NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pre-meeting briefing

Redacted

Ocrelizumab for treating primary progressive multiple sclerosis (ID938)

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

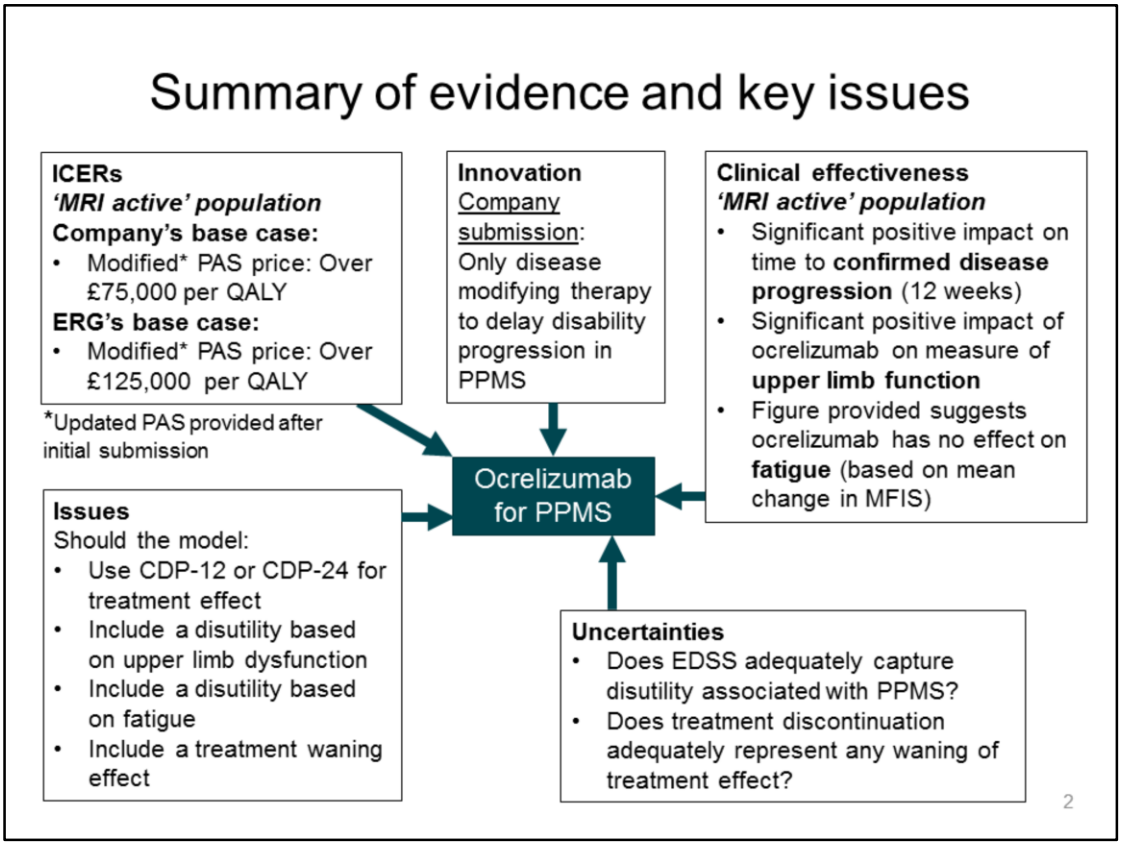
- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

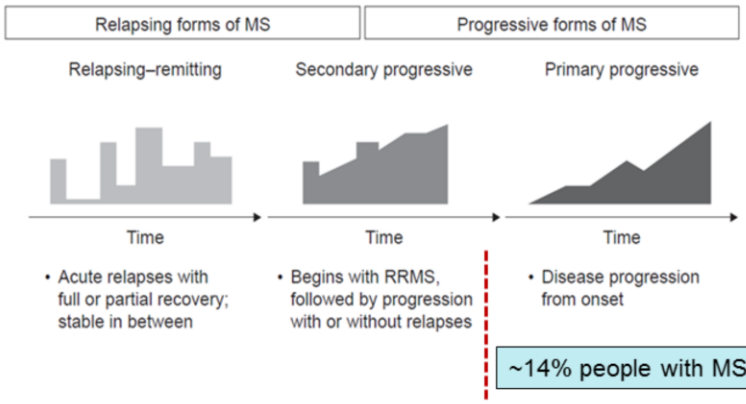
The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

1


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 confirmed disease progression (12 weeks)
• 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?
2

Multiple sclerosis

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



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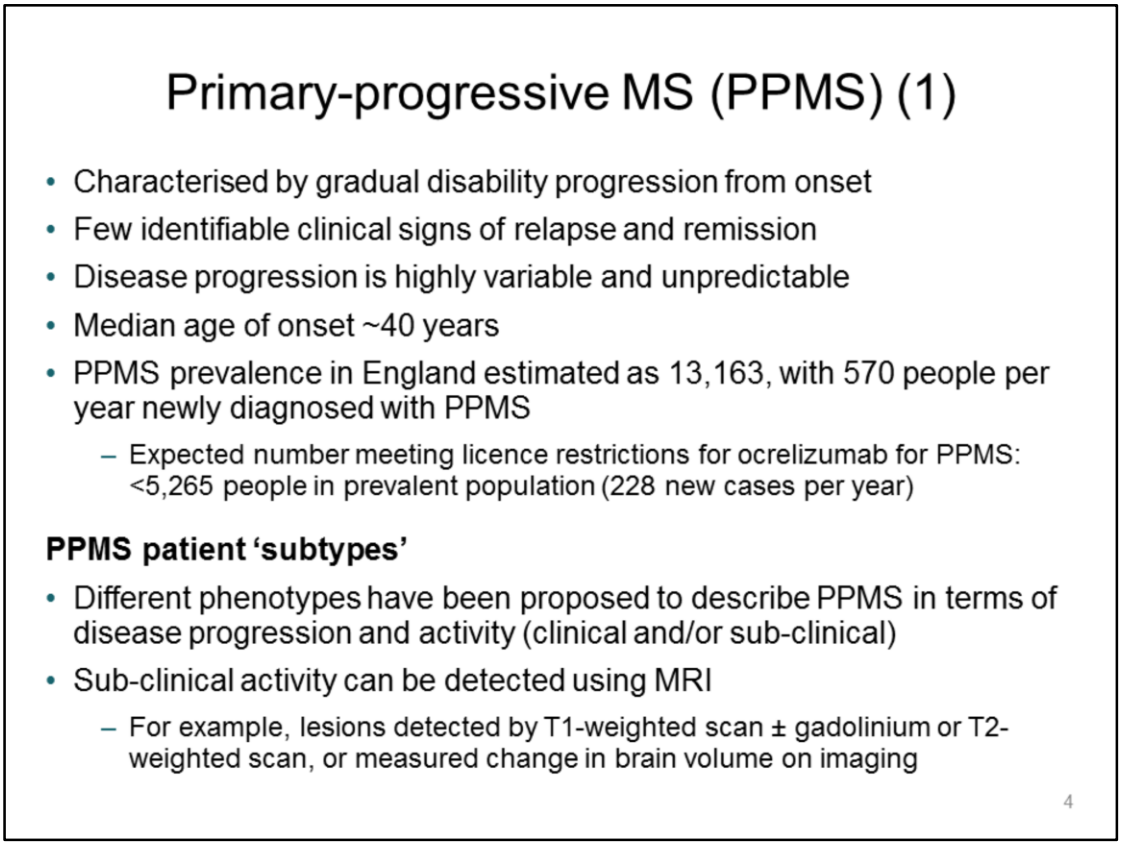
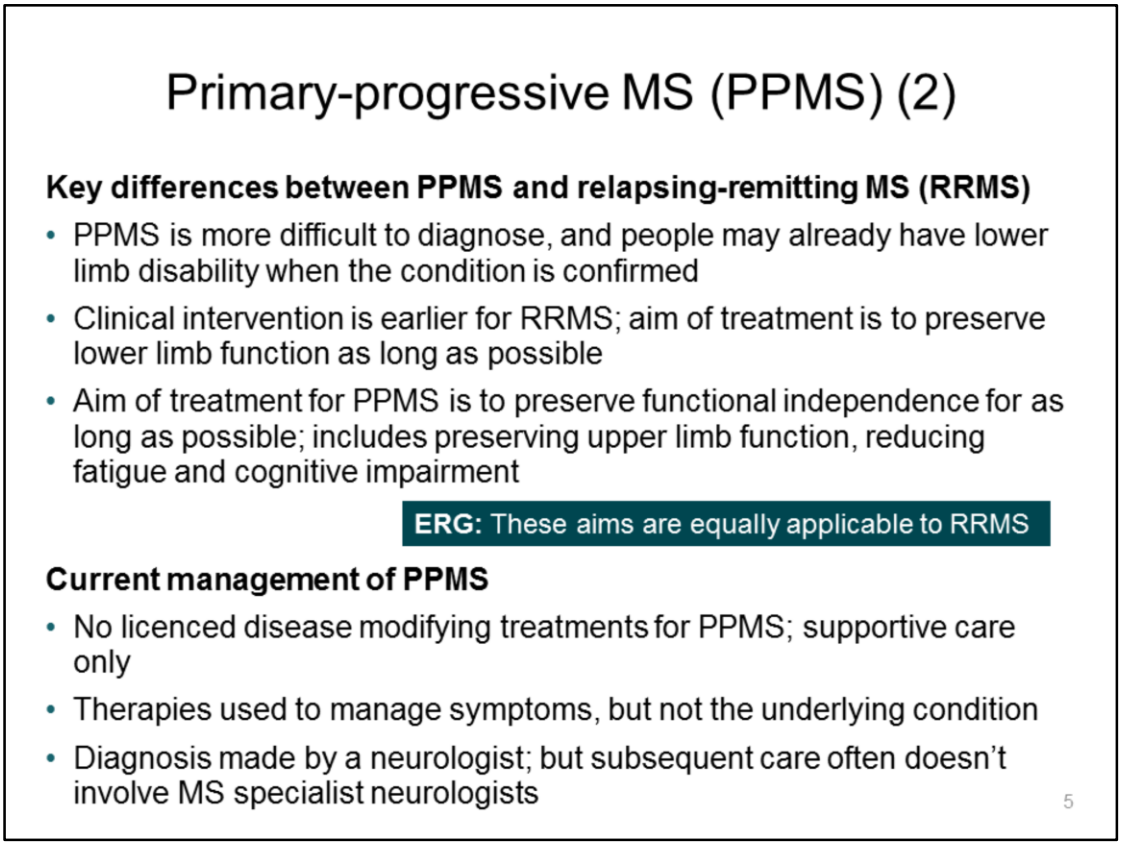
Source: Company submission, document B, section B.1.3.1.



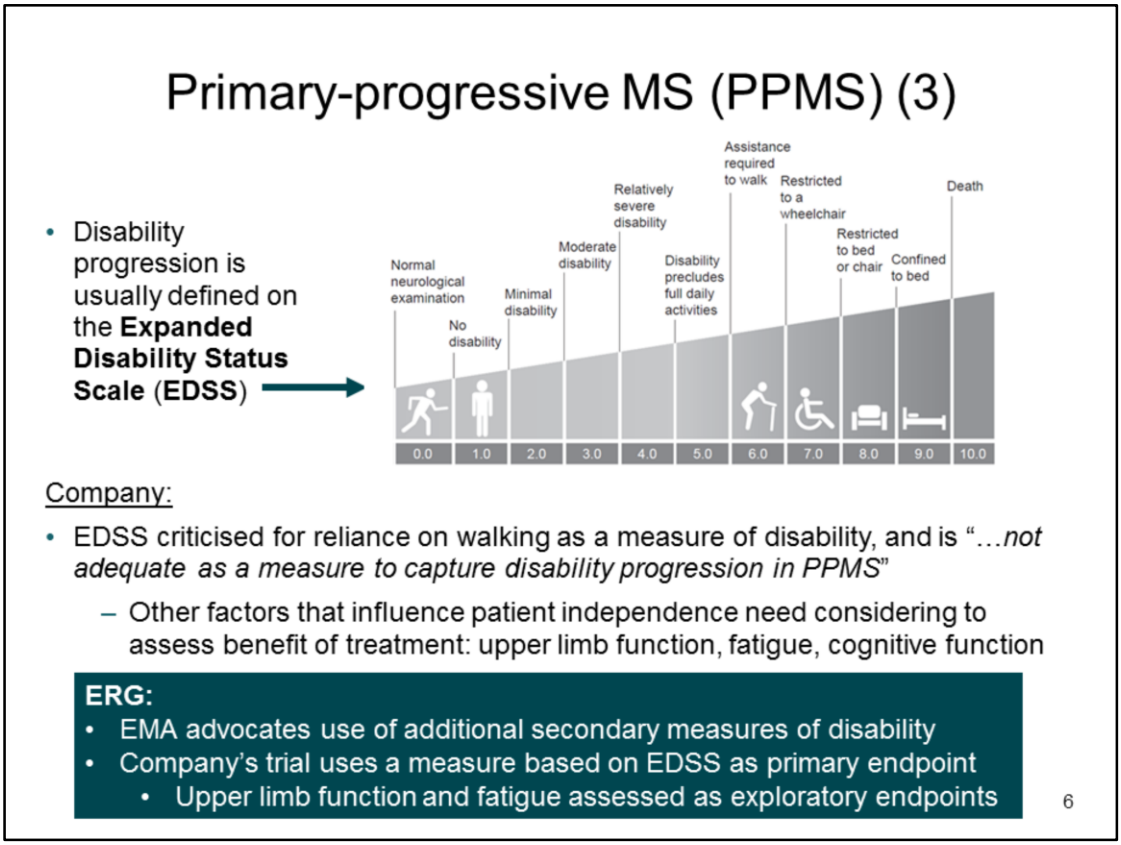
Source: Company submission, section B.1.3.

Further detail on PPMS phenotypes, as per the 'Lublin consensus statement', can be found in the company submission, document B, section B.1.3.2



Source: Company submission, document B, section B.1.3.2; Professional organisation submission from the Association of British Neurologists

Further details of therapies for the management of MS symptoms can be found in the company submission, document B, section B.1.3.4, table 4 (page 30). The ERG commented that this is based on Spanish guidelines and highlighted differences to UK practice (ERG report, section 2.2., page 28).



Source: Company submission, document B, section B.1.3.2; ERG report, section 2.1

A full description of the EDSS scores and domains can be found in the company submission, document B (table 3, page 20).

Company suggest that the EDSS scale is particularly insensitive to impairment to upper limb function and cognition at the higher end; for example, people may be stable on the EDSS (are restricted to a wheelchair; EDSS score of 7) but have progressive loss of upper limb/cognitive function that is not captured by an increasing EDSS score. Company submission, document B, section B.1.3.2.

Ocrelizumab (Ocrevus)

Marketing authorisation	Ocrelizumab is indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity
Mechanism	Humanised monoclonal antibody that selectively depletes CD20+ B cells
Administration and dose	Intravenous (IV) infusion • First 600 mg dose administered as two 300 mg infusions 2 weeks apart • Subsequent doses are administered as a single 600 mg infusions every 6 months A minimum interval of 5 months should be maintained between each dose
Cost	List price: £4,790 per 300 mg vial 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)

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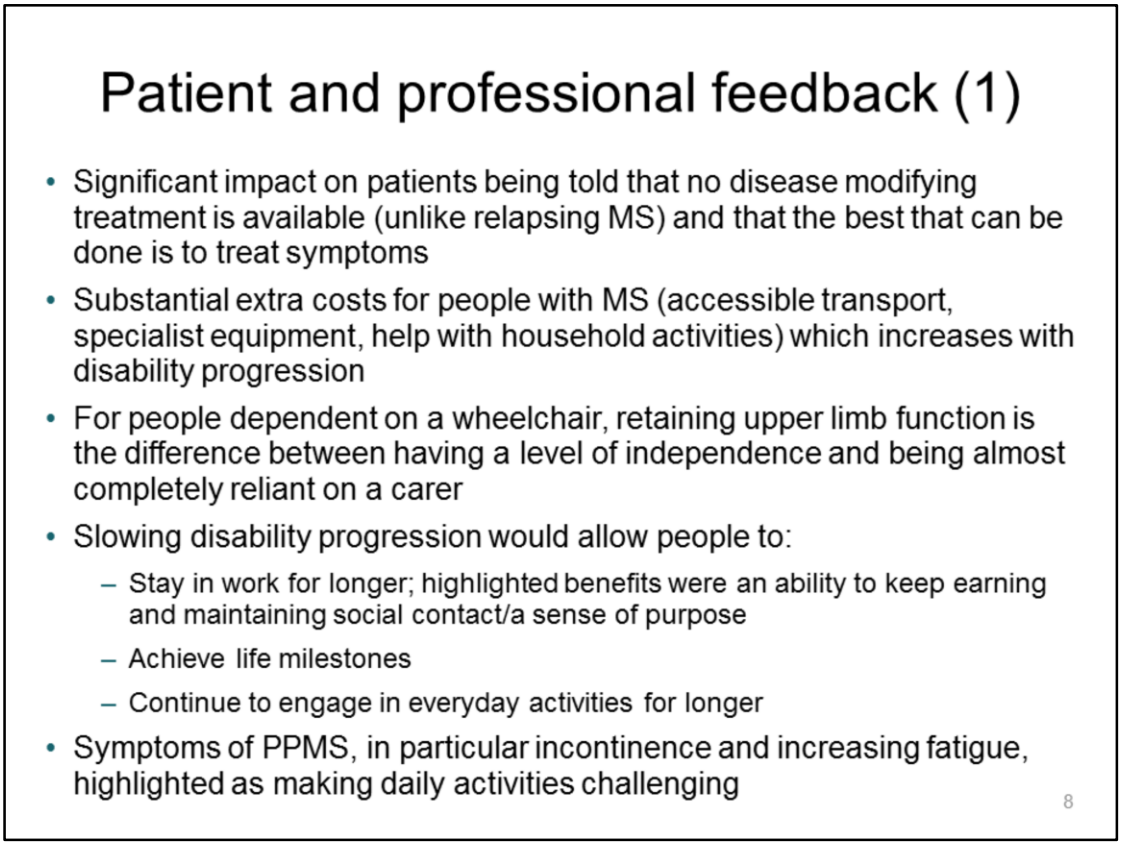
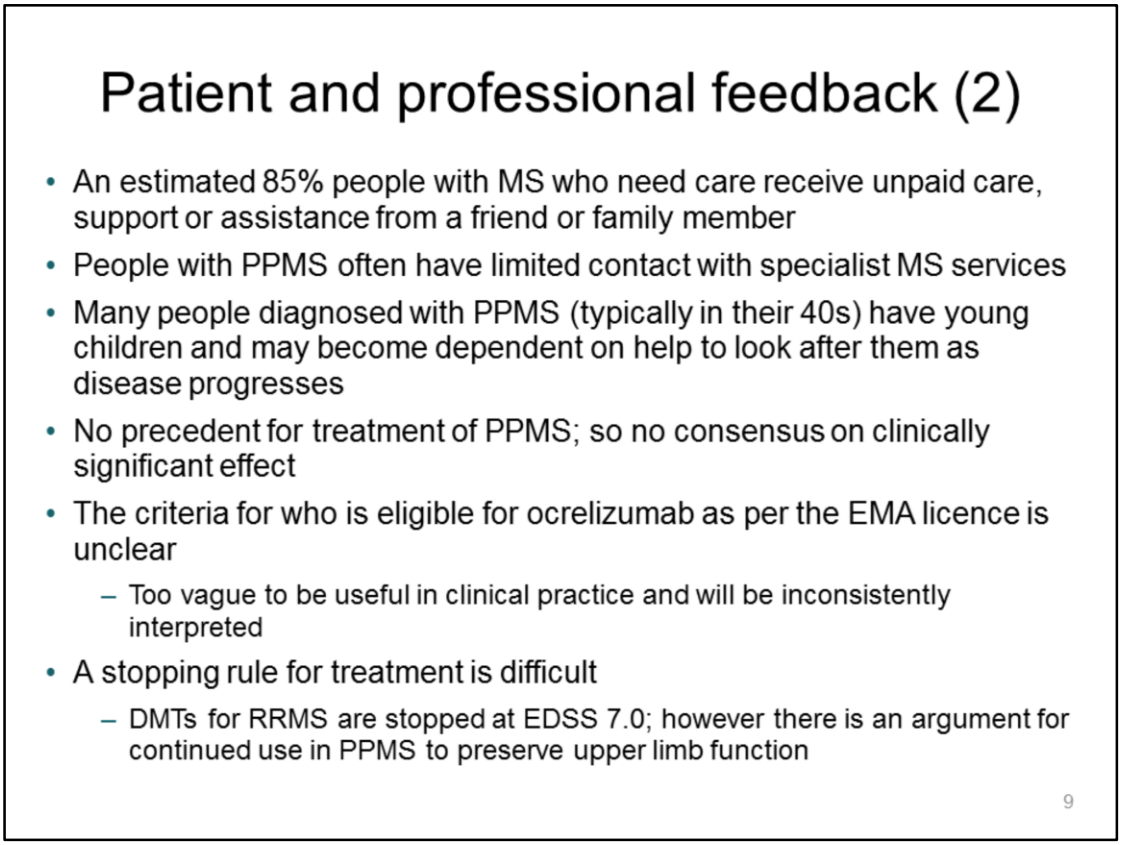
Source: Company submission, document B, section B.1.2



Source: This section summarises comments from:

- Association of British Neurologists
- MS Society
- Multiple Sclerosis Trust
- NHS England
- Patient expert statement
- Clinical expert statement



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- MS Society
- Multiple Sclerosis Trust
- NHS England
- Patient expert statement
- Clinical expert statement

Company's decision problem and deviations from final scope

	Final NICE scope	Company submission	Company rationale	ERG comments
Population	People with primary progressive multiple sclerosis (PPMS)	Restricted to people with: • early PPMS • imaging features characteristic of inflammatory activity ('MRI active')	Consistent with MA granted by the EMA	• ERG disagree with definition of 'early PPMS' used • 'MRI active' as defined does not reflect NHS practice *[Further comments on this in subsequent slide]* • No evidence presented for people >55 years old
Outcomes	• Disability • Disease activity • Patient-reported outcomes • Cognition and visual disturbance • Mortality • Adverse effects of treatment • Health-related quality of life	As per scope	-	Generally matches scope – although visual disturbance not measured as a separate outcome

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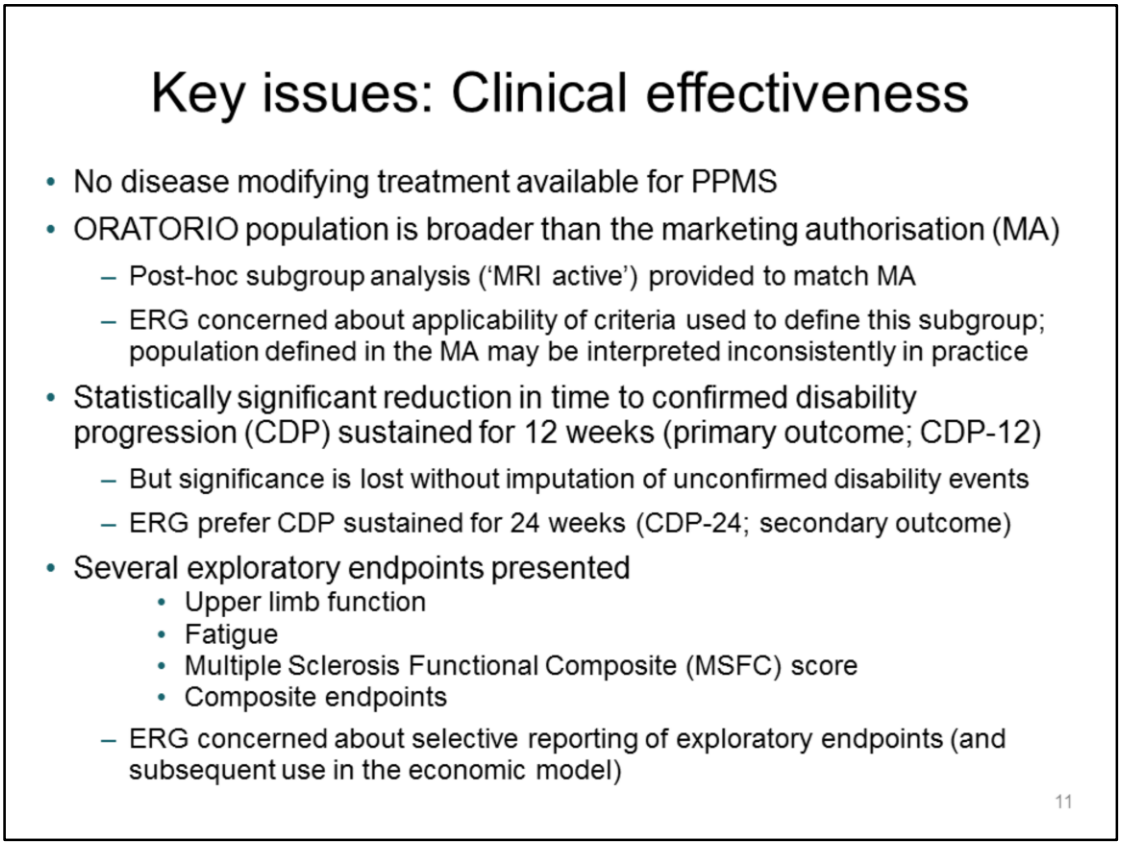
Source: Company submission, document B, section B.1.2 (table 1); ERG report, sections 3.1 and 3.4.

Company modified their indication (initially adults with PPMS) during scientific assessment on the basis that subgroup analysis showed more favourable results in younger patients and those presenting with T1-gadolinium enhancing lesions at baseline. ERG report, section 3.1 (page 29).

ERG commented that the marketing authorisation criteria of "early disease in terms of disease duration and level of disability" and "with imaging features characteristic of inflammatory activity" is vague and subjective. In the absence of more precise eligibility criteria for ocrelizumab, these criteria are at risk of being interpreted differently across the NHS.



Confirmed disability progression (CDP): Time to event of disability progression confirmed after 12 weeks (CDP-12) or 24 weeks (CDP-24)

Clinical evidence: ORATORIO trial

	WA25046 (ORATORIO)
Design	Phase III, multicentre, randomised, parallel-group, double blinded, placebo controlled
Population	• Diagnosis of PPMS (according to revised McDonald criteria) • 18 to 55 years • EDSS at screening: 3.0 to 6.5 • From onset of MS symptoms, disease duration of: – <15 years if EDSS at screening >5.0 – <10 years if EDSS at screening ≤5.0
Intervention	Ocrelizumab 600 mg (n=488; 24 from UK) • two 300 mg infusions separated by 14 days, every 24 weeks
Comparator	Placebo (n=244; 5 from UK)
Outcomes	• Confirmed disability progression: • sustained for at least 12 weeks (CDP-12) [Primary outcome] • sustained for at least 24 weeks (CDP-24) • Change in timed 25 foot walk • Change in T2 lesion volume and total brain volume • SF-36 physical component summary score

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Source: Company submission, document B, section B.2.3.1.

- Patients were enrolled at 182 investigational sites across 29 countries (Europe, North America, Australia and New Zealand, Latin America). There were five UK sites (company submission, document B, table 8, page 39)
- Patients were randomised between March 2011 and December 2012
- Study comprised screening period then 120 weeks double-blind treatment (5 full doses)

<u>Key exclusion criteria:</u>

- History of relapsing or secondary progressive MS
- Inability to complete MRI
- Previous treatment with B-cell targeted therapy or other medicine for treatment of MS
- Systemic corticosteroid therapy within 4 week prior to screening

<u>Exploratory endpoints:</u>

Clinical

- Time to sustained increase (≥20%) in 9-hole peg test (9-HPT)

Imaging

- Number of new/enlarging T2 lesions

- Change in cortical grey matter volume
- Change in white matter volume
- Change in T1 lesion volume

Patient reported outcomes

- Change in EQ-5D score
- Change in fatigue (on Modified Fatigue Impact Scale [MFIS])

Source: Company submission, document B, table 8 (page 39)

Extended control treatment period (company submission, document B, section B.2.6.5)

Post-hoc analysis (in response to EMA queries about efficacy).

'Extended control period data' comprises data from the double-blind controlled period plus any additional efficacy data from the extended control treatment period (up to point of clinical cut-off or first open label dose).

Open label extension

No data available.

Summary

Populations in the company's submission

Population	
ITT (intention to treat)	• Entire enrolled population from ORATORIO • Does not match marketing authorisation • Power calculations for the planned analyses were calculated for this population
'MRI active'	• Post-hoc subgroup to match marketing authorisation population • Used in economic model (base case)
'MRI active ≤50 years'	• Post-hoc subgroup analysis • Used in economic model (scenario analysis)

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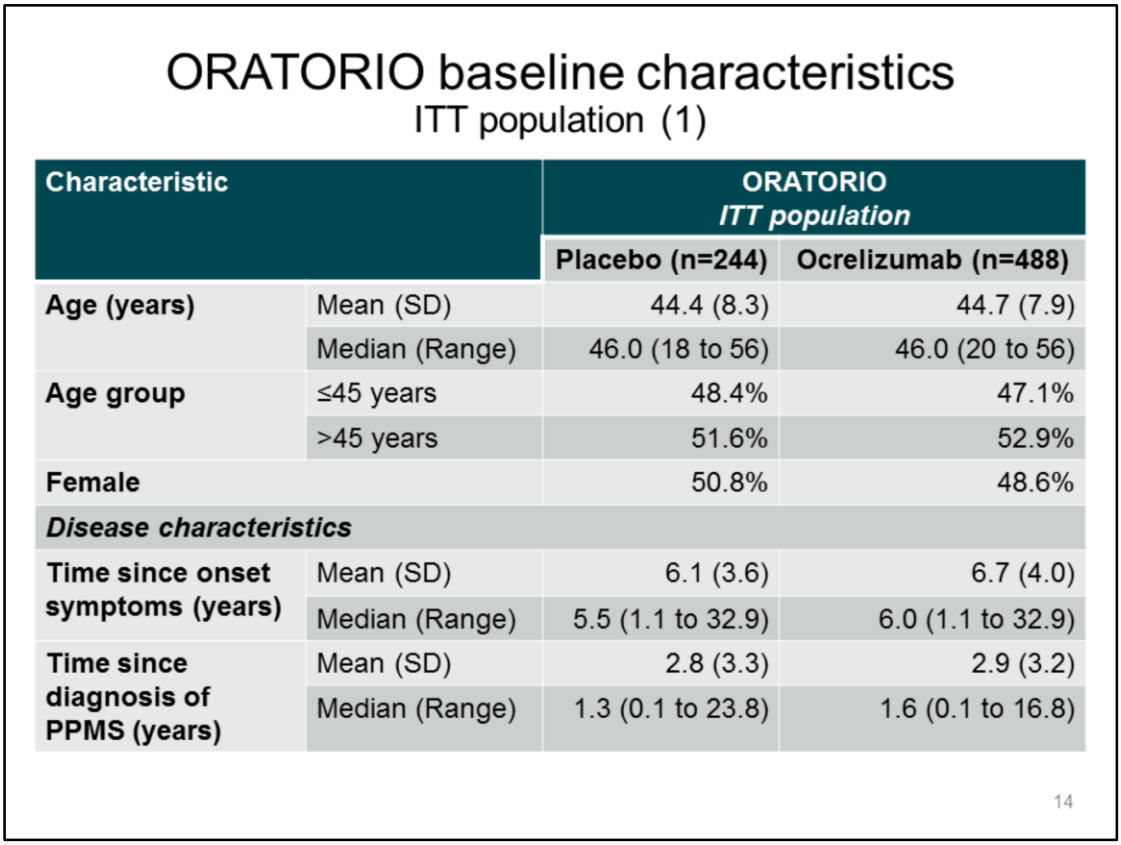

ORATORIO baseline characteristics
ITT population (1)

Characteristic		ORATORIO *ITT population*	
		Placebo (n=244)	Ocrelizumab (n=488)
Age (years)	Mean (SD)	44.4 (8.3)	44.7 (7.9)
	Median (Range)	46.0 (18 to 56)	46.0 (20 to 56)
Age group	≤45 years	48.4%	47.1%
	>45 years	51.6%	52.9%
Female		50.8%	48.6%
Disease characteristics			
Time since onset symptoms (years)	Mean (SD)	6.1 (3.6)	6.7 (4.0)
	Median (Range)	5.5 (1.1 to 32.9)	6.0 (1.1 to 32.9)
Time since diagnosis of PPMS (years)	Mean (SD)	2.8 (3.3)	2.9 (3.2)
	Median (Range)	1.3 (0.1 to 23.8)	1.6 (0.1 to 16.8)

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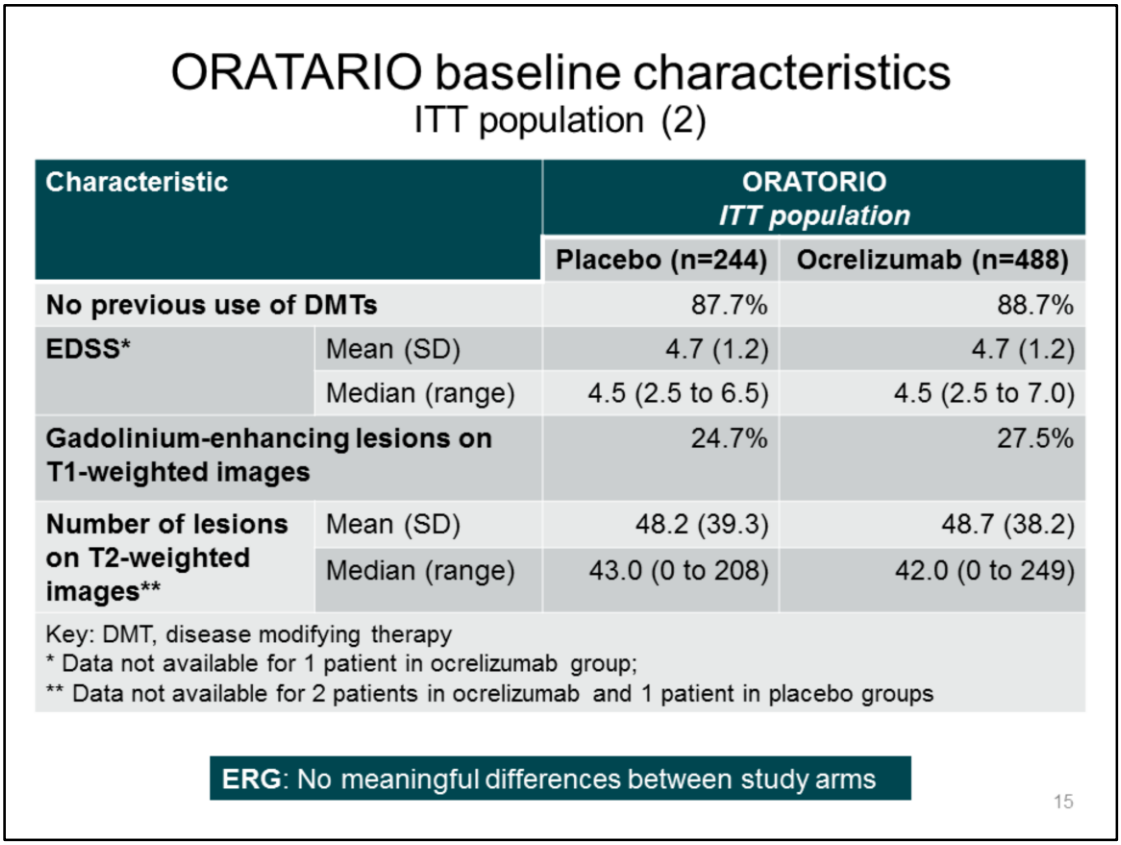
Source: Company submission, document B, section B.2.3.2, table 9

The full table of characteristics of participants across the study groups can be found in the company submission, document B, table 9 (page 42).



ORATARIO baseline characteristics

ITT population (2)

Characteristic		ORATORIO *ITT population*	
		Placebo (n=244)	Ocrelizumab (n=488)
No previous use of DMTs		87.7%	88.7%
EDSS*	Mean (SD)	4.7 (1.2)	4.7 (1.2)
	Median (range)	4.5 (2.5 to 6.5)	4.5 (2.5 to 7.0)
Gadolinium-enhancing lesions on T1-weighted images		24.7%	27.5%
Number of lesions on T2-weighted images**	Mean (SD)	48.2 (39.3)	48.7 (38.2)
	Median (range)	43.0 (0 to 208)	42.0 (0 to 249)

Key: DMT, disease modifying therapy
* Data not available for 1 patient in ocrelizumab group;
** Data not available for 2 patients in ocrelizumab and 1 patient in placebo groups

ERG: No meaningful differences between study arms

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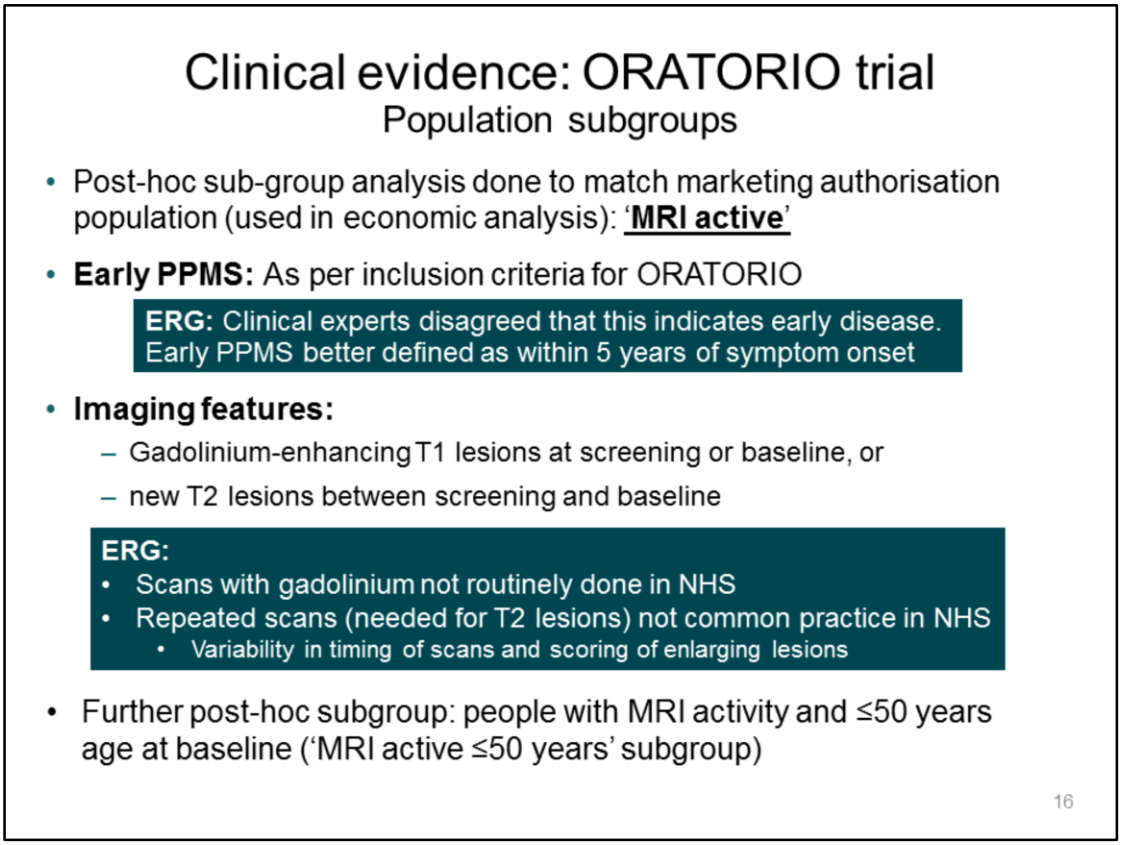
Source: Company submission, document B, section B.2.3.2, table 9; ERG report, section 4.2



Source: Company submission, document B, section B.2.6.7 and section B.2.7.2; ERG report, section 3.1.

MA: "adult patients with **early PPMS** in terms of disease duration and level of disability, and with **imaging features** characteristic of inflammatory activity"

'Early PPMS' ORATORIO inclusion and exclusion criteria :

- EDSS≤6.5
- Onset symptoms: <15 years (if EDSS>5.0), or <10 years (if EDSS≤5.0)

Enlarging T2 lesions were not measured at screening or baseline.

Pre-planned subgroups for analysis in the ORATORIO trial:

- Age (≤45 vs >45 years)
- Sex (male vs female)
- Baseline EDSS (≤5.5 vs >5.5)
- Region (USA vs ROW)
- Presence of gadolinium-enhancing T1 lesions at baseline MRI scan
- Prior MS DMTs with the exception of corticosteroids

- Duration since onset of MS symptoms (≤3 years, 3 to ≤5 years, 5 to ≤10 years, >10 years)
- Weight (≤75 vs >75 kg at baseline)
- BMI (<25 vs ≥25 kg/m2 at baseline)

Treatment effect (for CDP-12) favoured ocrelizumab in all subgroups, although effect was not statistically significant (study not powered for efficacy differences in subgroups). Company submission, document B, section B.2.3.1, table 8 (page 40) and section B.2.7. (page 69)

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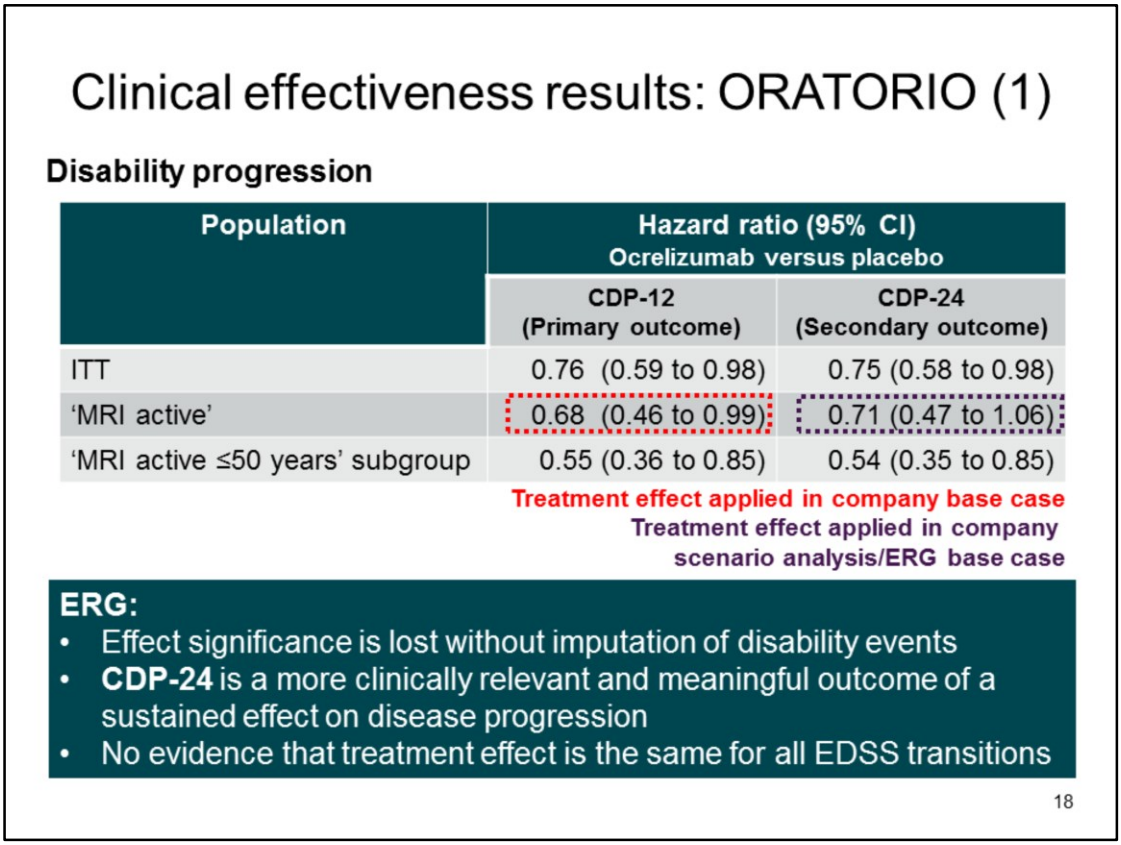
ORATORIO baseline characteristics

'MRI active' subgroup

Characteristic		ORATORIO *'MRI active' subgroup*	
		Placebo (n=104)	Ocrelizumab (n=189)
Age (years)	Mean (SD)	[redacted]	[redacted]
Female		[redacted]	[redacted]
Time since onset symptoms (years)	Mean (SD)	[redacted]	[redacted]
Time since diagnosis of PPMS (years)	Mean (SD)	[redacted]	[redacted]
No previous use of DMTs		[redacted]	[redacted]
EDSS	Mean (SD)	[redacted]	[redacted]
Gadolinium - enhancing lesions on T1 at:	Baseline	[redacted]	[redacted]
	Screening or baseline	[redacted]	[redacted]

ERG: No major imbalances apparent between study arms

Source: ERG report, section 4.2 (table 4)



Source: Company submission, document B, sections B.2.6.2, B.2.6.3 and B.2.7.2; ERG report, sections 4.4 and 4.5.1.

Analysis included **imputed events** if an initial EDSS disability progression event occurred, but treatment was discontinued before it could be confirmed. Analysis of 12-week CDP based only on un-imputed events changed the HR to 0.82 (p-value to 0.1477). ERG report section 4.4, page 51.

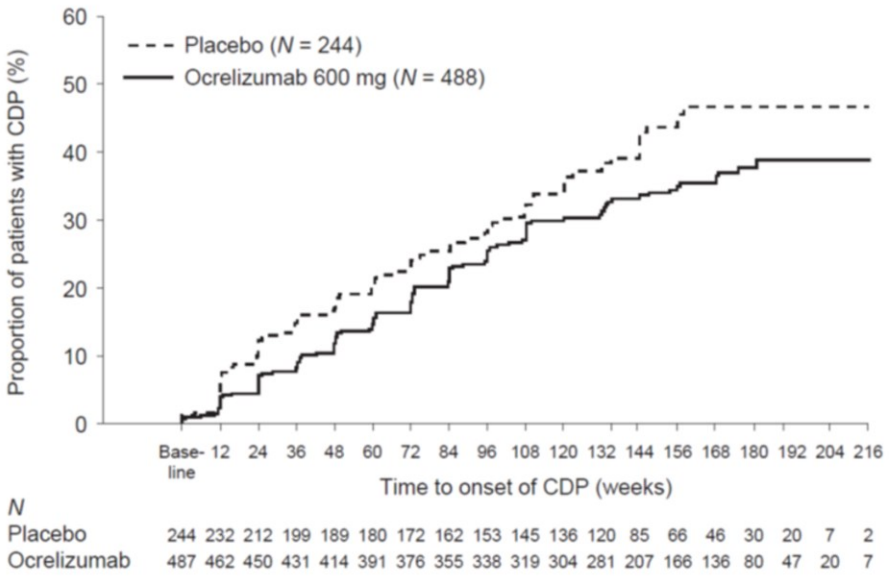
CDP-24 as the ERG's preferred outcome

EDSS can be affected temporarily by factors other than disease progression including variations due to relapses (relatively rare in PPMS, ~5% patients) or deterioration due to intercurrent illnesses (e.g. infections) or psychological factors. While these periods of deterioration can last for months they would generally be expected to have improved back to baseline by 6 months. ERG report, section 4.3, table 5 (page 46).

Further ERG analysis suggests that the hazard ratio changes with length of follow up, and that the use of a single size of effect for all EDSS transitions is an oversimplification. Full analysis can be found in the ERG report, section 4.8 (page 70).

Clinical effectiveness results: ORATORIO (2)

Time to 12-week CDP in ORATORIO (ITT population)



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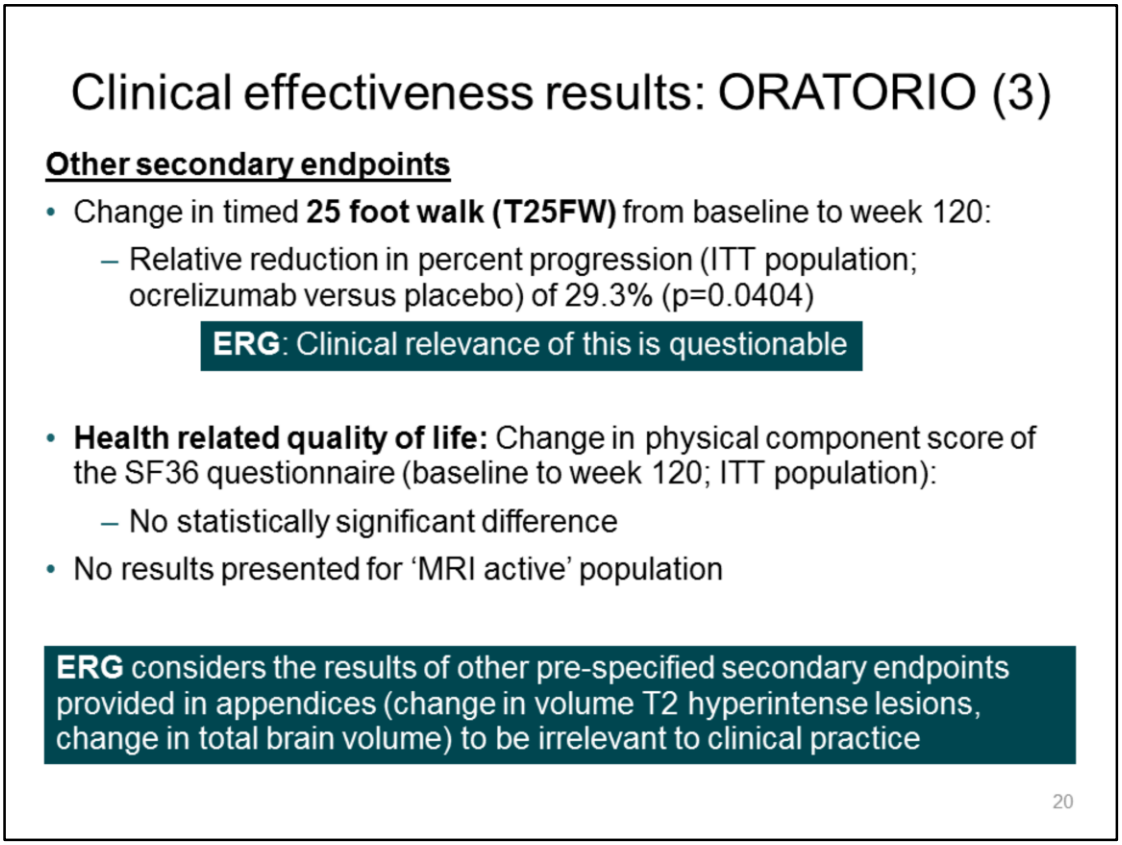
Source: Company submission, document B, section B.2.6.2. (figure 10)

The ERG noted that the treatment arms separate and then appear to converge (weeks 84 to 120) and that it is unlikely that the same transitions (between EDSS states) are being compared across time points. Further ERG analysis suggested that the hazard ratio between treatment arms changes with time, and the use of a single effect size for all EDSS transitions is likely to be 'a considerable oversimplification'. See ERG report, section 4.8 for full analysis.



Source: T25FW: Company submission, appendix K, section 1.1.1. ERG report, section 4.5.1 (page 56)
Health related quality of life: Company submission, appendix K, section 1.3. ERG report, section 4.5.1 (page 56)
Other pre-specified secondary outcomes: ERG report, section 4.5.1 (page 56)

Clinical effectiveness results: ORATORIO (4)

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

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)
- **Composite endpoints:** Ocrelizumab increased the proportion of people with No Evidence of Progression (p=0.0006) and No Evidence of Progression and Active Disease (p<0.001)

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Sources: Company submission, document B, sections B.2.6.4 and B.2.6.7 (9-HPT); ERG report, section 4.1.4 and section 4.3 (table 5)
Company submission, appendix K, section 1.6.1. (MSFC)
Company submission, appendix K, section 1.7.1 (PASAT)
Company submission, document B, section B.2.6.1 (Composite endpoints)
ERG report, section 4.5.1.

9-hole peg test (9-HPT)
Assesses upper limb function by measuring the time taken to place 9 pegs in holes in a block, and then remove them (repeated 4 times, twice for each arm).
ERG comment that it is a widely used and validated outcome measure in MS, although their clinical expert commented that it is a poor surrogate measure of disability. The ≥20% threshold has been used in previous studies but is not validated at all stages of disease. Outcome does not test the ability of upper limbs to do meaningful tasks which would cause loss of independence (for example, feeding and dressing). ERG report, section 4.3 (table 5).

Composite endpoints (Company submission, document B , section B.2.6.4)
No Evidence of Progression (NEP)

Combined absence of 12-week confirmed progression on Disability (EDSS), upper limb function (9-HPT) and ambulation (T25FW).

No Evidence of Progression or Active Disease (NEPAD)

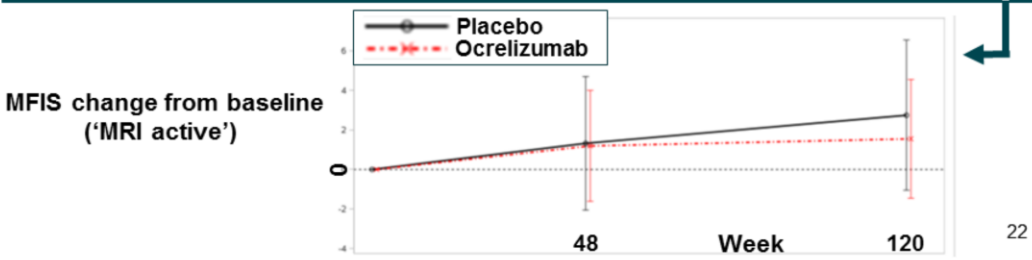
NEP plus no brain MRI-measured disease activity.

Clinical effectiveness results: ORATORIO (5)

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

Population	Change in fatigue from baseline to week 120		Difference in adjusted 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:
- MFIS used in economic model - the proportion of people with clinically meaningful fatigue (>38) – not specified in study protocol
- **'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



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Source: Company submission, document B, section B.2.6.4, adapted from figure 24A, section B.2.6.7; ERG report, section 4.5.1 and section 4.1.4.

Modified Fatigue Impact Scale (MFIS)
Scores range from 0 to 84 (higher score indicates higher fatigue).
Company use score of >38 to indicate clinically important level of fatigue for economic modelling.
ERG report, section 4.1.4. (page 37)

Exploratory outcomes not reported in company submission:
- Proportion of patients with confirmed disability progression at Week 120
- Change from baseline in EDSS score
- Cortical grey matter brain volume and white matter volume (presented in subgroup analyses only)
- MFIS subscale scores from baseline to Week 120.
- Change from baseline in total non-enhancing T1 lesion volume.

ERG report, section 4.1.4. (page 37)

Clinical effectiveness results: ORATORIO (6)

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

- Only intended to generate hypotheses - no formal conclusions should be drawn
  - Incorporation of 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

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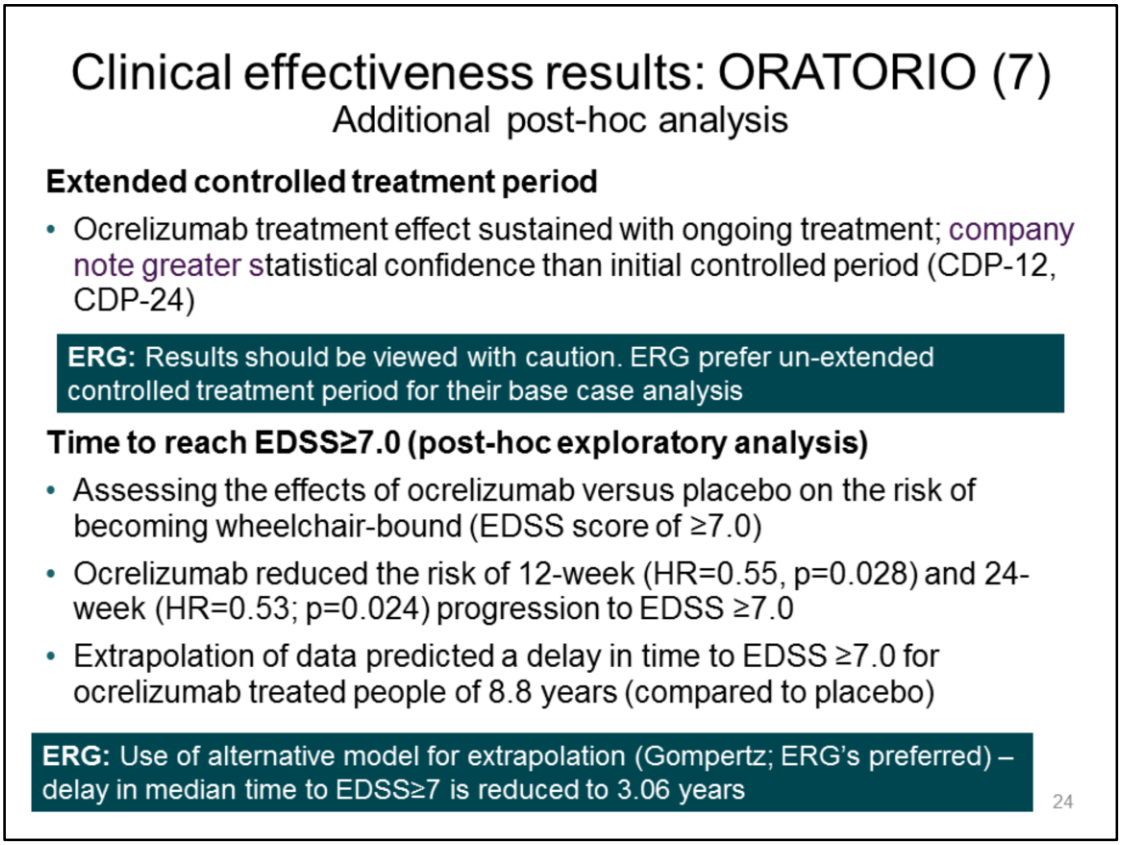

Source: Company submission, document B, section B.2.6.5.; ERG report, section 4.8.

Risk of becoming wheelchair bound (defined as reaching an EDSS score of 7.0) suggested to be a particular concern for people with an EDSS score of 4.0 to 6.0 (majority of people in the ORATORIO trial)

During ***double blind treatment period*** ocrelizumab reduced the risk versus placebo of 12-week (HR: 0.61; p = 0.1046) and 24-week (HR: 0.60; p = 0.0959) confirmed disease progression to EDSS ≥ 7.0.

ORATORIO: Adverse events (AEs)

Event	Placebo (n=239)	Ocrelizumab (n=486)
Any AE	90.0%	95.1%
Serious AE	22.2%	20.4%
AE leading to withdrawal from treatment	3.3%	4.1%
Death	0.4%	0.8%
Infusion related reactions (IRRs; ≥1)	**25.5%**	**39.9%**
Serious IRRs	0.0%	1.0%
Infection	67.8%	69.8%
Upper respiratory tract infection	**5.9%**	**10.9%**
Malignancy	**0.8%**	**2.3%**
Relapses	11.3%	4.9%

- 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)

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Source: Company submission, document B, section B.2.10. ERG report, section 4.5.1. (page 59)

Further details on adverse events in ORATORIO can be found in the company submission, document B, section B.2.10.

Key issues: cost effectiveness

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

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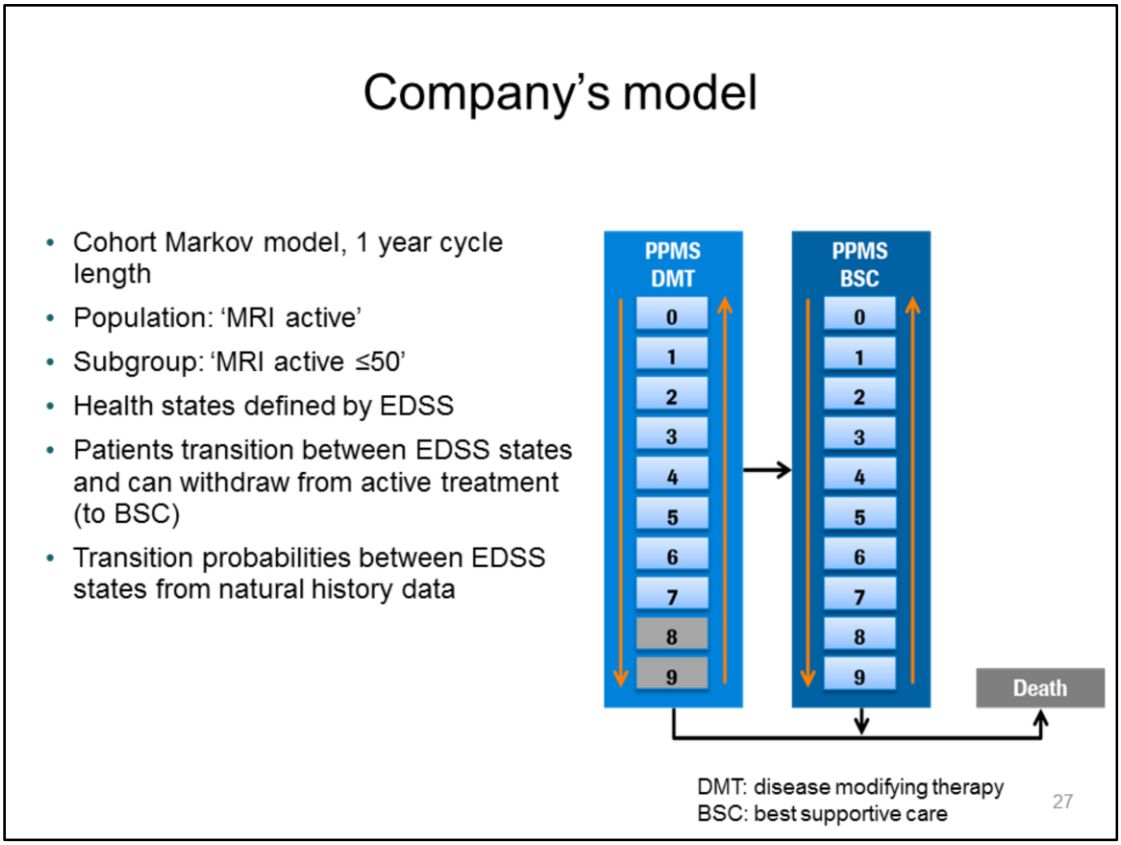
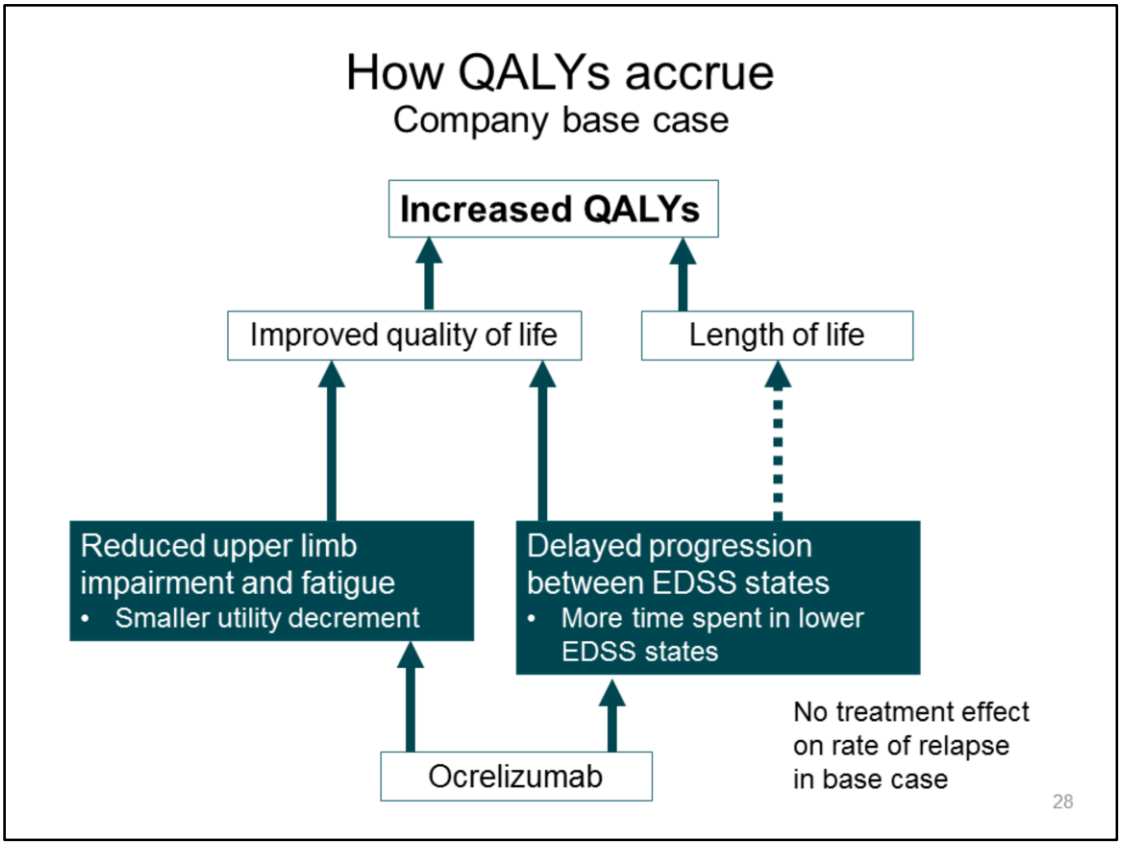


Source: Company submission, document B, figure 28 (page 94), section B.3.3.3 (page 104)

Patient level data from ORATORIO used to inform baseline distribution of EDSS states (3.0 to 7.0). Company submission, document B, section B.3.3.1.

Ocrelizumab treatment is discontinued when people progress to EDSS ≥8.

People can regress to less severe EDSS stage, based on observed natural history data. No treatment effect is applied to these transitions (in line with previous RRMS appraisals). Company submission, document B, sections B.3.3.2. and B.3.6.2.



No direct treatment effect on mortality, but some indirect effect as a result of delaying disability progression. ERG report, section 5.2.11.

Model assumptions (1)

Factor	Company base case	Company's justification	ERG preferred
Upper limb function not adequately captured by EDSS	Utility decrement applied to EDSS states for **upper limb impairment** Effect of ocrelizumab in reducing upper limb impairment taken from ORATORIO data	Regression analysis of EQ-5D data showed that clinically meaningful upper limb dysfunction (as measured by 20% increase in 9-HPT) impacted EQ-5D independent of EDSS	Utility decrement not included ***Further detail in later slides***
Impact of fatigue on functioning is not adequately captured by EDSS	Utility decrement applied to EDSS states for **fatigue** Effect of ocrelizumab in reducing fatigue taken from ORATORIO data	Regression analysis of EQ-5D data showed that clinically meaningful fatigue (as measured by MFIS score >38) impacted EQ-5D independent of EDSS	Utility decrement not included ***Further detail in later slides***

9-HPT, 9-hole peg test; EDSS, Expanded disability status scale; MFIS, Modified fatigue impact scale

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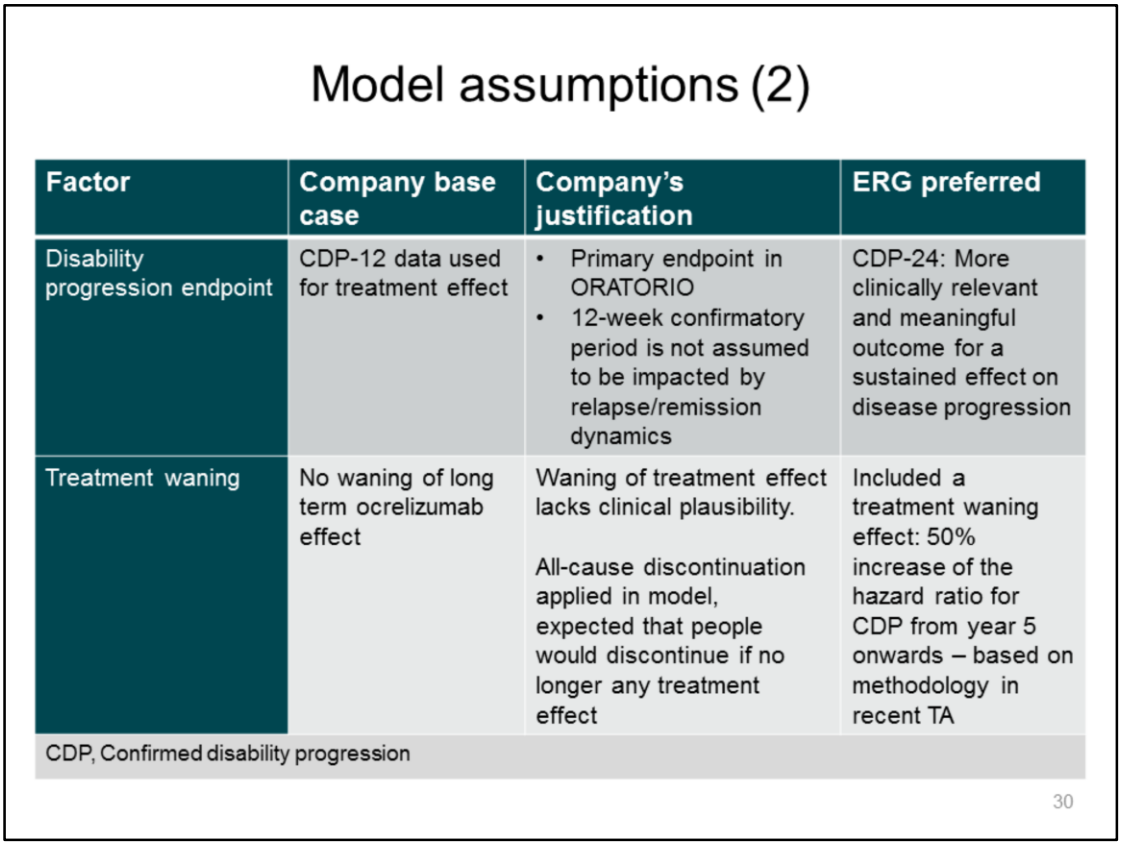
Source: Company submission, document B, section B.3.6.2

The ERG considered the following to be reasonable assumptions:

- Treatment effect is applied to EDSS progression but not regression
- Cost of disease management per EDSS health state based on estimates from RRMS patients
- Only adverse events with 'considerably higher' frequency in the ocrelizumab arm were included in the model. Adverse events were assumed to be similar in the ITT, MRI active, and MRI active ≤50 populations.

ERG report, section 5.2.11.



Model assumptions (2)

Factor	Company base case	Company's justification	ERG preferred
Disability progression endpoint	CDP-12 data used for treatment effect	• Primary endpoint in ORATORIO • 12-week confirmatory period is not assumed to be impacted by relapse/remission dynamics	CDP-24: More clinically relevant and meaningful outcome for a sustained effect on disease progression
Treatment waning	No waning of long term ocrelizumab effect	Waning of treatment effect lacks clinical plausibility. All-cause discontinuation applied in model, expected that people would discontinue if no longer any treatment effect	Included a treatment waning effect: 50% increase of the hazard ratio for CDP from year 5 onwards – based on methodology in recent TA

CDP, Confirmed disability progression

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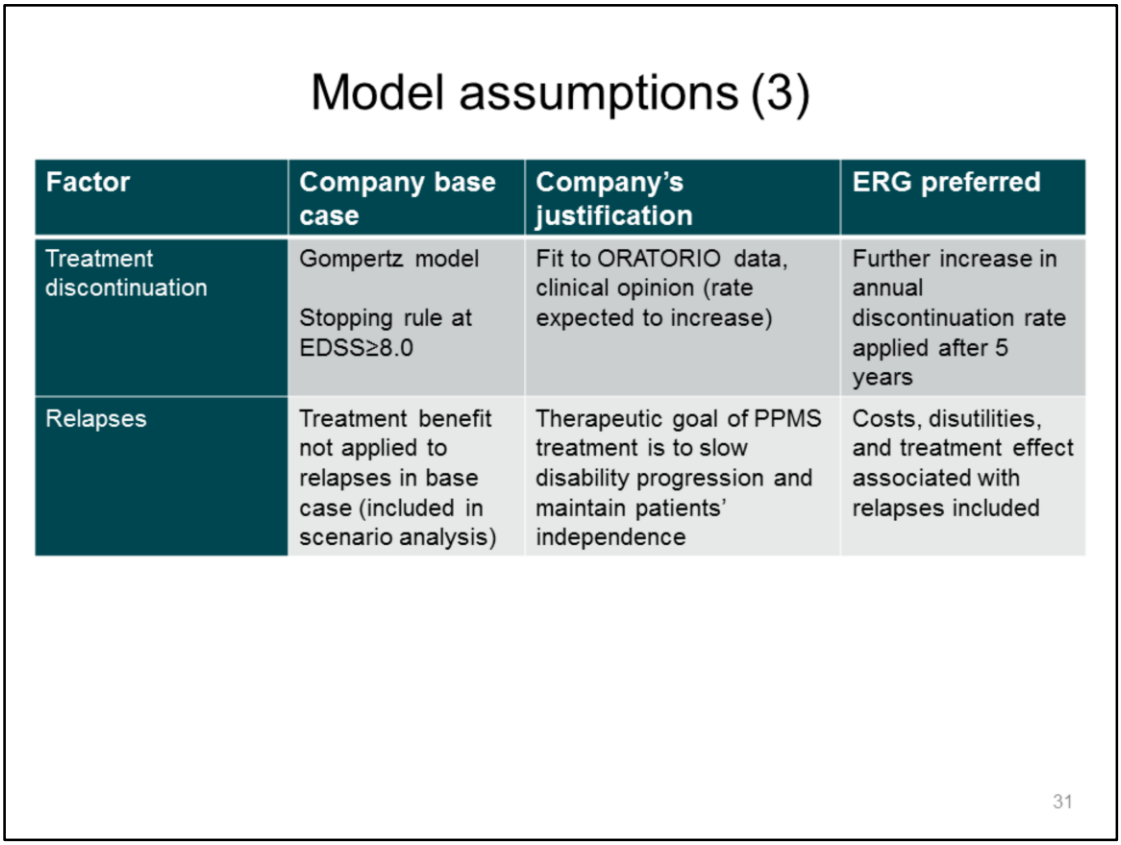
Source: Company submission, document B, section B.3.6.2; ERG report, section 5.2.6.



Model assumptions (3)

Factor	Company base case	Company's justification	ERG preferred
Treatment discontinuation	Gompertz model Stopping rule at EDSS≥8.0	Fit to ORATORIO data, clinical opinion (rate expected to increase)	Further increase in annual discontinuation rate applied after 5 years
Relapses	Treatment benefit not applied to relapses in base case (included in scenario analysis)	Therapeutic goal of PPMS treatment is to slow disability progression and maintain patients' independence	Costs, disutilities, and treatment effect associated with relapses included

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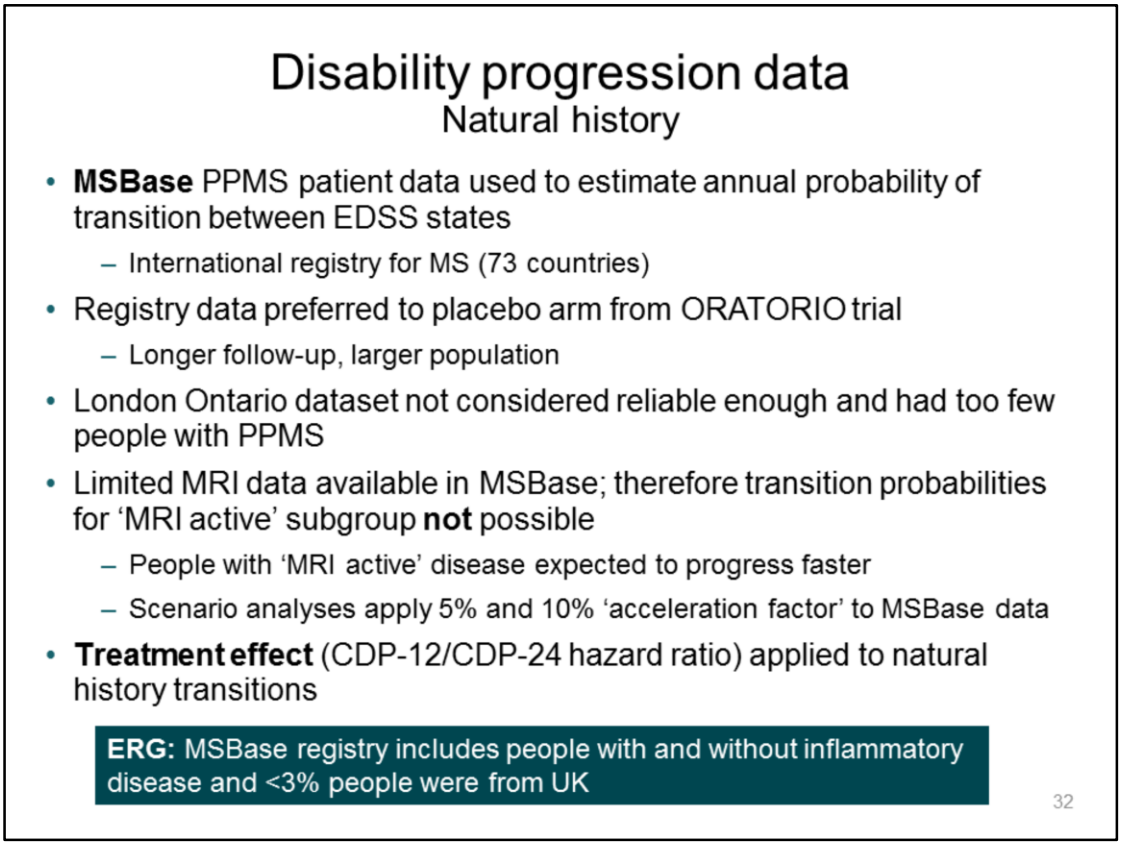
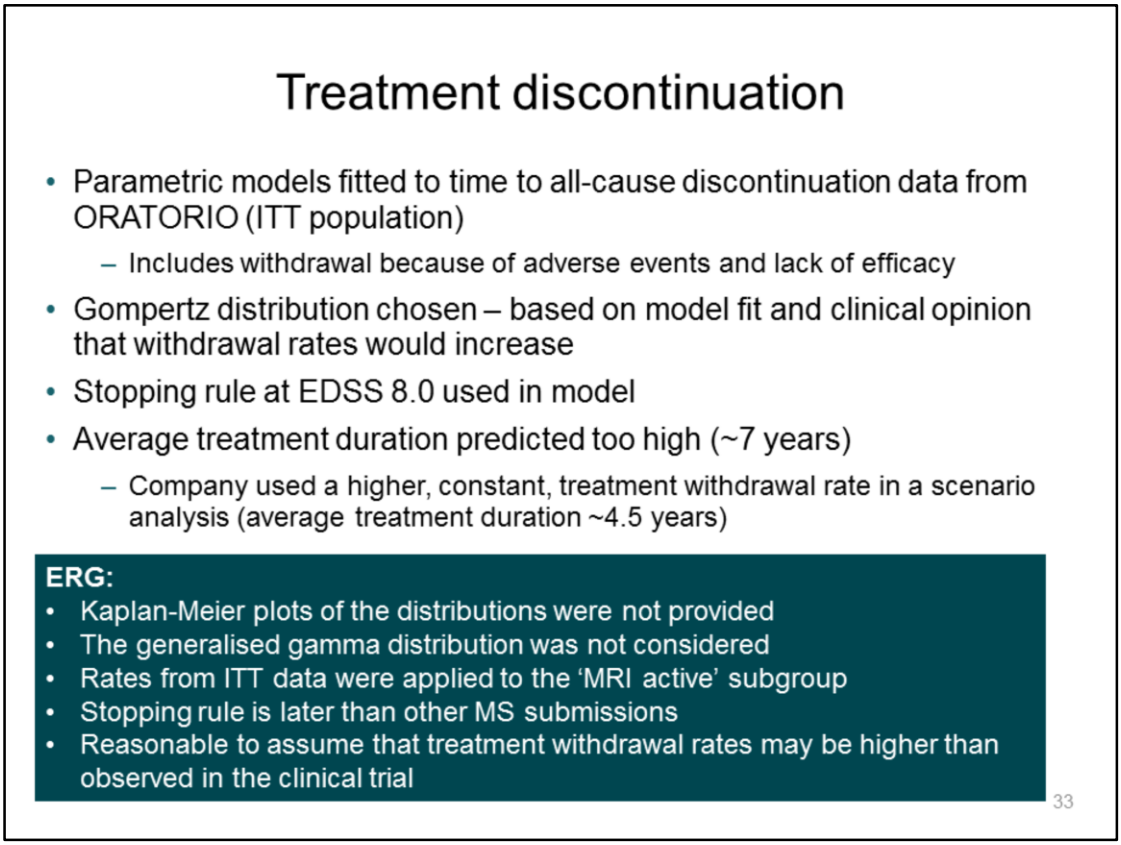
Source: Company submission, document B, section B.3.6.2 and section B.3.3.3



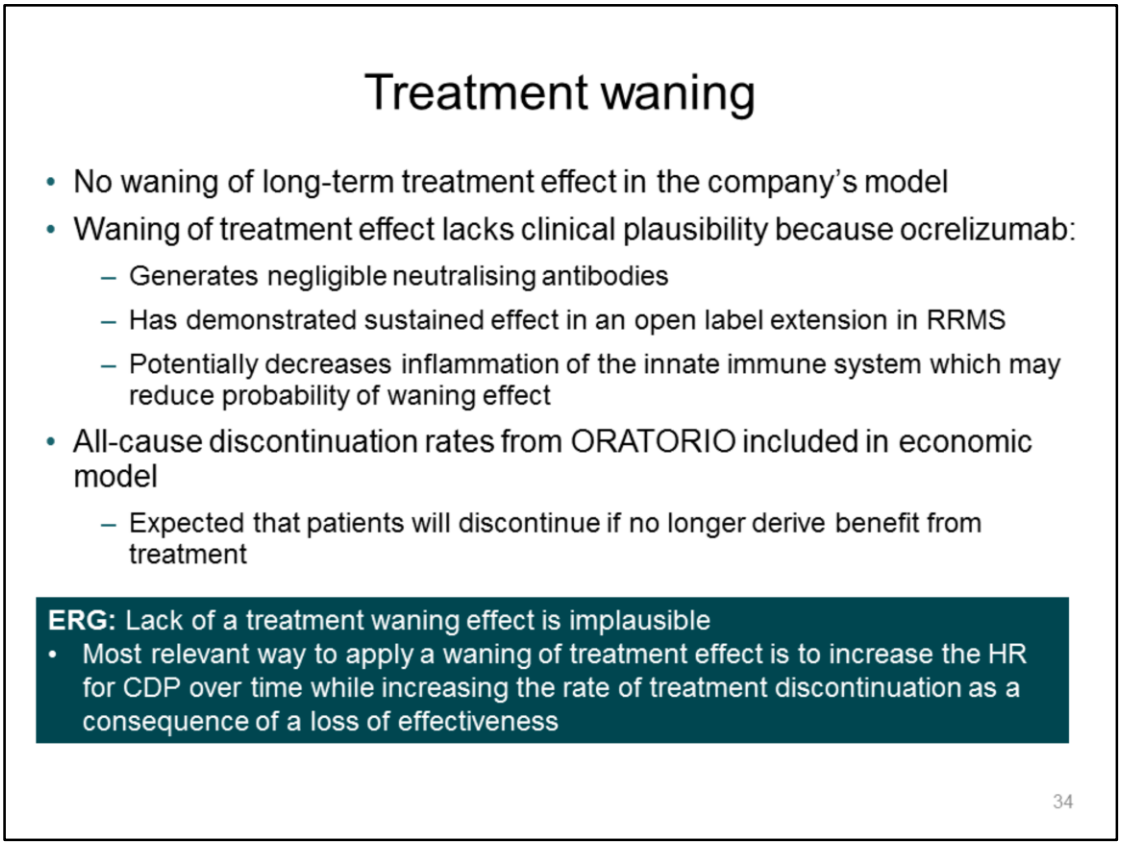
Source: Company submission, document B, section B.3.3.2.; ERG report, section 5.2.6.

Treatment effect (hazard ratio) applied in model ('MRI active'):
CDP-12: 0.68 (company base case)
CDP-24: 0.71 (ERG's base case / company scenario analysis)



Source: Company submission, document B, section B.3.3.5; ERG report, section 5.2.6., section 5.2.11.

Model fit statistics (AIC and Log Likelihood) were provided for distributions fitted to all-cause discontinuation data from ORATORIO: Exponential, Weibull, Log Logistic, Log normal and Gompertz. Company submission, document B. section B.3.3.5. (table 50).



Source: Company submission, document B, section B.3.3.6; ERG report, section 5.2.6.

Adverse events in economic model

- Only adverse events that occurred more frequently in the ocrelizumab arm of ORATORIO with a difference >3% are included in the model
  - Malignancies also included because of their high cost and impact on health related quality of life
- Adverse events assumed constant over time
- Probability of adverse events calculated from ITT population and applied to 'MRI active' and 'MRI active ≤50' in model

Adverse event	Ocrelizumab		Placebo	
	3-year probability	Yearly probability	3-year probability	Yearly probability
Infusion related reaction	39.9%	15.6%	0%	0%
Malignancy	2.3%	0.8%	0.8%	0.3%
Upper respiratory tract infection	10.9%	3.8%	5.9%	2.0%

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

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Source: Company submission, document B, section B.3.3.7; ERG report, sections 4.5.2 and 5.2.7.

Health related quality of life (1)

Baseline utility by EDSS state

- EQ-5D-3L collected in ORATORIO and pooled between trial arms to derive values for each health state
- Utility values for EDSS states not captured in ORATORIO were taken from published 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
- Disutility for caregivers was also included; derived from TA127

EDSS	Utility values ORATORIO	Utility values Orme et al.	Caregiver disutility
0	NA	0.837	0.000
1	NA	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	NA	-0.082	-0.107
9	NA	-0.228	-0.140
	Base case utility values		

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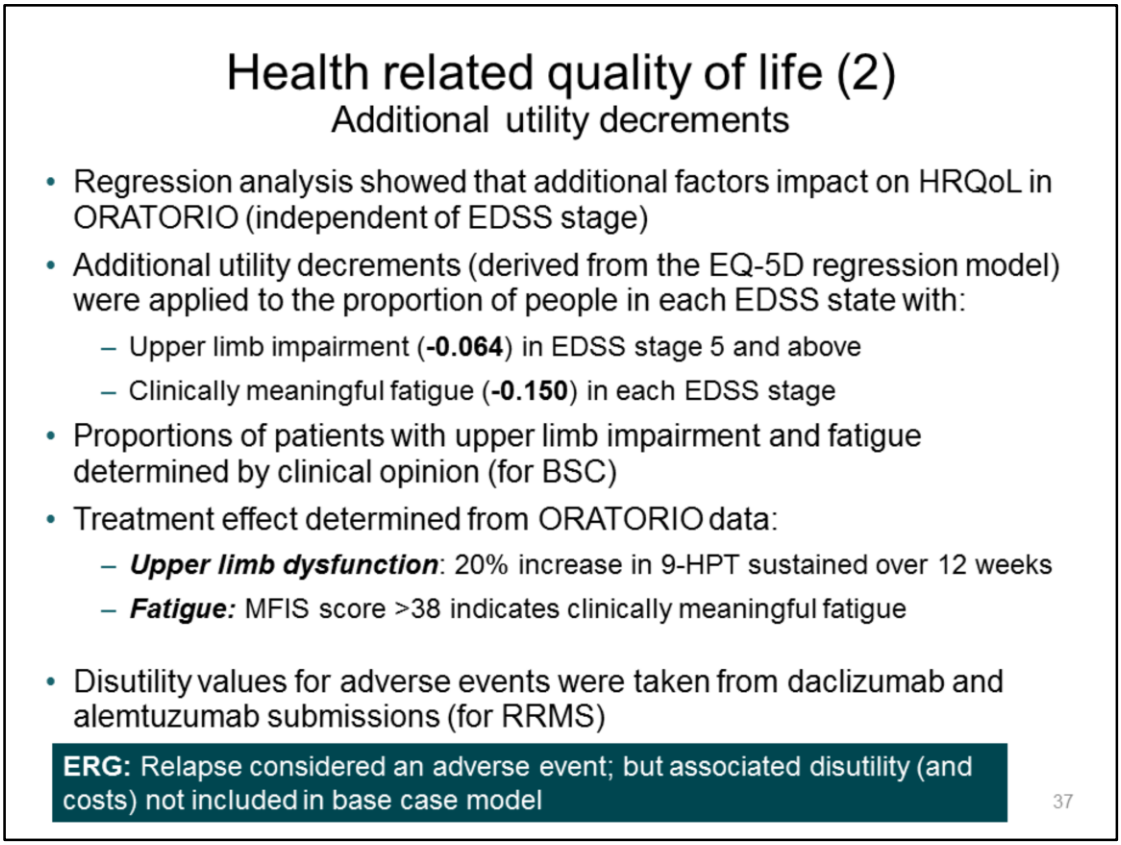
Source: Company submission, document B, sections B.3.4.1, B.3.4.5

TA127: Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis. Published August 2007.
Carer disutilities: These values were obtained from TA127 and were derived from a population of carers providing care for people with Alzheimer's disease and adjusted to reflect the time spent providing care for people with multiple sclerosis, as seen in the UK MS survey. ERG report, section 5.2.9 (page 101)

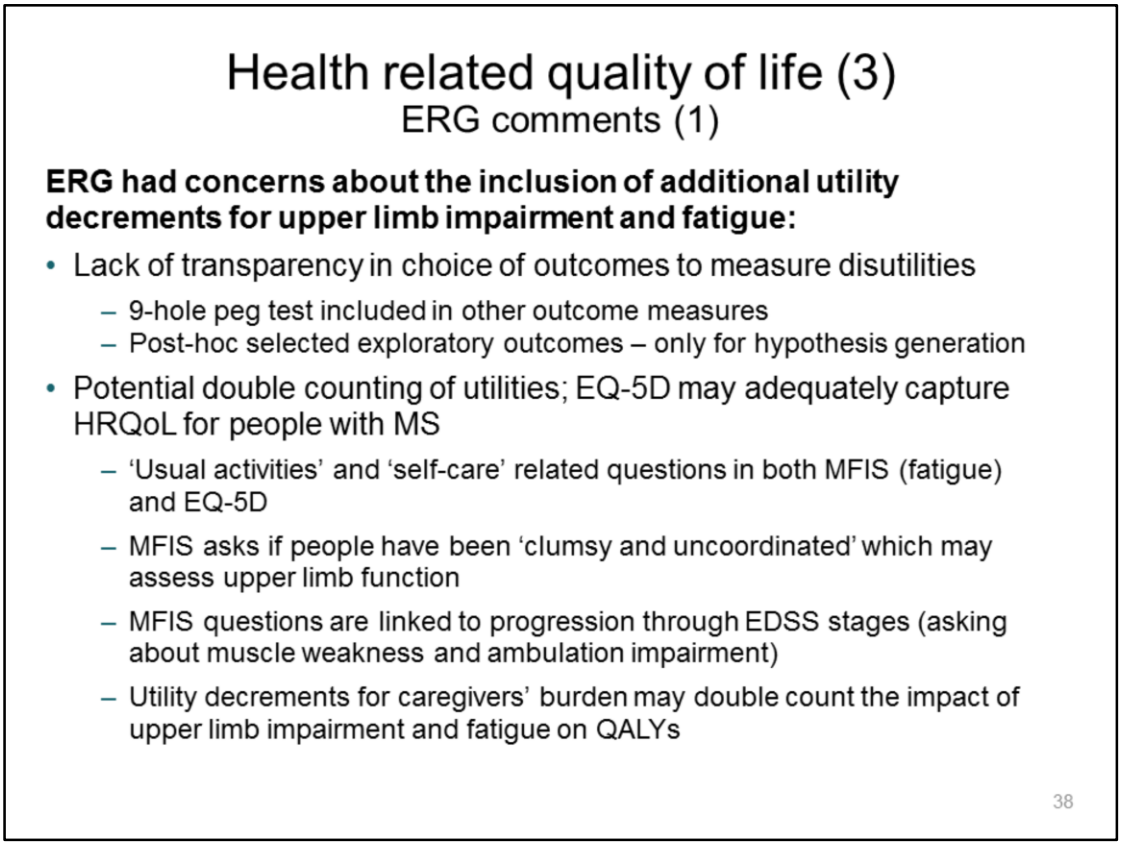


Source: Company submission, document B, sections B.3.4.1, B.3.4.5 and B.3.4.4.

After removal of factors without a significant interaction with EQ-5D, the **regression analysis model** included EDSS, upper limb impairment (as measured using 9-HPT) and clinically meaningful fatigue (defined as an MFIS score over 38). Further details can be found in the company submission, document B, section B.3.4.1 (page 110).

Treatment effect on upper limb impairment: (from ORATORIO):
As measured by the 9-HPT, a hazard ratio of 0.52 (95%CI: 0.32 to 0.85) was applied for the MRI active population. This HR represents the results of a 20% increase in the 9-HPT sustained over 12 weeks as seen in ORATORIO.

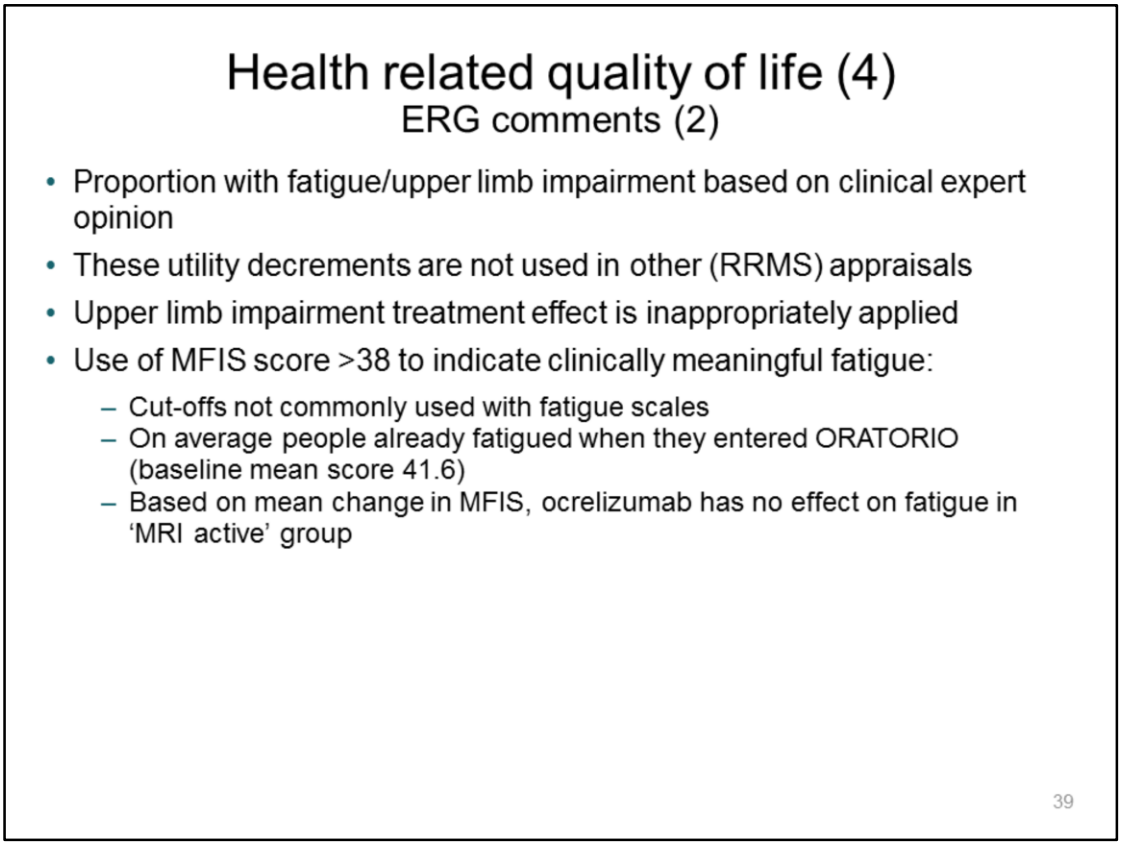
Treatment effect on fatigue: (from ORATORIO):
Relative risk reduction for people having clinically meaningful fatigue (defined as MFIS score >38) was determined from the ORATORIO trial. Data is academic in confidence. ERG report, section 5.2.9.



Source: ERG report, section 5.2.9.

- The 9-hole peg test (9-HPT) result was included in two outcomes: 20% increase in 9-HPT sustained over 12 weeks and Multiple Sclerosis Functional Composite score (MSFC). MSFC showed no difference between treatment arms.
- Unclear to the ERG why upper limb function should be a more important outcome for people with PPMS than people with RRMS (utility decrement for upper limb function not used in RRMS appraisals).

Full details of the ERG's concerns about inclusion of utility decrements for upper limb impairment and fatigue can be found in the ERG report, section 5.2.9. (page 98)



Source: ERG report, section 5.2.9.

Proposed Managed Access Agreement (MAA)

- MAA includes data collection and commercial access arrangement (CAA price)
- Will allow people with PPMS access to ocrelizumab while clinical uncertainty is addressed
- Commercial agreement underpinning the proposed MAA addresses cost effectiveness and triggering of Budget Impact Test
  - **Proposed CAA price** for ocrelizumab in PPMS

Proposed data collection

Phase IIIb study (WA40404)	
Design	Multi-centre, Randomised, Double Blind, Placebo Controlled Study
Population	Adults with PPMS; EDSS 3 to 8; Age 18 to 65
Outcomes	• Primary endpoint: 9-HPT (upper limb function) • Key secondary endpoint: 12-week CDP • Other secondary endpoints are to be determined
Subgroup analysis	• Different inflammatory profiles at baseline • Different age groups at baseline • Other pre-specified subgroups to be determined

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Source: Company submission, document B, section B.2.11.

Phase IIIb study planned in PPMS as part of the EMA Risk Management Plan for ocrelizumab.

- First patient expected by end of 2018.
- Clinical study report in 2014.

Open label extension of ORATORIO also still underway.

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Company's base case results

Population	Deterministic ICER (£/QALY)		Probabilistic ICER (£/QALY)	
	Modified PAS price	Proposed MAA price	Modified PAS price	Proposed MAA price
MRI active	£78,316	[redacted]	£84,249	[redacted]
MRI active ≤50 years	£47,857	[redacted]	£54,341	[redacted]

ERG: No comment provided on discrepancy between deterministic and probabilistic ICERs

Sensitivity analyses

Deterministic

- Results most sensitive to CDP-12 treatment effect and discount rates
- Cost of drug administration in years 2+, treatment effect on fatigue, and disutility for upper limb impairment also influenced results, but to a lesser degree

Probabilistic

- Probability ocrelizumab is cost-effective at a £30,000 ICER threshold:
  - PAS price:0% (*MRI active* and *MRI active ≤50 years*)
  - Proposed-MAA price: [redacted] (*MRI active*) / [redacted] (*MRI active ≤50 years*)

Source: Company submission, document B, section B.3.7.

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Company's scenario analyses ('MRI active')

Scenario		'MRI active' ICER (£/QALY)	
		Modified PAS price	Proposed MAA price
Base case		**£78,316**	[redacted]
Increase in transition rates between EDSS states (MSBase):	5%	£75,764	[redacted]
	10%	£73,479	[redacted]
Only progressions between EDSS states allowed		£68,143	[redacted]
Treatment discontinuation set to 'real world' scenario		£75,520	[redacted]
Stopping rule set to EDSS:	7.0	£77,739	[redacted]
	9.0	£80,679	[redacted]
EDSS utilities all from Orme et al.		£87,194	[redacted]
Combination: • Progression only transitions • 5% increase in transition rates between EDSS states • 'Real world' treatment discontinuation • Stopping rule at EDSS 7.0		£61,606	[redacted]

Source: Company submission, document B, section B.3.8.3 (table 69)

A full list of the company's scenario analyses and results can be found in the company submission, document B, section B.3.8.3 (table 69).

'Real world' treatment discontinuation scenario uses a higher, constant rate of discontinuation to predict average time on treatment more in keeping with the company's clinical expert's expectations (~4.5 years).

Several of the company's scenario analyses were repeated by the ERG (for example, using CDP-24 for the treatment effect, excluding disutilities from upper limb dysfunction and fatigue from the model). Results are shown on the next slide.

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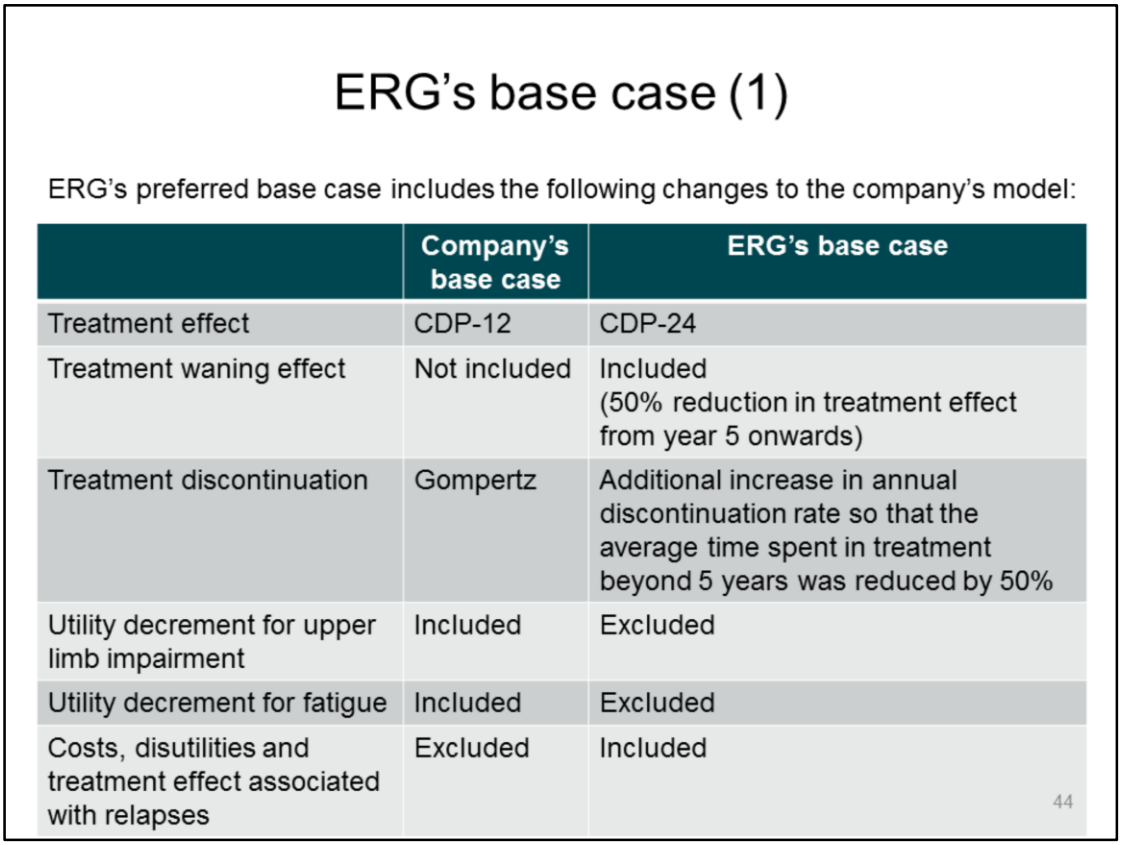
ERG's scenario analyses in company's model ('MRI active')

Scenario		'MRI active' ICER (£/QALY)
		Modified PAS price
-	**Base case**	**£78,316**
SA1	CDP-24 used for treatment effect	£86,824
SA2	50% decrease in treatment effect from year 5	£103,923
SA3	Increase in annual discontinuation from 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 would have preferred to use 20% increase in 9-HPT sustained for 24 weeks, but the data was not available

Source: ERG report, section 5.3.1.



ERG's base case (1)

ERG's preferred base case includes the following changes to the company's model:

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

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Source: ERG report, section 5.3.2.

Treatment waning effect selected by the ERG as most appropriate method from those used in recent technology appraisals. ERG report, section 5.2.6.

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ERG's base case (2)

Population	Deterministic ICER (£/QALY)		Probabilistic ICER (£/QALY)	
	Modified PAS price	Proposed MAA price	Modified PAS price	Proposed MAA price
MRI active	£129,877	[redacted]	£145,161	[redacted]

One-way sensitivity analyses

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

Probabilistic sensitivity analysis

- Probability ocrelizumab is cost-effective at a £30,000 ICER threshold:
  - PAS price: 0%
  - Proposed-MAA price: [redacted]

Source: ERG report, section 5.3

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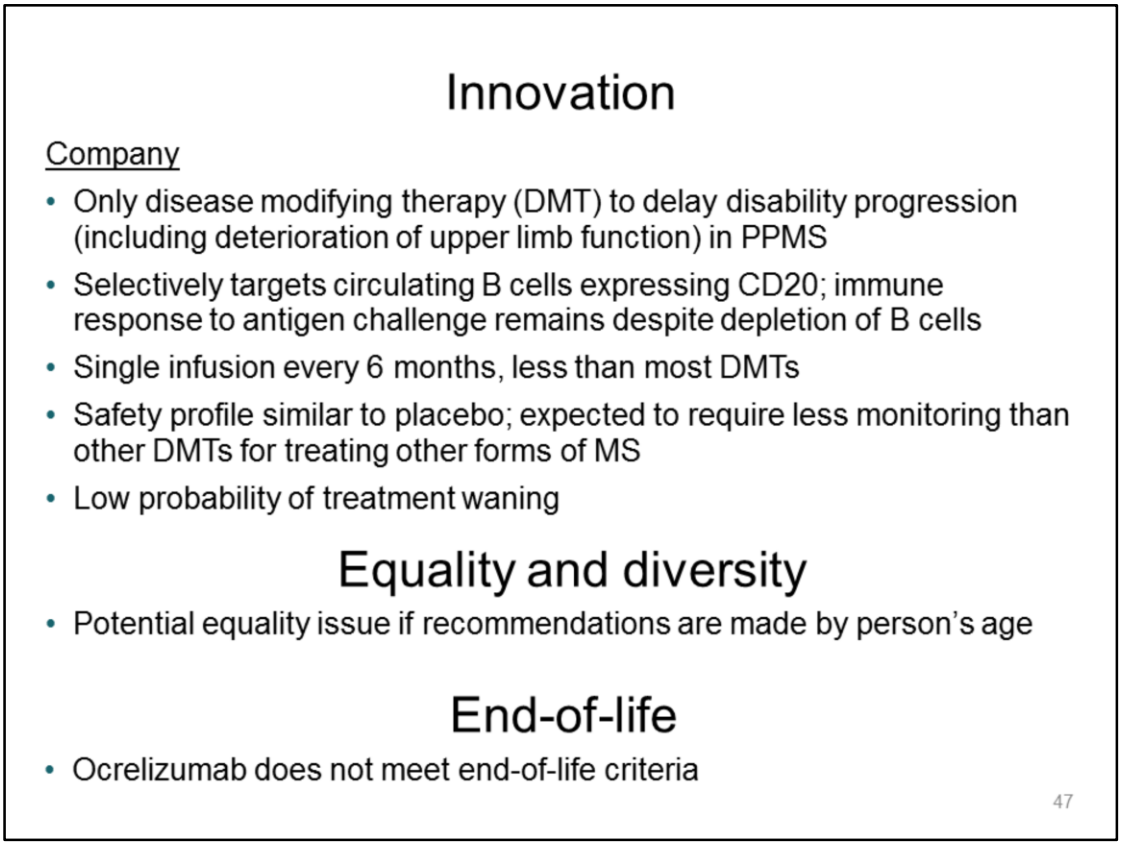
Exploratory analyses in ERG's base case

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

Source: ERG report, section 5.3.2 (table 59)



Source: Company submission, document B, section B.2.12 (Innovation), section B.2.13.2 (end-of-life)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

ID938 Ocrelizumab for Primary Progressive Multiple Sclerosis

Document B

Company evidence submission

File name	Version	Contains confidential information	Date
ID938 Ocrelizumab PPMS Roche submission document B [ACIC]	1	Yes	26/02/2018

Contents

Tables

Figures

Abbreviations

9-HPT	9-hole peg test
ABN	Association of British Neurologists
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
ANCOVA	Analysis of covariance
BMI	Body mass index
BSC	Best supportive care
CDP	Confirmed disability progression
CHMP	Commission for Human Medicinal Products
CI	Confidence interval
CNS	Central nervous system
DMT	Disease-modifying therapies
DOH	Department of Health
EDSS	Expanded disability status scale
EMA	European Medicines Agency
EPAR	European Public Assessment Report
Gd	Gadolinium
HR	Hazard ratio
ITT	Intent-to-treat
IRR	Infusion-related reaction
IV	Intravenous
JCV	John Cunningham virus
KM	Kaplan Meier
LLF	Lower limb function
LOCF	Last observation carried forward
MFIS	Modified fatigue impact scale
MMRM	Mixed-effect model repeated measure
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSIF	Multiple sclerosis international federation
NEDA	No evidence of disease activity
NEP	No evidence of progression
NR	Not reported
PASAT	Paced Auditory Serial Addition Test
PCS	Physical component score

PPMS	Primary progressive multiple sclerosis
QALY	Quality adjusted life years gained
RCT	Randomised controlled trial
R&D	Research and Development
ROW	Rest of world
RRMS	Relapsing-remitting multiple sclerosis
SAE	Serious adverse event
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey
SOC	System organ class
SPMS	Secondary progressive multiple sclerosis
T25FW	Timed 25-foot walk
ULF	Upper limb function
ULN	Upper limit of normal
USD	US Dollars

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Ocrelizumab is indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity (see section 5.1 of the Summary of Product Characteristics [SmPC]) [1].

Imaging features characteristic of inflammatory activity are described as T1 Gd-enhancing lesions and/or active [new or enlarging] T2 lesions in section 5.1 of the SmPC.

The patient population of the pivotal phase III study was broader than the marketing authorisation, and included patients without imaging features characteristic of inflammatory activity. The submission focuses on evidence from the phase III study in line with the marketing authorisation in patients with active disease, i.e. the subgroup of patients with T1 Gd-enhancing lesions and/or active [new or enlarging] T2 lesions.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with primary progressive multiple sclerosis	People with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity	In line with marketing authorisation
Intervention	Ocrelizumab	As per scope	
Comparator(s)	Established clinical management without ocrelizumab	As per scope	
Outcomes	• disability (for example, expanded disability status scale [EDSS], or time to walk 25 feet) • disease activity • patient-reported outcomes including fatigue, cognition and visual disturbance • mortality • adverse effects of treatment • health-related quality of life.	As per scope	
Subgroups to be considered	If the evidence allows subgroups of people with or without inflammation will be considered.	Pre-specified subgroup analysis in people with and without T1 Gd-enhancing lesions, and in patients younger or older than 45 years are presented in Appendix E. Post hoc subgroup analysis in patients aged 50 or younger with imaging features characteristic of inflammatory activity.	The marketing authorisation only covers patients with imaging features characteristic of inflammatory activity (i.e. T1 Gd-enhancing lesions and/or active [new or enlarging] T2 lesions). Additional post hoc analysis is presented as these patients benefited most from treatment with ocrelizumab and reflect early PPMS.
Special considerations including issues related to equity or equality	Not applicable	Subgroup analyses related to age may introduce equity concerns if recommendation is to restrict to people of a certain age category.	Age was a key predictor of ocrelizumab treatment effect in the pivotal phase III study, with younger patients benefiting most from treatment [1]. This is likely related to the underlying pathology and disease course of PPMS; the optimal treatment window is in patients with early disease in terms of disease duration, level of disability, and active inflammation.

B.1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	UK approved name: ocrelizumab Brand name: Ocrevus®
Mechanism of action	Ocrelizumab is a recombinant humanised monoclonal antibody that selectively binds to and depletes CD20+ B cells [2] [3]. B cells have been independently implicated in the pathophysiology of MS through their role in antigen presentation, cytokine production, autoantibody production and ectopic lymphoid follicle-like structures in the central nervous system [4, 5]. Ocrelizumab is the first medicine to have demonstrated efficacy in delaying progression in PPMS.
Marketing authorisation/CE mark status	Marketing authorisation by the European Medicines Agency (EMA) was granted in January 2018.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Ocrelizumab is indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity. Ocrelizumab is also indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS), with active disease defined by clinical or imaging features. This indication is assessed separately by NICE (ID937).
Method of administration and dosage	The initial 600 mg dose is administered as two separate intravenous infusions; first as a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion [1]. Subsequent doses of ocrelizumab thereafter are administered as a single 600 mg intravenous infusion every 6 months. The first subsequent dose of 600 mg should be administered six months after the first infusion of the initial dose. A minimum interval of 5 months should be maintained between each dose of ocrelizumab [1]. The following two premedications must be administered prior to each ocrelizumab infusion to reduce the frequency and severity of infusion-related reactions (IRRs) 100 mg intravenous methylprednisolone (or an equivalent) approximately 30 minutes prior to each ocrelizumab infusion; Antihistamine, approximately 30–60 minutes prior to each ocrelizumab infusion.

	In addition, premedication with an antipyretic (e.g. paracetamol) may also be considered approximately 30-60 minutes prior to each ocrelizumab infusion [1].
Additional tests or investigations	The SmPC recommends hepatitis B virus (HBV) screening in all patients before initiation of treatment with ocrelizumab as per local guidelines [1]. If progressive multifocal leukoencephalopathy (PML) is suspected dosing with ocrelizumab must be withheld. Evaluation including MRI scan preferably with contrast (compared with pre-treatment MRI), confirmatory cerebro-spinal fluid (CSF) testing for John Cunningham (JC) viral deoxyribonucleic acid (DNA) and repeat neurological assessments, should be considered. If PML is confirmed, treatment must be discontinued permanently [1].
List price and average cost of a course of treatment	List price is £4,790 per 300 mg vial. The average cost per patient per year is £19,160 based on twice yearly 600 mg infusions. Net price incorporating the patient access scheme (PAS) approved by the Department of Health (DoH) is [redacted] [redacted]
Patient access scheme (if applicable)	The PAS is a simple discount and is approved by the DoH and PASLU. [redacted]

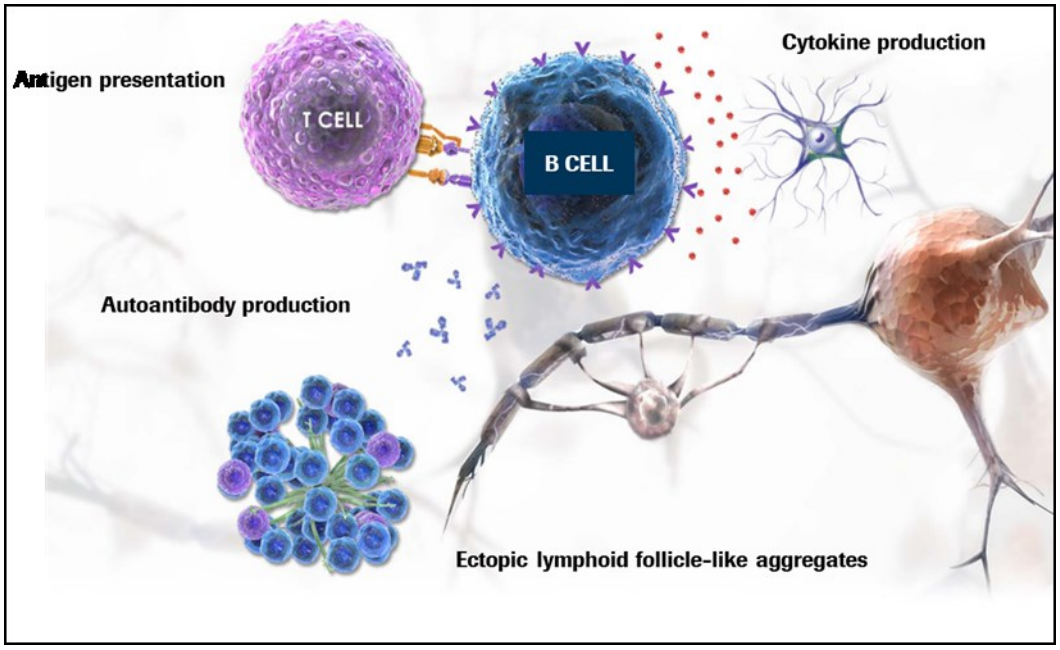
B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview – Clinical presentation and characteristics of the disease

Multiple sclerosis (MS) is a chronic autoimmune disease characterised by inflammation of the central nervous system (CNS) that leads to demyelination, axonal loss and progressive neuronal degeneration. Disease progression results in irreversible disability and cognitive impairment [6, 7]. Life expectancy for patients with MS is 5–10 years shorter than for the general population [8, 9], with approximately 50% of patients dying from complications in the advanced stage of MS [10].

B cells have been independently implicated in the pathophysiology of MS through their role in antigen presentation, cytokine production, autoantibody production and ectopic lymphoid follicle-like structures in the central nervous system [11].

Figure 1: Functional roles of B cells in MS



Studies have suggested that the innate immune system may play an important role in the progression of MS by influencing the effector function of T and B cells [12]. For instance, persistent activation of microglial cells, the most common immune cells in the central nervous system, has been observed in the chronic phase of relapsing-remitting experimental autoimmune encephalomyelitis (EAE), the mouse model of MS, and a correlation has been observed between activated microglial cells and loss of neuronal synapses [13]. Studies are

ongoing to further elucidate the role of activated microglia in the pathogenesis of MS progression.

In addition to immune-mediated inflammatory mechanisms, magnetic resonance imaging (MRI) studies reveal a much more widespread and global damage of the brain and spinal cord, which may initially be clinically silent [14, 15]. This subclinical activity can be a precursor of clinical events. For example, a T1-weighted gadolinium (Gd)-enhanced brain scan highlights areas of active inflammation, where the blood-brain barrier has become permeable to Gd, indicating active lesions that are new or enlarging [7]. A change in the T1 lesion volume correlates strongly with disability progression [16]. In T2-weighted scans, lesions appear as hyperintense white areas, providing information on lesion load and an indication of disease burden [17, 18].

B.1.3.2 The natural course of MS and patient subtypes

MS is a disease spectrum with three main presenting phenotypes based on the relative presence and clinical dominance of either episodic active neuro-inflammation with associated disability or disability progression independent of neuro-inflammation [19, 20]:

- relapsing-remitting (RRMS);
- secondary progressive (SPMS) and
- primary-progressive (PPMS).

The clinical course of MS is thus defined as either relapsing or progressive (see Figure 3) [21]. Relapsing and progressive forms of MS show distinct features apparent over the evolution of disability although both are characterised by an underlying disease progression that occurs and continues from the onset of the disease [22]. All forms of MS are further categorised as either active (with subclinical and/or clinical events) or not active [21, 23].

Patients with MS may have a broad range of neurological symptoms or signs, depending on the location and degree of inflammation in the central nervous system. MS is associated with autonomic, visual, motor and sensory symptoms, which can include fatigue, numbness, tingling, pain, weakness, vision loss, gait impairments, imbalance, and bowel and bladder dysfunction.

PPMS

Approximately 14% of MS patients are diagnosed with **PPMS** which is characterised by a gradual disability progression from onset with minimal discernible clinical signs of neuro-inflammation typified by relapses and remissions [24]. Typical symptoms of

progressive disease include increasing difficulty with walking, fatigue and cognitive impairment, with variable symptoms in other systems [25, 26]. Spastic paraparesis is a symptom commonly experienced by patients with PPMS, and is associated with impaired mobility, weakness, stiffness and clumsiness. For patients with PPMS, particularly those who are wheelchair-restricted, loss of residual arm and hand function would have a devastating impact on their quality of life as it can significantly limit the ability to perform activities of daily living and level of independence [27]. A recent survey of patients with MS suggested that upper limb function is more important than lower limb function to maintain independence. Progression is multi-dimensional, and some current disease-scoring tools do not adequately capture the impact of all aspects of impairment.

PPMS median age of onset (~40 years [28]) typically negatively impacts adults at their most productive time of life. Relative to relapsing forms of MS, PPMS is associated with older age at onset [29, 30]. To diagnose PPMS, patients require, in addition to one year of disease progression, two of the following three findings: evidence for dissemination of lesions in space in 1) the brain or 2) spinal cord or 3) identification of oligoclonal bands in the cerebrospinal fluid (CSF) [31]. The complex nature of diagnosis of PPMS often leads to delayed diagnosis [3-6].

Delayed diagnosis and an unrelenting progressive disease course together with the current lack of licensed disease-modifying treatments (DMTs) for PPMS would necessitate the focus of any new treatment to be the preservation of patient independence (upper limb function) rather than just patient mobility (lower limb function) [32].

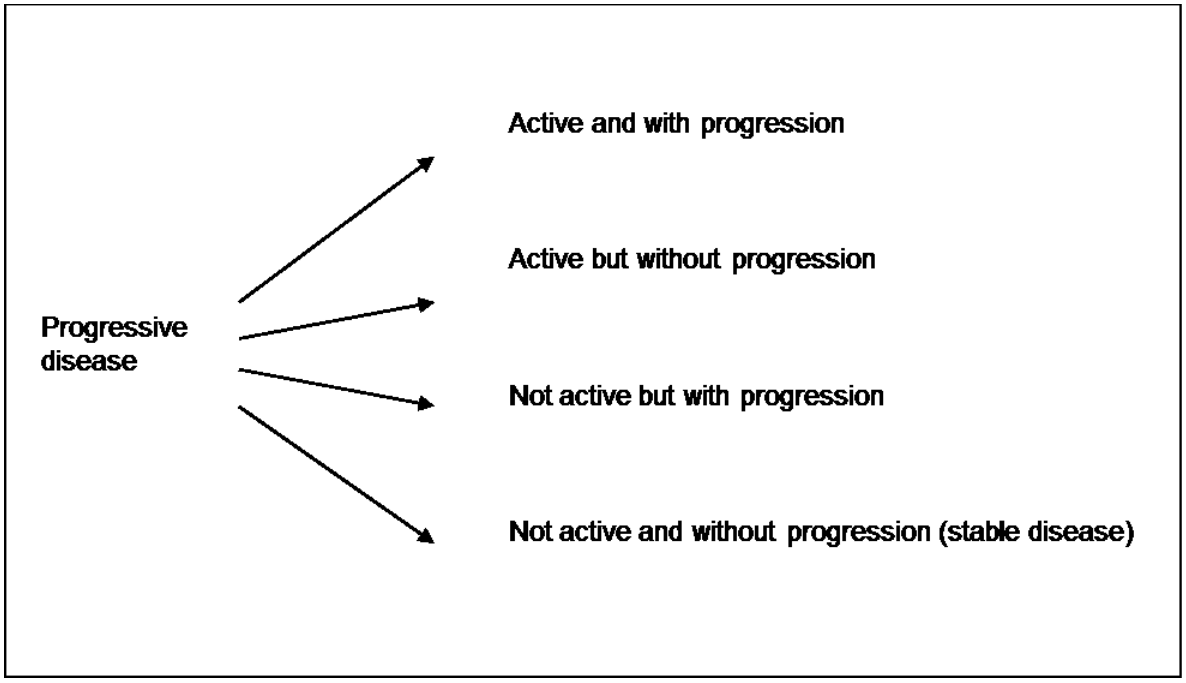
Importantly, there are currently no approved therapies that prevent further disability progression, including loss of upper extremity function in more advanced PPMS patients, and this population has been recognised as underserved with very limited therapeutic options [27].

PPMS is not well characterised, and the course of PPMS disease progression is highly variable and unpredictable, making the assessment of disease progression difficult. Whilst MS phenotypes can be categorised as progressive or relapsing, these categories do not provide any temporal indication of the disease process, and rate of progression has not always been considered.[*] Different phenotypes have been proposed in recent years to

[*] When the pivotal ORATORIO study of ocrelizumab in PPMS was designed, there was limited understanding about the disease course and different phenotypes in PPMS. Trial patients were not assessed for rate of progression prior to enrolment. A new Phase IIIb study will further characterise

describe the natural course of disease relating to clinical and sub-clinical activity and progression (Figure 2). A comprehensive assessment of disease activity and progression detected by clinical relapses or imaging (Gadolinium-enhancing lesions or new or enlarging T2 lesions) as well as progression of disability can provide meaningful additional descriptors in progressive disease. In general, disease progression is linked to the accumulation of disability, but other measures such as relapse rates and a variety of MRI techniques are also valuable. Overall, disability accumulation is more rapid for patients with PPMS than in other forms of MS [21].

Figure 2: PPMS disease modifiers (phenotypes) as per Lublin consensus statement



Adapted from Lublin et al 2014 [21].

Some patients with PPMS (approximately 10% of people diagnosed with PPMS; Table 33) experience relapses, which manifest with a temporarily accelerated disease course, and periods of remission (this form of disease used to be classified as progressive relapsing MS), but they have similar long-term rates of disability accumulation, compared with other patients with PPMS [33]. Most studies suggest that PPMS is part of the spectrum of MS phenotypes and that differences are relative rather than absolute [21, 24, 34].

patients with PPMS by level of activity and progression, and evaluate the efficacy and safety of ocrelizumab in different phenotypes. See Data Collection Arrangement Appendix for further details.

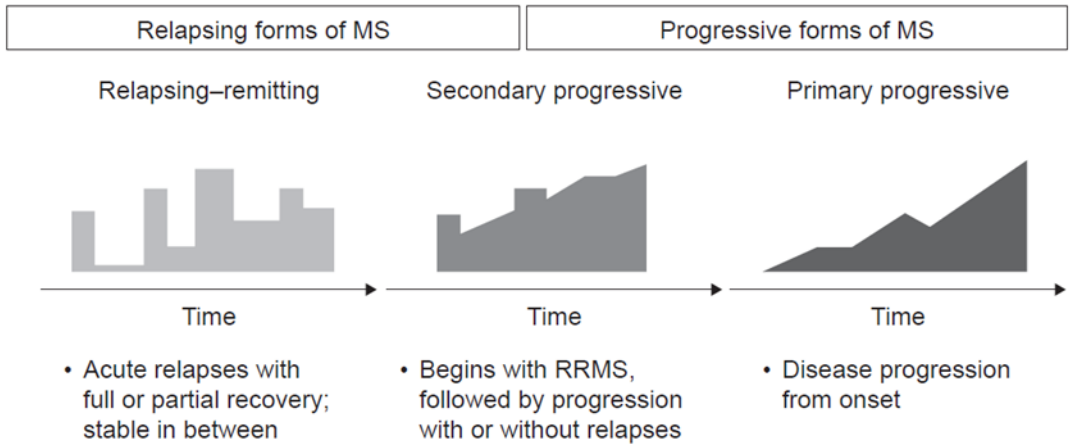
RRMS and SPMS

RRMS is the most common phenotype of MS, with an incidence of approximately 86% at diagnosis [35]. Patients with RRMS experience unpredictable and recurring clinical episodes of acute neurological dysfunction (relapses) that are driven by acute neuro-inflammation. This is followed by a recovery of function (remission) in some patients although studies have shown that over 25% of patients will have residual disability following a relapse [36]. A relapse is a clinically evident 'attack' of neuro-inflammation and demyelination, characterised by gradual onset of symptoms over days, stabilising over days or weeks and then gradually resolving, either completely or partially [37]. Current pharmacological management in RRMS includes the use of DMTs, aimed at reducing the frequency and/or severity of relapses and/or slowing disability progression. MS disease should be controlled as early as possible and experience with DMTs indicates that there is a window of opportunity where early use may control the disease in some patients [38, 39].

In RRMS, disability worsening occurs as a result of incomplete recovery from relapses [23]; a higher number of relapses in the first 2 years after disease onset is significantly associated with worse outcomes (higher probability and shorter time for attaining disability levels) [40].

Most patients with RRMS will eventually transition to **SPMS**, in which there is a period of steady disease progression with less discernible clinical signs of acute neuro-inflammation after an initial period of neuro-inflammatory-driven relapsing-remitting disease. Prior to the widespread use of highly efficacious DMTs, most patients with RRMS were thought to eventually develop SPMS [6], [41]. A study by Ahrweiller et al. demonstrated that 35% of patients with SPMS would experience at least one relapse [42].

Figure 3: Typical disease course for relapsing and progressive forms of MS



The Expanded Disability Status Scale (EDSS)

Clinical disease activity is defined primarily by clinical relapse or progression of disability on the Expanded Disability Status Scale (EDSS) [43, 44] and may include impairment of cognition detectable with neuropsychological testing [45]. These symptoms represent damage to the central nervous system (CNS) in the form of lesions that disrupt nerve function [46].

The Kurtzke Expanded Disability Status Scale (EDSS) is a clinician-administered scale used to assess the clinical severity and the functional deficit in MS. It is widely used in both clinical trials and routine practice to assess disability in patients with MS [47].

Disability is evaluated on the basis of neurological examination, the ability to walk specified distances, with or without assistance, and assessment of self-care. EDSS scores range from 0 to 10, with 0.5 unit increments that represent increasing levels of disability, with the scale ranging from 0 (representing normal neurological function) to the highest score of 10 (representing death due to MS), as shown in Figure 4 [47, 48].

The scoring is based on examination by a neurologist. Broadly, EDSS steps 1.0 to 4.5 refer to patients with MS who are able to walk without any aid. Scores are based on measures of impairment in eight functional systems; pyramidal (weakness or difficulty moving limbs), cerebellar (ataxia, loss of coordination or tremor), brainstem (problems with speech, swallowing and nystagmus), sensory (numbness or loss of sensations), bowel and bladder function, visual function, cerebral functions, and 'other'. Each functional system is scored on a scale of 0 (no disability) to 5 or 6 (more severe disability). EDSS steps 5.0 to 9.5 are defined by impairment to walking. A score of 7 is considered an important milestone as it represents the need for a wheelchair.

The EDSS has well recognised shortcomings [49-51]. It is based on neurological examination which is inherently subjective, and due to the complex scoring rules and time constraints in MS clinics, may not be fully implemented in practice. As a result, the scale has poor reliability within and between raters thereby creating considerable "noise" in real world measurements [50]. EDSS is a non-linear ordinal scale, such that increments do not have the same level of impact depending on where on the scale they occur. The upper end of the scale (scores 7–9) in particular is less sensitive to change, i.e. a 1-point increase between 7 and 8 ('essentially restricted to wheelchair' to 'essentially restricted to bed') has a much larger impact on a patient's HRQoL and costs than a 1-point increase between 3 and 4 ('fully ambulatory' to 'able to walk without aid for 500 metres'). The scale is therefore sometimes criticized for its reliance on walking as the main measure of disability.

A further shortcoming of the EDSS is that it captures cognitive impairment poorly [52]. Cognitive impairment is common in patients with MS (40–65%) and includes deficits in attention, information processing, episodic memory and executive functions; dementia and language deficits are less common [53, 54]. These impairments may occur at any time during the disease course, including patients with early disease and tends to worsen with increasing disability and disease duration [54].

Despite these limitations, the EDSS is widely accepted by regulators as a measure of disease progression [50, 51] based on clinical research that has mostly focussed on RRMS. There has never been a focus on PPMS-specific and relevant measures of disease progression because most clinical development programmes have focussed on RRMS.

Figure 4: Visual depiction of the Expanded Disability Status Scale (EDSS)

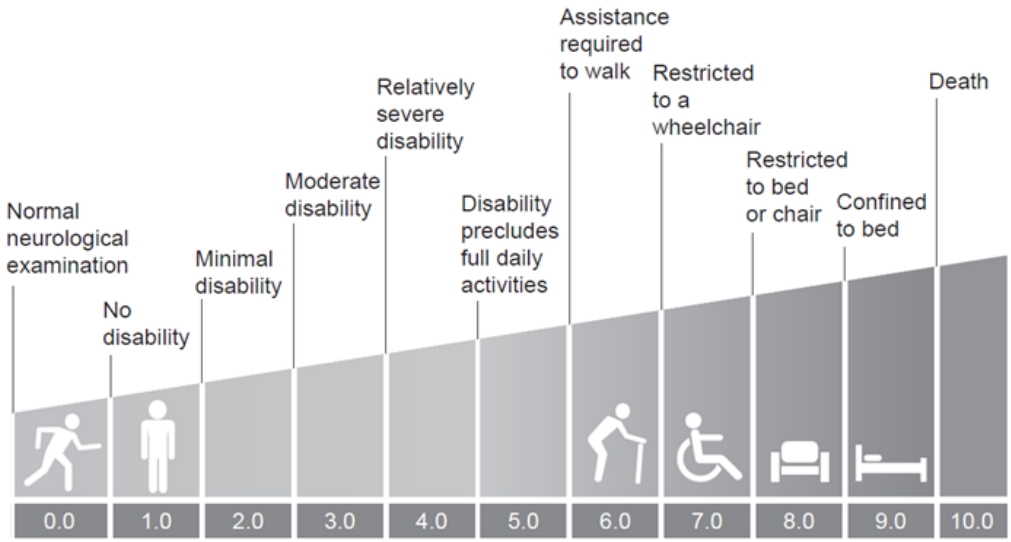


Table 3 Description of EDSS scores and domains

Score	Description	
1.0	No disability, minimal signs in one FS	Neurological impairment
1.5	No disability, minimal signs in more than one FS	
2.0	Minimal disability in one FS	
2.5	Mild disability in one FS or minimal disability in two FS	
3.0	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking	
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking	
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500 m	Ambulatory impairment
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300 m	
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200 m	
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100 m	

6.0	Requires a walking aid - cane, crutch, etc. - to walk about 100 m with or without resting	
6.5	Requires two walking aids - pair of canes, crutches, etc. - to walk about 20 m without resting	
7.0	Unable to walk beyond approximately 5 m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day	Ambulatory disability
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorized wheelchair	
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms	
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self care functions	
9.0	Confined to bed. Can still communicate and eat	
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow	
10.0	Death due to MS	

Adapted from Kurtzke 1983 [47]

Multi-dimensional disability in PPMS

The advantages and disadvantages of the EDSS scale in assessing disability in MS are well known [55]. Higher scores on the EDSS are primarily driven by impairment of walking ability. As mentioned previously, preserving upper limb function is more important than lower limb function for patients with PPMS [56]. Therefore, preserving upper limb function is clinically relevant and a suitable therapeutic goal in PPMS. However, the multi-dimensionality of progression (encompassing impairment to upper limb function and cognition) is limited in the EDSS scale's narrow assessment [55]. The EDSS scale is insensitive at the higher end and patients may seem to be stable according to the EDSS scale (e.g. in a wheelchair/EDSS score 7) but still experience progressive loss in upper limb or cognitive function that is not adequately captured by EDSS.

An additional approach to defining worsening or control of MS (especially in patients with progressive forms of the disease) would be the evaluation of additional patient relevant outcome measures which capture upper limb function, fatigue and cognition. In such cases, the EDSS may be complemented with tests of upper extremity dexterity (e.g. 9-hole peg test; 9-HPT). The 9-HPT and T25FW test have been combined with the EDSS in PPMS studies; the resultant composite endpoint has greater sensitivity to clinical progression than the EDSS alone [57].

Manual dexterity is an important predictor of overall activity and participation within the community – upper limb dysfunction in MS contributes to a reduced ability to perform activities of daily living, resulting in decreased independence and quality of life [58].

Dysfunctions of the upper extremities occur in at least 66% of people with MS, and approximately 44% experience problems with activities of daily living [59].

The 9-HPT is a standardised test of upper extremity function which requires a patient to take nine pegs from a shallow container, one at a time, placing them into holes in a plastic or wooden block, and then removing them one at a time and placing them back into the container [60]. This task is repeated four times in total, twice with the dominant hand and then twice with the non-dominant hand. Scores are calculated from the time taken to complete the four trials. Research has shown that reproducibility within subjects and between test operators is high, [61] and adverse changes in the 9-HPT scores are associated with greater long-term disability levels [62],[63].

Fatigue is the most commonly reported symptom in MS, and is considered by many patients to be the most debilitating symptom. In a qualitative assessment of the factors surrounding employment, fatigue was the most pervasive symptom (63% rated it as the most troublesome symptom), affecting both physical and mental aspects of patients' jobs [64]. A fatigue cascade has been described by patients, in which fatigue and general exhaustion or tiredness appear to trigger a cascade of other symptoms, both physical and cognitive. The downstream effects included increased clumsiness, decreased cognitive function, stuttering, shaking or muscle spasms, numbness/tingling, headaches, and blurred vision. A UK survey of 100 patients with MS indicated that fatigue was one of the factors directly related to the effects of MS on the ability to work (as well as handwriting, balance and walking difficulties) [65].

The impact of fatigue on physical, cognitive and psychosocial functioning can be measured by the MFIS Modified Fatigue Impact Scale (MFIS). On a scale of 0–84; a score of at least 38 represents a clinically meaningful level of fatigue [66].

Sub-clinical disease activity

Disease activity commonly occurs in the absence of clinical activity [67, 68]. Subclinical loss of brain tissue reflects ongoing inflammation or neurodegeneration but may go unnoticed, owing to neurological repair mechanisms, where the ‘neurological reserve’ compensates for damaged tissue [46].

MRI offers a sensitive way to detect clinically silent disease activity and on-going tissue damage, even in the absence of clinically detectable disease progression. MS lesions in the CNS can be identified and monitored, using techniques such as: [21, 69, 70]

- T1-weighted scan with or without gadolinium (Gd) dye injected into the bloodstream (asymptomatic new or enlarging T1 lesions)
- T2-weighted scan (asymptomatic new or enlarging T2 lesions)

Brain volume loss (BVL) is a measure of neurodegeneration in patients with MS; [71] it can be measured using MRI techniques. BVL is more rapid in patients with MS than in people without MS (the mean annual rate of BVL is 0.5%–1.35% in patients with MS, compared with the normal age-related annual rate of BVL in people without MS of 0.1%–0.3%) [71].

Combining clinical and subclinical measures can predict relapses and future disability progression over the long term [46, 72].

Composite endpoints

Several composite endpoints have been proposed in PPMS in recent years with a view to capturing different aspects of disability and/or disease activity. The Multiple Sclerosis Outcomes Assessment Consortium (MSOAC) was launched in 2012 to develop more sensitive and meaningful disability progression measures in PPMS. The consortium consists of academia, patient, industry and regulatory representatives [63, 73, 74]. It is yet to publish its conclusive findings and recommendations.

No evidence of progression (NEP)

No evidence of progression (NEP) is a composite endpoint used to evaluate the proportion of PPMS patients with stable clinical disease. NEP is defined as no CDP-12 of ≥1.0 /≥0.5 points on the EDSS (if the baseline score is ≤5.5/>5.5 points, respectively), no 12-week sustained increase of ≥20% on the T25FW test and no 12-week sustained increase of ≥20% on the 9-HPT.

A limitation of NEP is that a proportion of patients with PPMS have relapses and/or MRI activity, which are not included in the NEP composite [21].

No evidence of progression and active disease (NEPAD)

No evidence of progression and active disease (NEPAD) is a combination of NEDA and NEP used for the assessment of patients with PPMS. NEPAD can be considered to be an expanded version of NEDA incorporating assessments of hand/arm function and walking speed, or an expanded version of NEP, in which relapses and MRI activity are combined with the three NEP endpoints. Compared with NEDA and NEP, the NEPAD outcome may

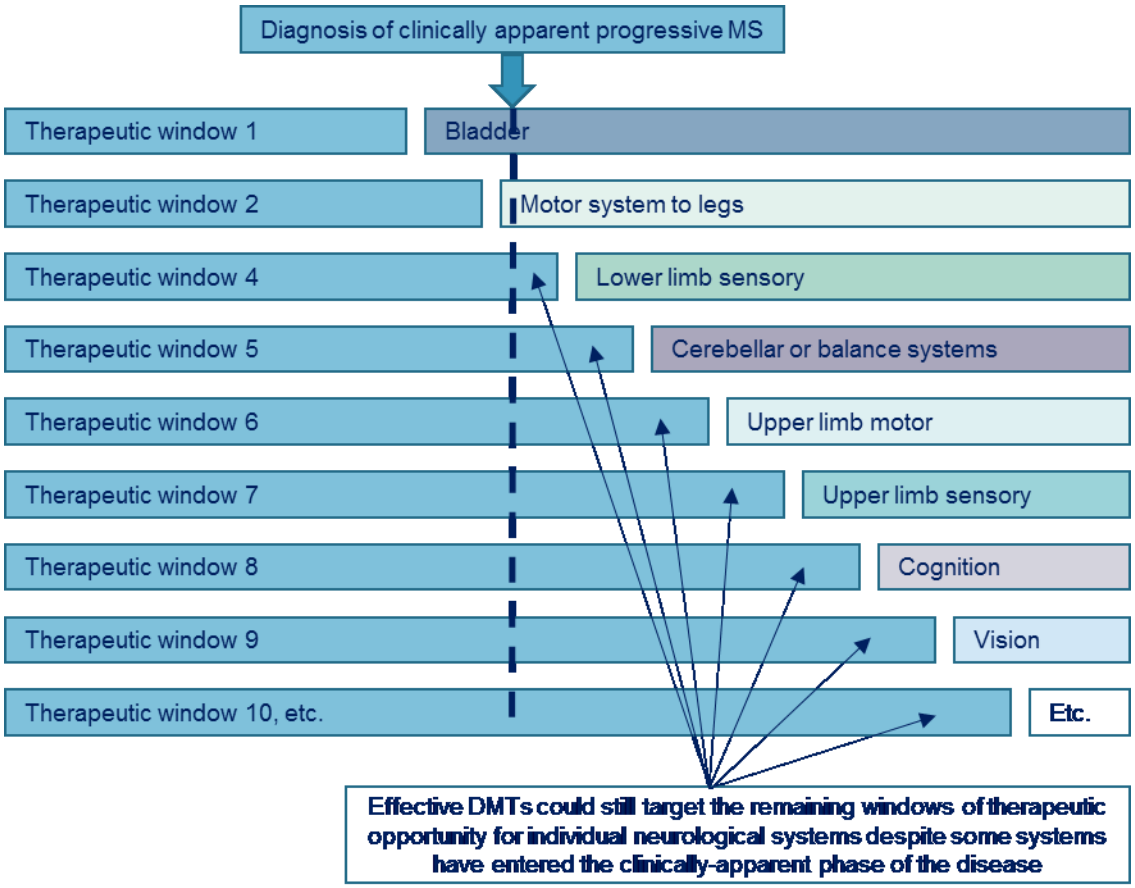
represent a more comprehensive measure of the absence of clinical and MRI features of disease progression and activity in patients with progressive forms of MS.

NEPAD status is defined as having no evidence of progression (no CDP-12 of ≥ 1 points/≥0.5 points on the EDSS (if the baseline score is ≤5.5 points/>5.5 points, respectively); no 12-week sustained increase of ≥20% on the T25FW test; and no 12-week sustained increase of ≥20% on the 9-HPT), no brain MRI activity (no new/enlarged T2 lesions and no Gd-enhancing T1 lesions) and no protocol-defined relapse.

Functional reserve hypothesis

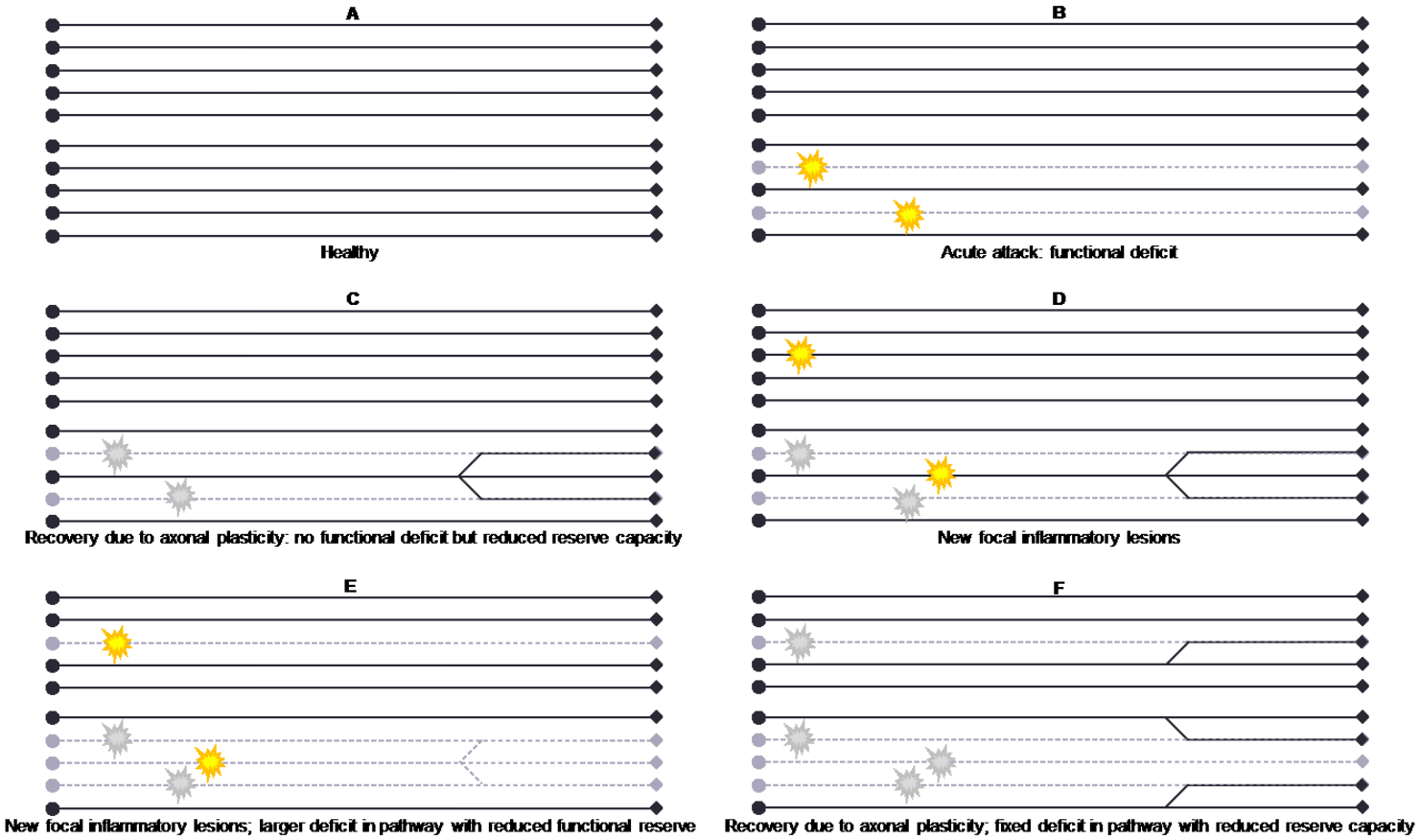
The functional reserve hypothesis suggests that neuronal domains may enter the clinically-apparent progressive phase of the disease at different rates depending on the length of the axons in the pathway and the reserve capacity of that pathway, i.e. its ability to compensate for ongoing or future damage. This hypothesis predicts that different neuronal domains will have different length-dependent therapeutic windows in which to respond to anti-inflammatory therapies that suppress ongoing inflammatory demyelinating lesions (Figure 5). The neuronal domains that have not entered the clinically-apparent progressive phase of the disease, due to preservation of functional reserve, may respond to anti-inflammatory therapies with a delay in the effect due to the delayed onset of clinical expression of neurodegenerative axonal loss; the so-called therapeutic lag. In contrast, the neuronal domains that have already entered the clinically-apparent progressive phase of the disease, due to loss of functional reserve, may fail to respond to anti-inflammatory therapies. Ultimately, longer axons (lower limbs) are damaged more easily and earlier than shorter axons (upper limbs) [75].

Figure 5: The therapeutic window in progressive MS



Adapted from [114].

Figure 6: Functional reserve and capacity



Loss of functional reserve predisposes pathways to manifest earlier with clinically-apparent progressive MS. Schematic example representation of the sequential paths to permanent functional deficit associated with delayed axonal loss following accumulation of focal inflammatory lesions. Compared to normal tissue (A) the initial impact of multiple focal inflammatory lesions affecting the lower neuronal pathway (B) may trigger a loss of 40% of its functioning neuroaxonal units x, which is able to recover function. Based on animal experiments this is hypothesised to be due to axonal plasticity, and axonal sprouting, from surviving neuroaxonal units (C). However, the loss of reserve capacity in the lower pathway makes it more susceptible to damage from further focal inflammatory lesions (D), with greater loss of function (D and E) and the inability to recover completely (F) leading to the emergence of clinically-apparent progressive disease.

Adapted from [114].

The importance of age

Aging is associated with gradual loss of brain volume in the general population. This general decrease in brain volume, combined with accumulated damage from brain lesions in PPMS, may impact the functional reserve capacity in older patients.

A recent meta-analysis of studies in MS observed a trend whereby older patients experience lower benefit from active treatment with respect to worsening of EDSS [76]. The meta-analysis included more than 28,000 MS patients in 38 clinical trials covering 13 categories of immunomodulatory drugs. The analysis predicted that patients beyond approximate 53 years of age may no longer derive benefit, as measured by worsening in EDSS, from active treatment.

The impact of age on response to treatment needs to be viewed in the wider context of multi-dimensional disability and therapeutic windows. Older patients may still benefit from active treatment if the clinical benchmark is preserving upper limb function. Indeed, in the absence of functioning lower limbs, the ability to use one's upper limbs becomes even more critical.

Summary of key differences between PPMS and RRMS

Following the revised McDonald diagnostic criteria of 2010, the diagnosis of RRMS has become easier by combining the clinical history characterised by episodes of new onset neurological symptoms that typically improve over time (relapses), with radiological findings. The clinical picture of RRMS is understood to be the result of a mostly neuro-inflammatory process. There is typically minimal accumulated disability at diagnosis of RRMS relative to PPMS.

Due to significant R&D investment since the late 1990s, there are now effective disease modifying treatments available to treat RRMS to the point where relapse activity is largely halted and recovery from accumulated pre-existing disability is no longer the exception but the norm.

Because of these two factors, clinical intervention is typically early and in many cases precedes the onset of lower limb fixed disability. Existing clinical guidelines recommend the use of disease-modifying treatments in RRMS in ambulant patients. The goal of treatment in RRMS is thus to preserve lower limb function for as long as possible until walking aids give way to obligatory wheelchair use which then triggers the discontinuation of disease modifying treatment in accordance with the ABN guidelines.

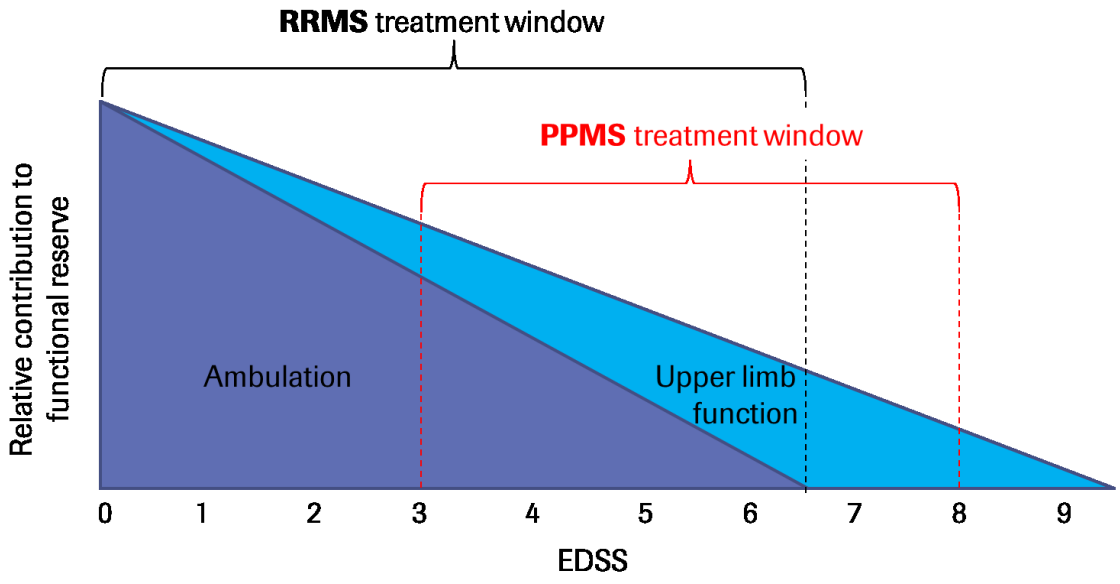
The well-established measure of disability progression in RRMS is centred on the EDSS scale and works well because incremental changes in the EDSS scale adequately reflect the dominant manifestation of RRMS related disability i.e. progressive lower limb disability.

In contrast, PPMS is more difficult to diagnose due to the clinical absence of well-formed episodic new-onset neurological symptoms that improve over time (relapses). A period of clinical observation is typically required to demonstrate the insidious progression of disability in the absence of clinical relapses in order the confirm the diagnosis retrospectively, which by then may already be accompanied by varying levels of pre-existing fixed lower limb disability i.e. EDSS scores of 3-4.

PPMS is understood to be the result of a mostly neuro-degenerative process. Due to the differences in the pathological disease processes between RRMS and PPMS and the greater technical challenges of impacting the underlying disease processes in PPMS, the goal of treatment in PPMS is to preserve functional independence for as long as possible. This would mean continuing treatment beyond a significant loss of lower limb function, in order to preserve residual upper limb function for as long as possible. Fatigue and cognitive impairment are other important factors that negatively impacts patients' independence which are particularly relevant in PPMS.

As such the EDSS score alone is not adequate as a measure to capture disability progression in PPMS. As mentioned earlier, other important aspects that impact patients' independence and HRQoL like upper limb function, fatigue and cognitive function need to be considered when assessing the clinical benefit of a disease modifying therapy in PPMS.

Figure 7: Differential treatment windows and goals in RRMS and PPMS



Proposal for Managed Access Agreement

As described in previous sections, there is considerable uncertainty in PPMS associated with the natural course of disease and therapeutic windows. The understanding of the disease has evolved in recent years leading to new concepts such as the Lublin phenotypes and functional reserve hypothesis.

We propose a Managed Access Agreement (MAA) for ocrelizumab in PPMS that would allow patients with PPMS to have access to this innovative therapy whilst addressing clinical uncertainty. The new Phase IIIb study would form the basis of data collection proposed under the MAA (see Section B.2.11 and the Data Collection Arrangement Appendix). The commercial arrangement that underpins the proposed MAA would address the cost effectiveness and triggering of the Budget Impact Test of ocrelizumab in PPMS (see PAS appendix).

This approach is similar to MAAs in oncology via 'use in Cancer Drugs Fund (CDF)' recommendations (12 CDF-type MAAs agreed by NICE and NHS England so far [77-88]), MAAs in ultra-orphan indications via the Highly Specialised Technology (HST) program (three HST-type MAAs agreed by NICE and NHS England so far [89-91]), and also a recent MAA for a treatment in systemic lupus erythematosus [92].

B.1.3.3 Epidemiology

There are currently no accurate data on the exact number of people with MS in the UK, but estimates have been made by taking data from Mackenzie et al (who reported on the incidence and prevalence of multiple sclerosis in the UK 1990–2010 from the General Practice Research Database [93]) and adapting it to overall prevalence from the MS Society [94]. The prevalence of MS in England in 2016 was estimated to be 89,030 patients and incidence 4,040 patients. The Mackenzie study estimated that the number of people with MS in the UK was growing by around 2.4% per year, due to people with MS living longer [93]. Through extrapolation, the prevalence of MS in England in 2018 would be approximately 93,355 patients.

Approximately 14.1% of patients with MS have PPMS. Hence, the prevalence of PPMS in England in 2018 would be 13,163 patients, and each year approximately 570 people are newly diagnosed with PPMS.

Ocrelizumab is licensed for patients with early PPMS with MRI activity. In the ORATORIO study, 40% of patients had MRI activity at screening/baseline (as measured by Gd-

enhancing lesions or new T2 lesions). Hence, approximately 5,265 prevalent patients and 228 incident patients in 2018 have MRI active disease.

The license restriction to early disease is not currently quantifiable due to the broad scope for interpretation, but would be expected to further reduce the population eligible for ocrelizumab. Another important aspect that limits the patient population to be treated with ocrelizumab, especially in the early years after availability of the first DMT in PPMS, is the capacity of MS clinics to identify and screen PPMS patients for eligibility.

More information on epidemiology and the estimated number of patients eligible for ocrelizumab in PPMS is provided in the Budget Impact Analysis.

B.1.3.4 The clinical pathway of care

There is no cure for MS [95, 96]. Optimal treatment requires intervention early in the course of MS with effective therapies – accumulating evidence shows this to be critical for maintaining neurological function and preventing subsequent disability [97].

Whilst a number of clinical guidelines and technology appraisals are available, which describe and recommend approaches to the management of RRMS and use of DMTs, treatment of **progressive** forms of MS remains highly challenging:

RRMS: Most patients receive treatment with DMTs over the lifetime of their disease. The aim of treatment with DMTs is to delay progression of disability, reduce the number and severity of relapses and diminish the impacts on HRQoL.	PPMS: Effective treatment of progressive MS is a long-standing challenge. Traditionally, patients with PPMS have been treated with therapies to manage their symptoms but not the underlying disease course. Ocrelizumab is the first and only DMT to be licensed in PPMS and be shown to slow disability progression.

Over the last decades, several other disease-modifying therapies have been investigated in patients with PPMS, including glatiramer acetate, [98] mitoxantrone, [99] IFNβ-1a IM, [100] IFNβ-1b, [101] rituximab [102] and fingolimod [103] but they did not demonstrate significant impact on clinical progression and/or did not meet their primary endpoints. Data on disability progression from randomised controlled trials (RCTs) of DMTs in the treatment of patients with PPMS are summarised in Table 5.

In addition to DMTs, patients with MS are managed symptomatically, in order to prevent complications where possible. Recommended symptomatic treatments and rehabilitation therapies for patients with MS are summarised in Table 4.

Table 4: Therapies for the Management of MS Symptoms

Symptom	Treatment Options
Relapses	• Methylprednisolone • Adrenocorticotrophin hormone is an option where there is no administration route for methylprednisolone • Following a severe disabling attack, the appropriateness of multidisciplinary rehabilitation therapy should be evaluated if symptoms persist after drug therapy • Plasmapheresis (following a severe disabling attack that does not respond to corticosteroids)
Fatigue	• Amantadine • Energy-saving rehabilitation strategies
Spasticity	• Baclofen • Tizandine (second line; added to or instead of baclofen) • Diazepam (third line) • Gabapentin • Nabiximols (where no clinical improvement is seen with other treatments or they are poorly tolerated) • Local application of botulinum toxin A (focal spasticity) • Physiotherapy
Impaired mobility	• Dalfampridine
Cognitive impairment	• Cognitive rehabilitation
Neuropathic pain	• Gabapentin • Carbamazepine • Amitriptyline • Pregabalin
Bladder dysfunction	• Oxybutynin (urge incontinence) • Tolterodine (urge incontinence) • Desmopressin (bladder dysfunction and nocturia) • Pelvic floor rehabilitation • Intermittent bladder catheterization
HRQoL	• Multidisciplinary rehabilitation therapy

[104]

Table 5: Disability Progression in Patients with PPMS Treated with DMTs in RCTs

DMT	Study design	Results[a]	Trial phase
Interferon beta 1a IM [100] (Avonex)	• Randomised controlled trial • Weekly Interferon beta 1a IM 30 µg or 60 µg or placebo for 2 years • *N* = 50	• No treatment effect on time to sustained progression in disability	Phase 2 Exploratory trial
Interferon beta 1b SC [101] (Betaseron)	• Randomised controlled trial • Interferon beta 1b SC, 8 MIU every other day or placebo for 2 years • N = 73	• 24-week CDP: Interferon beta 1b, SC, 27.8% versus placebo, 37.8% • Difference was not statistically significant	Phase 2 Exploratory trial
Glatiramer acetate [98]	• Multicentre, double-blind, randomised trial • Glatiramer acetate 20 mg or placebo for 3 years • N = 943	• Trial stopped by DSMB at interim analysis, after approximately 1 year • Non-significant delay in time to sustained accumulated disability, glatiramer acetate vs placebo • HR 0.87, 95% CI 0.71–1.07 • p = 0.1753	Phase 3 Pivotal trial
Rituximab [102]	• Multicentre, double-blind, randomised trial • 2 x 1000 mg IV rituximab infusions every 24 weeks, through 96 weeks or placebo • N = 439	• 96-week CDP: • Rituximab, 30.2% versus placebo, 38.5% • p = 0.14	Phase 2/3 Pivotal trial
Fingolimod [103]	• Multicentre, double-blind, randomized trial • Fingolimod 1.25 mg daily (later reduced to 0.5 mg/day) or placebo for 3 years (maximum 5 years) • N = 970	• 12-week CDP at year 3, Kaplan-Meier estimates: Fingolimod, 77.2% (95% CI 71.87–82.51) • Placebo, 80.3% (95% CI 73.31–87.25) • Risk reduction: 5.05% (HR 0.95, 95% CI 0.80–1.12) • p = 0.544	Phase 3 Pivotal trial

[a] CDP was not defined consistently across trials.
CDP, confirmed disability progression; CI, confidence interval; DMT, disease-modifying therapy; DSMB, data and safety monitoring board; HR, hazard ratio; IM, intramuscular; IV, intravenous; MIU, million international units; PPMS, primary progressive multiple sclerosis; RCT, randomised controlled trial; SC, subcutaneous.

B.1.3.5 Burden of disease

MS has a substantial negative impact on health-related quality of life (HRQoL) [105-107]. Patients with MS have significantly lower HRQoL scores than do patients who have other chronic diseases, such as chronic ischaemic heart disease, gastro-oesophageal reflux disease, Crohn's disease, non-insulin-dependent diabetes mellitus or ulcerative colitis [108]. Relapses, higher levels of disability and progressive disease are associated with significant reductions in HRQoL [109].

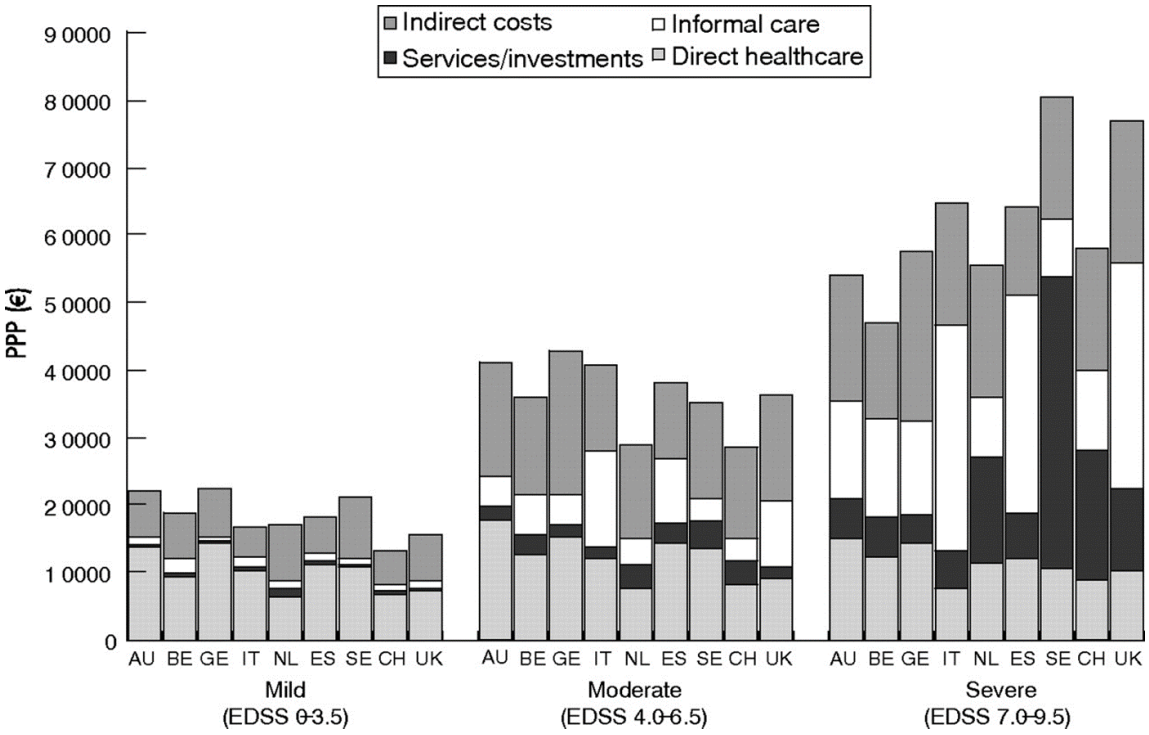
The range of physical dysfunctions associated with PPMS (such as fatigue, limb weakness, deterioration of upper limb function, loss of sensation, and spasticity) affect performance of many daily living activities (ADL) such as dressing, bathing, self-care, and writing, thus reducing functional independence and self-rated quality of life [110]. Indeed, it has been reported that the highest prevalence of upper limb disability found in the group with progressive disease.

Patients with MS are less likely to be employed, are more likely to require time off work when they are employed, and are more likely to retire early than people without MS [111-113]. Progressive disease has a greater impact on employment than RRMS [114], and patients with PPMS experience a significantly worse burden of disease than patients with RRMS [115].

Caregivers of patients with MS also experience high levels of distress, have reduced quality of life [116, 117] and may find that their employment is affected [116].

MS is a chronic disease that requires lifelong treatment. Resource utilisation associated with MS is significant and increases as a person’s level of disability increases [118, 119]. Costs are to some extent driven by direct medical costs, of which DMTs are a key component [120, 121]. However, indirect costs, arising mostly from productivity losses, account for more than half of the total economic burden of MS [122-124] (See Figure 8).

Figure 8: Cost per patient according to severity of disease



Patients are grouped into mild disease (Expanded Disability Status Scale (EDSS) 0–3.5), moderate disease (EDSS 4.0–6.5) and severe disease (EDSS 7.0–9.5), and total mean annual cost per patient (PPP) is calculated from the societal perspective. AU, Austria; BE, Belgium; CH, Switzerland; ES, Spain; GE, Germany; IT, Italy; NL, The Netherlands; SE, Sweden; UK, United Kingdom.

B.1.3.6 Unmet need in PPMS

There is a clear unmet need in the field of PPMS for a DMT that has a benefit–risk profile which supports initiation at any time during the disease course of MS, which preserves neurological function, inhibits the accumulation of irreversible disability and improves HRQoL.

Until now, no drugs have been successfully developed for the treatment of the severely debilitating condition, PPMS [125]. Ocrelizumab provides a treatment option that addresses the unmet need in PPMS by improving HRQoL - delaying disability progression in both lower limb function (reducing deterioration in walking speed) and upper limb function. It is also the first DMT to demonstrate near-complete suppression of subclinical disease activity as measured by MRI.

Furthermore, the safety profile coupled with the need for just two infusions per year means that ocrelizumab will require a low healthcare utilisation with infrequent monitoring; therefore, the introduction of ocrelizumab as a treatment for PPMS in people with imaging features characteristic of inflammatory activity will not introduce an unnecessary burden to the healthcare system.

B.1.4 Equality considerations

Efficacy results presented in this submission include a subgroup analysis in patients with inflammatory activity aged 50 years or younger (as referred to in section B.1.3.4; see also 'MRI Active ≤50' subgroup described in Section B.2.7). Subgroup analyses of the ORATORIO study suggested that age is a key indicator of clinical benefit from ocrelizumab in PPMS. Younger patients with imaging features characteristic of inflammatory activity derived the greatest benefit from treatment with respect to delaying confirmed EDSS worsening for 12 and 24 weeks, and delaying progression of upper limb impairment. As such, these results informed the approved indication in patients with early PPMS in the EU. The clinical benefit of treating patients older than 50 years with ocrelizumab appears more uncertain.

We recognise that this subgroup analysis may raise equality concerns. The decision to present this subgroup was informed by evidence from the pivotal Phase III ORATORIO study and was the subject of extensive discussions with health regulatory authorities [126]. The post-hoc analysis with age cut-off of 50 years was chosen to be as inclusive as possible.

A proxy for age was not identified in the ORATORIO data. Disease duration may have been an intuitive proxy, but the baseline patient characteristic of 'duration since MS symptom onset (years)' did not correlate well with treatment effect. This is likely due to the subjective nature of this variable, as it may be impacted by recall bias and is likely complicated by the delayed diagnosis of PPMS.

Older patients may still benefit from active treatment if the clinical benchmark is preserving upper limb function. Indeed, in the absence of functioning lower limbs, the ability to use one's upper limbs becomes even more critical. Analyses show that both EDSS scores (lower limb function being a major contributor) and 9-HPT (measure of upper limb function) contribute to the overall quality life of patients, and as such ocrelizumab provides considerable benefits for PPMS patients irrespective of age.

Proposal for Managed Access Agreement

To clarify the benefits of ocrelizumab in older patients with PPMS, the efficacy and safety of ocrelizumab in PPMS patients with a later disease course, defined by EDSS and age, will be evaluated in the planned Phase IIIb study with upper limb function as primary endpoint (see section B2.11 for more details).

We propose a Managed Access Agreement (MAA) for ocrelizumab in PPMS that would allow patients with PPMS to have access to this innovative therapy whilst addressing clinical uncertainty. The new Phase IIIb study would form the basis of data collection proposed under the MAA (see Data Collection Arrangement Appendix). The commercial arrangement that underpins the proposed MAA would address the cost effectiveness and triggering of the Budget Impact Test of ocrelizumab in PPMS (see PAS appendix).

This approach is similar to MAAs in oncology via 'use in Cancer Drugs Fund (CDF)' recommendations (12 CDF-type MAAs agreed by NICE and NHS England so far [77-88]), MAAs in ultra-orphan indications via the Highly Specialised Technology (HST) program (three HST-type MAAs agreed by NICE and NHS England so far [89-91]), and also a recent MAA for a treatment in systemic lupus erythematosus [92].

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

The efficacy and safety of ocrelizumab in adults with primary progressive multiple sclerosis (PPMS) has been demonstrated in the ORATORIO study (WA25046; clinicaltrials.gov identifier NCT01194570).

Table 6: Summary of clinical effectiveness evidence

Study	ORATORIO / WA25046 / NCT01194570				
Study design	Phase III, multicentre, randomised, parallel-group, double blinded, placebo controlled study				
Population	Patients who were diagnosed with PPMS in accordance with the 2005 revision of McDonald criteria				
Intervention(s)	Ocrelizumab 600 mg				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X
	No			No	
Rationale for use/non-use in the model	This study is used in the model as it is the only available evidence for ocrelizumab in PPMS. The trial comparison (placebo added to best supportive care) is generalisable to UK routine practice.				
Reported outcomes specified in the decision problem	• disability: CDP12, CDP24, 9-HPT, T25FW • disease activity: MRI activity (T2 lesions, gadolinium (Gd) – enhancing T1 lesions, brain volume) • patient reported outcomes: MFIS, MSFC, PASAT • mortality • adverse events • health-related quality of life: SF-36, EQ-5D				
All other reported outcomes	composite disability progression (CDP12, 9-HPT, T25FW)				

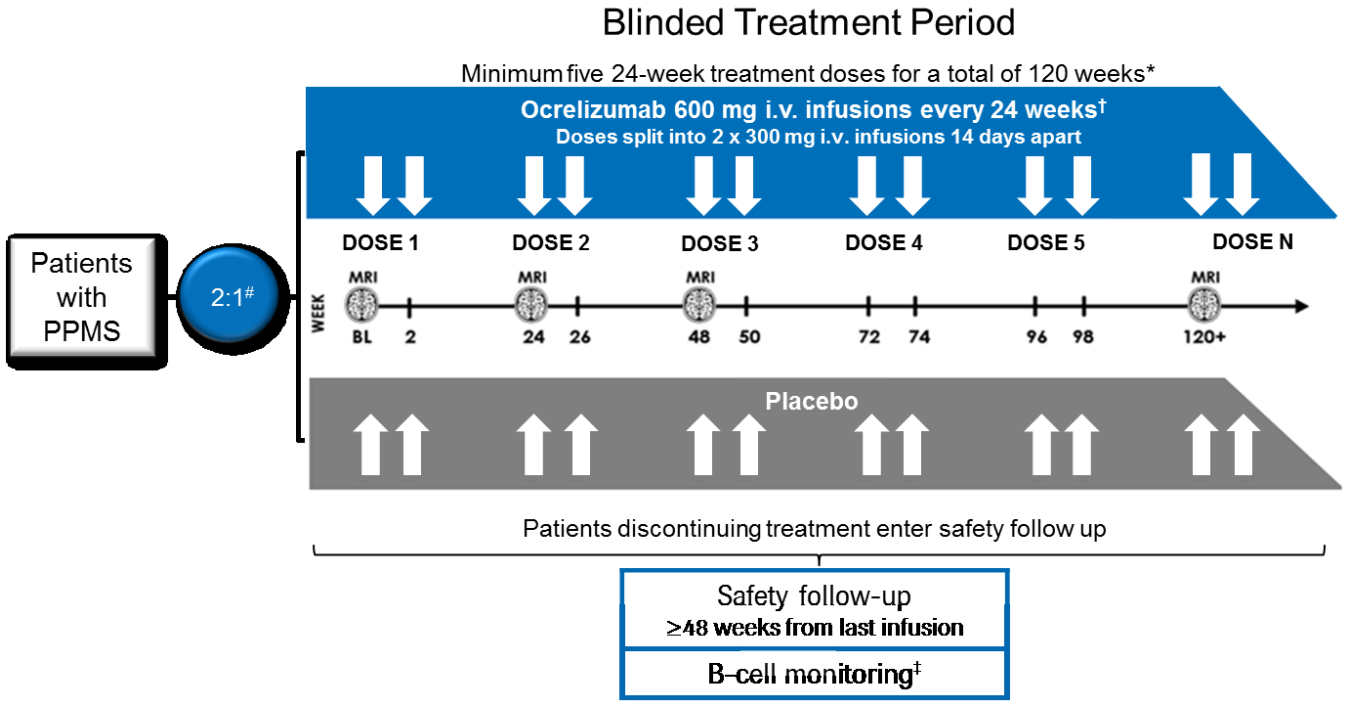
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

ORATORIO is a phase III, multicentre, randomised, parallel-group, double blinded, placebo controlled study, and supports the licence application for PPMS. Data were collected by the site investigators, queries were responded to by site personnel, and the data were analysed by F. Hoffman-La Roche; the aggregated and individual results of the participants were reviewed by F. Hoffman-La Roche and the ORATORIO steering committee.

B.2.3.1 Trial design

Patients were randomly assigned, in a 2:1 ratio, to receive ocrelizumab or blinded placebo, by means of intravenous infusion. Ocrelizumab was administered at a dose of 600 mg every 24 weeks: this was split as 2 x 300 mg doses given 14 days apart (i.e. Day 1 and Day 15 of every 24-week period). The design of the ORATORIO study is shown in Figure 9.

Figure 9: ORATORIO study design



Abbreviations: BL, baseline; i.v., intravenous; MRI, magnetic resonance imaging; MS, multiple sclerosis; PRMS, progressing-relapsing MS; R, randomisation; ROW, rest of world;

*The blinded treatment period may be extended until database lock

#2:1 randomisation stratified by age (≤45 vs >45) and region (US vs ROW)

†Patients received methylprednisolone prior to each ocrelizumab infusion or placebo infusion.

‡Continued monitoring occurs if B cells are not repleted

The study consisted of a screening period, followed by 120 weeks of double-blind treatment (representing five full doses).

Patients who withdrew prematurely from treatment were encouraged to enter safety follow-up (SFU) followed by B cell monitoring. Patients did not receive any study treatment during this period. Patients were followed in SFU for at least 48 weeks from the date of last ocrelizumab/placebo infusion. Additionally, telephone interviews were performed every 4 weeks.

An open label extension (OLE) was planned, but at the time of the clinical cut-off the OLE had not started, hence data was not available in the CSR. NB: Patients who withdrew from the blinded treatment period would not be eligible for OLE.

Patients were randomised into the study between 3 March 2011 and 27 December 2012. Patients were treated for a variable duration, with the clinical cut-off date occurring after a minimum of 120 weeks and approximately 253 events had been accrued, resulting in at least five treatment doses per patient. The study follow-up visits were performed every 12 weeks, starting from the date of the patient's last visit, until at least 48 weeks had elapsed since the date of last ocrelizumab/placebo infusion. Telephone interviews were conducted every 4 weeks from Week 8 onward to systematically identify any new or worsening neurological symptoms to trigger an unscheduled visit. Unscheduled visits for the assessment of potential relapses, new neurological symptoms or safety events could occur at any time.

A summary of the methodology of the ORATORIO study is given in Table 8

A total of 732 patients were randomized into the study, of which 725 received at least one dose of placebo or ocrelizumab.

There were five investigator sites in the UK, recruiting a total of 29 patients

Table 7: Summary of patients per site for United Kingdom

Site location	Placebo arm (N=244)	Ocrelizumab arm (N=488)
Barts and the London NHC Trust, London	2 (0.8%)	9 (1.8%)
Walton Center For Neurology & Neurosurgery; Clinical Trials Unit, Liverpool	2 (0.8%)	5 (1.0%)
Uni Hospital Queens Medical Centre; Neurology, Nottingham,	0	5 (1.0%)
Royal Victoria Infirmary; Neurology Dept., Newcastle Upon Tyne	0	3 (0.6%)
Kings College Hospital; Neurology	1 (0.4%)	2 (0.4%)
United Kingdom total	5 (2.0%)	24 (4.9%)

Table 8: Summary of trial methodology

Trial number (acronym)	ORATORIO (WA25046)
Location	Patients were enrolled at 182 investigational sites across 29 countries (Europe, North America, Australia and New Zealand, Latin America). There were five UK sites.
Trial design	Phase III, multicentre, randomised, parallel-group, double blinded, placebo controlled study

Eligibility criteria for participants	***Key inclusion criteria***
	• Diagnosis of PPMS in accordance with the revised McDonald criteria (2005)
	• Ages 18-55 years, inclusive
	• EDSS at screening from 3.0 to 6.5 points
	• Disease duration from the onset of MS symptoms:
	  ○ less than 15 years in patients with an EDSS at screening > 5.0
	  ○ less than 10 years in patients with an EDSS at screening ≤ 5.0
	
	Key exclusion criteria
	• History of relapsing remitting multiple sclerosis, secondary progressive, or progressive relapsing multiple sclerosis at screening
	• Inability to complete an MRI (contraindications for MRI included but were not restricted to weight ≥140 kg, pacemaker, cochlear implants, intracranial vascular clips, surgery within 6 weeks of entry into the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, etc.)
	• Previous treatment with B-cell targeted therapies or other medications potentially used for the treatment of MS
	• Systemic corticosteroid therapy within 4 weeks prior to screening

Settings and locations where the data were collected	• Secondary or tertiary care
Trial drugs **Permitted and disallowed concomitant medication**	Intervention (n=488): Ocrelizumab 600 mg administered as two 300 mg IV infusions separated by 14 days (subsequently referred to as one treatment dose), at a scheduled interval of every 24 weeks Comparator (n=244): Placebo
Primary outcomes (including scoring methods and timings of assessments)	Time to onset of confirmed disability progression over the treatment period, defined as increase in the EDSS score that is sustained for at least 12 weeks (based on regularly scheduled visits; CDP-12)
Other outcomes used in the economic model / specified in the scope	Secondary endpoints were tested in the following hierarchical order providing that each preceding end point reached a significance level of $p<0.05$: • time to onset of confirmed disability progression sustained for at least 24 weeks (CDP-24) • change in timed 25-foot walk from baseline to Week 120

	• change in the total volume T2 hyperintense brain lesions on MRI from baseline to Week 120 • percentage change in total brain volume from Week 24 to Week 120, • change in the Physical Component Summary score of the Short-Form 36 Health Survey (SF-36), version 2, from baseline to Week 120 Exploratory endpoints included: *Clinical* • time to a sustained increase of (≥ 20%) in the 9-HPT *Imaging* • total number of new or enlarging T2 hyperintense lesions detected by brain MRI from baseline to Week 120 • percentage change in cortical grey matter volume from baseline to Week 120 • percentage change in white matter volume from baseline to Week 120 • change from baseline in total non-enhancing T1 lesion volume on MRI scan of the brain *Patient-reported outcomes* • change in quality of life, as measured by EQ-5D score from baseline to Week 120 • change in fatigue, as measured by the Modified Fatigue Impact Scale (MFIS) total score and subscale scores from baseline to Week 120
Pre-planned subgroups	The primary and the following secondary efficacy endpoints (predefined: time to onset of 12- and 24-week CDP; change in T25-FW from baseline to Week 120; changes in total volume of T2 lesions were summarised and analysed by predefined subgroups: • Age (≤45 vs >45 years) • Sex (male vs female) • Baseline EDSS (≤5.5 vs >5.5) • Region (USA vs ROW) • Presence of gadolinium-enhancing T1 lesions at baseline MRI scan • Prior MS DMTs with the exception of corticosteroids • Duration since onset of MS symptoms (≤3 yrs, 3 to ≤5 yrs, 5 to ≤10 yrs, >10 yrs) • Weight (≤75 vs >75 kg at baseline) • BMI (<25 vs ≥25 kg/m^2 at baseline)

B.2.3.2 Baseline characteristics

Demographic characteristics of the ITT population were well balanced between groups. Consistent with the epidemiology of PPMS, the majority of the patients were Caucasian (>90% in both groups), with a median age of 46 years (range 18 to 56 years). Consistent with the sex prevalence for PPMS, approximately half of the patients were male in both groups (49% in the placebo group and 51% in the ocrelizumab group). Demographic characteristics of the safety population were consistent with those of the ITT population.

Baseline disease characteristics for PPMS were similar across both treatment groups. The median duration of disease in terms of time from symptom onset was almost 6 years in both groups with a median time since diagnosis of 1.3 years (placebo group) and 1.6 years (ocrelizumab group). The majority of patients (placebo 88% vs ocrelizumab 89%) had not received any MS disease-modifying treatment prior to baseline in the previous 2 years. Baseline disease characteristics for PPMS and EDSS score for the safety population were consistent with those for the ITT population.

Baseline MRI assessments showed that the majority of patients had no T1 Gd-enhancing lesions (placebo 75% vs ocrelizumab 73%). The volume and number of T2 lesions were similar between the groups. Normalised brain volume was also similar between the two groups. Baseline MRI characteristics for the safety population were consistent with those for the ITT population.

A total of 75% of patients in the placebo group and 81% of patients in the ocrelizumab group reported comorbidities that were active at baseline. The most common by System Organ Class (SOC) were Psychiatric Disorders (placebo 28% vs ocrelizumab 26%; most commonly depression, insomnia, and anxiety), Musculoskeletal and Connective Tissue Disorders (placebo 28% vs ocrelizumab 24%: most commonly back pain, osteoarthritis, and intervertebral disc protrusion), and Nervous System Disorders (placebo 24% vs ocrelizumab 23%: most commonly headache, migraine, and muscle spasticity). Results for the safety population were similar.

Table 9: Characteristics of participants in the studies across treatment groups

	Placebo (n=244)	Ocrelizumab (n=488)
Baseline characteristic		
Age, years		
Mean	44.4±8.3	44.7±7.9
Median (range)	46.0 (18 to 56)	46.0 (20 to 56)
Age group, n (%)		
<18	0	0
≥ 18 to 65	244 (100)	488 (100)
>65	0	0
≤ 45	118 (48.4)	230 (47.1)
>45	126 (51.6)	258(52.9)
Sex, n (%)		
Female	124 (50.8)	237 (48.6)
Male	120 (49.2)	251 (51.4)
Region		
ROW	210 (86.1)	421 (86.3)
USA	34 (13.9)	67 (13.7)
Race, n (%)		
American Indian or Alaska Native	0	5 (1.0)
Black or African American	5 (2.0)	9 (1.8)
White	235 (96.3)	454 (93.0)
Other	4 (1.6)	51 (10.5)
Unknown	0	18 (3.7)
Weight, kg		
n	243	486
Mean	72.81 ±15.13	72.46±17.11
Median (range)	72.00 (45.0 to 136.0)	71.00 (40.2 to 135.9)
Disease Characteristics		
Time since onset of MS symptoms, years†		
Mean	6.1±3.60	6.7±4.0
Median (range)	5.5 (1.1 to 32.9)	6.0 (1.1 to 32.9)
Time since diagnosis of PPMS, years‡		
Mean	2.8±3.3	2.9±3.2
Median (range)	1.3 (0.1 to 23.8)	1.6 (0.1 to 16.8)
No previous use of DMT, n (%)§	214 (87.7)	433 (88.7)
Patients received steroids as MS therapy, n (%)	45 (18.4)	89 (18.2)
Score on EDSS¶		
Mean	4.7±1.2	4.7±1.2
Median (range)	4.5 (2.5 to 6.5)	4.5 (2.5 to 7.0)
Gadolinium-enhancing lesions on T1-weighted images		
Yes	60/243 (24.7)	133/484 (27.5)
No	183/243 (75.3)	351/488 (72.5)
No. of lesions on T2-weighted images**		
Mean	48.2±39.3	48.7±38.2
Median (range)	43.0 (0 to 208)	42.0 (0 to 249)
Total volume. of lesions on T2-weighted images, cm^3 **		
Mean	10.9±13.0	12.7±15.1
Median (range)	6.2 (0 to 81.1)	7.3 (0 to 90.3)
Normalised brain volume, cm^3 ††		
Mean	1469.9±88.7	1462.9±84.0
Median (range)	1464.5 (1216.3 to 1701.7)	1462.9 (1214.3 to 1711.1)

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; PPMS; primary progressive MS; SD, standard deviation

± Plus–minus values are means ±SD. Patients were stratified according to geographic region (United States vs. rest of the world) and age (≤45 vs. >45 years).

† Data were not available for 14 patients in the ocrelizumab group and 7 patients in the placebo group.
‡ Data were not available for 2 patients in the ocrelizumab group and 1 patient in the placebo group.
§ Shown are data for patients with no use of disease-modifying therapy in the 2 years before trial entry.
¶ Scores on the EDSS range from 0 to 10, with higher scores indicating greater disability. Data were not available for 1 patient in the ocrelizumab group.
‖ A breakdown of the categorical numbers of gadolinium-enhancing lesions on T1-weighted images is provided in Table S7 in the Supplementary Appendix [127].
** Data were not available for 2 patients in the ocrelizumab group and 1 patient in the placebo group.
†† The analysis was performed with the use of SIENA/X.22 Data were not available for 6 patients in the ocrelizumab group and 1 patient in the placebo group.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

A description of the statistical analyses for ORATORIO is given in Table 10.

The participant flow and disposition for patients in ORATORIO is given in Appendix D.

Table 10: Summary of statistical analyses in ORATORIO

Hypothesis objective	• H0 (null hypothesis): There was no difference in the time to CDP between the ocrelizumab and placebo groups • H1 (alternative hypothesis): There was a difference in the time to CDP between the ocrelizumab and placebo groups The null hypothesis was tested at α = 0.05 level (two-sided test) stratifying by geographic region (US versus ROW) and age (≤45 versus >45). If the test result was statistically significant at α <0.05 level (two-sided test), it was concluded that the ocrelizumab group demonstrated a superior effect of increasing time to confirmed disability progression of patients, when compared with the placebo arm. Similar hypotheses were also tested for the secondary efficacy parameters.
Statistical analysis	Primary efficacy endpoint analysis The primary efficacy endpoint was tested at a two-sided significance level of α <0.05; p-values were based on a log-rank test stratified by geographic region and age. Overall hazard ratio was estimated using a stratified Cox regression model with the same stratification factors used in the log-rank test Secondary endpoint analysis The five secondary endpoints were tested in a hierarchical order, providing that each preceding end point reached a two-sided alpha significance level of p<0.05. • Time to onset of CDP for ≥ 12/24 weeks: log-rank test for p value, Cox regression for estimation of HR • Change in T25-FW relative ratio to baseline at Week 120: ranked ANCOVA with LOCF for p value; MMRM for treatment estimates • T2 lesion volume relative ratio to baseline at Week 120: ranked ANCOVA with LOCF for p value; MMRM for treatment estimates • % change in brain volume from Week 24 to Week 120: MMRM • Mean change from baseline in SF-36 PCS: MMRM Predefined exploratory analyses The statistical analysis plan accompanying the protocol stated that five MRI-derived endpoints, seven clinical and two pharmacokinetic/dynamic endpoints were planned to be assessed. Most of these endpoints had not yet been analysed at the time of the primary analysis and publication of the primary manuscript.
Sample size, power	Data from a previous Phase II/III study in patients with PPMS was used to

calculation	calculate the sample size for the ORATORIO study[102]. The two-year progression rate among patients receiving ocrelizumab was predicted to be 30% compared with 43% among patients receiving placebo. It was assumed the study would require a one-year accrual period with a 3.5 year maximum treatment period; it was also assumed that the drop-out rate over a 2-year period would be 20%. Using a two-sided log-rank test, a total sample size of 630 patients was calculated to provide 80% statistical power to maintain type I error rate of 0.01 (or approximately 92% power for type I error rate of 0.05) with 253 events expected to occur.
Analysis populations	The intent-to-treat (ITT) population comprised all patients who were randomly assigned to treatment. All efficacy endpoints were analysed using the ITT population. The per-protocol (PP) population comprised all patients in the ITT population adhering to the protocol. Patients were excluded if they significantly violated the inclusion or exclusion criteria or deviated from the study plan. The per-protocol (PP) population was used for the primary and some secondary efficacy analyses in order to evaluate the influence of major protocol violators and as a sensitivity check to the ITT analysis. The safety population comprised all patients who received at least one dose of study drug (ocrelizumab or placebo). All summaries of safety data were produced from the safety population. Within the safety population, there were four patients randomised to the placebo group who received ocrelizumab; these patients were summarised in the ocrelizumab-treated group.
Data management, patient withdrawals	The secondary endpoints of T25FW and volume of lesions on T2-weighted images often produce data which is not normally-distributed, and can include outlier values which are quite extreme. Therefore, robust hypothesis testing was performed using the ranked analysis of covariance (ANCOVA) method. The last-observation-carried-forward method was used to impute missing values. A mixed-effect model repeated measure (MMRM) approach that was based on log-transformed data was used to provide estimates of expected change from baseline and treatment effect. Log transformation was predicted to approximately normalise data on the basis of experience from phase 3 studies in patients with RMS and from assessment of the distributions for T25FW and the volume of lesions on T2-weighted images within the blinded ORATORIO data. For brain volume, p values and estimates were based on MMRM analysis of percent change from baseline. Ranked ANCOVA and MMRM analyses were adjusted for baseline values, geographic region, and age.
Sub-groups	The primary and the following secondary efficacy endpoints (time to onset of 12- and 24-week CDP; change in T25FW from baseline to Week 120; changes in total volume of T2 lesions were analysed by predefined subgroups: • Age (≤45 vs >45 yrs) • Sex (male vs female) • Baseline EDSS (≤5.5 vs >5.5) • Region (USA vs ROW) • Presence of gadolinium-enhancing T1 lesions at baseline MRI scan • Prior MS DMTs with the exception of corticosteroids • Duration since onset of MS symptoms (≤3 yrs, 3 to ≤5 yrs, 5 to ≤10 yrs, >10 yrs) • Weight (≤75 vs >75 kg at baseline) • BMI (<25 vs ≥25 kg/m^2 at baseline) To further investigate the independence of potential treatment effect modifying factors, a multivariate Cox regression analysis was performed.

	The Cox model contained all pre-specified subgroup factors as main and treatment interaction effects, with the exception of weight, due to its high correlation with BMI. Continuous variables (age, EDSS, duration since MS symptom onset, BMI) were included as linear covariates.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The risk of bias in the Phase III ORATORIO trial was assessed based on the Cochrane Risk of Bias tool, and is summarised in Appendix D.13.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Overview of efficacy

The data discussed in this section has been taken from the primary analysis for ORATORIO (clinical cut-off date 24 July 2014), in which a total of 732 patients were randomised.

In ORATORIO, ocrelizumab treatment was associated with significantly reductions in disability progression assessed by EDSS, relative to placebo. The study met its primary endpoint with a 24% reduction in the risk of 12-week CDP in the ocrelizumab group compared with placebo (hazard ratio 0.76 [95% CI: 0.59 to 0.98], p=0.0321).

In the study, ocrelizumab demonstrated beneficial effects and statistically significant improvements when compared with placebo, across a wide range of clinical (disability) and subclinical (MRI) outcome measures.

Results of the secondary and exploratory endpoints for disability and MRI outcomes supported the primary endpoint, demonstrating statistically significant efficacy of ocrelizumab vs placebo.

- Treatment with ocrelizumab resulted in a 25% reduction in the risk of 24-week CDP in the ocrelizumab group compared with placebo (hazard ratio 0.75 [95% CI: 0.58 to 0.98], p=0.0365)

- Treatment with ocrelizumab resulted in a smaller proportion of patients experiencing a 20% increase in time to complete 9-HPT, compared with placebo, at both 12 and 24 weeks (12 weeks: 83/488 vs 66/244; HR 0.56; 95% CI 0.441 to 0.78; p=0.0004) (24 weeks: 69/488 vs 57/244; HR=0.55 95% CI 0.38 to 0.77; p=0.0006)

- Patients in the ocrelizumab group experienced a significant mean decrease in fatigue as measured by the MFIS total score from baseline to Week 120 of -0.462 (95% CI: -2.145 to 1.222) compared with those in the placebo group who experienced a mean increase of 2.994 (95% CI: 0.658 to 5.330) (difference in adjusted means: -3.456 [95% CI: -6.048, to 0.863]; p=0.0091

- 43% of ocrelizumab-treated patients had No Evidence of Progression (NEP) versus 29% for placebo patients, which represents a 47% relative increase (p=0.0006)

- Ocrelizumab significantly increased the proportion of patients with No Evidence of Progression and Active Disease (NEPAD) at Week 120 compared with placebo (29.9% vs 9.4%; risk ratio ocrelizumab vs placebo [95% CI]: 3.15 [2.07–4.79]; p<0.001). This was reflected in superiority across all the individual components of NEPAD with ocrelizumab vs placebo from baseline to Week 120.

- The extrapolated time to median confirmed progression to EDSS ≥7.0 was 13.6 years for placebo-treated patients and 22.4 years for ocrelizumab-treated patients, corresponding to an expected delay in progression to EDSS ≥7.0 of 8.8 years.

- Treatment with ocrelizumab resulted in a 29% relative reduction in the T25FW progression rate from baseline to Week 120 compared with placebo (p=0.0404)

- Ocrelizumab decreased the percentage change in total volume of T2 hyperintense lesions from baseline to Week 120 (decrease of 3.4%) compared with an increase for patients on placebo (increase of 7.4%; p<0.0001)

- Treatment with ocrelizumab resulted in a 17.5% relative reduction in the rate of brain volume loss from Week 24 to Week 120, when compared with placebo (p=0.0206)

- Patients in the ocrelizumab group experienced a reduction of 0.73 points (not statistically significant) on the SF-36 Physical Component Summary Score (PCS) (a key secondary endpoint measuring change in quality of life) from baseline to Week 120 compared with placebo (-1.11 points; p=0.6034).

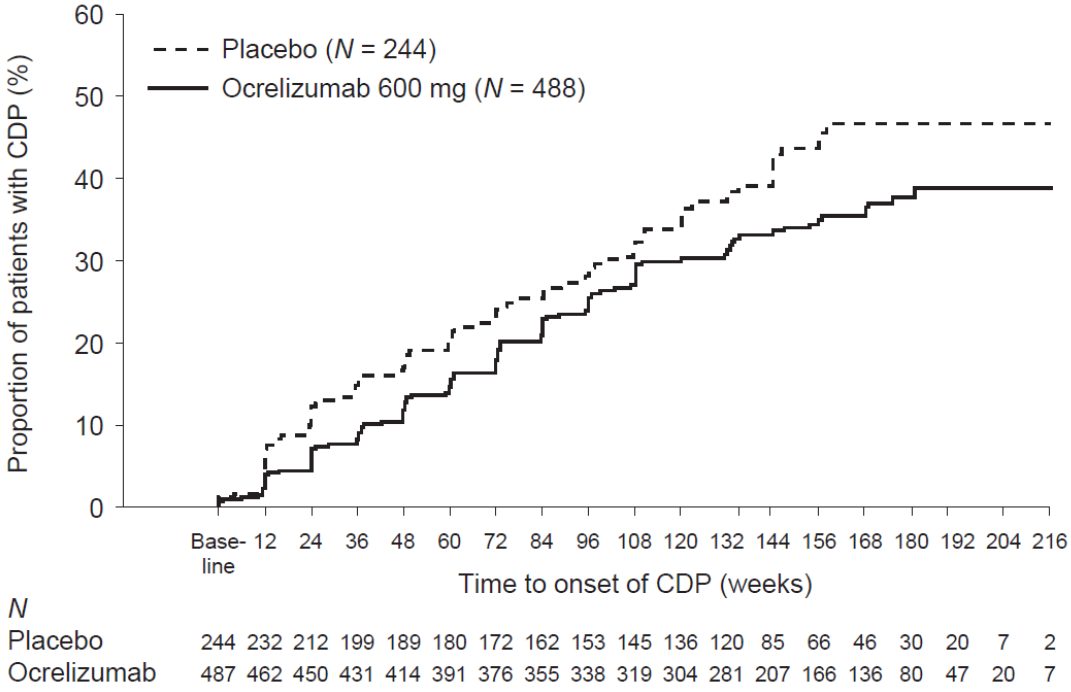
B.2.6.2 Primary efficacy endpoint

Time to onset of 12-week CDP

The study met its primary endpoint with a 24% statistically significant reduction in the risk of 12-week CDP in the ocrelizumab group compared with placebo (HR 0.76 [95% CI: 0.59,

0.98], p=0.0321). See Figure 10. The percentage of patients with 12-week CDP was 32.9% in the ocrelizumab group versus 39.3% in the placebo group. The Kaplan-Meier survival curves for time to onset of 12-week CDP show separation from 12 weeks, with a lower proportion of patients in the ocrelizumab group with CDP throughout the treatment period [128, 129].

Figure 10: Time to 12-week CDP in ORATORIO



The robustness of the results of the primary endpoint was analysed by performing various sensitivity analyses that evaluated the influence of relapses on disability progression outcomes. Sensitivity analyses were consistent with the primary analysis (treatment effect favouring ocrelizumab in each analysis).

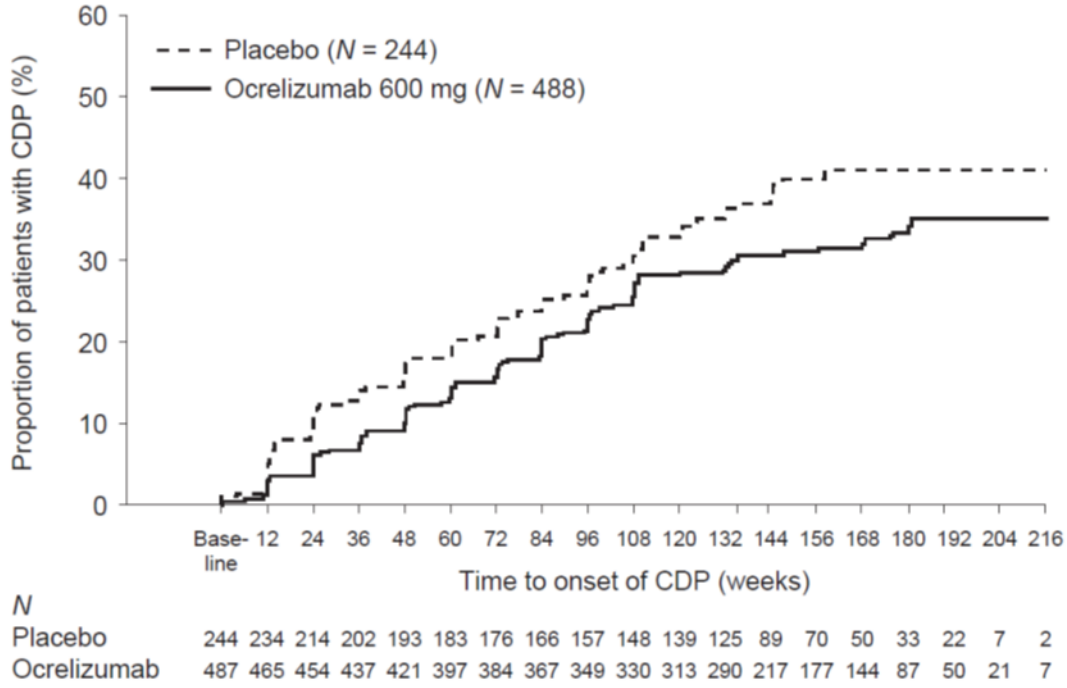
B.2.6.3 Secondary endpoints

Time to onset of 24-week CDP

Consistent with the primary endpoint, treatment with ocrelizumab led to a statistically significant 25% reduction in the risk of 24-week CDP compared with placebo (HR 0.75 [95% CI: 0.58, 0.98], p=0.0365). See Figure 11.

The percentage of patients with 24-week CDP was 29.6% in the ocrelizumab group versus 35.7% in the placebo group. The Kaplan-Meier survival curves for time to onset of 24-week CDP are shown [128, 129]. Again, consistent with the primary endpoint, the robustness of this finding is reflected in sensitivity analyses.

Figure 11: Time to 24-week CDP in ORATORIO



Other secondary endpoints

Further results of secondary endpoints of ORATORIO are given in Appendix K:

- change in timed 25-foot walk;
- percent change in total volume of T2 hypertintense lesions;
- percent change in total brain volume;
- change in quality of life as measured by SF-35 PCS

B.2.6.4 Exploratory endpoints

9 Hole Peg Test

The 9 Hole Peg Test (9-HPT) formed part of a composite endpoint (along with CDP by EDSS and T25FW). The relative contribution of the three components of the composite endpoint was analysed. The significant effect seen in the composite was found to be maintained in an analysis with the EDSS component removed and in further analyses with all components analysed alone. The results for the 9-HPT component are shown below [127, 129].

In terms of 9-HPT, 17.0% of patients in the ocrelizumab group had a confirmed 20% increase at 12 weeks compared with 27.0% in the placebo group, a risk reduction of 44% (HR: 0.56; 95% CI: 0.41–0.78; p = 0.0004.) This effect was maintained with the 24-week

measures 14.1% of patients had a confirmed 20% increase at 24 weeks compared with 23.4% in the placebo group, a risk reduction of 45% (HR: 0.55; 95% CI: 0.38–0.77).

Endpoint	Placebo (n=244)	Ocrelizumab (n=488)	Hazard ratio (95% CI)	p (log-rank)
20% increase in 9-HPT confirmed at 12 weeks	66 /244	83 /488	0.56 (0.41, 0.78)	0.0004
20% increase in 9-HPT confirmed at 24 weeks	57/244	69/488	0.55 (0.38; 0.77)	0.0006

Figure 12: Time-to-Onset of 12-Week Confirmed ≥20% Progression in 9-HPT in ORATORIO

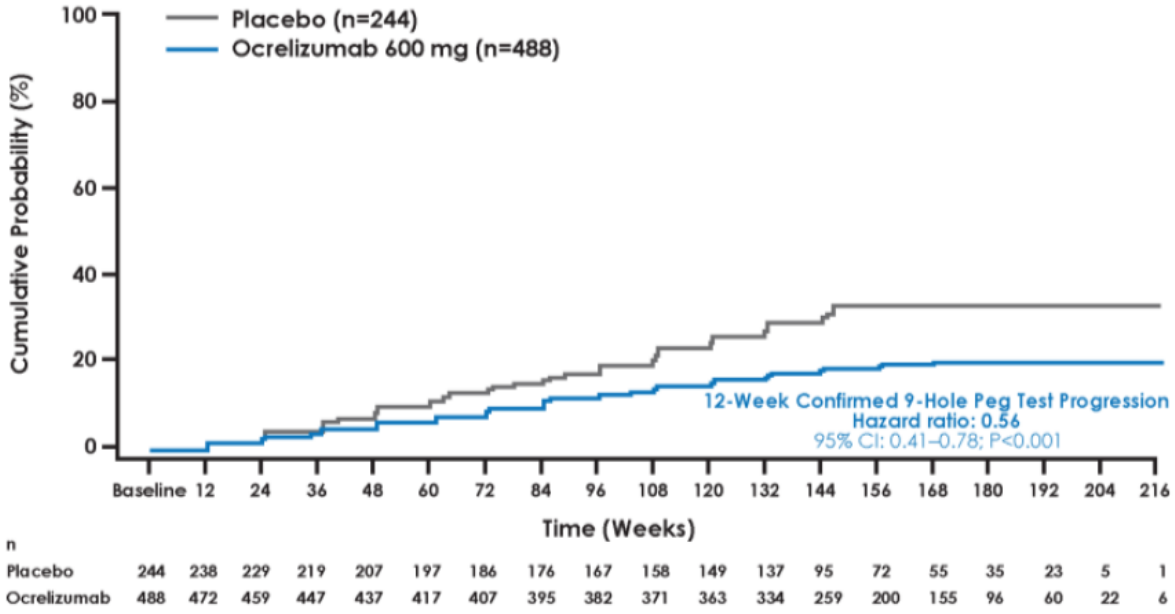
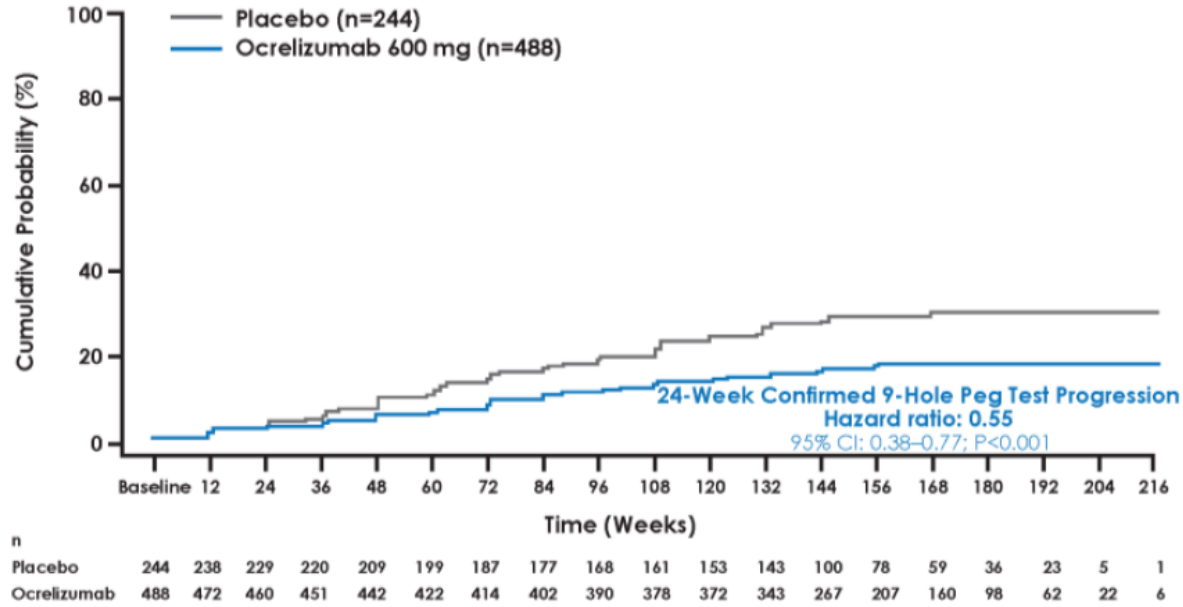


Figure 13: Time-to-Onset of 24-Week Confirmed ≥20% Progression in 9-HPT in ORATORIO



Modified Fatigue Impact Scale

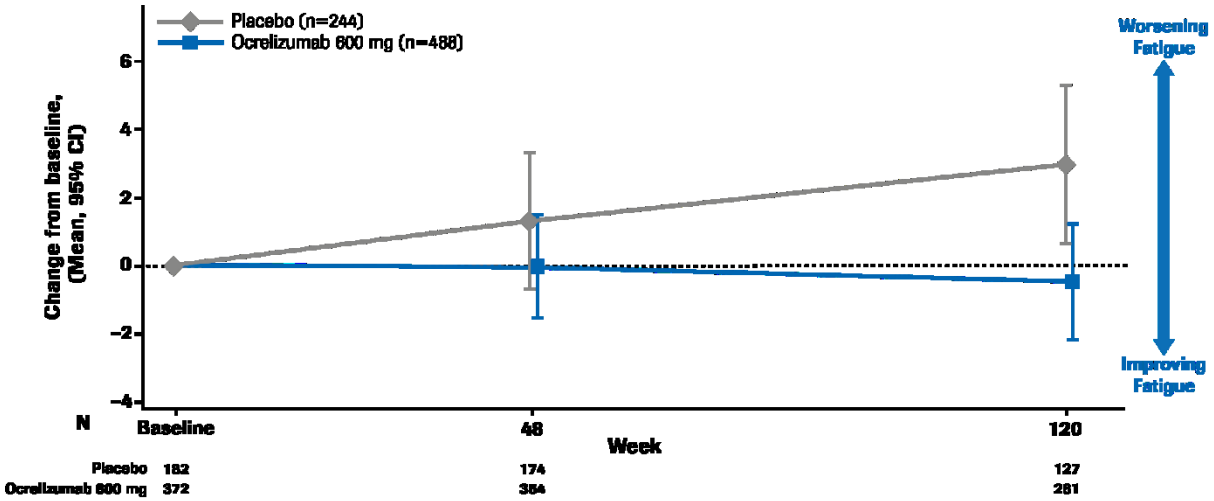
Patients in the ocrelizumab group experienced a significant mean decrease in fatigue as measured by the MFIS total score from baseline to Week 120 of -0.462 (95% CI: -2.145 to 1.222) compared with those in the placebo group who experienced a mean increase of 2.994 (95% CI: 0.658 to 5.330) (difference in adjusted means: -3.456 [95% CI: -6.048, to 0.863]; p=0.0091

Table 11: Baseline MFIS total and subscale scores

N=640	Mean (SD)	Median	Min, max
MFIS total score	41.6 (17.2)	43.0	0, 83
MFIS subscales			
Physical	22.6 (8.4)	24.0	0.36
Cognitive	14.7 (9.4)	14.0	0.40
Psychosocial	4.3 (2.2)	4.0	0.80

MFIS total scores range from 0 to 84, with higher scores indicating greater fatigue; scores ≥38 indicate a clinically important level of fatigue.

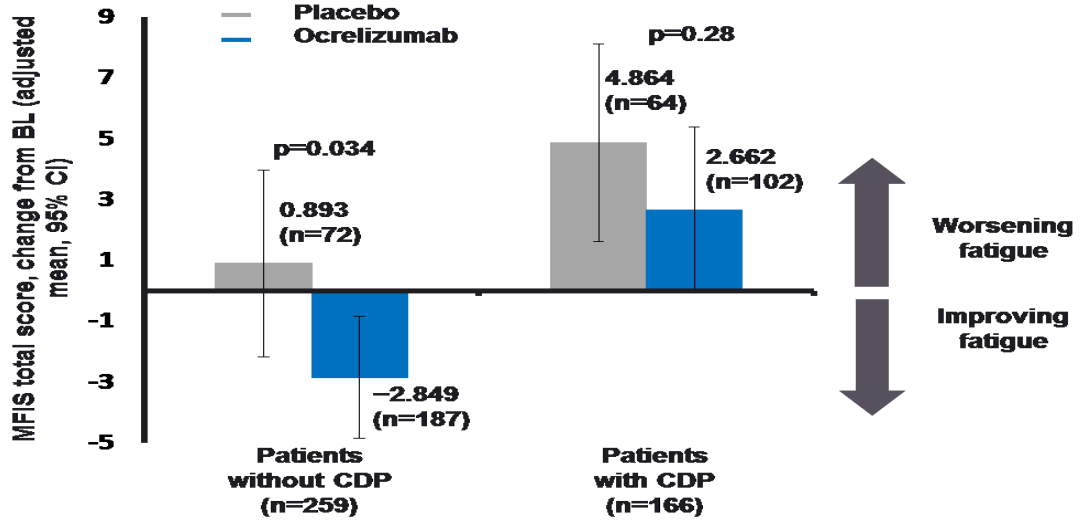
Figure 14: Change in MFIS total score from baseline to Week 120 in ORATORIO



The change in MFIS was analysed separately for each of the subscale components for physical, cognitive and psychosocial impact. Patients in the ocrelizumab group showed a consistent reduction in fatigue from baseline to Week 120 compared to those in the placebo group for all of the MFIS subscale components [129].

The relationship between CDP and fatigue in PPMS was explored and found that CDP is strongly associated with fatigue. Patients with CDP reported a significantly greater increase in the impact of fatigue on physical, cognitive and psychological functioning compared to patients without CDP. Even for patients who did not achieve 12-week CDP, those treated with ocrelizumab had greater reductions in fatigue than those receiving placebo. This suggests a beneficial effect of ocrelizumab on expressions of disease not captured by CDP [130].

Figure 15: Change in fatigue by CDP status from baseline to Week 120 in ORATORIO, stratified by treatment group

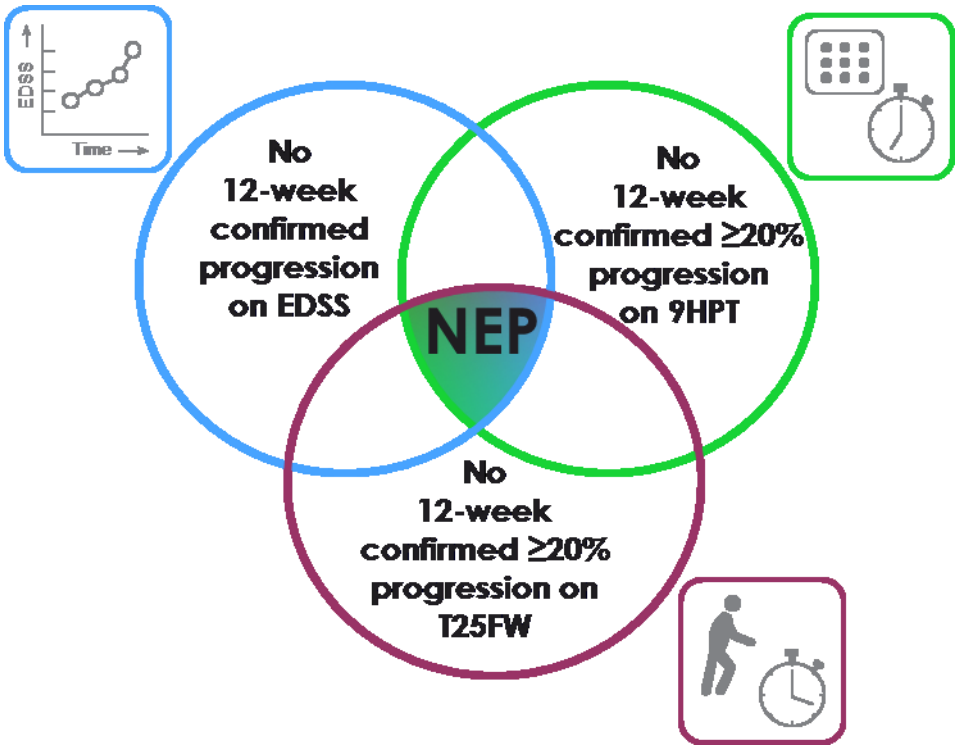


Pre-specified exploratory analysis: evaluation of No Evidence of Progression (NEP)

NEP is a composite endpoint to evaluate the proportion of PPMS patients with stable clinical disease. NEP assesses the combined absence of 12-week confirmed progression on measures of:

- Disability (EDSS)
- Upper limb function (9-HPT)
- Ambulation (T25FW

Figure 16: Definition of no evidence of progression (NEP) in PPMS



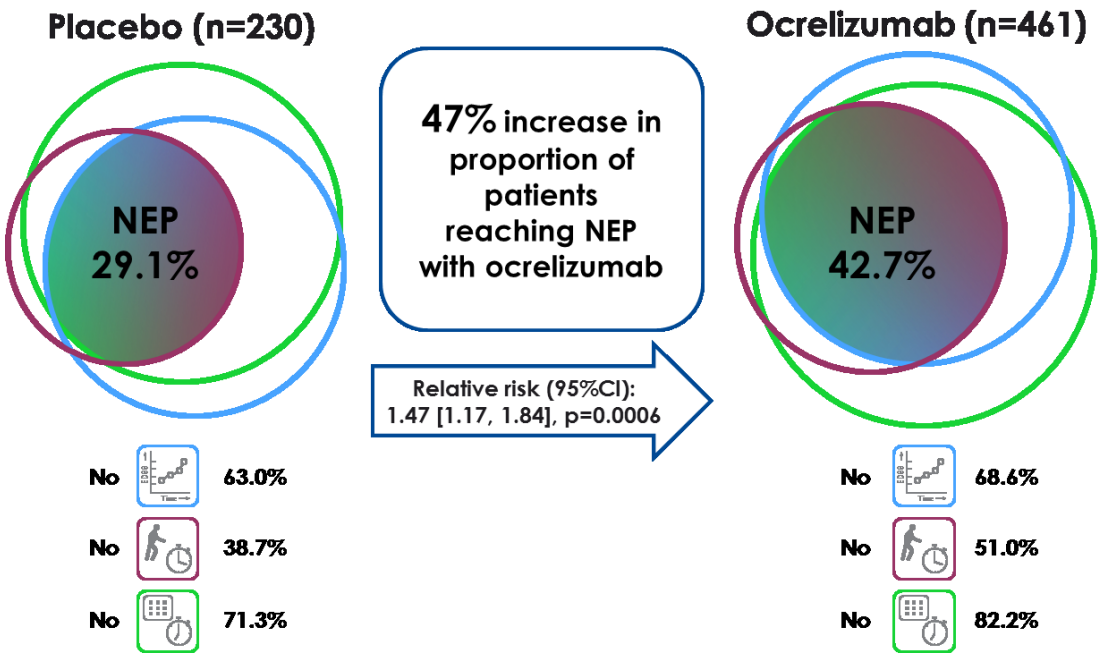
[131]

The NEP reference population was the ITT population excluding patients withdrawn for reasons other than efficacy failure or death prior to the Week 120 visit and without evidence of progression. Imputation was used for patients withdrawn from the treatment prior to the Week 120 visit and who had no event: patients withdrawn due to efficacy failure or death were considered as having event. Otherwise, they were considered as not having an event.

43% of ocrelizumab-treated patients had No Evidence of Progression (NEP) versus 29% for placebo patients, which represents a 47% relative increase (p=0.0006) (Figure 17).

Reaching NEP status is reflective of no worsening in three major components of MS disability and may represent an important outcome for patients with PPMS. The effect of ocrelizumab on NEP, a measure of overall absence of disability progression, including upper limb function and ambulation, is consistent with the primary and secondary efficacy outcomes observed in patients with PPMS in the ORATORIO trial [131].

Figure 17: NEP and its individual components in ORATORIO



[131]

Post-hoc exploratory analysis: evaluation of no evidence of progression or active disease (NEPAD)

No evidence of progression or active disease (NEPAD) is a novel endpoint that assesses the combined absence of composite disability progression (NEP) and clinical- and MRI-measured disease activity, and hence represents a more comprehensive measure than NEP [132].

NEPAD includes the following assessments:

- NEP, which assesses the combined absence of 12-week confirmed clinical progression

- No brain MRI-measured disease activity, including no new or enlarging T2 lesions and no T1 gadolinium-enhancing (Gd+) lesions [intrinsic descriptors of progressive MS phenotypes as per the Lublin revised consensus on MS disease course [21]]

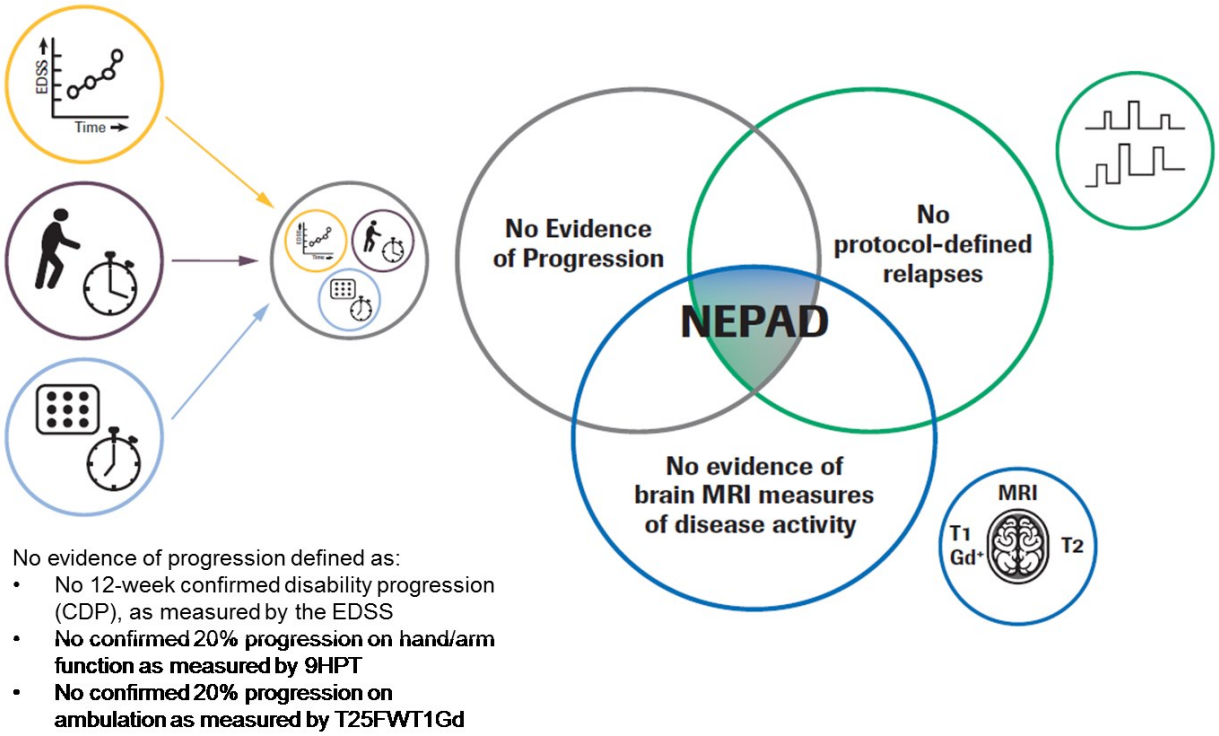
- No protocol-defined relapses

NEPAD also represents an extension of NEDA (no evidence of disease activity) [43] integrating aspects of disability burden (hand/arm function and ambulation impairment), which are central to the clinical course of progressive MS

A total of 234 PBO- and 465 OCR-treated patients were evaluated to assess the proportion of patients with NEPAD from baseline to Week 120 in an exploratory analysis of the ORATORIO trial.

In this analysis of the proportion of patients with NEPAD from baseline to Week 120, patients who withdrew early from study treatment (prior to having the Week 120 visit) for reasons other than 'lack of efficacy' or 'death', and who were NEPAD at time of study treatment discontinuation, were excluded. Sensitivity analyses were conducted, where patients excluded from the primary analysis were included and imputed as having NEPAD ('best case scenario') or evidence of progression or active disease (EPAD; 'worst case scenario').

Figure 18: Components of NEPAD



[132]

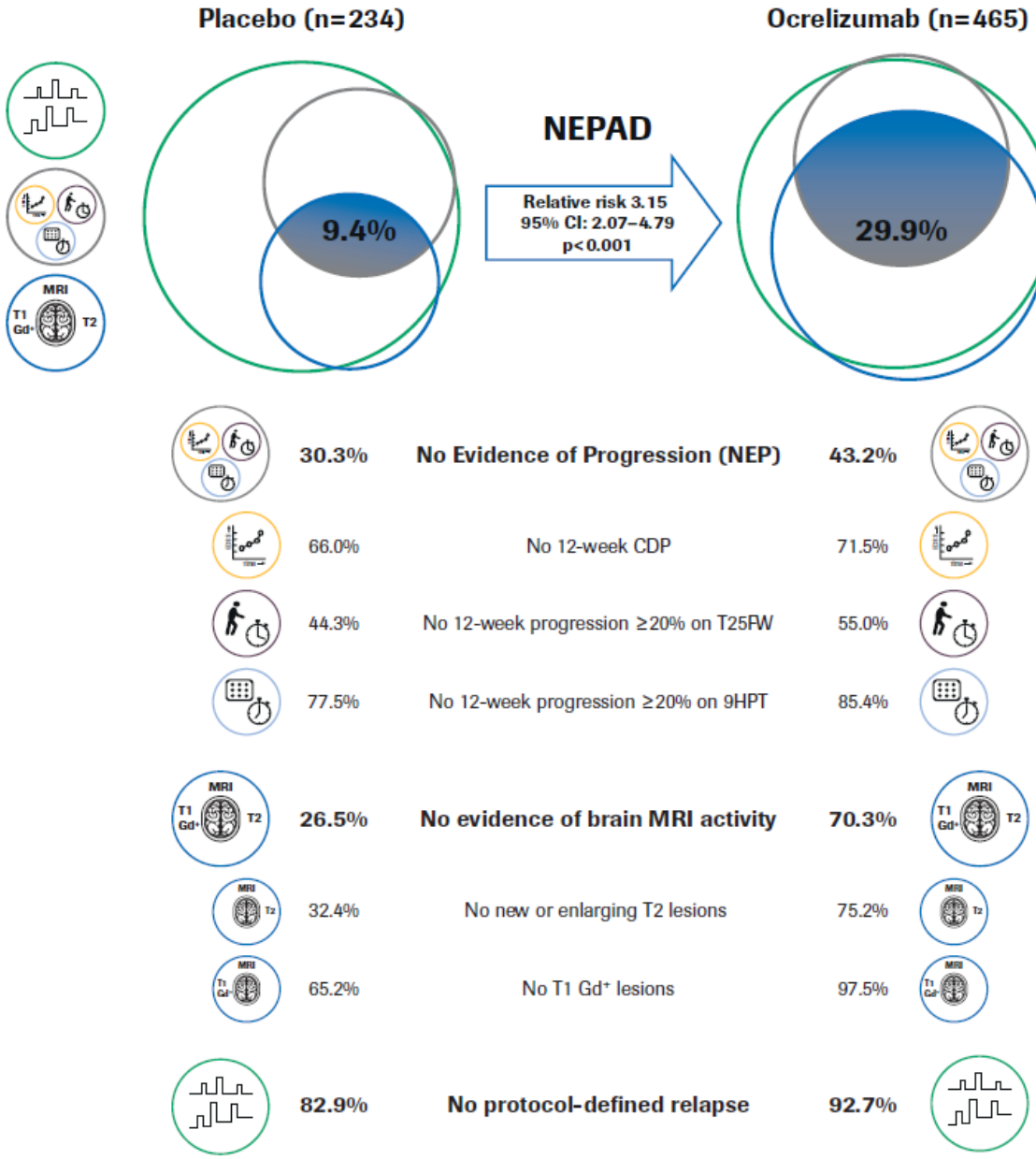
In ORATORIO, ocrelizumab significantly increased the proportion of patients with NEPAD at Week 120 compared with placebo (29.9% vs 9.4%; risk ratio ocrelizumab vs placebo [95% CI]: 3.15 [2.07–4.79]; p<0.001; Figure 19). This was reflected in superiority across all the individual components of NEPAD with ocrelizumab vs placebo from baseline to Week 120 [132].

Sensitivity analyses (imputing those patients who withdrew early for reasons other than 'lack of efficacy' or 'death' and who were NEPAD at time of study treatment discontinuation; placebo n=244, ocrelizumab n=487) were consistent with the primary results [132]

- NEPAD imputation of early discontinuers ('best case scenario'): ocrelizumab significantly increased the proportion of patients with NEPAD at Week 120 compared with placebo (33.5% vs 13.1%; risk ratio ocrelizumab vs placebo [95% CI]: 2.55 [1.80–3.60]; p<0.001)

- EPAD imputation of early discontinuers ('worst case scenario'): ocrelizumab significantly increased the proportion of patients with NEPAD at Week 120 compared with placebo (28.8% vs 9.0%; risk ratio ocrelizumab vs placebo [95% CI]: 3.17 [2.08–4.83]; p<0.001)

Figure 19: Proportion of patients with NEPAD (and the components of NEPAD) from baseline to Week 120 in ORATORIO



[131, 132]

Other exploratory endpoints

Further results of exploratory endpoints of ORATORIO are given in Appendix K:

- new or enlarging T2 hyperintense lesions
- SF-36 MCS
- MSCS
- PASAT

B.2.6.5 Extended controlled treatment period

To respond to queries from the EMA about the persuasiveness of the efficacy results from the ORATORIO trial, longer-term data taken from the extended controlled treatment period of the trial were analysed to demonstrate that the clinical benefit of ocrelizumab relative to placebo is sustained with ongoing treatment. This was a post-hoc analysis.

Data for the extended controlled treatment period comprised all efficacy data from the double-blind controlled treatment period of the ORATORIO trial, plus any additional efficacy data collected during either the controlled treatment period, from 24 July 2015 up to the clinical cut-off date of 20 January 2016, or the time when the patient received their first open-label dose of ocrelizumab, whichever came first. This represents an additional approximately 3 months of blinded data and an additional approximately 3 months of controlled follow-up during the time that patients were gradually unblinded and switched to the open-label extension (OLE).

Extended controlled treatment period: sustained risk reductions

These new data reveal that the superiority of ocrelizumab compared with placebo is sustained with ongoing treatment, and with higher statistical confidence than the initial controlled period.

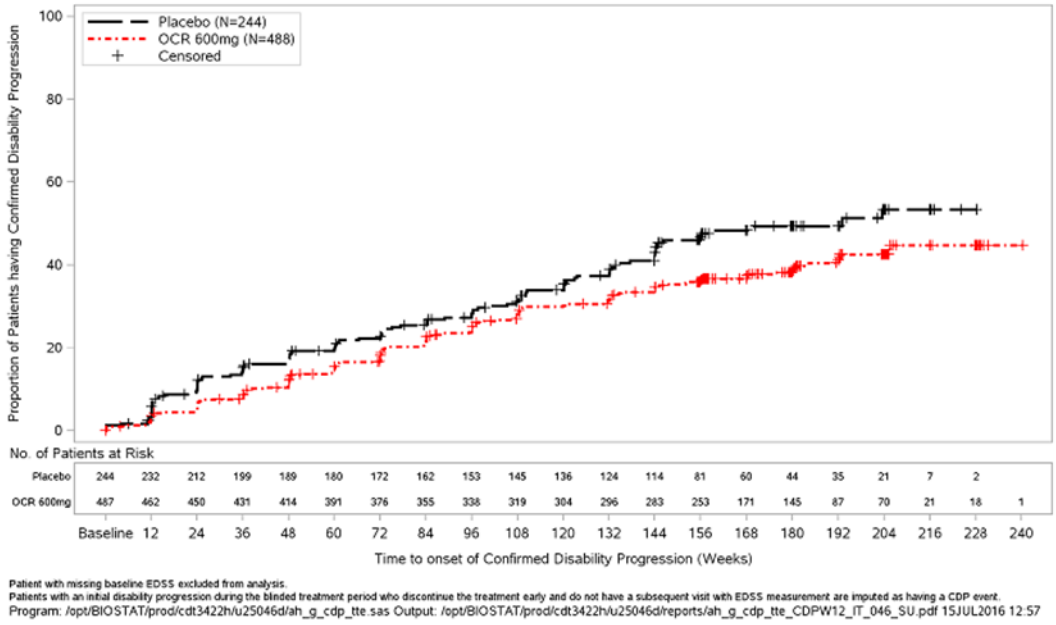
The extended controlled treatment period results for the key disability progression endpoints were:

- a 26% risk reduction for 12-week CDP (HR: 0.74; 95% CI: 0.58–0.95; p = 0.0151),
- a 30% risk reduction for 24-week CDP (HR: 0.70; 95% CI: 0.54–0.90; p = 0.0056),
- a 28% risk reduction for 12-week composite CDP (EDSS or T25FW test or 9-HPT; 185/488 vs 64/244 patients achieving NEP; HR for progression: 0.72; 95% CI: 0.60–0.87; p = 0.0005),
- a 32% relative risk reduction for 24-week composite CDP (227/488 vs 78/244 patients achieving NEP; HR for progression: 0.68; 95% CI: 0.56–0.82; p < 0.0001)

- and a 33% relative reduction in the percent progression in T25FW test over 144 weeks* (95% CI: 6.91–53.15; p = 0.1004) compared with placebo.

Kaplan–Meier plots of time to onset of 12-week CDP during the extended controlled treatment period (Figure 20) show separation between the ocrelizumab and placebo groups from 12 weeks. The plots show the benefits of ongoing treatment with ocrelizumab. The estimates at Week 144 and beyond indicate increasing separation between treatment arms, with confidence intervals excluding point estimates of the other arm

Figure 20: Time to onset of 12-week CDP during the extended controlled treatment period of ORATORIO



Compared with the ITT analysis, in the analysis from the extended controlled treatment period the differences were greater between the ocrelizumab and placebo groups for the 12-week CDP and 24-week CDP endpoints, NEP, and the T25FW test.

Extended controlled treatment period: delays in reaching high disability levels (EDSS ≥7) in PPMS

The clinical relevance of the primary endpoint result can be further contextualised by analysing a subset of progression events that reach a particularly meaningful milestone for patients, such as time to wheelchair use. A patient's perceived two-year risk of being wheelchair dependent (which is particularly pertinent to patients with an EDSS score of 4 to

* The T25-FW test data for the extended period were analysed using data transformations and methods for handling of missing data – these analyses and original analyses showed continued separation between groups from week 24 through to week 144.

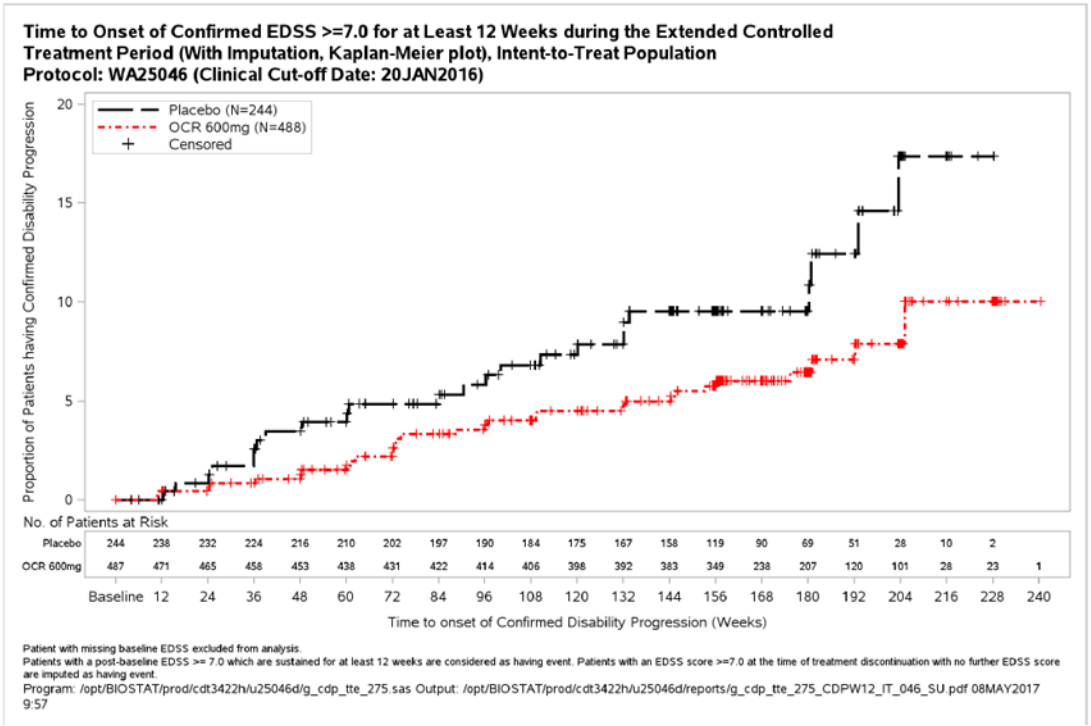
6, like the majority of patients included in the ORATORIO trial) is significantly associated with higher levels of stress, anxiety and depression [133].

Data from ORATORIO were used in a post hoc exploratory analysis to assess the effects of ocrelizumab versus placebo on the risk of becoming wheelchair-bound, defined as reaching an EDSS score of ≥7.0. A Kaplan-Meier analysis was used to estimate the risk of 12- and 24-week confirmed progression to EDSS ≥7.0 in the ITT population (placebo, n = 244; ocrelizumab, n = 488) during the double-blind and the extended control periods of the trial.

In this post hoc analysis, patients treated with ocrelizumab had a lower risk of progressing to wheelchair use than patients treated with placebo. During the double-blind treatment period, ocrelizumab numerically reduced the risk versus placebo of 12-week (5.1% vs 7.8%; HR: 0.61; p = 0.1046) and 24-week (4.7% vs 7.4%; HR: 0.60; p = 0.0959) progression to EDSS ≥ 7.0. During the extended controlled period, ocrelizumab significantly reduced the risk versus placebo of 12-week (6.2% vs 9.8%; HR: 0.55; p = 0.0275) and 24-week (5.7% vs 9.4%; HR: 0.53; p = 0.0240) progression to EDSS ≥ 7.0 (see Figure 21).

Compared with placebo, ocrelizumab reduced the risk of patients becoming wheelchair-bound, defined as confirmed transition to EDSS ≥7.0. These results are consistent with the established benefit of ocrelizumab in reducing overall disability progression (12-week and 24-week CDP) in patients with PPMS.

Figure 21: Time to confirmed EDSS ≥7.0 for at least 12 weeks during the extended controlled period of ORATORIO



Extrapolation of confirmed progression to EDSS ≥7 data

In order to further characterise the potential long-term impact of ocrelizumab treatment, the 12-week confirmed progression to EDSS ≥ 7.0 data from the extended controlled treatment period of ORATORIO were extrapolated into the future, until 50% of patients were expected to have reached EDSS ≥7.0, using a Weibull regression. The extrapolated time to median confirmed progression to EDSS ≥7.0 was 13.6 years for placebo-treated patients and 22.4 years for ocrelizumab-treated patients, corresponding to an expected delay in progression to EDSS ≥7.0 of 8.8 years. Using an alternative method, which assumed exponential distribution and median time to EDSS ≥7.0 of 13 years, the observed HR of 13 years in the placebo group corresponds to a delay of 8.7 years with ocrelizumab, similar to the extrapolation using Weibull distribution (see Figure 22).

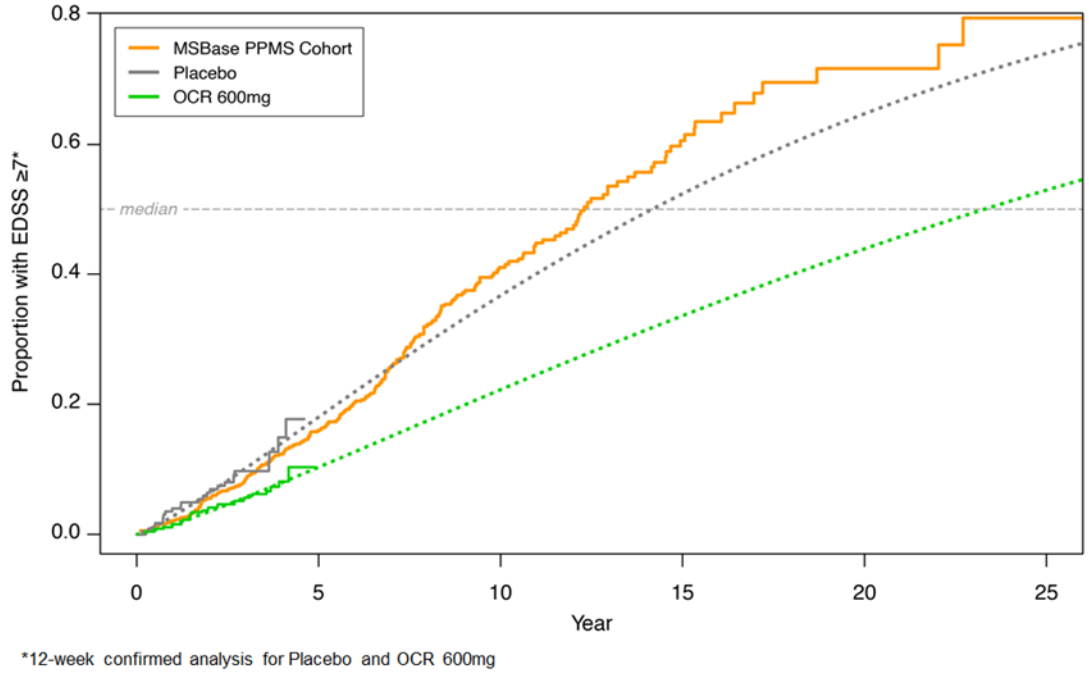
Further investigation of time to EDSS ≥ 7 using data from MSBase

In order to assess plausibility of the extrapolation analysis results, the time to EDSS ≥7.0 milestone was further investigated in an additional analysis of data in MSBase. MSBase is a longitudinal, observational registry that collects treatment and outcome information for patients with MS from routine clinical practice. MSBase was started in 2004, with an overall objective to facilitate the collection of epidemiological information through its unique web interface and to use the collected information to answer epidemiological questions, with the goal of improving the quality of care for patients with MS.

This observational registry represents real-world MS clinical practice, as all aspects of patient management are entirely at the discretion of the managing neurologist and his or her patient [134, 135]. Therefore, it is a suitable cohort on which to base assessment of the natural history of patients with progressive MS.

The natural history cohort in MSBase included adult patients with a PPMS diagnosis, baseline EDSS 3.0–6.5, a minimum of two EDSS assessments and no DMT use in the 2 years prior to baseline. The observed median time to EDSS ≥ 7.0 was 12.4 years, which is similar to the estimated 13.6 years for the extrapolated ORATORIO placebo arm.

Figure 22: Extrapolation of time to onset of confirmed EDSS gt7.0 for at least 12 weeks during the extended controlled treatment period of ORATORIO using a Weibull regression model



*12-week confirmed analysis for Placebo and OCR 600mg

Overall, patients included in the MSBase cohort were similar to those in the placebo arm of ORATORIO, with a median EDSS score of 4.5 (see Table 12).

Table 12: MSBase Natural History Cohort: Baseline[a] Patient Characteristics in Comparison with Those of Patients Included in the Placebo Arm of ORATORIO

Characteristic	Progressive MS in MSBase (N = 775)	ORATORIO Placebo arm (N = 244)
Age, years. Mean (SD)	43.4 (10.1)	44.4 (8.3)
Female. Number (%)	437 (56.4%)	124 (50.8%)
Time since onset of MS symptoms, years. Median (IQR)	5.8 (3.0, 10.8)	5.51 (3.31, 8.28)
Time since MS diagnosis, years. Median (IQR)	0.4 (0.0, 3.9)	1.34 (0.48, 3.89)
Score on first eligible EDSS.[a] Median (IQR)	4.5 (3.5, 6.0)	4.5 (3.5, 6.0)
DMT exposed. Number (%)		
Ever exposed in 2 years pre-baseline	0 (0.0%)	30 (12.3%)
Never exposed in 2 years pre-baseline	775 (100.0%)	214 (87.7%)

a Date of first diagnosis of progressive MS.
DMT, disease-modifying therapy; EDSS, expanded disability status scale; IQR, interquartile range; MS, multiple sclerosis; SD, standard deviation.

In summary, ocrelizumab significantly delayed time to wheelchair-confinement in the extended control period of ORATORIO. The extrapolated median time to reaching this major disability milestone in placebo patients was similar to that observed in MSBase registry.

Thus, it is expected that this observed benefit will translate to a meaningful long-term benefit for patients with PPMS.

B.2.6.7 Results in population matching the label: early PPMS with inflammatory activity

Informed by subgroup analyses presented to the Regulatory Authorities, ocrelizumab received marketing authorisation in January 2018 for the treatment of adult patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity [126].

With respect to the first requirement, early PPMS, the SmPC clarifies in Section 5.1 that patients included in ORATORIO were early in their disease course according to the trial's main inclusion and exclusion criteria.

With respect to the second requirement, imaging features characteristic of inflammatory activity, the SmPC clarifies in Section 5.1 that this refers to T1 Gd enhancing lesions and/or active (new or enlarging) T2 lesions.

To assess the proportion of patients in ORATORIO with imaging features characteristic of inflammatory activity, the presence of T1 Gd enhancing or active T2 lesions in placebo patients was assessed across all available MRI evidence collected during the trial (at screening, baseline, Week 24, Week 48 and Week 120). This approach best represents the proportion of patients with imaging features characteristic of inflammatory activity, since:

1. a single MRI scan only demonstrates acute cross-sectional MRI activity, such as Gd enhancing T1 lesions, while other imaging features (new or enlarging T2 lesions) require two scans

2. in the placebo arm there is no active treatment influencing MRI activity

The three imaging features characteristic of inflammatory activity can be defined as follows:

- Gd-enhancing T1 lesion count is a measure of acute inflammatory lesion activity on each MRI scan, associated with disruption of the blood–brain barrier

- 'New or enlarging' T2 lesion count is a measure of:

    - new focal inflammatory lesion activity in comparison with the previous scan (new T2) with no contact with T2 lesions detected on the previous scan

OR

- new focal inflammatory lesion activity (in comparison with the previous MRI scan) that appear to be confluent/overlapping with the limits of another lesion present on the previous scan (enlarging T2)

Importantly, ‘new and enlarging’ T2 lesions provide a marker for acute inflammatory activity in MS but do not capture chronic growth/expansion of persistent T2 lesions over time which happens as a consequence of chronic inflammatory activity in MS.

The imaging features described above are applied to the study population in the following ways.

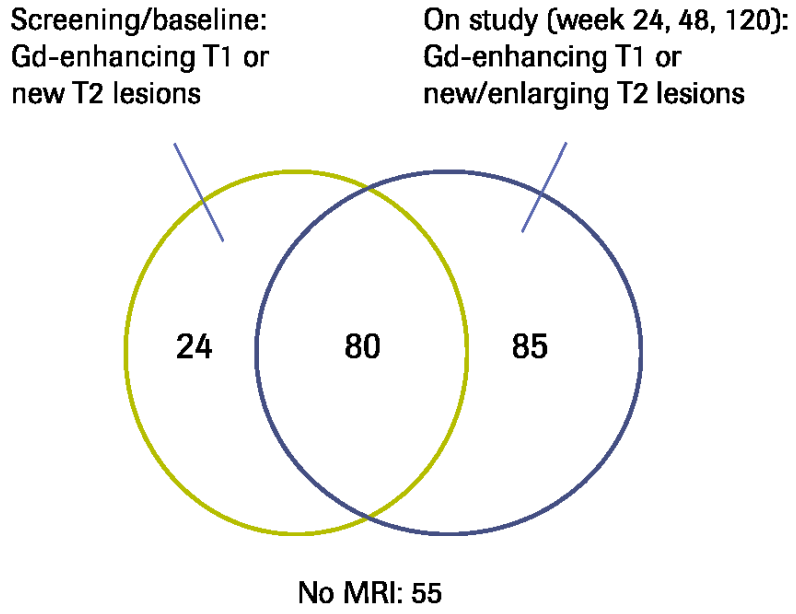
- Gd-enhancing T1 lesions at screening, baseline or on study
    - A patient was considered to have data if they had an evaluable result for Gd-enhancing T1 lesions from a brain MRI in the last 12 months prior to randomization, or at baseline or on study. ‘MRI Active’ was defined as Gd-enhancing T1 lesions > 0.
- New T2 lesions between screening and baseline
    - A patient was considered to have data if they had an evaluable result for T2 lesions in the 12 months prior to randomization and at baseline. Recorded data at screening were entered categorically as the number of T2 lesions present in the categories "0–5", "6–9" and "> 9" lesions. At baseline recorded data were number of T2 lesions from a brain MRI. To define MRI Activity the baseline number of T2 lesions was also grouped into categories of "0–5", "6–9" and "> 9". ‘MRI Active’ was defined as changes between screening and baseline from the category "0–5" to "6–9", from "0–5" to "> 9" and from "6–9" to "> 9".
- New/enlarging T2 lesions on study
    - A patient was considered to have data if they had an evaluable result for T2 lesions from a brain MRI. Recorded data were entered as the number of new or enlarging T2 lesions present relative to the previous scan. MRI Active was defined as new/enlarging T2 lesions > 0.

The number of patients in the placebo arm of ORATORIO with MRI activity at screening/baseline and/or on study is shown in Figure 23. A summary of MRI activity data by timepoint and aggregate for the placebo arm of ORATORIO is provided in Table 13.

In total, 77.5% of patients in the placebo arm of ORATORIO displayed imaging features characteristic of inflammatory activity at any time between screening and week 120 of the study.

Owing to randomisation and the baseline disease characteristics, it can be assumed that the patients in the ocrelizumab arm have the same general disease characteristics as the patients in the placebo arm.

Figure 23 Venn diagram of MRI activity in the placebo arm of ORATORIO



The efficacy of ocrelizumab in the population of ORATORIO with active disease reflective of the label can only be defined by MRI measurements at screening or baseline, since treatment with ocrelizumab suppresses MRI activity during the study.

As such, the subgroup that most closely resembles the label are patients with Gd-enhancing T1 lesions at screening or baseline, or patients with new T2 lesions between screening and baseline (henceforth referred to as the 'MRI active' subgroup). Lack of measurements for enlarging T2 lesions at screening/baseline does not allow an assessment of comparative efficacy in patients with enlarging T2 lesions. The 'MRI active' subgroup comprises 42.6% of patients in the placebo arm.

The efficacy of ocrelizumab in delaying disability progression as measured by CDP and 9-HPT in the 'MRI active' subgroup is numerically improved compared with the ITT population (Table 14, Table 15 and Table 16).

In contrast, the impact of ocrelizumab relative to placebo on change in fatigue as measured by MFIS was less pronounced in these subgroups (Figure 24).

Analyses were performed on the results from patients in the extended controlled treatment period (CDP-12 and CDP-24 only, not 9-HPT; Table 17 and Table 18). The results are broadly similar to the results observed during the double-blind controlled treatment period, with the CDP-24 results in the MRI active population improved.

Table 13 Summary of MRI Activity data by Timepoint and Aggregate for the Placebo Arm of ORATORIO

Description (for aggregate OR is applied)	T1 present		T2 new	T1 present / T2 new or enlarging timepoints			
	Screening	Baseline	Screen–baseline	Week 24	Week 48	Week 120	
T1 Gd-enhancing lesions	30/109 (27.5%)	60/243 (24.7%)	n/a	55/231 (23.8%)	43/218 (19.7%)	32/183 (17.5%)	n active / N, %
T2 new/enlarging lesions	n/a	n/a	n/a	106/233 (45.5%)	110/220 (50.0%)	113/183 (61.7%)	
T2 new lesions	n/a	n/a	37/117 (31.6%)	n/a	n/a	n/a	
T1, T2 at screening or baseline	**Yes**	**Yes**	**Yes**	No	No	No	**104/244 (42.6%)**
T1, T2 at screening, baseline, or week 24, 48, 120	Yes	Yes	Yes	Yes	Yes	Yes	189/244 (77.5%)

Gd, gadolinium; MRI, magnetic resonance imaging.

Table 14 Results for CDP-12 in 'MRI Active' population in ORATORIO

Population	Placebo (N = 244)		Ocrelizumab (N = 487)		HR (95% CI)	Log rank *p* value
	N (%)	Patients with event, n (%)	N (%)	Patients with event, n (%)		
ITT	244 (100)	96 (39.3)	487 (100)	160 (32.9)	0.76 (0.59–0.98)	0.0321
'MRI active' subgroup'	104 (42.6)	45 (43.3)	189 (38.8)	62 (32.8)	0.68 (0.46–0.99)	0.0448
Complement subgroup	140 (57.4)	51 (36.4)	298 (61.2)	98 (32.9)	0.84 (0.60–1.18)	0.3030

'MRI active' defined as gadolinium-enhancing T1 lesions at screening or baseline, or new T2 lesions between screening and baseline. Analysis based on Double-Blind Treatment Period (with Imputation).

Table 15 Results for CDP-24 in 'MRI active' population in ORATORIO

Population	Placebo (N = 244)		Ocrelizumab (N = 487)		HR (95% CI)	Log rank *p* value
	n (%)	Patients with event, n (%)	n (%)	Patients with event, n (%)		
ITT	244 (100)	87 (35.7)	487 (100)	144 (29.6)	0.75 (0.58–0.98)	0.0365
'MRI active' subgroup'	104 (42.6)	40 (38.5)	189 (38.8)	58 (30.7)	0.71 (0.47–1.06)	0.0917
Complement subgroup	140 (57.4)	47 (33.6)	298 (61.2)	86 (28.9)	0.79 (0.55–1.13)	0.1964

'MRI active' defined as gadolinium-enhancing T1 lesions at screening or baseline, or new T2 lesions between screening and baseline. Analysis based on Double-Blind Treatment Period (with Imputation).

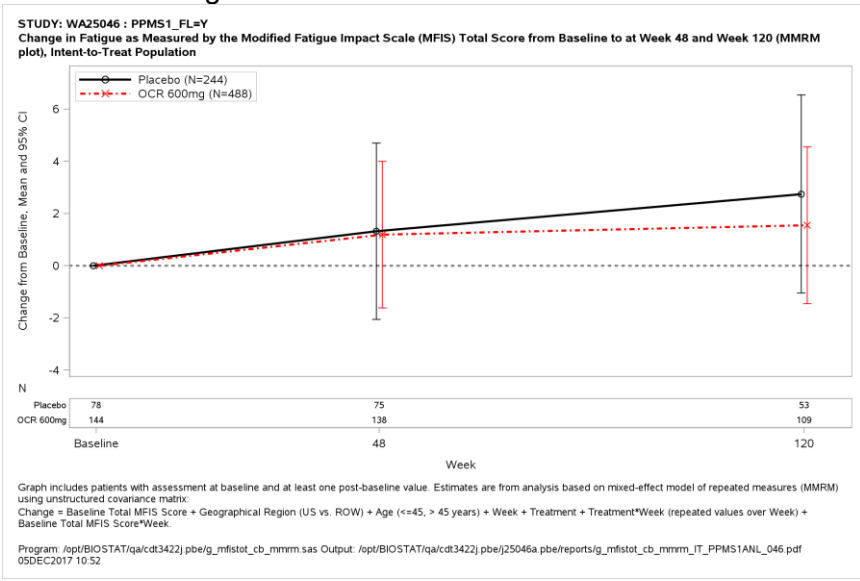
Table 16 Results for 20% Increase in 9-HPT (Sustained for 12 Weeks) in 'MRI active' population in ORATORIO

Population	Placebo (N = 244)		Ocrelizumab (N = 488)		HR (95% CI)	Log rank *p* value
	n (%)	Patients with event, n (%)	n (%)	Patients with event, n (%)		
ITT	244 (100)	58 (23.8)	488 (100)	74 (15.2)	0.56 (0.41–0.78)	0.0004
'MRI active'	104 (42.6)	26 (25.0)	189 (38.7)	31 (16.4)	0.52 (0.32–0.85)	0.0083
Complement	140 (57.4)	32 (22.9)	299 (61.3)	43 (14.4)	0.56 (0.36–0.86)	0.0079

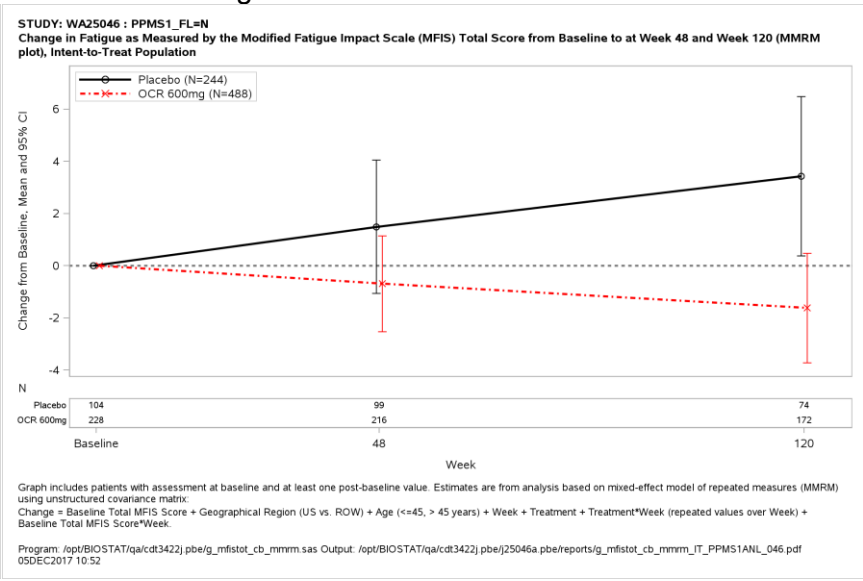
MRI active' defined as gadolinium-enhancing T1 lesions at screening or baseline, or new T2 lesions between screening and baseline.

Figure 24 Change in fatigue in 'MRI-active' population in ORATORIO

A. Patients meeting the criteria for 'Active'



B. Patients not meeting the criteria for 'Active'



'Active' defined as gadolinium-enhancing T1 lesions at screening or baseline, or new T2 lesions between screening and baseline. Analysis based on MFIS Total Score from Baseline to Week 48 and Week 120.

Table 17 CDP-12 for MRI-active population - extended control treatment period

Population	Placebo n (%)	Ocrelizumab n (%)	Hazard ratio	95% CI	Interaction test (p-value)
ITT	243 (100%)	486 (100%)	0.75	0.59, 0.96	
MRI active - Yes	104 (42.8%)	189 (38.9%)	0.69	0.47, 1.00	0.4101
MRI active - No	139 (57.2%)	297 (61.1%)	0.81	0.59, 1.10	

Cox model including Region of World and Age (≤45 vs >45) as strata (ITT and MRI active) or Region of World as strata (MRI active ≤50). With imputation due to withdrawal

Table 18 CDP-24 for MRI-active population – extended control treatment period

Population	Placebo n (%)	Ocrelizumab n (%)	Hazard ratio	95% CI	Interaction test (p-value)
ITT	243 (100%)	486 (100%)	0.70	0.55, 0.90	
MRI active - Yes	104 (42.8%)	189 (38.9%)	0.68	0.46, 0.99	0.6880
MRI active - No	139 (57.2%)	297 (61.1%)	0.72	0.52, 1.00	

Cox model including Region of World and Age (≤45 vs >45) as strata (ITT and MRI active) or Region of World as strata (MRI active ≤50). With imputation due to withdrawal

B.2.7 Subgroup analysis

The primary and the secondary efficacy endpoints were analysed by predefined subgroups:

- Age (≤45 vs >45 yrs)
- Sex (male vs female)
- Baseline EDSS (≤5.5 vs >5.5)
- Region (USA vs ROW)
- Presence of gadolinium-enhancing T1 lesions at baseline MRI scan
- Prior MS DMTs with the exception of corticosteroids
- Duration since onset of MS symptoms (≤3 yrs, 3 to ≤5 yrs, 5 to ≤10 yrs, >10 yrs)
- Weight (≤75 vs >75 kg at baseline)
- BMI (<25 vs ≥25 kg/m^2 at baseline)

There was a directionally consistent treatment effect favouring ocrelizumab in all subgroups (HR<1). None of the observed differences in the size of the treatment effect between subgroups were statistically significant. However, the study was not powered to demonstrate efficacy differences between these subgroups. Results of the predefined subgroup analyses are provided in Appendix E.

B.2.7.1 Multivariate analysis

To further investigate the independence of potential treatment effect modifying factors, a multivariate Cox regression analysis was performed. The Cox model contained all pre-specified subgroup factors as main and treatment interaction effects, with the exception of weight, due to its high correlation with BMI. Continuous variables (age, EDSS, duration since MS symptom onset, BMI) were included as linear covariates.

The main value of this analysis lies in the evaluation of potential treatment interactions, corrected for the potential prognostic effects of other baseline covariates. Trends were observed between treatment effect and T1 Gd-enhancing lesions, sex and age (Table 19).

Based on the findings from the multivariate analysis, all other secondary endpoints were analyzed by T1 Gd-enhancing lesions, sex, and age subgroups. Results of these subgroup analyses are provided in Appendix E.

Table 19 Subgroup interactions observed in ORATORIO multivariate analysis

	Trend (interaction p-value <0.2)	Weak trend (interaction p-value 0.2 - 0.3)
CDP-12	T1 Gd-enhancing lesions Sex	
CDP-24		T1 Gd-enhancing lesions Age

Following extensive discussions with the Regulatory Authorities [126], a subgroup of patients with inflammatory activity and aged 50 years or younger at baseline is also presented (see section B.2.7.2).

B.2.7.2 Subgroup analysis of patients with imaging features characteristic of inflammatory activity aged ≤50 years at baseline

As demonstrated in the multivariate analysis, age and presence of T1 Gd-enhancing lesions were key modifiers of treatment effect. The age-dependent effect on disease progression in ORATORIO was further assessed by age quartiles [126]. Efficacy was fairly stable in patients aged 50 or under, but patients in the fourth age quartile (>50 years at baseline) did not derive benefit as measured by progression on EDSS from active treatment.

The efficacy of ocrelizumab was further assessed in post hoc subgroup analysis defined by MRI activity **and** further restricted to patients who were ≤50 years of age at baseline. The cut-off of 50 years was informed by the before mentioned analysis by age quartiles. Patients belonging to this restricted subgroup demonstrated a better treatment response with respect to delaying confirmed disability progression in ORATORIO than the ITT population or MRI active subpopulation (Table 20, Table 21 and Table 22).

In contrast, the impact of ocrelizumab relative to placebo on change in fatigue as measured by MFIS was less pronounced in these subgroups Figure 26.

Age appeared to be correlated with MRI activity, as most patients (80%) with MRI activity were aged 50 or younger (Figure 25). The interaction between age and T1 Gd enhancing lesions at baseline with regard to predicting ocrelizumab treatment effect was further investigated by estimating the hazard ratio for CDP-12 within all four possible pre-defined subgroup combinations. It was difficult to conclude from this analysis whether younger age drives treatment effect in MRI active patients, or vice versa [126].

Analyses were performed on the results from patients in the extended controlled treatment period (CDP-12 and CDP-24 only, not 9-HPT; see Table 23 and Table 24).

Figure 25 Venn diagram of overlapping subpopulations defined by MRI activity and age in ORATORIO

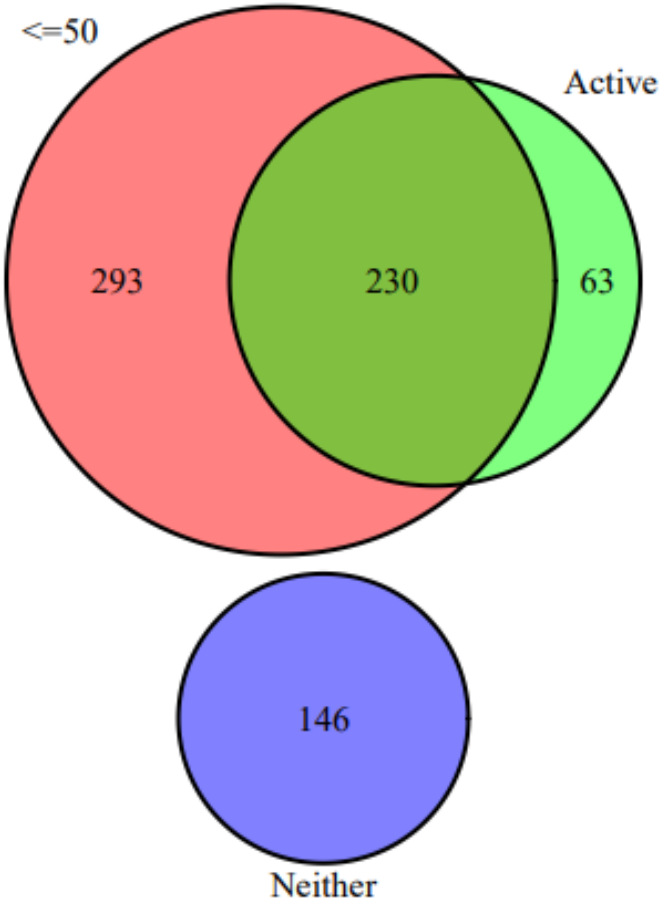


Table 20 Results for CDP-12 in 'Active ≤50 Years' Subgroup in ORATORIO

Population	Placebo (N = 244)		Ocrelizumab (N = 487)		HR (95% CI)	Log rank *p* value
	n (%)	Patients with event, n (%)	n (%)	Patients with event, n (%)		
ITT	244 (100)	96 (39.3)	487 (100)	160 (32.9)	0.76 (0.59–0.98)	0.0352
'MRI active ≤50 Years' subgroup	79 (32.4)	38 (48.1)	151 (31.0)	48 (31.8)	0.55 (0.36–0.85)	0.0058
Complement subgroup	165 (67.6)	58 (35.2)	336 (69.0)	112 (33.3)	0.91 (0.66–1.24)	0.5369

'Active' defined as gadolinium-enhancing T1 lesions at screening or baseline, or new T2 lesions between screening and baseline. Analysis based on Double-Blind Treatment Period (with Imputation).

Table 21 Results for CDP-24 in 'Active ≤50 Years' Subgroup in ORATORIO

Population	Placebo (N = 244)		Ocrelizumab (N = 487)		HR (95% CI)	Log rank *p* value
	n (%)	Patients with event, n (%)	n (%)	Patients with event, n (%)		
ITT	244 (100)	87 (35.7)	487 (100)	144 (29.6)	0.76 (0.58–0.99)	0.0403
'MRI active ≤50 Years' subgroup	79 (32.4)	35 (44.3)	151 (31.0)	44 (29.1)	0.54 (0.35–0.85)	0.0064
Complement subgroup	165 (67.6)	52 (31.5)	336 (69.0)	100 (29.8)	0.91 (0.65–1.27)	0.5687

'Active' defined as gadolinium-enhancing T1 lesions at screening or baseline, or new T2 lesions between screening and baseline. Analysis based on Double-Blind Treatment Period (with Imputation).

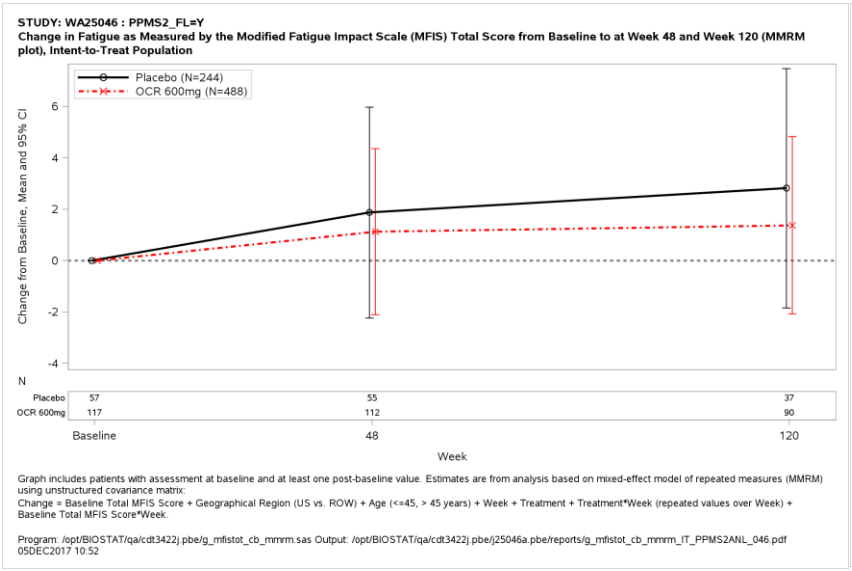
Table 22 Results for 20% Increase in 9-HPT (Sustained for 12 weeks) in 'Active ≤50 Years' Subgroup in ORATORIO

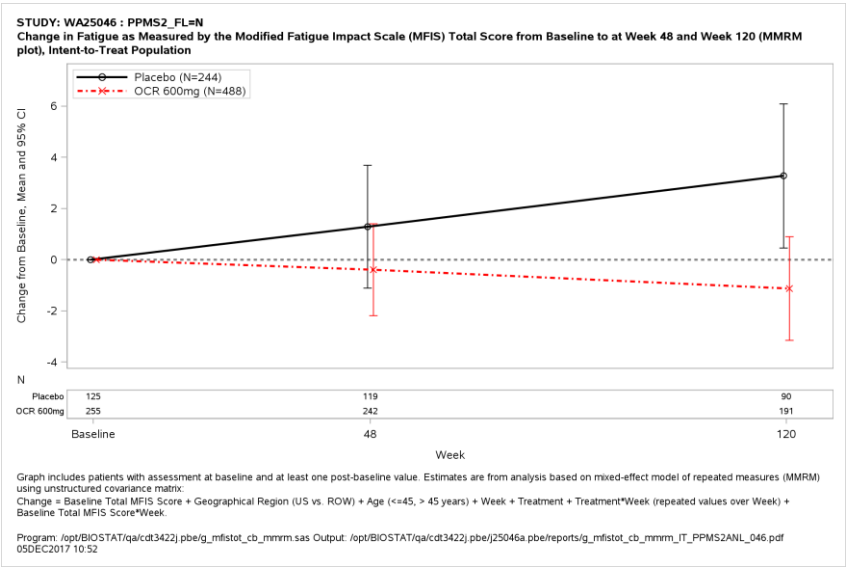
Population	Placebo (N = 244)		Ocrelizumab (N = 488)		HR (95% CI)	Log rank *p* value
	n (%)	Patients with event, n (%)	n (%)	Patients with event, n (%)		
ITT	244 (100)	58 (23.8)	488 (100)	74 (15.2)	0.56 (0.40–0.77)	0.0004
'MRI active ≤50 Years' subgroup	79 (32.4)	23 (29.1)	151 (30.9)	27 (17.9)	0.45 (0.27–0.76)	0.0022
Complement subgroup	165 (67.6)	35 (21.2)	337 (69.1)	47 (13.9)	0.62 (0.41–0.94)	0.0237

'Active' defined as gadolinium-enhancing T1 lesions at screening or baseline, or new T2 lesions between screening and baseline.

Figure 26 Change in Fatigue in 'Active ≤ 50 years' subgroup in ORATORIO

Patients meeting the criteria for 'MRI activity' B. Patients not meeting the criteria for 'MRI activity'





'Active' defined as gadolinium-enhancing T1 lesions at screening or baseline, or new T2 lesions between screening and baseline. Analysis based on MFIS Total Score from Baseline to Week 48 and Week 120.

Table 23 Subgroup analysis in extended control period – CDP-12

Population	Placebo n (%)	Ocrelizumab n (%)	Hazard ratio	95% CI	Interaction test (p-value)
ITT	243 (100%)	486 (100%)	0.75	0.59, 0.96	
MRI active <= 50 - Yes	79 (32.5%)	151 (31.1%)	0.56	0.37, 0.85	0.0793
MRI active <= 50 - No	164 (67.5%)	335 (68.9%)	0.88	0.65, 1.18	

Cox model including Region of World and Age (≤45 vs >45) as strata (ITT and MRI active) or Region of World as strata (MRI active ≤50). With imputation due to withdrawal

Table 24 Subgroup analysis in extended control period – CDP-24

Population	Placebo n (%)	Ocrelizumab n (%)	Hazard ratio	95% CI	Interaction test (p-value)
ITT	243 (100%)	486 (100%)	0.70	0.55, 0.90	
MRI active <= 50 - Yes	79 (32.5%)	151 (31.1%)	0.53	0.35, 0.81	0.1097
MRI active <= 50 - No	164 (67.5%)	335 (68.9%)	0.81	0.60, 1.10	

Cox model including Region of World and Age (≤45 vs >45) as strata (ITT and MRI active) or Region of World as strata (MRI active ≤50). With imputation due to withdrawal

B.2.8 Meta-analysis

No meta-analysis was performed, as only one trial (ORATORIO) met the scope of the NICE decision problem and is included in this submission.

B.2.9 Indirect and mixed treatment comparisons

No indirect or mixed treatment comparison was performed as only one trial (ORATORIO) met the scope of the NICE decision problem and is included in this submission.

B.2.10 Adverse reactions

B.2.10.1 Summary of safety data

Adverse events from ORATORIO are presented in this section. The safety population included all patients who received any study drug. Randomised patients who received incorrect therapy different from that intended were summarised in the group according to the therapy actually received. Patients who were not randomised, but who received study drug, were included in the safety population and summarised according to the therapy actually received.

A total of 725 patients received study drug and comprised the safety analysis population (239 patients in the placebo group, 486 patients in the ocrelizumab group). The proportion of patients who experienced at least one AE was similar between groups (placebo 90.0%, ocrelizumab 95.1%). The overall number of AEs per 100 patient years (100PY) was balanced (placebo 267.04, ocrelizumab 260.51) and remained similar for the two treatment groups over time during the controlled treatment period.

Table 25: Summary of adverse events in ORATORIO

n (%)	Placebo (n = 239)	Ocrelizumab (n = 486)
Any AE	215 (90.0%)	462 (95.1%)
Serious AE	53 (22.2%)	99 (20.4%)
Death	1 (0.4%)	4 (0.8%)
AE leading to withdrawal from treatment	8 (3.3%)	20 (4.1%)
IRR	61 (25.5%)	194 (39.9%)
Serious IRR	0	5 (1.0%)
IRRs leading to withdrawal from treatment	1 (0.4%)	2 (0.4%)
Infection	162 (67.8%)	339 (69.8%)
Serious infection	20 (8.4%)	34 (7.0%)
Malignancies	2 (0.8%)	11 (2.3%)

It was noted that some adverse events reported in the trial appeared to be disease-related symptoms, which were more prevalent in the placebo arm than in the ocrelizumab arm. A summary of adverse events related to study medication is provided (Table 26) and is incorporated in the economic analysis (see Section B.3.3.7.)

Table 26: Adverse events related to study medication by body system class (>2% in ocrelizumab arm)

System organ class	Placebo (N=239)	Ocrelizumab 600 mg (N=486)
Infusion-related reaction	60 (25.5)	194 (39.9)
Urinary tract infection	12 (5.0)	30 (6.2)
Nasopharyngitis	12 (5.0)	21 (4.3)
Upper respiratory tract infection	5 (2.1)	15 (3.1)
Bronchitis	2 (0.8)	12 (2.5)
Headache	10 (4.2)	13 (2.7)
Neoplasms benign, malignant and unspecified (incl, cysts and polyps)	2 (0.8)	6 (1.2)

NB. Neoplasms included here despite occurring <2% in ocrelizumab arm

- Overall, the proportion of patients experiencing AEs and SAEs associated with ocrelizumab, including serious infections, was similar to placebo
- As expected with monoclonal antibodies, a higher proportion of patients in the ocrelizumab group reported infusion-related reactions,
    - IRRs were the most frequently reported AE among ocrelizumab-treated patients; overall, 39.9% of ocrelizumab-treated patients and 25.5% patients receiving placebo reported at least one IRR
    - No fatal or life-threatening IRRs have been reported, and most IRRs were of mild to moderate severity, decreasing in both rate and severity with subsequent dosing
- Most infections were mild to moderate, and the rate of withdrawal due to infections was low in both groups; no opportunistic infections were reported in the ORATORIO study
- The imbalance observed in the incidence of malignancies needs to be contextualised with the totality of MS data and epidemiology data; no conclusion can be made based on this low number

Table 27: AEs by SOC reported by ≥10% of patients in either treatment in ORATORIO

n (%)	Placebo (n=239)	Ocrelizumab (n=486)
Overall patients with ≥1 AE	215 (90.0)	462 (95.1)
Infections and Infestations*	162 (67.8)	339 (69.8)
Nasopharyngitis	65 (27.2)	110 (22.6)
Urinary tract infection	54 (22.6)	96 (19.8)
Influenza	21 (8.8)	56 (11.5)
Upper respiratory tract infection	14 (5.9)	53 (10.9)
Bronchitis	12 (5.0)	30 (6.2)
Gastroenteritis	12 (5.0)	20 (4.1)
Injury, poisoning and procedural complications	104 (43.5)	263 (54.1)
Musculoskeletal and connective tissue disorders	98 (41.0)	181 (37.2)
Nervous system disorders	79 (33.1)	174 (35.8)
General disorders and administration-site conditions	60 (25.1)	130 (26.7)
Gastrointestinal disorders	60 (25.1)	126 (25.9)
Psychiatric disorders	59 (24.7)	89 (18.3)
Skin and subcutaneous disorders	44 (18.4)	99 (20.4)
Respiratory, thoracic and mediastinal disorders	35 (14.6)	87(17.9)
Metabolism and nutrition disorders	28 (11.7)	56 (11.5)
Renal and urinary disorders	30 (12.6)	51 (10.5)
Vascular disorders	26 (10.9)	54 (11.1)
Investigations	20 (8.4)	58 (11.9)

*For Infections and Infestations SOC only: events reported by at least 5% of patients in one treatment arm are presented

Table 28: SAE by SOC (≥1% of patients) in ORATORIO

n (%)	Placebo (n=239)	Ocrelizumab (n=486)
Overall patients with ≥1 SAE	53 (22.2)	99 (20.4)
Patients with infections and infestations	14 (5.9)	30 (6.2)
Injury, poisoning and procedural complications	11 (4.6)	19 (3.9)
Nervous system disorders	9 (3.8)	18 (3.7)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	7 (2.9)	8 (1.6)
Gastrointestinal disorders	3 (1.3)	10 (2.1)
Musculoskeletal and connective tissue disorders	6 (2.5)	6 (1.2)
General disorders and administration-site conditions	3 (1.3)	6 (1.2)
Renal and urinary disorders	3 (1.3)	5 (1.0)

B.2.10.2 Deaths

Five deaths were reported:

- 0.4% in the placebo arm: road traffic accident

- 0.8% in the ocrelizumab arm: pulmonary embolism, pneumonia, pancreas carcinoma, pneumonia aspiration

B.2.10.3 Malignancies

Thirteen malignancies were reported:[129]

- 0.8% in the placebo arm: one cervix adenocarcinoma in situ and one basal cell carcinoma
- 2.3% in the ocrelizumab arm: four breast cancers, one endometrial adenocarcinoma, one anaplastic large cell lymphoma, one malignant fibrous histiocytoma, one metastatic pancreatic cancer, and three basal cell carcinomas

Incidence rates of malignancies in ocrelizumab-treated patients were within the range of epidemiological data and other clinical trials in MS. (See Appendix F).

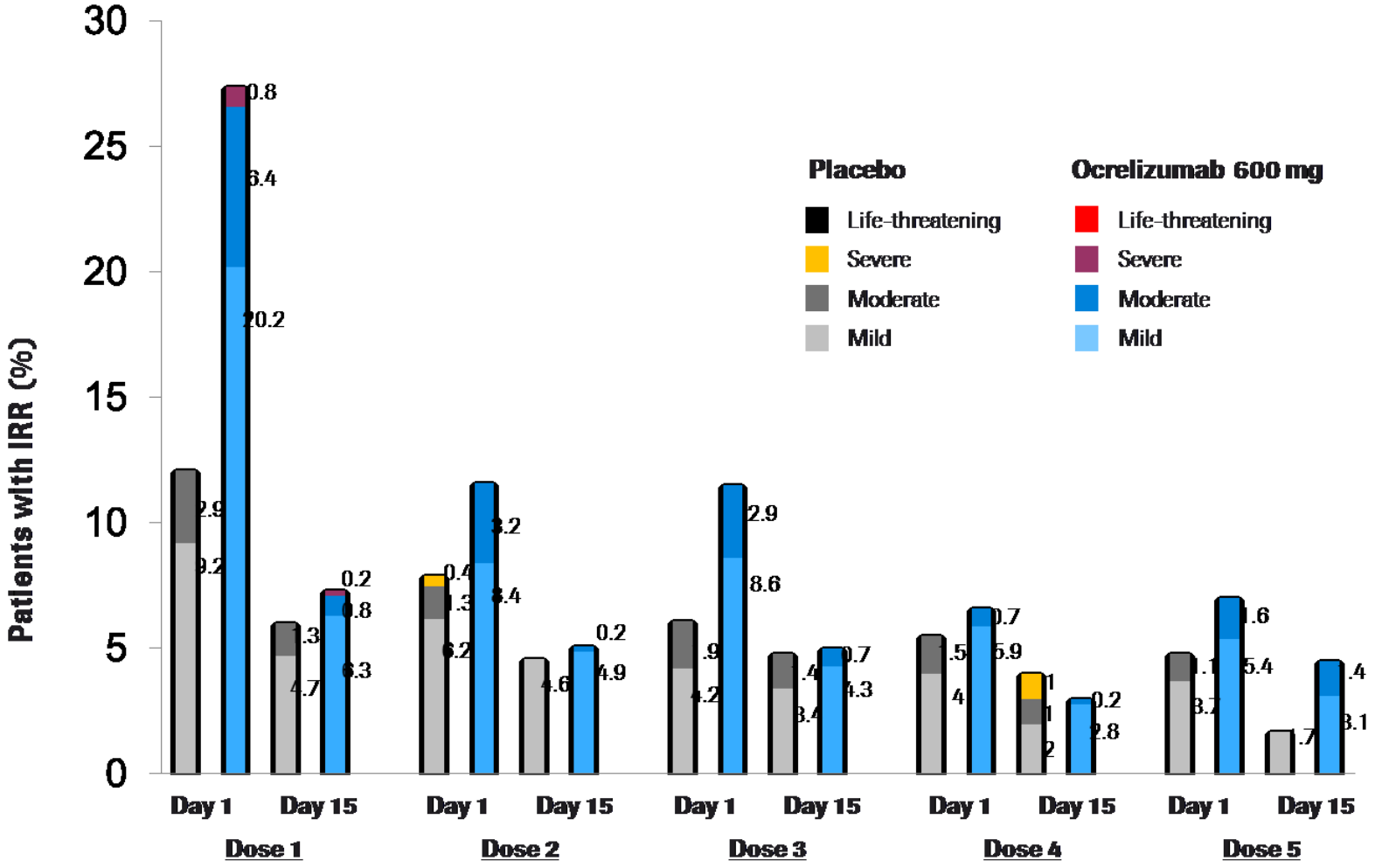
B.2.10.4 Infusion-related reactions (IRRs)

IRRs included all events occurring during infusion, shortly post-infusion (in clinic) or within 24 hours post-infusion:[127-129]

- IRRs were the most frequently reported AE among ocrelizumab-treated patients; overall, 39.9% of ocrelizumab-treated patients and 25.5% patients receiving placebo reported at least one IRR
- During the first infusion of the first dose, a higher proportion of ocrelizumab-treated patients experienced IRRs (any grade) compared with placebo-treated patients (27.4% vs 12.1%, respectively)
- No fatal or life-threatening IRRs have been reported, and most IRRs were of mild to moderate severity, decreasing in both rate and severity with subsequent dosing

The incidence of IRRs was highest during the first infusion (Dose 1, Day 1) and decreased over time. A greater proportion of patients in each group experienced IRRs with the first infusion of each dose compared with the second infusion of that dose. The majority of IRRs in both groups were of Grade 1 or 2. There were 4 patients (1.7%) in the placebo group and 6 patients (1.2%) in the ocrelizumab group who experienced Grade 3 IRRs. Four of the 6 patients with Grade 3 IRRs in the ocrelizumab group experienced the event at the first infusion on Day 1, one patient at the second infusion on Day 15, and one patient at Dose 8, second infusion [129].

Figure 27: Infusion Related Reactions by Most Extreme Intensity (Grade) and dose



[127, 136]

The most frequent symptoms associated with an IRR in the ocrelizumab group (in ≥10% of patients with an IRR) included pruritus, flushing, rash, pyrexia, headache, and throat irritation. The symptoms associated with ≥10% of IRRs in the placebo group included headache, flushing, nausea, fatigue, and dizziness. The symptoms of IRRs reported at first infusion of ocrelizumab/placebo were representative of symptoms experienced with subsequent infusions and were consistent with the overall IRR symptoms reported [129].

Table 29: Most frequent IRRs occurring in ≥10% of ocrelizumab-treated patients in ORATORIO

n (%)	Placebo (n=239)	Ocrelizumab (n=486)
Total number of patients with IRRs	61 (25.5)	194 (39.9)
Pruritus	2 (3.3)	56 (28.9)
Flushing	10 (16.4)	46 (23.7)
Rash	1 (1.6)	40 (20.6)
Headache	21 (34.4)	31 (16.0)
Pyrexia	4 (6.6)	26 (13.4)
Throat irritation	1 (1.6)	26 (13.4)

All IRRs were manageable through premedication, infusion adjustment (slowing, interrupting, or discontinuing the infusions), and symptomatic treatment. The addition of antihistamines with methylprednisolone as premedication appeared to decrease the incidence of IRRs. The incidence of IRRs after the first infusion was highest in the premedication subgroup that received methylprednisolone alone, compared with those who received methylprednisolone plus analgesics/antipyretics, methylprednisolone plus antihistaminics and methylprednisolone plus analgesics/antipyretics and antihistaminics [129, 136].

Table 30: Incidence of IRRs after the first infusion in ocrelizumab-treated patients who received premedication in ORATORIO

Premedication	n/N (%)
Methylprednisone alone	29/59 (49.2)
Methylprednisone plus analgesics/antipyretics	9/21 (42.9)
Methylprednisone plus antihistaminics	4/24 (16.7)
Methylprednisone plus analgesics/antipyretics and antihistaminics	91/382 (23.8)

Over the controlled treatment period, a total of 0.4% (n=1) of patients in the placebo group and 0.4% (n=2) in the ocrelizumab group withdrew from treatment due to an IRR. In the ocrelizumab group, one patient experienced an IRR at the first infusion of the first dose and the other patient at the first infusion of the second dose [129].

B.2.10.5 Infections

The proportion of patients in the ORATORIO study reporting an infection was 67.8% and 69.8% in the placebo and ocrelizumab groups, respectively. Overall rates of infection were 73.8 and 71.7 per

100PY in the placebo and ocrelizumab groups, respectively. Infections reported in at least 10% of patients and reported more frequently in the ocrelizumab group than in the placebo group were URTI and influenza.

Most infections were mild to moderate, and the rate of withdrawal due to infections was low in both groups. The proportion of patients with serious infections was 5.9% in the placebo group and 6.2% in the ocrelizumab group. Rates of serious infections were 2.9 per 100 patient years in the placebo group and 3.0 per 100 patient years in the ocrelizumab group. Among herpes virus-related infections, only oral herpes was more common in patients treated with ocrelizumab (2.3%) compared with placebo (0.4%); all cases were mild to moderate.

Table 31: Infections and serious infections in ORATORIO

n (%)	Placebo (n=239)	Ocrelizumab (n=486)
Total number of patients with ≥1 AE	162 (67.8)	339 (69.8)
Most frequently reported infections		
Nasopharyngitis	65 (27.2)	110 (22.6)
Urinary tract infection	54 (22.6)	96 (19.8)
Influenza	21 (8.8)	56 (11.5)
Upper respiratory tract infection	14 (5.9)	53 (10.9)
Herpes infections		
Herpes zoster	2 (0.8)	6 (1.2)
Oral herpes	1 (0.4)	11 (2.3)
Herpes simplex	2 (0.8)	3 (0.6)
Nasal herpes	1 (0.4)	1 (0.2)
Herpes zoster oticus	1 (0.4)	0
Withdrawal due to infections	3 (1.3)	4 (0.8)
Arthritis infective	1 (0.4)	0
Hepatitis viral	1 (0.4)	0
Infectious colitis	0	1 (0.2)
Meningitis aseptic	1 (0.4)	0
Pneumonia	0	1 (0.2)
Urinary tract infection	0	1 (0.2)
Viral infection	0	1 (0.2)
Patients with ≥1 serious infection event	14 (5.9)	30 (6.2)

No opportunistic infections were reported in the ORATORIO study. Two deaths were related to infections (<1%) in the ocrelizumab group (aspiration pneumonia and pneumonia); these deaths were considered unrelated to treatment per investigator and related to treatment per sponsor (reviewed by an Independent Data Monitoring Committee) [137].

B.2.10.6 Relapses

All patients with new or worsening neurological symptoms were referred to the examining investigator, who independently assessed the EDSS (for assessment of disease progression or protocol defined relapse). Treating investigators who considered new or worsening neurological

symptoms to be consistent with an MS relapse completed a dedicated eCRF electronic form “MS Relapse” independent of the EDSS assessment by the examining investigator

A greater proportion of placebo patients reported clinical relapses compared with the ocrelizumab patients (Placebo 16.3%, ocrelizumab 6.6%). The majority of patients with a relapse reported one relapse (Table 57). Within each group, the number of clinical relapses per year remained similar over 3 years.

Table 32: Proportion of patients with a clinical relapse – controlled treatment period (safety population)

	Placebo (n=239)	Ocrelizumab (n=486)
Patients with relapses n Proportion 95% relapses per patient	 39 16.3% (11.9%, 21.6%)	 32 6.6% (4.5; 9.2%)
Number of relapses per patient 0 1 2 ≥ 3 Total Number of Relapses	 200 (83.7%) 28 (11.7%) 8 (3.3%) 3 (1.3%) 57	 454 (93.4%) 28 (5.8%) 3 (0.6%) 1 (0.2%) 37

The majority of the relapses reported (63 of 94 relapses; 67%) fulfilled the definition of a protocol-defined relapse. As with clinical relapses, a greater proportion of the patients in the placebo group reported protocol-defined relapses compared with the ocrelizumab group, generally with a similar number of protocol-defined relapses per year.

Table 33: Proportion of patients with a protocol-defined relapse – controlled treatment period (safety population)

	Placebo (n=239)	Ocrelizumab (n=486)
Patients with relapses n Proportion 95% relapses per patient	 27 11.3% (7.6%, 16.0%)	 24 4.9% (3.2%, 7.3%)
Number of relapses per patient 0 1 2 ≥ 3 Total Number of Relapses	 212 (88.7%) 21 (8.8%) 4 (1.7%) 2 (0.8%) 36	 462 (95.1%) 21 (4.3%) 3 (0.6%) 0 27

Two patients in the placebo group (0.8%) and 5 patients in the ocrelizumab group (1.0%) had a MS relapse that fulfilled the criteria of an SAE (i.e., required hospitalisation).

B.2.10.7 Treatment exposure

Overall, there was good compliance regarding administration of ocrelizumab infusions.

The majority of patients received 6 or more doses (Placebo 71%, ocrelizumab 83%) with the median number of doses received during the controlled treatment period being 6 doses for the placebo group and 7 doses for the ocrelizumab group. The median ocrelizumab cumulative dose was 4200 mg.

Table 34: Exposure to ocrelizumab/placebo during the double-blind treatment period

	Placebo (n=486)	Ocrelizumab 600 mg (n=486)
Treatment duration, weeks, n (%)		
0–23	12 (5.0%)	25 (5.1%)
24–47	11 (4.6%)	13 (2.7%)
48–71	15 (6.3%)	13 (2.7%)
72–95	13 (5.4%)	11 (2.3%)%)
96–119	16 (6.7	20 (4.1%)
120–143	56 (23.4%)	108 (22.2%)
144–167	43 (18.0%)	113 (23.3%)
168–191	42 (17.6%)	115 (23.7%)
192–215	29 (12.1%)	60 (12.3%)
216+	2 (0.8%)	8 (1.6%)
Number of doses, n (%)		
1	12 (5.0%)	25 (5.1%)
2	11 (4.6%)	13 (2.7%)
3	15 (6.3%)	13 (2.7%)
4	13 (5.4%)	11 (2.3%)
5	18 (7.5%)	22 (4.5%)
6	54 (22.6%)	109 (22.4%)
7	44 (18.4%)	114 (23.5%)
8	44 (18.4%)	107 (22.0%)
9	26 (10.9%)	65 (13.4%)
10	2 (0.8%)	7 (1.4%)
Mean number of doses (SD)	6.1 (2.2)	6.6 (2.1)
Median	6.0	7.0
Mean cumulative dose, mg (SD)	0.0 (0.0)	3867.5 (1244.2)
Median	0.0	4200.0
Min-max	0–0	19–6000

Most patients (> 99%) received more than 80% of the planned ocrelizumab dose at each infusion. The following number of patients received less than 80% of the planned dose: 3 patients on Dose 1 Day 1, 2 patients on Dose 2 Day1, 1 patient on Dose 5 Day 15, and 1 patient on Dose 8 Day 15.

Nearly all patients (> 99%) received the protocol-mandated steroid pre-treatment prior to each ocrelizumab infusion.

B.2.10.8 Anti-drug antibodies (ADA)

Analysis of ADAs was based on the safety population and were summarised descriptively over the blinded treatment period by treatment group. The incidence of treatment-induced ADAs was low (<2%) in the ocrelizumab group. Out of the 481 patients who received ocrelizumab and had an ADA assay result from a post-baseline sample during the controlled treatment period, 9 patients (1.9%) showed treatment-induced ocrelizumab ADAs (see Table 35). Of note:

- One patient was randomised to the placebo group but assigned to the ocrelizumab group in the safety population because of a dispensing error at Week 96 only, when ocrelizumab was dispensed instead of placebo. This patient was negative at baseline but tested positive at Weeks 12 and 48 prior to receiving ocrelizumab. Results at Weeks 72, 96 and 144 were negative for this patient. Because the positive ADA result occurred prior to the patient receiving ocrelizumab at Week 96, the positive ADA result was not considered to be strictly treatment-induced.

- One patient in the ocrelizumab group with treatment-induced ocrelizumab ADAs at Weeks 24, 96, 120, 144 and 168, tested positive for neutralising antibodies to ocrelizumab at Weeks 144 and 168. This patient did not experience any MS relapse, CDP event or IRRs. SAEs of Grade 2 cholelithiasis (Day 116; resolved Day 375 without a change in dose) and Grade 3 acute pancreatitis (Day 303; resolved Day 327 with interruption of dose) were observed in this patient. Except for all samples up to Week 2, serum ocrelizumab concentrations were lower than the minimal reportable titre of 1.30 for all pre-infusion and Week 84 timepoints.

There was a low baseline prevalence of ocrelizumab ADAs in both treatment groups (<1%).

Nine additional patients (3.8%) in the placebo group tested ADA positive for ocrelizumab post-baseline; one of these patients tested positive for neutralising antibodies to ocrelizumab following a positive ADA result at the treatment withdrawal visit. These results represent untreated false positives as the ADA tests were designed to have an untreated positive rate of 5% in the screening assay and 1% in the confirmatory assay.

A summary of ocrelizumab concentrations at timepoints where ADA samples were collected is included.

Table 35: Baseline prevalence and post-baseline incidence of anti-drug antibodies to ocrelizumab – controlled treatment period (safety population)

	Placebo (n=239)	Ocrelizumab (n=486)
Baseline prevalence of ADAs		
Baseline evaluable patients	227	464
Patients with a positive sample at baseline	1 (0.4%)	1 (0.2%)
Patients with no positive samples at baseline	226	463
Post-baseline incidence of ADAs		
Post-baseline evaluable patients	239	481
Patients positive for ADA	9 (3.8%)	9 (1.9%)
Treatment-induced ADA	9	9
Treatment-enhance ADA	0	0
Patients negative for ADA	230	472
Treatment unaffected	1	1

Baseline is the ADA assessment with the highest titre prior to the first infusion of ocrelizumab. All data from the treatment and treatment-free period included.
Baseline evaluable patient = a patient with an ADA assay result from a baseline sample(s).
Post-baseline evaluable patient = a patient with an ADA assay result from at least one post-baseline sample.
Number of patients positive for ADA = the number (and percentage) of post-baseline evaluable patients determined to have treatment-induced ADA or treatment-enhanced ADA during the study period.
Treatment-induced ADA = a patient with negative or missing baseline ADA result(s) and at least one positive post-baseline ADA result.
Treatment-enhanced ADA = a patient with positive ADA result at baseline who has one or more post-baseline titre results that are at least 0.60 t.u. greater than the baseline titre result.
Transient ADA = ADA positive result detected (a) at only one post-baseline sampling timepoint (excluding last timepoint) OR (b) at 2 or more timepoints during treatment where the first and last ADA positive samples are separated by a period of <16 weeks, irrespective of any negative samples in between.
Persistent ADA = ADA positive result detected (a) at the last post-baseline sampling timepoint, OR (b) at 2 or more time points during treatment where the first and last ADA positive samples are separated by a period ≥16 weeks, irrespective of any negative samples in between.
Number of patients negative for ADA = number of post-baseline evaluable patients with negative or missing baseline ADA result(s) and all negative post-baseline results, or a patient who is treatment unaffected.
Treatment unaffected = A post-baseline evaluable patient with a positive ADA result at baseline and (a)where all post-baseline titre results are less than 0.60 t.u. greater than the baseline titre result, OR (b) where all post-baseline results are negative or missing. For any positive sample with titre result less than the minimum reportable titre or any positive sample where a titre cannot be obtained, titre value is imputed as equal to the minimum reportable titre.
The percentage (%) is calculated by the number of evaluable patients at baseline or post-baseline respectively.

The data from the ORATORIO safety population is the most robust safety evidence available for the PPMS population. Safety in subgroups was not assessed, since a larger pool of patients is preferable in order to detect any safety signals.

B.2.11 Ongoing studies

Patients in the ORATORIO study were allowed to switch to ocrelizumab after the randomised controlled period ended. Data from the open label extension of ORATORIO is yet to read out.

Planned study

As part of the EMA Risk Management Plan for ocrelizumab, a new Phase IIIb study is planned in PPMS. The study protocol is under development. An overview of the study design is provided below. We propose that this study forms the basis of data collection under the proposed MAA for

ocrelizumab. More information on how this new study addresses the clinical uncertainty of ocrelizumab in PPMS is provided in the Data Collection Arrangement Appendix.

Table 36 Characteristics of planned Phase IIIb study, WA40404

Study Design	Multi-centre, Randomised, Double Blind, Placebo Controlled Study
Timelines	First patient in expected by end of 2018 Clinical Study Report in 2024
Population	Adults with Primary Progressive Multiple Sclerosis Later in their Disease Course* * EDSS 3 to 8, Age 18 - 65
Intervention	Ocrelizumab
Comparator	Placebo
Outcomes	Primary endpoint: 9-HPT Key secondary endpoint: 12-week confirmed disability progression Other secondary endpoints are to be determined.
Subgroup analysis	• Different inflammatory profiles at baseline • Different age groups at baseline • Other pre-specified subgroups to be determined

Source: Ocrelizumab European Public Assessment Report [126]

B.2.12 Innovation

Ocrelizumab is a glycoengineered humanised monoclonal antibody specifically for chronic administration that selectively targets circulating B cells expressing CD20, a cell-surface antigen that is expressed on mature B cells but not B cell progenitor cells in the bone marrow or terminally differentiated plasma cells. Adaptive immune responses to antigen challenge remain largely intact despite the depletion of circulating B cells [3].

- Ocrelizumab is the only DMT to demonstrate delays in disability progression (including delays to deterioration in upper limb function) in patients with PPMS [128] and therefore has the potential to establish a new standard of care in this form of the disease. Furthermore, ocrelizumab is the only DMT to consistently demonstrate **efficacy** across all disease outcomes in RRMS and PPMS.
- Ocrelizumab is administered as a single 600 mg IV infusion every six months [1]. The **frequency of administration** over a 12-month period is less than DMTs used for other types of MS, and may mitigate the risk of non-adherence as seen with other DMTs that have logistical and resource intensive administration schedules.

- In addition, the **safety profile** of ocrelizumab in the ORATORIO trial was similar to placebo with a distinct absence of burdensome and complex safety monitoring requirements. Patients receiving ocrelizumab are not expected to require additional routine JCV, cardiovascular or laboratory tests, or other safety monitoring like MRI screening (compared to other intravenously infused and orally administered DMTs for the treatment of other forms of MS[1]).
- There is a low probability of long-term **treatment waning** with ocrelizumab compared to other DMTs. This is based on the identification and assessment of all relevant biologically plausible contributory factors and the associated evidence following literature review and repeated consultation with clinical experts:
    - As a humanised antibody, the immunogenicity of ocrelizumab is significantly reduced compared to DMTs used for other types of MS Table 35. This is likely to reduce the probability of long-term treatment waning effects due to the formation of neutralising and inhibitory anti-drug antibodies.
    - [redacted]
    - Furthermore, data from pre-clinical investigations suggest that ocrelizumab decreases inflammation of the innate immune system which may also reduce the probability of a treatment waning effect. In the EAE model, a widely accepted animal model of human MS disease, anti-CD20 therapy reduced microglial activation and lesion formation, with immunohistochemistry for MHCII also demonstrating a reduced volume of brain microglial activation which was accompanied by a reduction in T-cell recruitment and demyelination [138]. This is in contrast to the lack of effect seen in relation to microglial activation with DMTs used for other types of MS [139]).

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Findings from ORATORIO

Overall, the study provided robust evidence that ocrelizumab demonstrated consistent efficacy on clinical measures of disease progression (disability as measured by EDSS; upper limb function

measured by 9-HPT; fatigue) and on subclinical measures of disease progression (T2 hyperintense lesion volume and whole brain volume) against a placebo comparator. The result of the primary endpoint was confirmed by the secondary endpoints (with the exception of SF-36 PCS) and treatment effects achieved were clinically relevant. Importantly for patients with PPMS, treatment with ocrelizumab has been shown to delay the loss of upper limb function, as assessed by 9-HPT.

The safety profile of ocrelizumab 600 mg, administered every 24 weeks by infusion to patients with PPMS, was similar to that of placebo, with the exception of a greater proportion of patients with IRRs observed with ocrelizumab (expected with a monoclonal antibody administered intravenously). The proportion of patients with infections was similar in both groups although more upper respiratory tract and oral herpes infections were reported with ocrelizumab. An imbalance in the incidence of malignancies, with a cluster in female breast cancers, was observed, however incidence rates were within expected epidemiological ranges for MS (see Appendix F).

The incidence of ADAs in the ocrelizumab group was low (<2%), indicating limited likelihood of developing drug resistance over the long term.

Informed by subgroup analysis, the label for ocrelizumab is for treatment in patients with early PPMS with imaging features characteristic of inflammatory activity. The results in the population that reflects the label indicated numerical improvements in disability progressions, as expressed by CDP-12, CDP-24 and 9-HPT (see Section B.2.6.7).

The subgroup of patients that responded best to treatment with ocrelizumab, as defined by confirmed disability progression on EDSS, were younger patients (<50 years). However, analyses of other endpoints in ORATORIO lend support to the functional reserve hypothesis. In analyses of worsening of 9-HPT (confirmed 20% increase in 9-HPT for at least 12 weeks or 24 weeks), considerable benefit was observed in patients treated with ocrelizumab irrespective if they were younger or older. Thus, the trend of lower benefit with respect to worsening of EDSS in older patients, but retained benefit in delaying upper limb worsening across all age groups may be explained by the fact that while older patients may have accumulated more permanent disability with respect to lower limb function (a major contributor to the EDSS score and therefore the confirmed EDSS worsening assessment), the shorter neuronal pathway for the arms may be less likely to have accumulated sufficient focal lesions and axonal loss to exhaust its reserve capacity.

B.2.13.2 Validity

Internal validity

The internal validity of this study is supported by the rigid adherence to the EMA guidance (EMA/CHMP/771815/2011, Rev. 2) on recommended study design and endpoints in the clinical investigation of medicinal products for the treatment of multiple sclerosis.

The study was unblinded when the last enrolled patient completed at least 120 weeks (5 doses) of study treatment and approximately 253 CDP events had occurred. Analyses of study conduct indicated the double-blind design was effectively maintained. The majority of patients received 6 or more doses of study drug (Placebo 71%, ocrelizumab 83%). In addition, there was good compliance of ocrelizumab IV infusions, with over 99% of patients receiving more than 80% of their planned dose at each infusion. A higher number of patients in the placebo group prematurely discontinued treatment compared with ocrelizumab (Placebo 34%, ocrelizumab 21%), mostly driven by the higher incidence of withdrawals due to lack of efficacy (Placebo 11%, ocrelizumab 4%) [129].

MS treatment trials of at least 2 years' duration have been used to show a treatment effect on disability progression, although it is widely acknowledged that progressive MS studies may necessitate a longer blinded treatment period to enable successful demonstration of efficacy [75]. A variable duration, event driven design with a minimum 120-week treatment period in this study was anticipated to adequately demonstrate a significant treatment effect on the primary efficacy endpoint.

External validity

The ORATORIO study was designed prior to the publication of the 'Lublin phenotypes' in PPMS which define progressive disease phenotype on the basis of the presence or absence of disease activity and progression. The ORATORIO study did not fully measure MRI activity or rate of progression prior to patient enrolment. We believe that the study included predominantly actively progressing PPMS patients; however, further data collection may be beneficial to identify patient phenotypes that benefit most from treatment with ocrelizumab, and further elucidate the age-dependency of treatment benefits. The proposed MAA will address these clinical uncertainties using data collected from the planned Phase IIIb study. The new Phase IIIb study will further characterise patients with PPMS by level of activity and progression, and evaluate the efficacy and safety of ocrelizumab in different phenotypes.

The EDSS scale, used in ORATORIO to measure the primary endpoint of confirmed disability progression, accurately reflects deterioration of lower limb function as a proxy for mobility preservation. However, mobility preservation as a treatment goal is of greater relevance to RRMS

than PPMS. The treatment goal for patients with PPMS is the preservation of functional independence; as a proxy, this could be measured by upper limb disability progression.

Disability in PPMS is a multi-dimensional measure. The current EDSS scale is biased in its greater focus on lower limb function rather than upper limb function. Only one state (EDSS score of 8) addresses upper limb disability exclusively. This is not adequate to accurately assess the potentially significant contribution of early upper limb function preservation in the overall preservation of functional independence in PPMS. Consultation with clinical experts revealed that they believe EDSS underestimates the broader disability in PPMS patients. Some patients may appear stable on EDSS but experience deterioration in other functions that affect their independence.

Upper limb function and fatigue, as measured by 9-HPT and MFIS, are not routinely measured in all MS clinics. However, dissemination of the ORATORIO study results and increasing general awareness of the importance of these disease facets are likely to encourage adoption of these measures in routine practice.

In summary, we propose an MAA for ocrelizumab in which access is allowed for patients with high unmet need. In addition, the clinical uncertainties in PPMS identified by the regulatory authorities are going to be addressed in the planned Phase IIIb study.

Life expectancy

The average life expectancy for patients with MS is 5–10 years less than that for the general population [6, 8, 9].

Ocrelizumab does not meet end-of-life criteria.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic review (SR) was conducted to identify cost-effectiveness studies in MS (see Appendix G for details). Thirty-three unique studies were identified in RRMS, as well as 7 previous NICE appraisals in RRMS. However, no studies were identified with a focus on patients with PPMS, highlighting a paucity of economic data for this patient group.

Separate from the SR, one report was identified from the website of the US organisation the Institute for Clinical and Economic Review assessing the cost-effectiveness of DMTs in MS, including for PPMS [140]. As this report is relevant to the decision problem it is summarised here (Table 37). The PPMS economic analysis included in the report compared ocrelizumab with BSC and used natural history based on SPMS (London Ontario dataset) due to paucity of data in PPMS, and did not allow improvements in EDSS. The cost and mortality risk by EDSS-defined health states were assumed to be the same for patients with RRMS, SPMS or PPMS, and utilities were based on SPMS. Treatment effect on CDP-24 was applied in the model. No ICER was calculated for ocrelizumab as the drug price was not available at the time of analysis.

Table 37: Summary of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
[140]	2017	Markov model – 10 health states (EDSS 1-9 and death); lifetime horizon; US payer perspective	Mean age at baseline 42 years, mean proportion male 47%	Ocrelizumab: 3.33 BSC: 2.75	Ocrelizumab: NR BSC: $264,760 (USD)	NR
Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; NR, not reported						

B.3.2 Economic analysis

Due to the absence of published economic evaluations and NICE appraisals in PPMS, a de novo model was developed to assess the cost-effectiveness of ocrelizumab in PPMS. Cost-effectiveness models in RRMS, especially the established ScHARR model developed for NICE, were deemed relevant as reference for the new PPMS model given that the natural disease history and types of events involved in PPMS and RRMS are analogous. However, the treatment goal and definition of disability is fundamentally different in PPMS (see section B.1.3.3) and necessitates adaptation of the established RRMS model structure as described below.

The features of neurological disability in PPMS and their relative impact on HRQoL of people with MS have been more clearly acknowledged in recent years. Whilst loss of ambulatory function is a distinctive feature of all forms of MS and the key driver of the EDSS score, PPMS is also characterised by loss of functionality in the arms. There is a qualitative difference in level of disability and associated functionality between PPMS and RRMS. In people with RRMS lower limb impairment is the key manifestation of disability and upper limb function is generally sufficiently preserved. In contrast, in people with PPMS accumulated disability is manifested by progressive loss of both lower and upper limb function. Therefore, the impact of upper limb function is an important aspect of independence and HRQoL for people with PPMS that is less prominent in RRMS (see Section B.3.4.1 Health-related quality-of-life data from clinical trials). The different domains of the EQ-5D have been shown to be impacted by disability severity to different degrees, in particular the “Self-care” and “Usual activities” domains are negatively impacted by severe disability, lending support to the treatment goal in PPMS being preservation of patients’ independence[56].

In addition, the impact of fatigue on patients’ physical, cognitive, and psychosocial functioning are more prevalent at higher EDSS levels (EDSS >4) and therefore more relevant for a typical PPMS patient than RRMS patient [141]. The EDSS score has been shown to be insensitive to changes in these patient-relevant factors [52].

The explicit consideration of the intensity of upper limb impairment and fatigue, and improvement in their functionality as demonstrated in ORATORIO, require the adaptation of the model structure to also account for the relationship between such factors and EDSS and their impact on HRQoL via disutilities.

There has also been a gradual recognition that although rare, relapses occur in people with PPMS. The PPMS patient phenotypes described by Lublin et al [21] include relapses in the definition of active disease. Relapses were observed in some patients in the ORATORIO study and captured as adverse events (Section B.2.10). The therapeutic goal of pharmacological treatment in PPMS is to slow disability progression and maintain patients’ independence. As such, the PPMS model does not apply benefits of treatment to relapses in the base case, as would occur in an RRMS model. Scenario analysis explores the impact of incorporating relapses in the economic model (see Section B.3.3.3).

B.3.2.1 Patient population

The SmPC states that ocrelizumab is indicated for the treatment of adult patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

The population of the ORATORIO study that reflects the label indication is the primary population of interest in the economic analysis (see Section B.2.6.7). Inflammatory activity is defined as presence of T1 Gd enhancing or new T2 lesions at screening/baseline, and represents about 40% of the ITT population of ORATORIO.

In addition, subgroup analysis is conducted in patients with early PPMS with inflammatory activity aged 50 years or under as younger patients were demonstrated to benefit most from treatment with ocrelizumab in the ORATORIO study (see Section B.2.7.2) [1].

B.3.2.2 Model structure

A Markov state-transition model was designed to reflect the natural history of PPMS based on disability progression. The natural history of PPMS is most commonly described as progression towards increasing levels of disability in several functional and clinically relevant dimensions, deriving from progressive loss of neurological function. The Kurtzke Expanded Disability Status Scale (EDSS) has been the standard for measuring both the degree of current neurologic disability and its progression over time in clinical trials in MS [142] [47]. A full description of the EDSS scale and its limitations can be found in Section B.1.3.2.

Transitions between health states

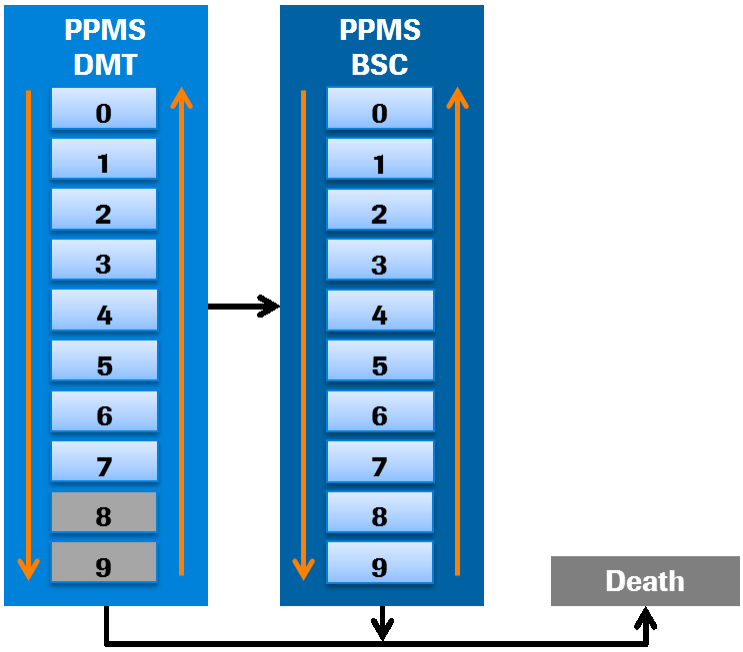
Patients enter the model on active treatment and start in one of the ten EDSS states. The distribution of EDSS scores at baseline in the model was taken from the ORATORIO study.

In each annual cycle patients may:

1. transition between EDSS states in PPMS;
2. withdraw from active treatment and continue to receive best supportive care (BSC);
3. transition to death.

A schematic of the model diagram is depicted in Figure 28.

Figure 28: Model structure



Orange arrows indicate direction in which patients may move along the EDSS scale. Grey boxes in 'PPMS DMT' = these indicate the stages at which treatment is discontinued.

The probability of changing EDSS state (disability progression) in the model was determined by natural history data obtained from PPMS patients in the MSBase database (underlying disease progression of patient not on disease modifying therapy) (see Section B.3.3.2). PPMS natural history data from MSBase indicates that in rare cases disability severity on the EDSS scale can improve temporarily. These rare observations of EDSS improvements in the real world were not excluded from the MSBase data set for the base case analysis, but a scenario is included with adjustment to not allow EDSS improvements. Treatment with ocrelizumab was assumed to delay the progression of disease and treatment effects in the form of hazard ratios were derived from the ORATORIO study, using CDP-12 in the base case, and applied to the natural history data probabilities of worsening in EDSS. The probabilities of improving EDSS are assumed to be unaffected by treatment.

Cost of disease management and HRQoL (utilities) associated with each EDSS state are applied in the model. As per previous NICE appraisals in RRMS, caregiver disutilities per EDSS state were also accounted for in the model (see Section B.3.4.5).

Two further drivers of the impact of treatment on HRQoL are incorporated in the model within the EDSS structure, based on equations describing the association of EDSS, upper limb function and fatigue with utilities (see Section B.3.1.4). Upper limb impairment and fatigue are incorporated in the model assuming an event rate for each EDSS state. The disutility of impairment in upper limb function and impact of fatigue on physical, cognitive and psychosocial functioning were quantified

using regression analysis of the clinical measures (9-HPT and MFIS respectively) and the EQ-5D data collected in the ORATORIO study. The ORATORIO study demonstrated that ocrelizumab slowed the loss of upper limb function and reduced the impact of fatigue (as measured by 9-HPT and MFIS, respectively) compared with placebo, and the reduced rates of upper limb impairment and fatigue in the ocrelizumab cohort of the model translate into reduced disutility in relevant health states.

Treatment withdrawal due to all-causes is included in the economic model and is derived from the ORATORIO study. The most frequently experienced AEs, or rare AEs with a particularly high cost and utility impact, were included in the model and incurred costs and disutilities (see Section B.3.3.7).

In the EDSS scale, score 10 is defined as death due to MS. Deaths are accrued in the model as a result of progression through states 0-9 (alive states), as mortality is EDSS dependent. Death rates in the model are estimated using age and gender specific rates obtained from England life tables and applying a MS risk multiplier dependent on the particular EDSS score

No direct treatment effect on mortality was assumed.

In summary (see Table 38 for more details):

- The model structure consists of 11 possible health states (EDSS 0 to 9 and death [EDSS 10]), each stratified by the probability of people being treated with ocrelizumab or receiving BSC alone

- People move between EDSS states based on transition probabilities derived from natural history data for patients not treated with DMTs.

    - Transition probabilities for people in the ‘PPMS, DMT’ group are derived applying a relative risk of progression to the natural history data. The relative risk is obtained from the ORATORIO study as expressed by CDP-12

- Mortality in the model is driven by disease progression, adjusted for age, gender and MS-specific mortality multipliers

    - Treatment effect is applied to natural history EDSS transitions in the ‘PPMS, DMT’ group, but not directly to mortality estimates

- Each EDSS health state is assigned specific disease management costs (i.e. BSC costs) and utilities, including caregiver disutilities

- EDSS states are associated with different rates of upper limb impairment and fatigue; such rates drive adjustments in the utility associated with each EDSS state. The cohort treated with ocrelizumab benefits from decreased rates of fatigue and upper limb disability - both indirectly through slowing of EDSS progression and directly through treatment effect demonstrated on 9-HPT and MFIS - and is associated with fewer disutility.

- Costs and disutilities associated with drug-related adverse events are assigned to each cohort based on data from the ORATORIO study.

Model perspective

The model was developed from the UK National Health Services and Personal and Social Services perspective (NHS-PSS). The scope of the model includes pharmacological treatments, medical and other professional care as well as other elements of government-funded Personal and Social Services. The model base case perspective does not include the value of care provided informally by family or friends of patients. A scenario analysis is included to explore the impact of including these indirect costs.

Table 38: Features of the economic analysis

	Previous appraisals	**Current appraisal**	
Factor	**n/a**	**Chosen values**	**Justification**
Time horizon	n/a	50 years	Lifetime horizon to ensure all costs and benefits for a chronic disease such as PPMS are captured. In line with majority of RRMS appraisals.
Source of natural history progression	n/a	See Table 43	Long-term registry data was considered most robust in reflecting a chronic disease course over a lifetime, and the MSBase registry analysis was specific for PPMS. Registry approach in line with previous RRMS appraisals.
Source of mortality multiplier	n/a	See Table 49	Pokorski et al, extrapolated for EDSS states. In line with majority of RRMS appraisals.
Source and application of treatment effect	n/a	CDP-12 (Table 47), 9-HPT (Table 53), MFIS (Table 54) from ORATORIO study	CDP-12 was the primary endpoint in the ORATORIO study and was considered more robust than CDP-24 due to the increased number of events in both arms. Applying CDP-24 is explored in sensitivity analysis. Treatment effect on 9-HPT and MFIS were included due to independent effect on EQ-5D.
Treatment waning effect	n/a	Not applied (see Section B.3.3.6)	Not considered clinically plausible for ocrelizumab.
Source and application of treatment withdrawal	n/a	See Section B.3.3.5	Annual probability of all-cause discontinuation from ORATORIO study. Choice of distribution (Gompertz) informed by model fit and clinical opinion.
Stopping rule	n/a	EDSS ≥8 (see Section B3.2.3)	ABN clinical guideline recommends treatment in RRMS to cease once patients are non-ambulatory. The treatment goal in PPMS is different and is aimed at preserving patients' independence; hence the importance of continuing treatment for longer to maintain upper limb function.

Source of patient utilities	n/a	See Table 52	Trial-based EQ-5D regression analysis supplemented by PPMS specific utilities from Orme et al 2007 [106] for EDSS health states not included in ORATORIO study. Approach in line with majority of RRMS appraisals.
Source of caregiver disutilities	n/a	See Table 56	Based on maximum disutility in Alzheimer's disease and adjusted using time spent caring for MS patient at different EDSS health states. In line with majority of RRMS appraisals.
Source of disease management costs	n/a	See Table 60	Based on estimates from Tyas et al 2007 [143] in RRMS inflated to 2016 (direct medical and partial non-medical). Approach in line with majority of RRMS appraisals. The PPMS decrement reported in the regression analysis by Tyas et al was not applied due to lack of clinical plausibility of resulting negative costs for EDSS ≤5.

B.3.2.3 Intervention and comparator

Effective treatment of PPMS is a long-standing challenge. Five other DMTs (fingolimod, glatiramer acetate, IFNB-1a, IFNB-1b, and rituximab) have been evaluated in RCTs in PPMS, but none have demonstrated benefit over placebo (Section B.1.3). Thus, the only treatment demonstrating clinical benefit in PPMS is ocrelizumab which was licensed in January 2018. People with PPMS have traditionally been managed symptomatically, or not at all. Current BSC consists of symptom control, physical therapy, psychiatric and social support.

The model compares the following two treatment strategies, as per the NICE decision problem:

- Ocrelizumab in addition to BSC as per established clinical management, until discontinuation of ocrelizumab because of tolerability, adverse events or other reasons;
- BSC as per established clinical management.

Anecdotal evidence of off-label use of DMTs in PPMS is rare and not included in the model. This conservative approach may have resulted in an underestimation of the costs in the comparator arm.

Discontinuation rules

As the treatment goal in PPMS is to preserve independence, a stopping rule as the one applied in RRMS (i.e. EDSS ≥7) is not desirable as it would prevent patients from benefiting optimally from treatment at later stages of the disease course. The economic analysis in PPMS therefore applies a later stopping rule at EDSS ≥8 (i.e. patients essentially restricted to bed or chair) to maximise on the opportunity to preserve upper limb function for as long as is possible even in wheelchair-bound patients.

In addition to the EDSS-dependent stopping rule, all-cause discontinuation rates derived from the ORATORIO study are applied each year to the ocrelizumab cohort (see Section B.2.6).

B.3.3 Clinical parameters and variables

Whenever possible, patient level data from the ORATORIO study were used to inform clinical parameters and variables in the economic analysis. Further information regarding this trial is presented in depth in Section B.2.6.

B.3.3.1 Baseline patient characteristics

Patient level data from the ORATORIO study were used for baseline EDSS distribution, age, and gender (Table 39). Demographic data for the 'MRI active' and 'MRI active ≤50' subgroups were assessed and found to be similar to the ITT population, apart from age in the 'MRI active ≤50' subgroup. Given the similarity between the subgroups and ITT, baseline demographic data for the subgroups have not been incorporated into the model. The impact of lower baseline age in the 'MRI Active ≤50' subgroup is explored in scenario analysis.

Table 39 Baseline patient characteristics used in model (ITT population)

Characteristic		ITT population n=731	MRI active subgroup n=293	MRI active ≤50 subgroup n=230
Age (years)		44	43	40
Gender (% male)		51	50	50
EDSS (%)	0	0	0	0
	1	0	0	0
	2	0	0	0
	3	27	25	26
	4	27	28	30
	5	16	19	17
	6	30	28	27
	7	0	0	0
	8	0	0	0
	9	0	0	0

B.3.3.2 Disability progression

Identification of PPMS natural history dataset

A suitable dataset is needed to inform transition probabilities between EDSS scores reflecting the natural course of disease progression in PPMS in patients not treated with disease modifying therapies. The ORATORIO study included a placebo arm, however the use of clinical trial data to inform disease progression parameters in modelling has often been challenged. Due to the chronic, lifetime nature of MS and the relatively short duration and small sample size of trials, the most robust way to estimate natural history is to use longitudinal observational data, i.e. registry data.

Previous NICE appraisals in RRMS preferred the use of observational data in the real-world setting to fully characterise the disease course, such as the London Ontario and British Columbia datasets [144-150].

Roche collaborated with the Sylvia Lawry Centre for Multiple Sclerosis Research (SLCMSR), who have access to the London Ontario dataset from Canada and the international MSBase dataset [134] , to identify PPMS specific natural history. The analysis of London Ontario data did not result in outputs usable for economic modelling as some EDSS states were deemed not to be reliable by the SLCMSR statistician and had few PPMS patients (n = 219). The London Ontario dataset was hence not considered further.

MSBase is an international registry for MS. A minimum dataset is required to be uploaded for initial registration of patients. Following this initial visit, at least an annual follow-up visit is required. Key data are collected prospectively in MSBase, including EDSS. MSBase is an observational database that represents real-world MS clinical practice as patient management is dictated by individual doctors and their patients [134].

MSBase is made up of 352 members, 240 clinics, and 73 countries and contains a total of 45,197 patient records. The registry contains 2,786 primary progressive (2074) / progressive relapsing (712) patients (6% of total patients included in the registry). MSBase data has informed multiple publications, including papers on comparative efficacy, discontinuing DMTs and the natural history of MS and related factors [151-153]

Suitability assessment of MSBase registry

Following the approach of the Scientific Advisory Group behind the UK risk sharing scheme (RSS) in RRMS [154], key selection criteria were used to assess natural history datasets:

- Availability of EDSS measurements
- Access to unprocessed (actual) scores with no data smoothing or manipulation
- Prospective data collection
- Database size
- Follow-up length
- Broad setting matching health system and MS prevalence

These criteria provide a clear and rational basis by which to assess the suitability of different natural history datasets for the economic model in PPMS (Table 40).

Table 40 Comparison of ORATORIO placebo arm data with MSBase data

Key selection criteria	ORATORIO placebo arm	MSBase
Availability of EDSS measurements	Yes	Yes
Access to unprocessed (actual) scores with no data smoothing or manipulation	Yes	Yes (analysis conducted by MSBase)
Prospective data collection	Yes	Both prospective and retrospective
Database size	244 patients (1,968 EDSS observations)	1,079 patients (8,401 EDSS observations)*
Follow-up length – mean (median) in weeks	140 (144)	421 (336)
Broad setting matching health system and MS prevalence	Restricted trial population (e.g. eligibility criteria specifying EDSS score 3-6 at screening)	Broad population included in observational database (represents real world MS practice as patient management is dictated by individual doctors and their patients)

* after application of inclusion / exclusion criteria for statistical modelling

Compared with the ORATORIO placebo arm data, the MSBase dataset includes a greater number of patients/EDSS observations, longer follow-up, and a patient population reflective of real world practice. For a chronic disease, it is desirable to use natural history data with as long a follow-up as possible to be able to better characterise the disease course over time.

Therefore, the MSBase dataset represents a broader and fuller characterisation of the natural history of PPMS than what can be observed in the clinical trial and is the most appropriate source for the economic model.

Statistical modelling of MSBase data

A protocol was developed in collaboration with MSBase to generate transition probabilities for the EDSS transition probability matrix in the economic model. The statistical approach was similar to that reported in Palace et al 2014 [154].

Key analysis highlights:

- Continuous multi-state Markov model (based on Palace et al 2014)
- Transition matrices for the 10-state disability (EDSS) Markov model (EDSS 0-9)
- Model specification = no covariates (unadjusted)
- Unit = longest DMT free period in the DMT naive, PPMS state
- Baseline = first recorded EDSS in DMT naive & PPMS state
- Data = MSBase global - extract date 10th December 2016

Inclusion criteria:

- Aged 18 or over
- Minimum 2 years of follow-up in DMT naive PPMS state
- Minimum 2 EDSS scores during follow-up

Exclusion criteria:

- Excluding EDSS 10 from dataset

The characteristics of the PPMS analysis set obtained from MSBase are summarised below.

Table 41 Population characteristics of MSBase PPMS analysis set

Characteristic	PPMS analysis set
Clinic or population-based cohort	Clinic
Data collection period (time period)	June 1976 to December 2016
Recording disability scores	Both prospective and retrospective
Number of patients	1079
Females: n (%)	596 (55.2)
Age at analysis baseline, years: mean (SD); median (quartiles)	51.0 (10.2); 51.3 (44.9, 58.4)
Age at onset of PPMS, years: mean (SD); median (quartiles)	42.9 (10.2); 43.5 (35.9, 50.2)
Age at diagnosis of PPMS, years: mean (SD); median (quartiles)	47.9 (10.1); 48.3 (41.6, 54.8)
Disease duration at analysis baseline, years: mean (SD); median (quartiles)*	8.2 (7.6); 5.7 (2.6, 11.3)
Patients who experienced a relapse in the analysis period: n (%)	88 (8.2)
First eligible EDSS: median (quartiles)	4 (3, 6)
Follow-up: mean (SD); median (quartiles)	8.10 years (6.47) 6.72 (3.99, 10.49)
Time to reach EDSS 6, years: median	6.71

* Defined as time since first symptoms

Estimation of EDSS transition probabilities

EDSS scores over time were used to estimate annual probabilities in a transition matrix that form the baseline risks for disability progression. Table 42 below illustrates the number of adjacent data points used in the estimation of transition probabilities. The transition probability matrix in PPMS is presented in Table 43. The unadjusted transition matrix allows for improvements in EDSS, as observed in the raw data.

Clinical opinion indicated that some improvements in EDSS can occur in PPMS patients, but only at the lower end of the EDSS scale which is most sensitive to change, and only small (up to 2 steps on EDSS) improvements were clinically plausible.

The model fit statistic, Akaike information criterion (AIC), shows that the unadjusted model (presented here) is the optimal choice as it has the lowest AIC. Covariates such as age and sex were explored but did not provide a better fit (Table 44).

Table 42 Number of observed transitions between EDSS scores in PPMS

		To EDSS									
		0	1	2	3	4	5	6	7	8	9
From EDSS	0	10	7	3	4	2	0	1	0	0	0
	1	3	61	50	13	9	1	4	1	1	0
	2	7	28	358	115	64	16	11	1	0	0
	3	1	6	62	593	212	48	32	4	2	0
	4	0	3	28	84	1056	229	141	3	2	0
	5	0	2	2	10	101	641	279	8	2	0
	6	3	1	1	7	30	93	2142	231	27	1
	7	0	0	0	0	3	0	69	854	115	6
	8	0	2	0	0	0	0	2	31	376	22
	9	0	0	0	0	0	0	0	0	8	56

Source: MSBase analysis

Table 43 Transition probability matrix in PPMS

		To EDSS									
		0	1	2	3	4	5	6	7	8	9
From EDSS	0	0.4068	0.2929	0.2242	0.0611	0.0132	0.0016	0.0002	0.0000	0.0000	0.0000
	1	0.0842	0.2617	0.4204	0.1735	0.0512	0.0076	0.0012	0.0000	0.0000	0.0000
	2	0.0138	0.0903	0.4409	0.2998	0.1264	0.0238	0.0048	0.0002	0.0000	0.0000
	3	0.0017	0.0164	0.1318	0.4008	0.3326	0.0905	0.0252	0.0010	0.0000	0.0000
	4	0.0001	0.0016	0.0182	0.1088	0.5181	0.2429	0.1046	0.0054	0.0002	0.0000
	5	0.0000	0.0002	0.0024	0.0209	0.1718	0.3922	0.3807	0.0299	0.0018	0.0000
	6	0.0000	0.0000	0.0001	0.0010	0.0127	0.0653	0.8011	0.1103	0.0093	0.0002
	7	0.0000	0.0000	0.0000	0.0000	0.0005	0.0038	0.0813	0.7766	0.1335	0.0043
	8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0042	0.0817	0.8599	0.0541
	9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002	0.0046	0.0955	0.8998

Source: MSBase analysis

Table 44 Model fit for transition probability matrix

Model	AIC
Unadjusted	14761.97
Age (continuous)	14766.83
Sex	14788.74
Age (continuous) + Sex	14776.41

Source: MSBase analysis

As the label for ocrelizumab in early PPMS specifies patients with imaging features characteristic of inflammatory activity, an assessment was made of the completeness of MRI data collected in the

MSBase registry. Limited MRI data were available in MSBase and therefore transition probabilities specifically reflecting the 'MRI active' subgroup could not be generated.

Patients with MRI active disease may be expected to progress faster than the general population with PPMS. Hence a scenario is included that explores the impact of applying a 5% or 10% acceleration factor to the MSBase matrix to mimic faster progression in patients with MRI active disease (see Appendix L).

The MSBase registry data contain rare observations of EDSS improvements in PPMS. However, PPMS is a progressive disease and large improvements in EDSS or improvements at the higher end of the EDSS scale may not be considered clinically plausible. For example, it is unlikely that a patient using a wheelchair (EDSS 7) is able to walk with an aid again (EDSS 6). Therefore, scenario analysis is included with the matrix constrained to allow progression only (see Appendix L).

For the 'MRI active ≤50' subgroup a separate transition probability matrix was generated using MSBase data with baseline age ≤50 as covariate (Table 45 and Table 46).

Table 45 Number of observed transitions between EDSS scores in PPMS patients ≤50 yrs

		To EDSS									
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
From EDSS	**0**	7	3	3	2	2	0	1	0	0	0
	1	3	35	24	8	6	0	2	1	0	0
	2	5	10	195	62	37	8	6	1	0	0
	3	1	4	33	321	127	26	12	4	2	0
	4	0	1	14	47	577	113	63	3	0	0
	5	0	0	1	3	45	315	130	8	1	0
	6	1	0	1	2	11	40	861	99	9	0
	7	0	0	0	0	2	0	28	353	56	6
	8	0	0	0	0	0	0	1	18	193	11
	9	0	0	0	0	0	0	0	0	3	43

Source: MSBase analysis

Table 46 Transition probability matrix in PPMS patients aged ≤50

From EDSS	To EDSS									
	0	1	2	3	4	5	6	7	8	9
0	0.4143	0.3203	0.2021	0.0496	0.0122	0.0013	0.0002	0.0000	0.0000	0.0000
1	0.1259	0.2967	0.3855	0.1384	0.0463	0.0062	0.0010	0.0000	0.0000	0.0000
2	0.0143	0.0693	0.4693	0.2812	0.1375	0.0236	0.0046	0.0002	0.0000	0.0000
3	0.0017	0.0121	0.1369	0.3646	0.3661	0.0923	0.0250	0.0011	0.0000	0.0000
4	0.0001	0.0012	0.0198	0.1081	0.5396	0.2309	0.0944	0.0056	0.0003	0.0000
5	0.0000	0.0001	0.0023	0.0184	0.1558	0.4110	0.3761	0.0338	0.0024	0.0000
6	0.0000	0.0000	0.0001	0.0010	0.0124	0.0734	0.7767	0.1237	0.0124	0.0003
7	0.0000	0.0000	0.0000	0.0000	0.0005	0.0043	0.0813	0.7543	0.1539	0.0057
8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002	0.0054	0.1026	0.8303	0.0614
9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0025	0.0409	0.9555

Source: MSBase analysis

Similar to the approach taken with the MSBase matrix, scenario analysis is included allowing for progression only (see Appendix L).

Application of treatment effect on slowing of disease progression

The effects of treatment are handled in the model by an instantaneous hazard rate relative to that of patients not on treatment in the PPMS natural history dataset. The relative treatment effect was only applied to forward transition probabilities, not to backward transitions (i.e. EDSS improvements). CDP-12 data in the respective subgroups were used in the base case model, as it was the primary endpoint in ORATORIO and the 12-week confirmatory period is not assumed to be impacted by relapse/remission dynamics, as suggested in RRMS. Application of CDP-24 data is explored in sensitivity analysis (Table 47).

Table 47: Treatment effects applied in the model

	'MRI active' subgroup	'MRI active ≤50' subgroup	'MRI active' subgroup – extended control period	'MRI active ≤50' subgroup – extended control period
CDP12	**0.68 (0.46 – 0.99)**	**0.55 (0.36 – 0.85)**	0.69 (0.47 – 1.00)	0.56 (0.37 – 0.85)
CDP24	0.71 (0.47 – 1.06)	0.54 (0.35 – 0.85)	0.68 (0.46 – 0.99)	0.53 (0.35 – 0.81)

In bold are data points used in base case economic analysis

B.3.3.3 Relapses

As described earlier, relapses occur in PPMS patients but are relatively rare events compared with relapsing form of MS. In the MSBase PPMS dataset 8% of patients experienced a relapse, and in the ORATORIO placebo arm 11% of patients experienced a protocol-defined relapse (see Section B.2.10.6). In ORATORIO relapses were reported as adverse events, and occurred less frequently in patients treated with ocrelizumab compared with BSC.

The therapeutic goal of pharmacological treatment in PPMS is to slow disability progression and maintain patients' independence. As such, the PPMS model does not apply benefits of treatment to relapses in the base case, as would occur in an RRMS model. Scenario analysis explores the impact of incorporating relapses in the economic model. This is done in the same way as in established RRMS models used in previous NICE appraisals, i.e. the impact of ocrelizumab is driven by both its impact on disability (by keeping patients in lower EDSS states for longer) and its direct effect on relapses.

Post hoc analysis was conducted to derive annualised relapse rate ratios, and indicated a 65% reduction in relapses with ocrelizumab treatment compared with placebo (Table 48). In line with the approach taken for modelling disease progression, registry data was considered most robust to derive natural history of annual relapse rates. MSBase data on time from first symptom to onset of first relapse in PPMS informed the annual relapse rate of 0.015, which was assumed to be constant per EDSS health state.

Cost and disutility associated with relapses were derived from the literature. The most commonly used sources in previous NICE RRMS appraisals were applied [106, 143], which suggested a typical relapse costs £2,001 (inflated from 2005 to 2016 using PSSRU [144-150] and is associated with a disutility of -0.071 lasting for 46 days.

Table 48 Annualised protocol-defined relapse rate, ITT population

Efficacy variable	Placebo (N=244)	Ocrelizumab 600 mg (N=488)
Total number of relapses	36	27
Total patient-years followed	636.4	
Unadjusted annualised relapse rate *	0.057	
Adjusted annualised relapse rate **	0.021	0.011
95% CI of adjusted annualised relapse rate	(0.014, 0.071)	(0.005, 0.025)
Adjusted annualised relapse rate ratio		0.350
95% CI of adjusted annualised relapse rate ratio		(0.190, 0.645)
p-value		0.0010

Negative binomial model.

* The total number of relapses for all patients in the treatment group divided by the total patient-years of exposure to that treatment.

** Adjusted by Geographical Region (US vs ROW) and Age (<=45, >45 years).

Log-transformed exposure time is included as an offset variable.

B.3.3.4 Mortality

Mortality was based on the general population, with the application of adjustable MS-specific mortality multipliers by EDSS. All-cause mortality rates for the general population were obtained from national life tables for [155] England and Wales from 2014–2016 [156]. A weighted average of the general population all-cause mortality rate is calculated based upon the female to male ratio of MS patients used in the model.

Increasing levels of disability are associated with increasing risk of death as shown by Sadovnick et al 1992. This Canadian study included 2,348 patients followed in MS specialty clinics between 1972 and 1985. MS patients were categorised as mild (EDSS ≤3.5), moderate (EDSS 4-7) and severe (EDSS ≥7.5) and reported a 160%, 184% and a 444% increase in the mortality, respectively. The fingolimod manufacturer submission to NICE [146] generated an equation to predict excess mortality for individual EDSS scores and this has been used in NICE MS appraisals ever since. The resulting relative risks by EDSS state are provided in Table 49. The probability of mortality per cycle is dependent on the starting age of the cohort.

No direct treatment effect on mortality is assumed; however, there will be an indirect impact on mortality of applying treatment effects to disability progression.

Table 49 MS mortality multipliers by EDSS

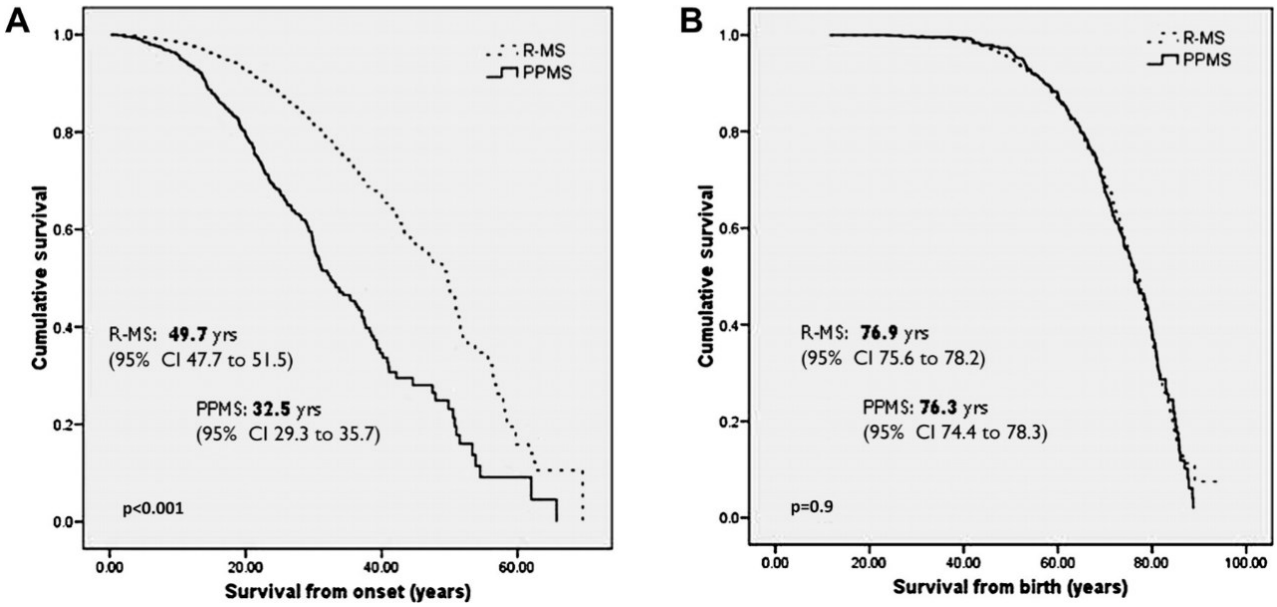
EDSS	0	1	2	3	4	5	6	7	8	9
Relative risk	1.00	1.43	1.60	1.64	1.67	1.84	2.27	3.10	4.45	6.45

Source: TA254 manufacturer submission [146]

Mortality multipliers in PPMS were assumed equal to those applicable to other types of MS, such as RRMS and SPMS, as they are assumed to be driven by disease progression primarily and not disease type. This assumption is supported by the study by Kingwell et al, 2012 [9]. This study analysed mortality data from 6,917 patients included in the British Columbia dataset between 1980 and 2007; approximately 10% of the sample were people with a diagnosis of PPMS. It highlighted that PPMS patients have a greater mortality risk than both the general population and patients with relapsing MS.

However, the study showed that although survival from onset may be longer for relapsing MS than for PPMS, survival age is similar. This is explained by PPMS patients being typically diagnosed at a more advanced stage; therefore the death rates in PPMS are likely driven by higher level of disability from onset rather than an independent increase in risk of death for each EDSS score compared with RRMS (Figure 29).

Figure 29 Survival curves for PPMS and RMS (British Columbia dataset)



Kaplan-Meier survival curves for (A) survival from onset (B) and survival age, Source: Kingwell et al, 2012

B.3.3.5 Treatment withdrawal

The ORATORIO study is the primary source for all-cause discontinuation of treatment. All-cause discontinuation includes withdrawal due to adverse events or lack of efficacy. Different distributions were fitted to the all-cause discontinuation data from the study to convert it to annual probabilities of withdrawal.

The model fit statistics, Akaike information criterion (AIC) and Log likelihood, indicate that the Exponential and Gompertz functions are the most appropriate fit to the data (Table 50). Clinical opinion indicated that withdrawal rates were expected to increase in the long-term. This was thought to be driven by the perception of relatively limited tangible benefits to patients of slowing down disability progression, as opposed to the benefits derived from high-efficacy DMTs in RRMS which can reverse disability. As such, the Gompertz function was deemed the optimal choice as the annual probability of withdrawal increases over time with this function.

However, clinical opinion deemed the average treatment duration predicted by the model, which is a combination of the stopping rule at EDSS 8 and all-cause discontinuation based on the Gompertz function, to be excessively high at just under 7 years.

The impact of a higher constant treatment withdrawal rate – 14% per year, informed by the yearly discontinuation rate at 10 years based on the Gompertz function, was explored in scenario analysis. This rate of discontinuation is broadly similar to 17% annual treatment withdrawal rates observed in the real world setting for rituximab in rheumatoid arthritis in the US. This could be considered an analog for ocrelizumab in PPMS as it is an example of another disease modifying therapy that slows

disease progression in a chronic disease. There are however differences between rheumatoid arthritis and PPMS, primarly the lack of alternative treatment options in PPMS which may encourage patients to stay on treatment even if the tangible benefits are perceived to be small.

The average treatment duration predicted by the model under this scenario (nearly 4 ½ years) matches expectations by clinical experts of ocrelizumab use in the real world.

Table 50 Model fit for all-cause discontinuation

Distribution	AIC	Log likelihood
Exponential	1213.37	-604.69
Weibull	1215.29	-604.65
Log logistic	1220.01	-607.00
Log normal	1249.42	-621.71
Gompertz	1214.10	-604.05

All-cause discontinuation data from the ITT population were applied to the 'MRI active' and 'MRI active ≤50' populations as rates during the study were similar.

On withdrawal of treatment, patients are assumed to follow the same transition probabilities as those assigned to BSC.

B.3.3.6 Treatment effect waning

Waning of long-term treatment effect has been a topic of long-standing discussion at NICE appraisals in RRMS ever since the first DMTs were approved. The relatively short trial durations compared with a lifetime of disease, and the occurrence of anti-drug neutralising antibodies in a considerable proportion of patients in the early DMT trials with interferon-beta has often led NICE committees to consider a scenario or base case with waning of treatment effect due to drug resistance or other factors. Most previous NICE committees have concluded that the plausible ICER range is somewhere between excluding and including waning assumptions.

No waning of long-term treatment effect has been assumed in the base case model for ocrelizumab due to the following unique features (see Section B.2.12):

1. Ocrelizumab is a humanised antibody engineered for long-term use and generates negligible neutralising antibodies, which are thought to play a role in developing drug resistance.

2. Ocrelizumab has demonstrated sustained treatment effect across different timepoints and different outcomes in the open label extension study in RRMS (see Appendix M). The open label extension data of ORATORIO in PPMS are not available yet but there is no reason to believe that the treatment effect of ocrelizumab will not be similarly sustained in PPMS.

3. Pre-clinical investigations suggest that ocrelizumab also decreases inflammation of the innate immune system which, together with the effects of ocrelizumab seen on the adaptive immune system, may reduce the probability of a treatment waning effect.

For the above reasons a scenario that includes waning of treatment effect lacks clinical plausibility for ocrelizumab. In addition, annual all-cause discontinuation rates based on data from ORATORIO are applied in the economic model and it would be expected that if patients no longer derive benefit from treatment they would discontinue.

B.3.3.7 Adverse events

The AE profile of ocrelizumab is broadly similar to placebo, with the differences between the arms being minor (less than 3% difference) for most AEs and many AEs occurring more frequently in patients treated with placebo than ocrelizumab (see Section B.2.10). This points towards many AEs being disease-related symptoms that are reduced in the ocrelizumab arm due to slowing of disease progression compared with placebo, and are not drug-related AEs. Including these AEs would result in double counting of costs and disutilities associated with EDSS health states, and would be favourable to ocrelizumab due to its treatment effect on slowing of disability progression.

Hence only those AEs occurring more frequently in the ocrelizumab arm with a difference >3% are included in the model arm. No infusion related reactions were included in the model for placebo, since these would not occur in routine practice in patients treated with BSC. As an exception malignancies were included due to their high cost and HRQoL impact. The rates of AEs in the 3-year study were converted to annual risk of AEs (Table 51).

The annual risk of AEs is assumed to be constant and applied to each year of the model time horizon. This assumption is supported by long-term experience with DMTs in RRMS which has shown that AEs can occur either soon after start of treatment (e.g. infusion related reactions) or can develop years later (e.g. malignancies).

Due to increased probability of detecting rare adverse events in larger cohorts of patients, the ITT safety data was applied to the 'MRI active' and 'MRI active ≤50' subgroups; the underlying assumption being that AEs are no different in subgroup populations compared with ITT.

Table 51 Adverse events from ORATORIO included in economic model

	Ocrelizumab		Placebo	
AE, %	**3-year probability**	**Yearly probability**	**3-year probability**	**Yearly probability**
Infusion related reaction	39.9	15.6	0	0
Malignancies	2.3	0.8	0.8	0.3
Upper respiratory tract infection	10.9	3.8	5.9	2.0

B.3.4 Measurement and valuation of health effects

Utility weights incorporated in the model covered four domains:

1. Patient utilities associated with disability as described by the EDSS states reached by the cohort over the time horizon of the model

2. Utility decrements associated with loss of upper limb functionality and fatigue, not captured in the EDSS score

3. Utility decrements associated with adverse events

4. Utility decrements associated with carer burden

B.3.4.1 Health-related quality-of-life data from clinical trials

Health-related quality of life data collected in patients in the trial was consistent with the NICE reference case. EQ-5D-3L was collected in ORATORIO at baseline and at each follow up visit. No statistically significant differences were observed between treatment arms and EQ-5D data was therefore pooled. The UK value set as described by Dolan et al [157] was used to translate the patient measurements into preferences from the perspective of the UK general public.

The relationships between health utilities and measures of disease activity and disability progression in PPMS are poorly understood [158]. A regression analysis model selection process was developed aimed at building the simplest model including all important factors. For each patient both scheduled and unscheduled assessments of EQ-5D were considered as long as relevant covariates were also available. No imputations for missing data were performed. The full model included EDSS, region of world, baseline Gd-enhancing lesion, age, sex, fatigue status, and upper limb impairment. After removal of factors without significant interaction with EQ-5D, the final model included EDSS, upper limb impairment (as measured by 9-HPT), and clinically meaningful fatigue (as defined by MFIS score >38) (Table 52) (see Appendix H for details).

The distribution of EDSS states during the duration of the ORATORIO study ranged from 2-7. For EDSS states not captured in the RCT or with very low numbers, health state utility values from published literature were used (see Section B.3.4.3). The impact of deriving the utility value for EDSS 7 from the literature is explored in scenario analysis, due to the low number of patients with EQ-5D measurement in this health state in ORATORIO.

Comparison of the utility estimates in the ‘MRI active’ and ‘MRI active ≤50’ subgroups with the ITT population indicated similar results and therefore subgroup EQ-5D data have not been included in the model (see Appendix H for more details).

Table 52 Utility values from ORATORIO study

Health state	Mean	95% CI	Standard error	Assessments / patients (n)
EDSS 2	0.7913	0.738, 0.845	0.0272	71 / 51
EDSS 3	0.7376	0.710, 0.765	0.0142	381 / 230
EDSS 4	0.6782	0.650, 0.707	0.0146	385 / 231
EDSS 5	0.6649	0.627, 0.703	0.0192	173 / 129
EDSS 6	0.6049	0.577, 0.633	0.0144	525 / 283
EDSS 7	0.4278	0.346, 0.510	0.0417	31 / 26
Upper limb impairment (12-week sustained 20% increase in 9-HPT)	–0.0641	-0.114, -0.014	0.0257	N/A
Fatigue and cognitive impairment (MFIS >38)	-0.1502	-0.174, -0.126	0.0121	N/A

Source: final EQ-5D regression model (see Appendix H)

Incorporation of disutility associated with upper limb impairment

Regression analysis of EQ-5D data collected in ORATORIO demonstrated that there are factors in PPMS other than EDSS that impact HRQoL, and the model was adjusted to account for these.

The adjustment for upper limb dysfunction was incorporated in the model assuming that this type of disability would apply from EDSS stage 5 and above, based on clinical advice that upper limb impairment is most prominent in these patients and confirmed by the statistically significant interaction test in the regression model. Clinical opinion suggested that upper limb dysfunction is closely associated with level of disability, affecting approximately 30% of patients on at least one side with EDSS 0-4, 50% of patients with EDSS 5–6 and 70% of patients with EDSS ≥7 (Table 53).

The ORATORIO data provide a partial picture of the proportion of patients by EDSS defined as having upper limb impairment in the placebo arm (see Appendix H). Only data for EDSS 2–6 were available and the patient numbers for some EDSS scores are low and estimates therefore uncertain. In general, a trend of increasing upper limb impairment with increasing EDSS level was observed, although trial estimates appear lower than those predicted by clinical opinion. Given the low patient numbers with upper limb impairment for some EDSS scores, clinical opinion was considered more credible as the basis for the estimated proportions. The impact of lower proportions of patients experiencing upper limb impairment is explored in scenario analysis.

Disutility (-0.0641, see Table 52) is applied to the proportion of patients experiencing upper limb impairment in each EDSS health state. The ORATORIO trial showed that preserving upper limb function is an important contribution of treatment. Clinically meaningful upper limb impairment, as measured by 20% increase in 9-HPT sustained over 12 weeks, was reduced by 48% with ocrelizumab compared with placebo in the MRI active population and 55% in the MRI active ≤50 subgroup (see Section B.2.6.4). This relative risk is applied in the ocrelizumab treated cohort from

EDSS 5 and above to the proportion of patients with upper limb impairment when not on therapy, and hence fewer patients treated with ocrelizumab experience the associated disutility.

Therefore, the impact of ocrelizumab is driven by both its impact on slowing EDSS progression (by keeping patients in earlier EDSS states for longer where lower proportions of patients have upper limb dysfunction than higher EDSS states) and its direct impact on upper limb dysfunction. This approach is similar to incorporation of relapses in established RRMS models, with both indirect and direct treatment effects applied. The overall impact of incorporating disutility associated with upper limb impairment is 0.982 or 0.546 fewer QALYs accrued in the placebo arm over the lifetime horizon of the model in the MRI active population or MRI active ≤50 subgroup, respectively (16% or 9% reduction, respectively).

Incorporation of disutility associated with fatigue

Fatigue is one of the most common disabling symptoms associated with MS. The prevalent nature of fatigue in MS patients was corroborated in the study by Thompson et al [141] which indicated that up to 96% of patients with MS experience some degree of fatigue. The degree to which these symptoms affect patients was correlated with level of disability as expressed by EDSS.

The Modified Fatigue Impact Scale (MFIS) assesses the impact of fatigue on physical, cognitive, and psychosocial functioning. The MFIS is considered a reliable measure to assess the burden of fatigue in people with MS. Clinically meaningful fatigue was defined as a total score of 38 and above [66]. However, it should be noted that cut-offs are not commonly used with fatigue scales and have not been extensively researched in PPMS.

Similarly to upper limb dysfunction, the impact of fatigue on physical, cognitive, and psychosocial functioning, as measured by MFIS, was shown to have a statistically significant independent effect on utility in PPMS. A decrement (-0.1502, see Table 52) was applied to utilities in the proportion of patients per EDSS health state experiencing clinically meaningful fatigue each year in the BSC cohort of the model (Table 54).

The proportion of patients assumed to experience clinically meaningful fatigue in each EDSS health state was informed by clinical opinion. This was generally supported by the proportion of patients by EDSS defined as fatigued (MFIS >38) in the placebo arm of the ORATORIO study, although trial estimates appeared higher (see Appendix H). The ORATORIO data only provide a partial picture as not all EDSS scores are observed in the trial. Given the low patient numbers who were fatigued for some EDSS scores, clinical opinion was considered more credible as the basis for the estimated proportions. The impact of higher proportions of patients experiencing clinically meaningful fatigue is explored in scenario analysis.

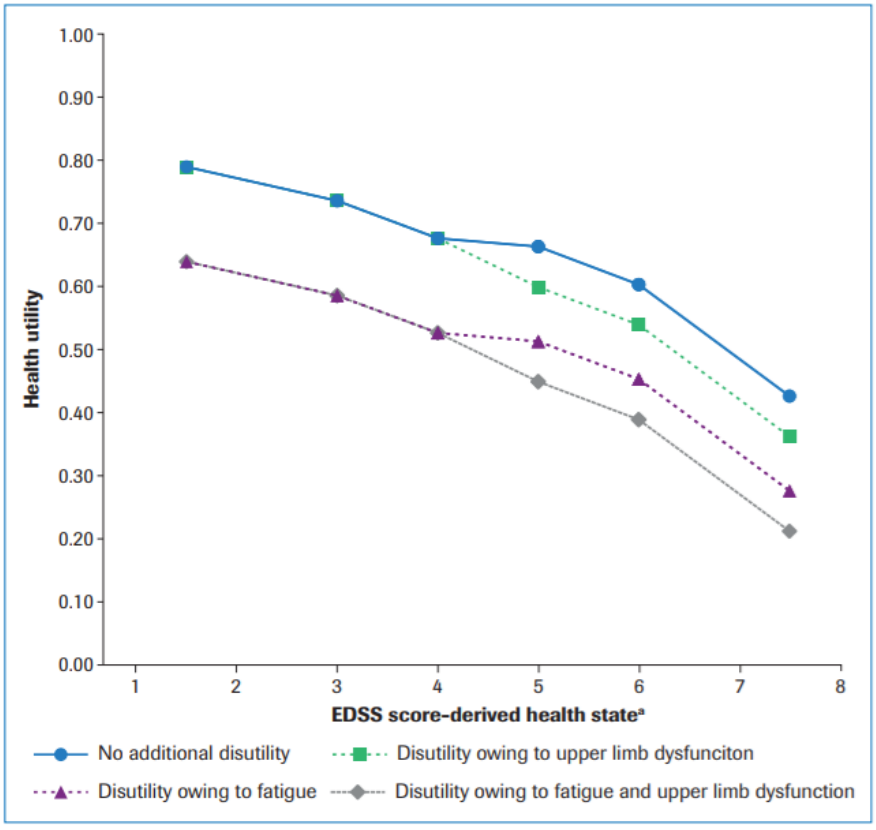
For people treated with ocrelizumab, a relative risk reduction in clinically meaningful fatigue, as measured by MFIS score >38 in ORATORIO, of [redacted] in the MRI active population and [redacted] in the MRI active ≤50 subgroup was applied to the fatigue impact decrement each year.

Therefore, the impact of ocrelizumab is driven by both its impact on slowing EDSS progression (by keeping patients in earlier EDSS states for longer where lower proportions of patients are affected by fatigue than higher EDSS states) and its direct impact on fatigue. This approach is similar to incorporation of relapses in established RRMS models, with both indirect and direct treatment effects applied. The overall impact of incorporating disutility associated with fatigue is 1.855 or 1.414 fewer QALYs accrued in the placebo arm over the lifetime horizon of the model in the MRI active population or MRI active ≤50 subgroup, respectively (27% or 22% reduction, respectively).

Summary

The overall impact of including disutilities of upper limb impairment and fatigue on EQ-5D by EDSS is illustrated below.

Figure 30 Impact of upper limb dysfunction and fatigue on EDSS-derived HSUVs in ORATORIO



Source: Daigl et al 2017 [158]

Table 53 Incorporation of upper limb impairment disutility

EDSS	0	1	2	3	4	5	6	7	8	9	Source
Proportion with upper limb impairment (BSC)	30%	30%	30%	30%	30%	50%	50%	70%	70%	70%	Clinical opinion
	20%	20%	20%	20%	25%	30%	40%	70%	70%	70%	Scenario informed by trial data and clinical opinion
Ocrelizumab treatment effect (12-week 9-HPT)	0.52	0.52	0.52	0.52	0.52	0.52	0.52	0.52	0.52	0.52	ORATORIO study*, MRI active population
	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	ORATORIO study*, MRI active ≤50 subgroup
Disutility						-0.064	-0.064	-0.064	-0.064	-0.064	ORATORIO regression analysis EQ-5D
Number of months per year that disutility is applied						12					Clinical opinion

* Assumed to apply to all health states

Table 54 Incorporation of fatigue impact disutility

EDSS	0	1	2	3	4	5	6	7	8	9	Source
Proportion with clinically meaningful fatigue (BSC)	10%	25%	30%	35%	40%	50%	55%	60%	60%	70%	Clinical opinion
	10%	25%	50%	55%	60%	70%	70%	70%	70%	70%	Scenario informed by trial data and clinical opinion
Ocrelizumab treatment effect (MFIS >38)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ORATORIO study*, MRI active population
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ORATORIO study*, MRI active ≤50 subgroup
Disutility	-0.150	-0.150	-0.150	-0.150	-0.150	-0.150	-0.150	-0.150	-0.150	-0.150	ORATORIO regression analysis EQ-5D
Number of months per year that disutility is applied						12					Clinical opinion

* Assumed to apply to all health states

B.3.4.2 Mapping

Mapping was not required as EQ-5D was collected in the ORATORIO study and various other sources of EQ-5D values in MS were identified in the literature.

B.3.4.3 Health-related quality-of-life studies

A SR was conducted in March 2016 and updated in March 2017 to identify HRQoL studies appropriate for application in economic analysis in MS. A total of 51 studies were identified reporting health state utility values (HSUV) for patients with MS according to EDSS score (43 full publications and 8 abstracts). Of these, 28 studies were consistent with the NICE reference case; however, 4 of these only contained two EDSS data points and are not further described here. The 24 relevant studies with sufficient HRQoL data are summarised in Appendix H.

The majority of relevant studies included a mixed population of patients with RRMS, SPMS, and PPMS (n=20 studies). A further two studies considered patients with RRMS only, and only two studies included HSUV in RRMS, SPMS and PPMS patients separately, highlighting the paucity of data in PPMS patients. Of the two studies in PPMS specifically, only one reported data for the entire EDSS spectrum [106].

A clear pattern was observed across the evidence base of decreasing overall utility with increasing EDSS score, to the point of negative values corresponding to worse than death at EDSS 9.

Key differences between utilities from ORATORIO study and the literature

As shown below, the trajectory of decreasing utility values per EDSS score in the EQ-5D analysis of the ORATORIO study was consistent with the two other studies that reported data for a similar EDSS spectrum in PPMS.

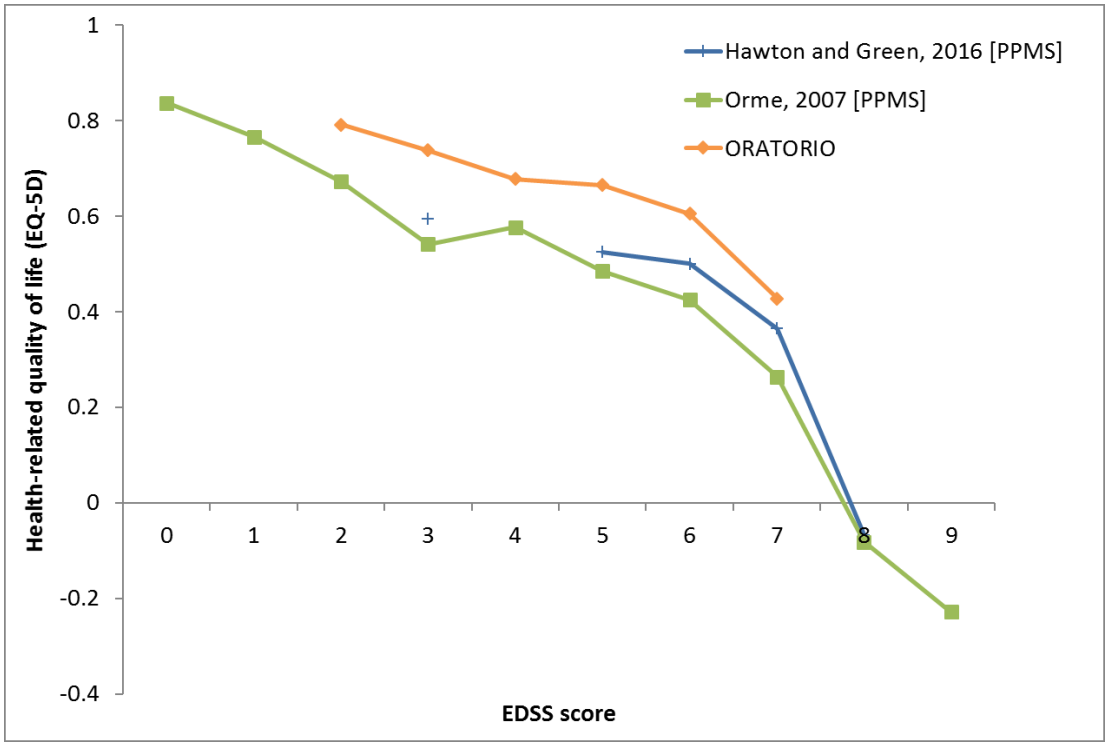
The health state utility values (HSUV) from the ORATORIO study, without adjustment for upper limb dysfunction or fatigue, are higher than those reported by the other two studies. This is likely due to the younger age at baseline in the ORATORIO study (44 years) compared with patients included in the MS Trust survey reported by Orme et al (51 years) or the study by Hawton and Green (51 years).

For the last 10 years there has been precedent in previous NICE appraisals in RRMS to use EQ-5D data elicited from patients via the MS Trust survey to supplement trial data [106]. To date this is the largest and most complete study among 2,048 patients with MS in the UK, and it includes separate utilities for patients with PPMS. Its limitations have been well described in previous NICE appraisals.

Utilities from the lower and upper end of the EDSS spectrum were derived from PPMS-specific decrements in Orme et al to supplement ORATORIO trial data (see Section B.3.4.5).

In scenario analysis the impact of using HSUV for PPMS entirely derived from the MS Trust survey (Orme et al, 2007 [106]) is explored.

Figure 31: Consistency of EDSS-dependent utility values



ORATORIO EQ-5D data without adjustment for upper limb dysfunction or fatigue

B.3.4.4 Adverse reactions

Disutilities associated with AEs and the duration of AEs were sourced from recent appraisals in RRMS or from the literature. For application of disutilities and costs, AEs were divided into serious and non-serious events in line with the approach taken in previous appraisals in RRMS. Information on IRRs was derived from the alemtuzumab appraisal and information on upper respiratory tract infection was derived from the daclizumab appraisal. Disutilities associated with malignancies was sourced from the literature using breast cancer as a proxy. Disutility for non-serious breast cancer was based on "recurrence free" health state and for serious breast cancer additional disutility was added assuming local recurrence [159].

Disutility applied in the model were calculated as a one off utility adjustment (loss), adjusted by the duration of the adverse event and expressed as utility adjustment on a yearly basis. The adjustments applied to utility were applied as a proportion of serious and non-serious events in

ORATORIO, with 20.4% of all adverse events being classified as serious and 79.6% as non-serious [129].

Table 55 Disutilities associated with adverse events

	Non-serious		Serious		
AE	**Disutility**	**Duration (days)**	**Disutility**	**Duration (days)**	**Average disutility***
Infusion related reaction	-0.011	5	-0.011	5	-0.0002
Malignancies	-0.176	365	-0.284	365	-0.1986
Upper respiratory tract infection	-0.2	7	-0.2	14	-0.0046

Source: manufacturer submission for daclizumab and alemtuzumab [159-161]

* It is assumed that for each type of AE 79.6% are non-serious and 20.4% are serious, based on average proportion of SAEs in ORATORIO.

B.3.4.5 Caregivers

Caregivers of patients with PPMS experience a substantial burden, particularly as patients become progressively more disabled. Previous NICE appraisals in RRMS have applied disutility for caregivers. A maximum utility decrement of 0.14 was derived from studies in Alzheimer's disease and adjusted according to time spent by friends and family caring for a person with MS at different EDSS health states as derived from the UK MS survey (Table 56). As would be expected, disutility is minimal for EDSS states 0–6 but once a patient becomes reliant on a wheelchair (EDSS 7) and particularly once a patient is bed-bound (EDSS 8-9), the impact on the caregiver's HRQoL increases significantly.

Table 56: Caregiver disutility by EDSS state

EDSS	Caregiver disutility
0	0.000
1	-0.001
2	-0.003
3	-0.009
4	-0.009
5	-0.020
6	-0.027
7	-0.053
8	-0.107
9	-0.140

Source: TA127 manufacturer submission [162]

B.3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

Trial-based HRQL data were used to derive HSUV for PPMS in the base case economic analysis. For the health states that lack trial data (EDSS 0-1 and 8–9), PPMS specific utility values from the regression analysis of the MS Trust survey were applied [106].

HRQoL impact per EDSS was assumed to be the same in ITT and subgroup populations.

In scenario analysis the impact of using HSUV for PPMS derived from the MS Trust survey (Orme et al, 2007), either entirely or for EDSS 0-1 and 7-9, is explored. Decrements for upper limb function and fatigue impact are applied as per the trial EQ-5D regression analysis.

Table 57: Health state utility values in economic analysis

	Base case		Scenario (All Orme et al)
EDSS	**Utility value**	**Source**	
0	0.837	Orme et al	0.837
1	0.766		0.766
2	0.791	ORATORIO	0.672
3	0.738		0.541
4	0.678		0.577
5	0.665		0.485
6	0.605		0.425
7	0.428		0.264
8	-0.082	Orme et al	-0.082
9	-0.228		-0.228

B.3.5 Cost and healthcare resource use identification, measurement and valuation

The total cost of care was estimated in the model as the sum of the following cost components:

1. Cost of disease modifying treatment consisting of drug acquisition, administration and monitoring costs for ocrelizumab

2. Cost of management of adverse events related to treatment

3. Cost of BSC, including healthcare, personal and social care costs, for each level of disability and associated dependency and needs in PPMS

The model assumes that the total cost of care will be reduced indirectly through disease modifying treatment because of delaying progression to more severe and hence costlier EDSS states. The model does not assume a direct impact of disease modifying treatment on the cost of BSC.

Costs of treatment, administration, monitoring and AE management are applied to the 'DMT treated' cohort until treatment discontinuation; after discontinuation, patients are assumed to receive BSC. No further pharmacological therapy is assumed other than treatment of symptoms.

For the comparison group, costs of care are those of BSC and are driven by model occupancy in each EDSS state, as described by natural history of PPMS. Management of adverse events related to placebo are also costed.

B.3.5.1 Intervention and comparators' costs and resource use

The drug acquisition costs for ocrelizumab are £19,160 per year at list price, and [redacted] per year at the net price approved by the DoH. Details about the proposed CAA price in PPMS is provided in the PAS appendix. The cost of symptomatic treatment as part of BSC is included under health state costs.

Resource use associated with administration and monitoring was based on the SmPC requirements and clinical expert opinion by a MS neurologist and MS nurse (Table 58). The first dose of ocrelizumab is administered as two separate infusions and therefore the administration costs for year 1 are higher than for subsequent years. Likewise, monitoring requirements for ocrelizumab in year 1 include MRI scanning prior to treatment initiation as per the marketing authorisation.

The costs of drug, administration, and monitoring were applied in the model each year to all patients that remained on treatment.

Table 58: Cost of drug administration and monitoring associated with ocrelizumab

Cost item	Cost (year 1)	Resource use (year 1)	Cost (year 2+)	Resource use (year 2+)	Source (year 2016/17)
Administration costs	£1,595.67	3x day case (£531.89 each)	£1,061.78	2x day case (£531.89 each)	AA30F. Medical care of patients with multiple sclerosis, with CC score 0-1. Day case.
	£19.41	Methylprednisolone for 1st 3 vials (£17.30) Chlorphenamine 10 mg QD (£1.95) Paracetamol 2x500 mg QD (£0.16)	£19.41	Methylprednisolone for 1st 3 vials (£17.30) Chlorphenamine 10 mg QD (£1.95) Paracetamol 2x500 mg QD (£0.16)	British National Formulary. MIMS.
	£1,615.08	Total	£1,081.19	Total	
Monitoring costs	£236.28	1 MRI for all patients, second MRI needed for 70% of patients to identify active T2 lesions (£146.03 per MRI)			Weighted average of RD01A and RD04Z. MRI Scan of one area, without contrast, 19 years and over and MRI scan of two or three areas, without contrast. Market research indicated that 30% of patients with PPMS have a recent MRI available (within last 12 months).
	£204.86	1 neurology visit	£152.30	1 neurology visit	WF01B and WF01A. Non-admitted Face to face attendance, first and follow up. 400 Neurology. Consultant led outpatient attendance.
	£55.00	1 MS nurse visit (£110 per hour, half hour visit)	£55.00	1 MS nurse visit (£110 per hour, half hour visit)	Hospital based nurse band 6.
	£6.74	2 full blood counts (£3.37 each)	£3.10	2 full blood counts	DAPS08. Phlebotomy
	£3.37	1 HBV test			
	£3.37	1 varicella zoster virus test			
	£558.58	Total	£293.86	Total	

Source: National schedule of reference costs; PSSRU unit costs [163, 164]

B.3.5.2 Health-state unit costs and resource use

A SR was conducted to identify evidence regarding the resource use and costs associated with the management and treatment of MS in the UK. Four studies were identified that reported resource use and costs by EDSS health states in line with the NICE reference case for health and social care (NHS and PSS) (Table 59). Only one of these reported costs by the full EDSS spectrum 0–9 [143], and another reported costs by EDSS 0-8 [109]. The other two studies reported cost data for pooled EDSS health states, EDSS 0–3 (mild disability), EDSS 4–6 (moderate disability), and EDSS 7–9 (severe disability). One study reported costs by disease type (RRMS, SPMS, and PPMS) [143], the others were based on mixed patient populations with MS. A clear trend was seen in the literature for increasing costs with increasing disability. In particular for patients with severe disability (EDSS 7–9) health and social care costs are high.

The publication by Tyas et al 2007 is based on the MS Trust survey, and contains the most complete and robust data on resource use and costs of MS by subtype in the UK. In line with the majority of previous NICE appraisals in MS this source was used to derive health state costs for PPMS [143].

The type of MS appears to have an impact on costs in the Tyas study, with SPMS having higher costs than RRMS but PPMS appearing to be associated with lower costs. The PPMS decrement suggested that zero or negative costs were incurred in patient with EDSS <6. Based on clinical advice sought, this was thought to be explained by PPMS patients in the past having been sub-optimally managed compared with RRMS as the lack of DMT treatment options resulted in patients not being seen as often by healthcare professionals. However, this situation is no longer considered to be representative of routine practice and costs were assumed to be driven primarily by level of disability and not disease type. Hence, the economic analysis utilises costs associated with RRMS obtained from Tyas et al 2007 [143].

The definition of what constitutes direct non-medical care, i.e. social care, was not consistent across studies or was unclear. What proportion of direct non-medical care in the MS Trust survey falls under the NHS and PSS perspective has often been a point of discussion by previous Committees in RRMS appraisals. The publication by Kobelt et al 2006 [118] is based on the MS survey like Tyas et al 2007, and provides more information on methodology and breakdown of items under direct non-medical costs. It indicates that around 25% of direct non-medical costs are professional social care in the community, as well as aids and home modifications likely borne by PSS. The rest is informal care costs (productivity loss by informal caregiver). In order to be consistent with the reference case, data from Tyas et al has been adjusted to include direct medical costs and 25% of direct non-medical costs in the base case economic model (inflated to 2016 using the PSSRU 2016

hospital & community health services inflation index) (Table 60). The impact of including or excluding all non-medical costs is explored in scenario analysis.

Further research was conducted by Roche to quantify the effect of disease severity (measured by EDSS) and type of MS (RRMS versus PPMS) on the cost of MS care from a NHS and PSS perspective (BOUNDS-MS study). A retrospective cross-sectional database was utilised which collected data from neurologists, MS patients and their carers during the years 2010-2016 (see Appendix N for more details about this research study). The main strength of the study was inclusion of resource use and cost data from recent years, hence it is expected to be reflective of today's management of MS in NHS/PSS. However, there were several key limitations of this study which precluded it from being applied in the base case. There was likely to be selection bias as only patients seen by a consulting neurologist were recruited into the study, as opposed to the general patient population reached through the national MS Survey. This resulted in small sample sizes and uncertain estimates in PPMS and at the higher end of the EDSS scale as these patients are generally no longer seen or treated by a neurologist. In addition, the number of resource use items and cost categories included in the study were more limited than the MS survey reported by Kobelt and Tyas, and this may have resulted in underestimation of the cost of management of MS. Due to these limitations this study is considered less robust than Tyas et al and its impact is explored in scenario analysis only.

Table 59: Summary of annual EDSS health state costs

	0	1	2	3	4	5	6	7	8	9	Reference
Health and social care*	510 (931)	455 (789)	358 (582)	334 (485)	501 (706)	503 (699)	652 (1210)	658 (953)	1660 (1723)		[109]
Inpatient	70 (25-229)				54 (17-146)			1838 (758, 5191)			[119]
Outpatient	346 (200-754)				698 (435, 1103)			435 (106, 986)			
Consultations	578 (404, 838)				923 (745, 1192)			826 (334, 1609)			
Investigations	82 (56, 123)				74 (49, 109)			29 (0, 147)			
MS treatments	5369 (4494, 6270)				5499 (4682, 6351)			2098 (0, 10491)			
Prescribed & OTC medications	269 (205, 378)				851 (685, 1398)			832 (535, 1101)			
Total direct medical costs	6714 (5760, 7717)				8101 (7153, 9072)			6059 (2907, 10735)			
Investments/ modifications	48 (16, 226)				1457 (1127, 1761)			2989 (1168, 4433)			
Professional care	0				950 (6885, 11462)			16430 (16763, 54939)			
Informal care	1865 (789, 5321)				7893 (6115, 10237)			21824 (9957, 34697)			
Total direct non-medical costs	1913 (811, 5038)				10299 (8170, 12772)			41242 (17653, 59378)			
Direct healthcare costs**	5400				7000			7700			[118]
Services/ investments**	400				1200			9000			
Informal care**	1100				7000			25200			
Direct medical costs, RRMS	250 (-3623, 4123)	85 (-1678, 1849)	213 (-1489, 1915)	850 (-1575, 3275)	806 (-927, 2539)	1419 (-195, 3032)	2162 (492, 3832)	6583 (4632, 8534)	10761 (8665, 12857)	15121 (9912, 20330)	[143]
Direct medical costs, SPMS	530	365	493	1130	1086	1699	2442	6863	11041	15401	
Direct medical costs, PPMS	0†	0†	0†	0†	0†	0†	645	5066	9244	13604	
Direct non-medical costs	2536 (-1745, 6817)	3462 (886, 6039)	4414 (1836, 6991)	6212 (3103, 9321)	4028 (1439, 6617)	6333 (3709, 8958)	6580 (3956, 9204)	10808 (7895, 13721)	15339 (12369, 18309)	10161 (4598, 15725)	

Amounts in table are in GBP (£).

* Costs reported on a 6-monthly basis not annual.

** Read from graph using WebPlotDigitizer software

† Negative costs constrained to zero.

Table 60: Disease management costs applied in the economic analysis

EDSS state	Cost (£) - NHS	Cost (£) – PSS*	Total cost (£), NHS and PSS perspective
0	313.72	795.59	1,109.31
1	106.66	1,086.10	1,192.76
2	267.29	1,384.76	1,652.05
3	1,066.65	1,948.82	3,015.47
4	1,011.43	1,263.66	2,275.09
5	1,780.67	1,986.78	3,767.46
6	2,713.05	2,064.27	4,777.32
7	8,260.86	3,390.68	11,651.54
8	13,503.74	4,812.14	18,315.88
9	18,975.00	3,187.70	22,162.71

Source: Tyas et al, 2007 [143]. Up-inflated to 2016/17 using healthcare inflation index published in PSSRU 2017.
* 25% of total non-medical costs was assumed to fall under PSS perspective

B.3.5.3 Adverse reaction unit costs and resource use

The cost of treating AEs, consistent with disutilities and durations of AEs, was sourced from the alemtumab and daclizumab appraisals in RRMS [160, 161]. Resource use and cost associated with malignancies was derived from the literature using breast cancer as a proxy. Non-serious malignancies were assumed to receive no chemotherapy and serious malignancies were assumed to be treated with chemotherapy [165].

Cost were not inflated from the year these estimates were reported as the difference is assumed to have a negligible impact on the overall results.

Table 61: Summary of AE management costs

	Non-serious		Serious		
AE	**Cost (£)**	**Resource use**	**Cost (£)**	**Resource use**	**Average cost***
Infusion related reaction	0.00	None	65.00	1 GP consultation	13.26
Malignancies	10,768	GP, nurse, Hospitalisation, Radiotherapy	22,980	GP, nurse, Hospitalisation, Chemotherapy, Radiotherapy	13,328
Upper respiratory tract infection	65.00	1 GP consultation	65.00	1 GP consultation	65.00

Source: manufacturer submission for daclizumab and alemtuzumab [160, 161] [165]
* It is assumed that for each type of AE 79.6% are non-serious and 20.4% are serious, based on average proportion of SAEs in ORATORIO.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

The list of variables used in the economic model and the measurement of uncertainty around them is presented below. When standard errors are not reported in the literature a standard assumption of 20% of the mean is used.

Table 62: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Demographics			
Age	44 years	Log Normal	B.3.3
Gender (male)	51%	Beta	
Baseline EDSS distribution	ORATORIO (Table 39)	Dirichlet	
Model structure			
Time horizon	50 years	Fixed	B.3.2
Cycle length	Yearly		
Discount rate for costs and outcomes	3.5%		
Half cycle correction	Yes		
Transition probabilities			
PPMS matrices	Values based on MSBase datasets (Table 43)	Dirichlet	B.3.3.2
Mortality multipliers	Values based on Pokorski et al (Table 49)	Log Normal	B.3.3.4
Treatment effect			
Disability progression	Values derived from ORATORIO for CDP-12	Lognormal for CIs from ORATORIO Scenario analysis	B.3.3.2
Upper limb function	Values derived from ORATORIO for 9-HPT	Lognormal for CIs from ORATORIO Scenario analysis	B.3.4.1
Fatigue	Values derived from ORATORIO for MFIS	Lognormal for CIs from ORATORIO Scenario analysis	B.3.4.1
All-cause discontinuation	Values based on Gompertz	Beta	B.3.3.5
Utilities			
Patient utility by EDSS	ORATORIO (ITT) (Table 52)	Cholesky covariance matrix	B.3.3 and Appendix D
Upper limb impairment disutility		Cholesky covariance matrix	B.3.4.1
Fatigue disutility		Cholesky covariance matrix	B.3.4.1
Caregiver disutility	Values based on previous RRMS appraisals (Table 56)	Beta	B.3.4.5
Resource use and cost			
EDSS health states	Values derived from Tyas et al (Table 60)	Gamma	B.3.5.2
Drug acquisition	Drug-specific	Fixed	B.3.5.1
Drug administration	Drug-specific	Gamma	B.3.5.1
Monitoring	Drug-specific	Gamma	B.3.5.1

AE management	Drug-specific	Fixed	B.3.5.3

B.3.6.2 Assumptions

Assumptions made in the base case are summarised below with justifications.

Table 63: List of model assumptions

Assumption	Justification
The population in ORATORIO is representative of UK population with early and active PPMS	The ORATORIO studies included 5 UK trial sites across the country. The randomised control period of the ORATORIO study ran from 2011 - 2015. It is therefore considered reflective of patients with early PPMS with inflammatory activity in the UK today.
Treatments effect is applied to EDSS progression but not regression	Treatment effect is only applied to EDSS progression; i.e. active treatment slows disease progression. This is in line with previous appraisals in RRMS.
Patients with PPMS can improve EDSS (backward transitions)	EDSS improvements are observed in the raw data from the MSBase registry. Clinical opinion suggests that small improvements may occur at the lower end of the EDSS scale, but large improvements or improvements at the higher end of the scale would not be plausible in PPMS. Scenario analysis is included with the MSBase transition matrices constrained to allow progression only. No treatment effect is applied to EDSS improvements.
Upper limb function is not adequately captured by EDSS	Upper limb function is increasingly recognized as an important disease facet and component of disability in MS [56, 63]. Regression analysis of EQ-5D data in the ORATORIO study indicated that clinically meaningful upper limb dysfunction (as measured by 20% increase in 9-HPT sustained for 12 weeks) impacted EQ-5D independent of EDSS. It was therefore considered valid to apply disutilities and treatment effect of ocrelizumab on slowing of upper limb impairment. Upper limb impairment could have implications for the cost of disease management, but no data is available in the literature. The full benefits of preserving upper limb function in terms of utilities and costs are therefore likely under-estimated in the economic analysis.
Impact of fatigue on functioning is not adequately captured by EDSS	Fatigue is a common symptom of MS and its impact on physical, cognitive, and psychosocial functioning is increasingly recognized [166]. Regression analysis of EQ-5D data in the ORATORIO study indicated that clinically meaningful fatigue (as measured by MFIS score >38) impacted EQ-5D independent of EDSS. It was therefore considered valid to apply disutilities and treatment effect of ocrelizumab on reducing fatigue.
No direct treatment effect on mortality	Literature has demonstrated that the risk of death is primarily dependent on the level of disability (EDSS). The duration of clinical trials in MS is not long enough to detect a direct impact of treatment on mortality. Instead, treatment influences mortality indirectly by slowing of disability progression. This approach is in line with previous RRMS appraisals.
Increasing rate of all-cause treatment withdrawal	Extrapolating an increasing rate of long-term all-cause discontinuation was supported by model fit statistics for the Gompertz function, and by clinical opinion. Clinical opinion considered patient expectations to play a key role in treatment withdrawal. The benefits of slowing disability progression may not

	appear immediately tangible to patients as the natural history of PPMS is higly variable on an individual patient level. Therefore, the real world treatment withdrawal rates are assumed to be higher than those observed during the trial.
No treatment waning for ocrelizumab	Long-term waning of treatment effect with DMTs has not been definitively proven nor disproven, and remains an area of debate. Open label extension data of up to four years is available for ocrelizumab in RRMS and demonstrates sustained treatment effect across CDP and MRI outcomes (see Appendix M). Open label extension data from ORATORIO in PPMS is yet to read out but there is no reason to believe the results are different from RRMS. Treatment waning is biologically implausible with ocrelizumab as it generates negligible neutralising antibodies, unlike other DMTs used in RRMS (see Section B.2.10.8).
Cost of disease management by health state	The cost of disease management per EDSS health state was based on estimates derived from RRMS patients. This was considered appropriate as application of the reported PPMS decrement would have resulted in negative costs for EDSS 0-5, which clinical experts deemed implausible. Clinical opinion supported the assumption that disease management costs are driven by level of disability (EDSS) and not by disease type.
Drug related AEs	Many of the reported AEs in ORATORIO occurred at similar or higher frequency in the placebo arm than ocrelizumab arm, and were considered to be disease-related symptoms. In order to avoid double-counting of costs and disutilites already accounted for in the EDSS health states, only AEs with considerably higher frequency in the ocrelizumab arm were included in the model. AEs were assumed to be similar in the ITT, MRI active, and MRI active ≤50 populations.

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The economic analysis indicates that [redacted] QALYs are accrued over a lifetime with ocrelizumab treatment, compared with [redacted] QALYs with BSC. The main benefit of disease modifying treatment is not in extending life but in improving the quality of life, as expressed by the incremental QALY gain of [redacted]

The base case analysis indicates an ICER of [redacted] at list price and £88,214 at DoH-approved PAS price, respectively (Table 64 and Table 65)

Results based on the proposed commercial arrangement for PPMS (referred to as ocrelizumab CAA price) are presented in the PAS appendix, and indicate an ICER of [redacted].

Table 64: Incremental analysis, base case MRI active (based on ocrelizumab list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 65: Incremental analysis, base case MRI active (based on ocrelizumab PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	88,214	88,214

Table 66: Probabilistic results, base case MRI active (based on ocrelizumab list price)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
BSC	[redacted]	[redacted]	-	-	-	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 67: Probabilistic results, base case MRI active (based on ocrelizumab PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
BSC	[redacted]	[redacted]	-	-	-	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	93,949	93,949

B.3.8 Sensitivity analyses

B.3.8.1 Deterministic sensitivity analysis

For one-way sensitivity analysis parameters were varied between the lower and upper boundary of the 95% confidence/credible interval or by 20% of the mean if a distribution was not available (values available in cost-effectiveness model). The ten parameters most sensitive to change were included in the tornado diagrams (Figure 32 and

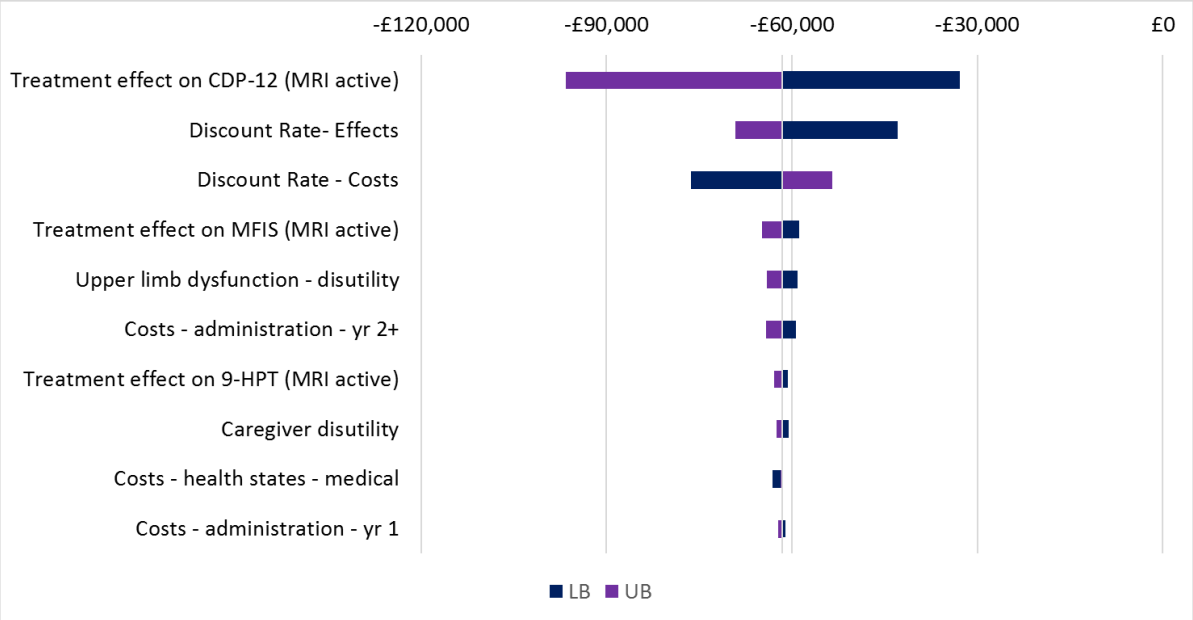
Figure 33).

Results were most sensitive to changes in the treatment effect on confirmed disability progression and discount rate for costs and effects, which is to be expected for a chronic disease such as PPMS in which the costs and benfits are accrued over a lifetime. Variation in the cost of drug administration in years 2+, treatment effect on fatigue, and distutillity for upper limb impairment also influenced cost-effectiveness results, but to a lesser degree.

Other parameters had relatively little impact on the overall results.

Figure 32 One way sensitivity analysis for ocrelizumab versus BSC (NMB, list price)

Figure 33 One way sensitivity analysis for ocrelizumab versus BSC (NMB, PAS price)



B.3.8.2 Probabilistic sensitivity analysis

All model variables that had a distribution assigned are presented in Table 62. Probabilistic sensitivity analysis was conducted with 1,000 iterations to determine the uncertainty surrounding the base-case ICERs.

The probabilistic results are broadly similar - albeit higher – than the deterministic results, lending support to the overall conclusions (Table 66 and Table 67).

At list price or DoH-approved PAS price there is 0% probability that ocrelizumab is cost-effective at a £30k ICER threshold (Figure 34 and

Figure 37).

The incremental cost-effectiveness planes indicate that ocrelizumab is mostly situated in the north-east quadrant, meaning it is more efficacious and costlier than BSC. Most of the simulations are located above the ICER threshold of £30,000 per QALY at the DoH-approved PAS price. A minority of simulations is situated in the north-west quadrant, meaning less efficacious and costlier than BSC (Figure 35, Figure 36, Figure 38, and Figure 39).

Based on the proposed CAA for ocrelizumab in PPMS the probability of being cost-effective at the ICER threshold of £30,000 per QALY increases to [redacted] (see PAS appendix). The probabilistic ICER based on the proposed CAA is [redacted] (see PAS appendix).

Figure 34 Cost-effectiveness acceptability curve for ocrelizumab versus BSC (list price)

Figure 35 Cost-effectiveness plane for ocrelizumab and BSC (list price)

Figure 36 Incremental cost-effectiveness plane for ocrelizumab versus BSC (list price)

Figure 37 Cost-effectiveness acceptability curve for ocrelizumab and BSC (PAS price)

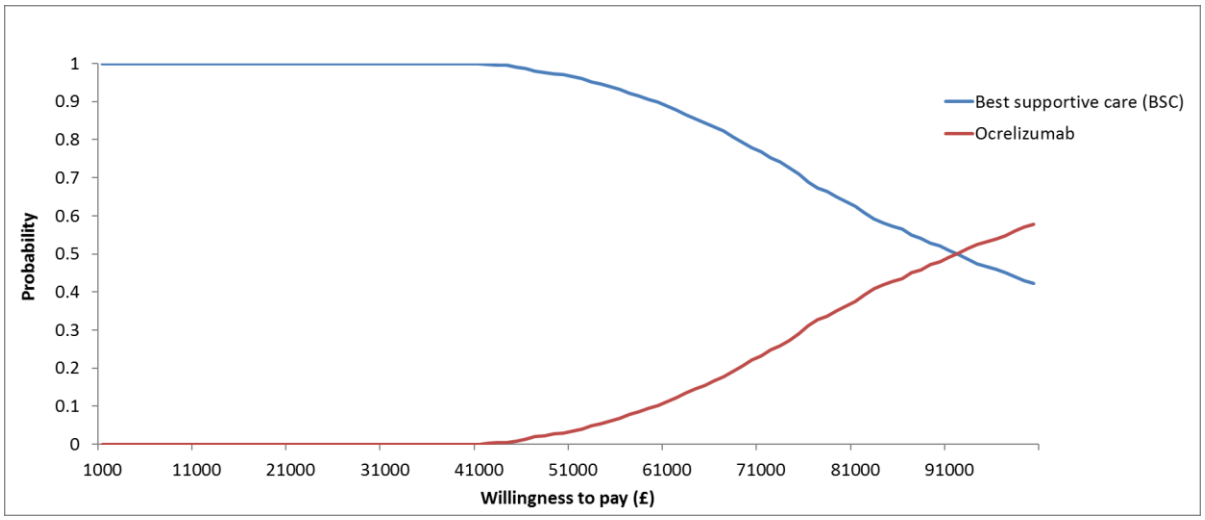


Figure 38 Cost-effectiveness plane for ocrelizumab and BSC (PAS price)

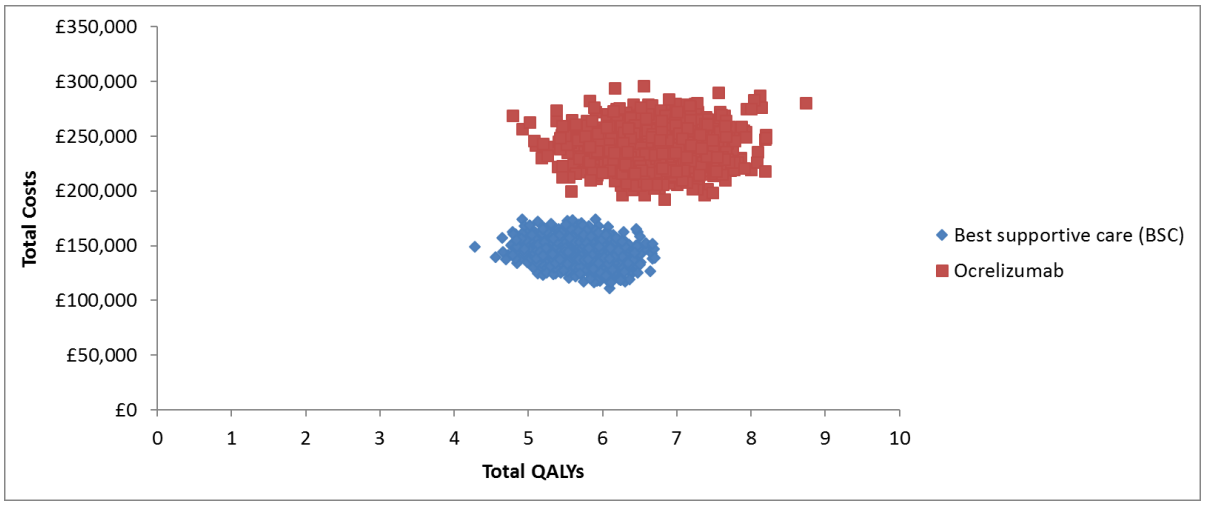
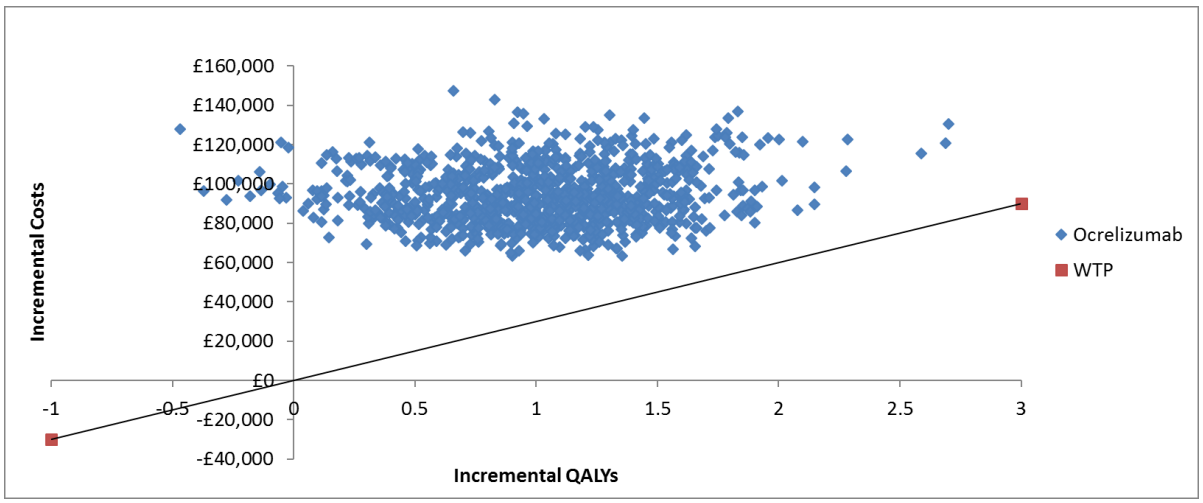


Figure 39 Incremental Cost-effectiveness Plane for ocrelizumab versus BSC (PAS price)



B.3.8.3 Scenario analysis

Scenario analysis was performed to test the sensitivity of the economic model to different model assumptions or input sources (Table 68 and Table 69). This included application of 5% and 10% acceleration factors to the MSBase natural history to mimic faster progression in MRI active disease, allowing progression-only transition probabilities in PPMS, and applying the natural history matrix for younger patients (50 year or younger) to the MRI active population. All of these scenarios lowered the ICER and the base case can therefore be considered conservative.

Efficacy was varied through application of CDP-24 and extended control period data. Results were sensitive to these adjustment and there was in particular a large difference between CDP-24 data from the controlled treatment period and the extended control period. CDP-12 is an equally robust measure of disability progression in PPMS as CDP-24, as relapses are rare in PPMS and the issue of confounding due to relapses that take long to resolve is not relevant. It was also the primary endpoint of ORATORIO and is therefore considered more statistically robust.

The cost-effectiveness results were sensitive to scenarios that resulted in variation of the treatment duration. A more stringent stopping rule (EDSS ≥7) and assumption of real world-like discontinuation improved the cost-effectiveness considerably.

The results were relatively insensitive to changes in the proportion of patients per EDSS health state who are assumed to suffer from upper limb impairment and fatigue. Application of utility values from Orme et al 2007 increases the ICER considerably, likely due to the limited ability to accrue a QALY gain as the utility values reported by Orme et al 2007 were generally lower than those observed in the ORATORIO study. The patients included in Orme et al 2007 likely reflect a population at a later disease course in terms of age and EDSS than the patients included in ORATORIO who reflect early disease. The ICER also increases if the impact of upper limb impairment and fatigue on HRQoL is excluded from consideration.

Finally, a combination of scenarios that adjusts natural history of PPMS to reflect faster progression and no EDSS improvement, and constrain the long-term costs of ocrelizumab by way of shorter treatment duration, result in ocrelizumab being cost-effective compared with BSC in the MRI active population based on the proposed CAA (see PAS appendix).

Table 68 Results of scenario analysis in MRI active population, based on list price

	Ocrelizumab		BSC		
Scenarios	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**ICER**

Base case MRI active	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natural history					
Acceleration factor set to 1.05 (MSBase matrix)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acceleration factor set to 1.1 (MSBase matrix)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natural history set to MSBase ≤50 for MRI active population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-only MSBase matrix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy					
Efficacy set to CDP-24 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extended control period CDP-12 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extended control period CDP-24 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs					
Include relapses (cost, disutilities, and treatment effect)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude direct non-medical costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Set health state costs to BOUNDS-MS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-term discontinuation set to real world scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stopping rule set to EDSS 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stopping rule set to EDSS 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utilities					
Set patient utilities to Orme et al	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of upper limb dysfunction per EDSS (trial based)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of fatigue per EDSS (trial based)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude upper limb impairment from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude fatigue impact from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Combination					
Progression-only MSBase matrix, 5% acceleration factor, real world long-term discontinuation, and stopping rule at EDSS 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 69 Results of scenario analysis in MRI active population, based on PAS price

	Ocrelizumab		BSC		
Scenarios	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**ICER**
Base case MRI active	[redacted]	[redacted]	[redacted]	[redacted]	**£88,214**
Natural history					

Acceleration factor set to 1.05 (MSBase matrix)	[redacted]	[redacted]	[redacted]	[redacted]	£85,391
Acceleration factor set to 1.1 (MSBase matrix)	[redacted]	[redacted]	[redacted]	[redacted]	£82,864
Natural history set to MSBase ≤50 for MRI active population	[redacted]	[redacted]	[redacted]	[redacted]	£81,202
Progression-only MSBase matrix	[redacted]	[redacted]	[redacted]	[redacted]	£76,914
Efficacy					
Efficacy set to CDP-24 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	£97,625
Extended control period CDP-12 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	£91,176
Extended control period CDP-24 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	£88,214
Costs					
Include relapses (cost, disutilities, and treatment effect)	[redacted]	[redacted]	[redacted]	[redacted]	£88,047
Exclude direct non-medical costs	[redacted]	[redacted]	[redacted]	[redacted]	£90,346
Set health state costs to BOUNDS-MS data	[redacted]	[redacted]	[redacted]	[redacted]	£87,497
Long-term discontinuation set to real world scenario	[redacted]	[redacted]	[redacted]	[redacted]	£85,125
Stopping rule set to EDSS 7	[redacted]	[redacted]	[redacted]	[redacted]	£87,619
Stopping rule set to EDSS 9	[redacted]	[redacted]	[redacted]	[redacted]	£90,817
Utilities					
Set patient utilities to Orme et al	[redacted]	[redacted]	[redacted]	[redacted]	£98,214
Proportion of upper limb dysfunction per EDSS (trial based)	[redacted]	[redacted]	[redacted]	[redacted]	£89,132
Proportion of fatigue per EDSS (trial based)	[redacted]	[redacted]	[redacted]	[redacted]	£88,280
Exclude upper limb impairment from model	[redacted]	[redacted]	[redacted]	[redacted]	£98,038
Exclude fatigue impact from model	[redacted]	[redacted]	[redacted]	[redacted]	£95,696
Combination					
Progression-only MSBase matrix, 5% acceleration factor, real world long-term discontinuation, and stopping rule at EDSS 7	[redacted]	[redacted]	[redacted]	[redacted]	£69,758

B.3.9 Subgroup analysis

The subgroup analysis in MRI active ≤50 indicates that [redacted] QALYs are accrued over a lifetime with ocrelizumab treatment, compared with [redacted] QALYs with BSC. The main benefit of disease modifying treatment is not in extending life but in improving the quality of life, as expressed by the incremental QALY gain of [redacted] This is a larger magnitude of benefit than in the MRI active population.

The base case analysis in MRI active ≤50 indicates an ICER of [redacted] at list price and £54,486 at DoH-approved PAS price, respectively (Table 70 and Table 71).

Results based on the proposed CAA for ocrelizumab in PPMS are presented in the PAS appendix, and indicate an ICER of [redacted].

Table 70: Incremental analysis, MRI active ≤50 subgroup (based on ocrelizumab list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 71: Incremental analysis, MRI active ≤50 subgroup (based on ocrelizumab PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	54,486	54,486

Table 72: Probabilistic results, MRI active ≤50 subgroup (based on ocrelizumab list price)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
BSC	[redacted]	[redacted]	-	-	-	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 73: Probabilistic results, MRI active ≤50 subgroup (based on ocrelizumab PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
BSC	[redacted]	[redacted]	-	-	-	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	61,241	61,241

B.3.9.1 Deterministic sensitivity analysis in subgroup MRI active ≤50

Parameters were varied between the lower and upper boundary of the 95% confidence/credible interval or by 20% of the mean if a distribution was not available (values available in cost-effectiveness model). The ten parameters most sensitive to change were included in the tornado diagrams (Figure 40 and

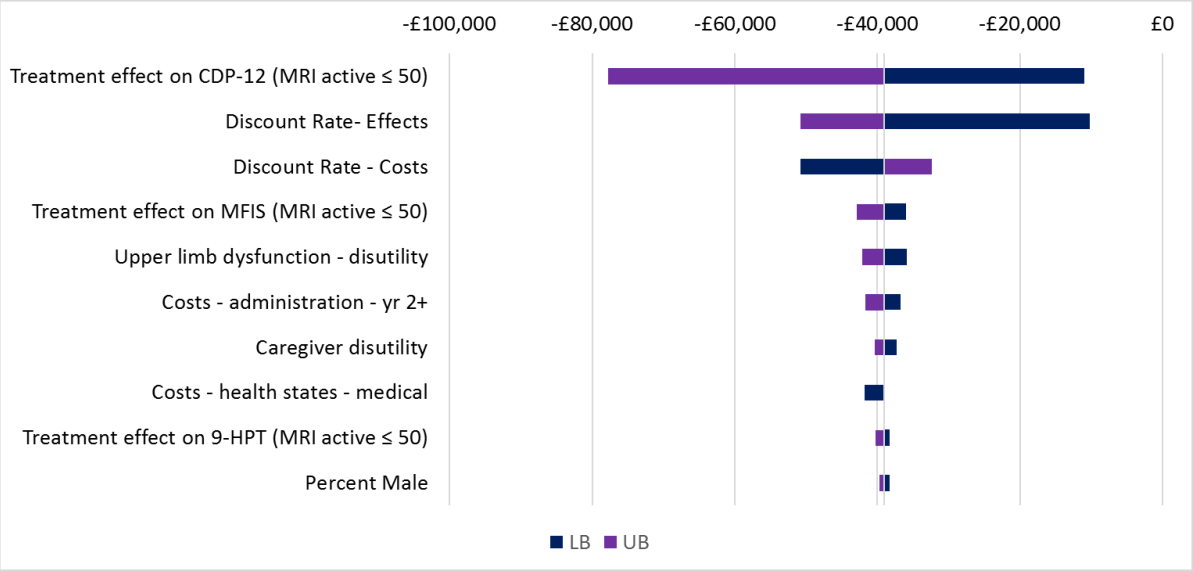
Figure 41).

Similar to the results in the MRI active population, results in the MRI active ≤50 subgroup were most sensitive to changes in the treatment effect on confirmed disability progression and discount rate for costs and effects, which is to be expected for a chronic disease such as PPMS in which the costs and benfits are accrued over a lifetime. Variation in the cost of drug administration in years 2+, treatment effect on fatigue, and distutillity for upper limb impairment also influenced cost-effectiveness results, but to a lesser degree.

Other parameters had relatively little impact on the overall results.

Figure 40 One way sensitivity analysis in MRI active ≤50 subgroup (list price)

Figure 41 One way sensitivity analysis in MRI active ≤50 subgroup (PAS price)



B.3.9.2 Probabilistic sensitivity analysis in subgroup MRI active ≤50

The probabilistic results are broadly similar - albeit higher - to the deterministic results, lending support to the overall conclusions Table 72 and Table 73).

At list price or DoH-approved PAS price there is 0% probability that ocrelizumab is cost-effective at a £30k ICER threshold (Figure 42 and

Figure 45).

The incremental cost-effectiveness planes indicate that ocrelizumab is mostly situated in the north-east quadrant, meaning it is more efficacious and costlier than BSC. Most of the simulations are located above the ICER threshold of £30,000 per QALY at the DoH-approved PAS price. One or two simulations out of a thousand are situated in the north-west quadrant, meaning less efficacious and costlier than BSC (Figure 43, Figure 44, Figure 46, and Figure 47).

Based on the proposed CAA for ocrelizumab in PPMS, the probability of being cost-effective at the ICER threshold of £30,000 per QALY increases to [redacted] (see PAS appendix). The probabilistic ICER based on the proposed CAA is [redacted] (see PAS appendix).

Figure 42 Cost-effectiveness acceptability curve for ocrelizumab versus BSC in MRI active ≤50 subgroup (list price)

Figure 43 Cost-effectiveness plane for ocrelizumab and BSC in MRI active ≤50 subgroup (list price)

Figure 44 Cost-effectiveness plane for ocrelizumab versus BSC in MRI active ≤50 subgroup (list price)

Figure 45 Cost-effectiveness acceptability curve for ocrelizumab versus BSC in MRI active ≤50 subgroup (PAS price)

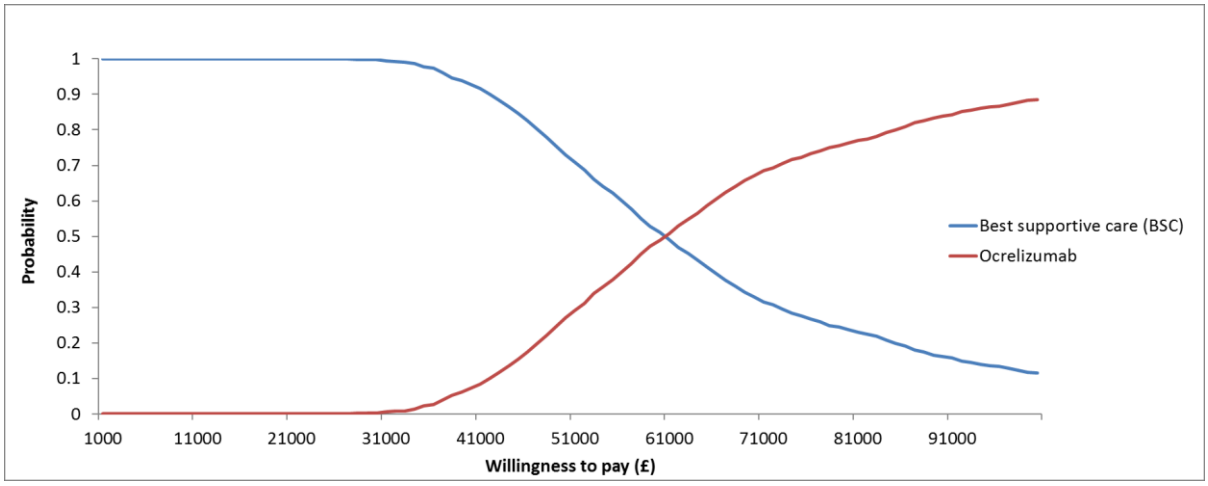


Figure 46 Cost-effectiveness plane for ocrelizumab and BSC in MRI active ≤50 subgroup (PAS price)

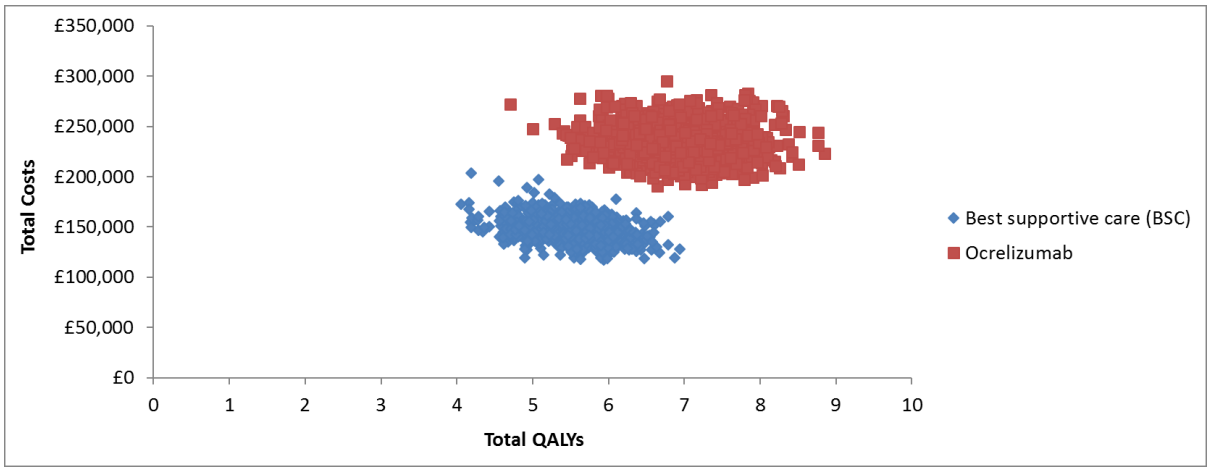
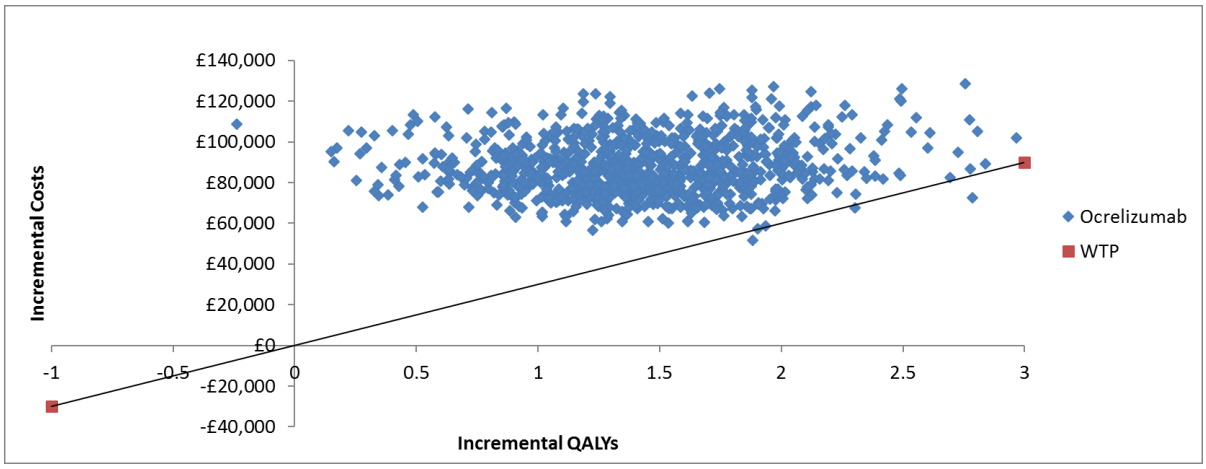


Figure 47 Cost-effectiveness plane for ocrelizumab versus BSC in MRI active ≤50 subgroup (PAS price)



B.3.9.3 Scenario analysis

Scenario analysis was performed to test the sensitivity of the economic model to different model assumptions or input sources (Table 74 and Table 75). This included application of the average age at baseline in the MRI active ≤50 subgroup in ORATORIO, 5% and 10% acceleration factors to the MSBase ≤50 natural history to mimic faster progression in MRI active disease, and allowing progression-only transition probabilities in PPMS. All of these scenarios lowered the ICER and the base case can therefore be considered conservative.

Efficacy was varied through application of CDP-24 and extended control period data. Results were relatively insensitive to these adjustment and contrary to the MRI active population the results were improved with CDP-24. CDP-12 is an equally robust measure of disability progression in PPMS as CDP-24, as relapses are rare in PPMS and the issue of confounding due to relapses that take long to resolve is not relevant. It was also the primary endpoint of ORATORIO and is therefore considered more statistically robust.

The cost-effectiveness results were sensitive to scenarios that resulted in variation of the treatment duration. A more stringent stopping rule (EDSS ≥7) and assumption of real world-like discontinuation improved the cost-effectiveness considerably.

The results were relatively insensitive to changes in the proportion of patients per EDSS health state who are assumed to suffer from upper limb impairment and fatigue. Application of utility values from Orme et al 2007 increases the ICER considerably, likely due to the limited ability to accrue a QALY gain as the utility values reported by Orme et al 2007 were generally lower than those observed in the ORATORIO study. The patients included in Orme et al 2007 likely reflect a population at a later disease course in terms of age and EDSS than the patients included in ORATORIO who reflect early disease, particularly so in the subgroup aged 50 or younger. The ICER also increases if the impact of upper limb impairment and fatigue on HRQoL is excluded from consideration.

At the proposed CAA price, ocrelizumab is cost-effective in all scenarios (see PAS appendix).

Table 74 Results of scenario analysis in MRI active ≤50 subgroup, based on list price

	Ocrelizumab		BSC		
Scenarios	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**ICER**
Base case MRI active ≤50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline characteristics					
Baseline age set to 40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natural history					

Acceleration factor set to 1.05 (MSBase matrix ≤50)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acceleration factor set to 1.1 (MSBase matrix ≤50)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-only MSBase matrix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy					
Efficacy set to CDP-24 (MRI active ≤50)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extended control period CDP-12 (MRI active ≤50)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extended control period CDP-24 (MRI active ≤50)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs					
Include relapses (cost, disutilities, and treatment effect)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude direct non-medical costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Set health state costs to BOUNDS-MS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Long-term discontinuation set to real world scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stopping rule set to EDSS 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stopping rule set to EDSS 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utilities					
Set patient utilities to Orme et al	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of upper limb dysfunction per EDSS (trial based)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of fatigue per EDSS (trial based)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude upper limb impairment from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude fatigue impact from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Combination					
Progression-only MSBase matrix, 5% acceleration factor, real world long-term discontinuation, and stopping rule at EDSS 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 75 Results of scenario analysis in MRI active ≤50 subgroup, based on PAS price

	Ocrelizumab		BSC		
Scenarios	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**ICER**
Base case MRI active ≤50	[redacted]	[redacted]	[redacted]	[redacted]	**£54,486**
Baseline characteristics					
Baseline age set to 40 years	[redacted]	[redacted]	[redacted]	[redacted]	£51,571
Natural history					
Acceleration factor set to 1.05 (MSBase matrix ≤50)	[redacted]	[redacted]	[redacted]	[redacted]	£52,506

Acceleration factor set to 1.1 (MSBase matrix ≤50)	[redacted]	[redacted]	[redacted]	[redacted]	£50,739
Progression-only MSBase matrix	[redacted]	[redacted]	[redacted]	[redacted]	£47,722
Efficacy					
Efficacy set to CDP-24 (MRI active ≤50)	[redacted]	[redacted]	[redacted]	[redacted]	£53,086
Extended control period CDP-12 (MRI active ≤50)	[redacted]	[redacted]	[redacted]	[redacted]	£55,944
Extended control period CDP-24 (MRI active ≤50)	[redacted]	[redacted]	[redacted]	[redacted]	£51,739
Costs					
Include relapses (cost, disutilities, and treatment effect)	[redacted]	[redacted]	[redacted]	[redacted]	£54,389
Exclude direct non-medical costs	[redacted]	[redacted]	[redacted]	[redacted]	£56,516
Set health state costs to BOUNDS-MS data	[redacted]	[redacted]	[redacted]	[redacted]	£53,076
Long-term discontinuation set to real world scenario	[redacted]	[redacted]	[redacted]	[redacted]	£52,346
Stopping rule set to EDSS 7	[redacted]	[redacted]	[redacted]	[redacted]	£53,858
Stopping rule set to EDSS 9	[redacted]	[redacted]	[redacted]	[redacted]	£55,883
Utilities					
Set patient utilities to Orme et al	[redacted]	[redacted]	[redacted]	[redacted]	£60,726
Proportion of upper limb dysfunction per EDSS (trial based)	[redacted]	[redacted]	[redacted]	[redacted]	£54,874
Proportion of fatigue per EDSS (trial based)	[redacted]	[redacted]	[redacted]	[redacted]	£54,755
Exclude upper limb impairment from model	[redacted]	[redacted]	[redacted]	[redacted]	£59,357
Exclude fatigue impact from model	[redacted]	[redacted]	[redacted]	[redacted]	£58,542
Combination					
Progression-only MSBase matrix, 5% acceleration factor, real world long-term discontinuation, and stopping rule at EDSS 7	[redacted]	[redacted]	[redacted]	[redacted]	£42,694

B.3.10 Validation

Validation of cost-effectiveness analysis

Two separate quality checks of the economic model were performed by external agencies. This included review of the implementation of calculations and testing of extreme values. Any modelling errors identified were corrected before submission.

The face validity of the model structure, inputs, and results was tested at an advisory board with clinical and health economic experts from the UK who are familiar with PPMS. The

experts confirmed the face validity of the economic analysis and supported broadening the definition of disability by including the impact of upper limb dysfunction and fatigue.

Cross-comparison of economic results between NICE appraisals was not possible due to lack of precedents in PPMS. One other economic analysis in PPMS has been published by the Institute for Clinical and Economic Review in the US [140]. This economic analysis is different from ours in a number of aspects:

i) it utilises ITT data from the ORATORIO study;

ii) it applies natural history based on SPMS patients from the London Ontario registry which does not allow EDSS improvements;

iii) it does not incorporate upper limb function and fatigue, and

iv) it applies utilities based on SPMS sourced from literature and US specific costs.

When applying ITT data, MSBase natural history allowing only progression, utilities from Orme et al 2007, and excluding upper limb function and fatigue in our economic model for comparison, the QALY gains are similar to the published estimates (Table 76).

Table 76 Cross-validation of cost effectiveness models in PPMS

	Roche model*, QALYs	US model, QALYs
BSC	[redacted]	2.75
Ocrelizumab	[redacted]	3.33
Incremental	[redacted]	0.58

* Assumptions set to resemble assumptions in US model: ITT data, MSBase allowing only progression, utilities from Orme et al 2007, and excluding disutilities for upper limb impairment and fatigue.

B.3.11 Interpretation and conclusions of economic evidence

A de novo economic analysis was performed to assess the cost-effectiveness of ocrelizumab compared to BSC in PPMS. The design of the economic model was based on the established RRMS models used in previous NICE appraisals in RRMS, with additional features bolted on to capture disease facets that are unique to, or more prominent in, PPMS.

Inclusion of disutilities associated with upper limb impairment and fatigue increases the QALY gain for ocrelizumab by 11% and 8% respectively in the MRI active population, and by 7% for each aspect in the MRI active ≤50 subgroup. These aspects contribute to preserving patients' independence and are important to consider when assessing the benefit of a disease modifying therapy in a disease area of high unmet need. The cost of upper limb

impairment and the cost of the impact of fatigue on physical, cognitive, and psychosocial functioning are not included in the model due to lack of data, and the ICER estimates may therefore be seen as conservative estimates.

A key strength of the economic analysis presented here was the use of clinical data from the ORATORIO study, such as the EQ-5D regression analysis. Another key strength was that analyses were conducted in populations to match the marketing authorization and identify a subset of patients who respond best to ocrelizumab. Subgroup data was sourced from the study and natural history relevant for the subgroup was applied, where possible, to reflect faster progression in early and active disease. Finally, a comprehensive list of scenarios was tested to explore the sensitivity of results to key assumptions.

A key limitation of the economic analysis was that despite best efforts, some input data for PPMS or the subpopulations were limited or lacking altogether, such as transition probabilities in patients with MRI active disease. There is a general paucity of utility and cost data in PPMS. Another limitation is that the subgroup analyses for 'MRI active' and 'MRI active ≤50' were post hoc analyses. These analyses were presented to the EMA during the regulatory process for ocrelizumab, and informed the license for adults with early PPMS (in terms of disease duration and level of disability) and with imaging features characteristic of inflammatory activity.

Although the license for ocrelizumab is not restricted to an age group, the EPAR includes an extensive discussion of the effect of age (and disease activity) on response to ocrelizumab, and suggests that younger patients with disease activity respond best to treatment with ocrelizumab. The cut-off of 50 years was selected because post hoc analysis in age quartiles indicated that patients aged over 50 years derived limited to no benefit in delaying disability progression as measured by EDSS from treatment. Hence, to maximize the patient cohort that could potentially derive benefit from ocrelizumab, 50 years' cut-off was chosen instead of the pre-specified cut-off of 45 years (median age in the trial was 46 and mean age was 44).

Age was also identified in a recently published meta-analysis in MS as a key predictor of response to DMTs. The analysis suggested that the average MS patient may not derive benefit from DMT treatment after age 53 [76].

The planned randomized controlled Phase IIIb study (WA40404) of ocrelizumab versus placebo will address the clinical uncertainty around benefit in older patients and the importance of upper limb function in more advanced disease. The study will include patients

with a later disease course (in terms of EDSS and age) and evaluate 9-HPT as primary endpoint.

In summary, the proposed CAA for ocrelizumab in PPMS would allow demonstration of cost-effectiveness of ocrelizumab in early and active PPMS whilst clinical uncertainty is addressed by the planned Phase IIIb study for a future re-appraisal by NICE.

We therefore believe that the proposed MAA for ocrelizumab in PPMS should allow access to an innovative new therapy for patients with no other treatment options.

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List of Appendices

Updated ICERs based on new ocrelizumab PAS

NEW Table 1: Incremental analysis, base case MRI active (based on modified ocrelizumab PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	78,316	78,316

NEW Table 2: Probabilistic results, base case MRI active (based on modified ocrelizumab PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	84,249	84,249

NEW Figure 1 One way sensitivity analysis for ocrelizumab versus BSC (NMB, modified PAS price)

NEW Figure 2 Cost-effectiveness acceptability curve for ocrelizumab and BSC (modified PAS price)

NEW Figure 3 Cost-effectiveness plane for ocrelizumab and BSC (modified PAS price)

NEW Figure 4 Incremental Cost-effectiveness Plane for ocrelizumab versus BSC (modified PAS price)

NEW Table 3 Results of scenario analysis in MRI active population, based on modified PAS price

	Ocrelizumab		BSC		
Scenarios	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**ICER**
Base case MRI active	[redacted]	[redacted]	[redacted]	[redacted]	£78,316
Natural history					
Acceleration factor set to 1.05 (MSBase matrix)	[redacted]	[redacted]	[redacted]	[redacted]	£75,764
Acceleration factor set to 1.1 (MSBase matrix)	[redacted]	[redacted]	[redacted]	[redacted]	£73,479
Natural history set to MSBase ≤50 for MRI active population	[redacted]	[redacted]	[redacted]	[redacted]	£71,985
Progression-only MSBase matrix	[redacted]	[redacted]	[redacted]	[redacted]	£68,143
Efficacy					

Efficacy set to CDP-24 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	£86,824
Extended control period CDP-12 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	£80,994
Extended control period CDP-24 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	£78,316
Costs					
Include relapses (cost, disutilities, and treatment effect)	[redacted]	[redacted]	[redacted]	[redacted]	£78,155
Exclude direct non-medical costs	[redacted]	[redacted]	[redacted]	[redacted]	£80,449
Set health state costs to BOUNDS-MS data	[redacted]	[redacted]	[redacted]	[redacted]	£77,599
Long-term discontinuation set to real world scenario	[redacted]	[redacted]	[redacted]	[redacted]	£75,520
Stopping rule set to EDSS 7	[redacted]	[redacted]	[redacted]	[redacted]	£77,739
Stopping rule set to EDSS 9	[redacted]	[redacted]	[redacted]	[redacted]	£80,679
Utilities					
Set patient utilities to Orme et al	[redacted]	[redacted]	[redacted]	[redacted]	£87,194
Proportion of upper limb dysfunction per EDSS (trial based)	[redacted]	[redacted]	[redacted]	[redacted]	£79,131
Proportion of fatigue per EDSS (trial based)	[redacted]	[redacted]	[redacted]	[redacted]	£78,375
Exclude upper limb impairment from model	[redacted]	[redacted]	[redacted]	[redacted]	£87,038
Exclude fatigue impact from model	[redacted]	[redacted]	[redacted]	[redacted]	£84,959
Combination					
Progression-only MSBase matrix, 5% acceleration factor, real world long-term discontinuation, and stopping rule at EDSS 7	[redacted]	[redacted]	[redacted]	[redacted]	£61,606

NEW Table 4: Incremental analysis, MRI active ≤50 subgroup (based on modified ocrelizumab PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,857	47,857

NEW Table 5: Probabilistic results, MRI active ≤50 subgroup (based on modified ocrelizumab PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	54,341	54,341

NEW Figure 5 One way sensitivity analysis in MRI active ≤50 subgroup (modified PAS price)

NEW Figure 6 Cost-effectiveness acceptability curve for ocrelizumab versus BSC in MRI active ≤50 subgroup (modified PAS price)

NEW Figure 7 Cost-effectiveness plane for ocrelizumab and BSC in MRI active ≤50 subgroup (modified PAS price)

NEW Figure 8 Cost-effectiveness plane for ocrelizumab versus BSC in MRI active ≤50 subgroup (modified PAS price)

NEW Table 6 Results of scenario analysis in MRI active ≤50 subgroup, based on modified PAS price

	Ocrelizumab		BSC		
Scenarios	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**ICER**
Base case MRI active ≤50	[redacted]	[redacted]	[redacted]	[redacted]	£47,857
Baseline characteristics					
Baseline age set to 40 years	[redacted]	[redacted]	[redacted]	[redacted]	£45,182
Natural history					
Acceleration factor set to 1.05 (MSBase matrix ≤50)	[redacted]	[redacted]	[redacted]	[redacted]	£46,065

Acceleration factor set to 1.1 (MSBase matrix ≤50)	[redacted]	[redacted]	[redacted]	[redacted]	£44,467
Progression-only MSBase matrix	[redacted]	[redacted]	[redacted]	[redacted]	£41,767
Efficacy					
Efficacy set to CDP-24 (MRI active ≤50)	[redacted]	[redacted]	[redacted]	[redacted]	£46,591
Extended control period CDP-12 (MRI active ≤50)	[redacted]	[redacted]	[redacted]	[redacted]	£49,175
Extended control period CDP-24 (MRI active ≤50)	[redacted]	[redacted]	[redacted]	[redacted]	£45,373
Costs					
Include relapses (cost, disutilities, and treatment effect)	[redacted]	[redacted]	[redacted]	[redacted]	£47,762
Exclude direct non-medical costs	[redacted]	[redacted]	[redacted]	[redacted]	£49,887
Set health state costs to BOUNDS-MS data	[redacted]	[redacted]	[redacted]	[redacted]	£46,446
Long-term discontinuation set to real world scenario	[redacted]	[redacted]	[redacted]	[redacted]	£45,916
Stopping rule set to EDSS 7	[redacted]	[redacted]	[redacted]	[redacted]	£47,258
Stopping rule set to EDSS 9	[redacted]	[redacted]	[redacted]	[redacted]	£49,129
Utilities					
Set patient utilities to Orme et al	[redacted]	[redacted]	[redacted]	[redacted]	£53,337
Proportion of upper limb dysfunction per EDSS (trial based)	[redacted]	[redacted]	[redacted]	[redacted]	£48,198
Proportion of fatigue per EDSS (trial based)	[redacted]	[redacted]	[redacted]	[redacted]	£48,093
Exclude upper limb impairment from model	[redacted]	[redacted]	[redacted]	[redacted]	£52,135
Exclude fatigue impact from model	[redacted]	[redacted]	[redacted]	[redacted]	£51,419
Combination					
Progression-only MSBase matrix, 5% acceleration factor, real world long-term discontinuation, and stopping rule at EDSS 7	[redacted]	[redacted]	[redacted]	[redacted]	£37,161

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Single Technology Appraisal

Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

Dear [redacted],

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on 26 February 2018 from Roche Products. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **05 April 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals [https://appraisals.nice.org.uk/request/47715 on 'NICE Docs/Appraisals'].

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Thomas Walker, Technical Lead (Thomas.Walker@nice.org.uk). Any procedural questions should be addressed to Donna Barnes, Project Manager (Donna.Barnes@nice.org.uk).

Yours sincerely

Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

A1. Please provide details of the reasons why participants 'withdrew consent' during the ORATORIO study (22 in the ocrelizumab arm and 21 in the placebo arm, as described in figure 2 in appendix D). Please also provide details of the 'other' reasons participants withdrew from the study (20 in the ocrelizumab arm and 13 in the placebo arm, as described in figure 2 in appendix D).

A2. Please explain why CDP-12 (confirmed disability progression for 12 weeks) rather than CDP-24 (confirmed disability progression for 24 weeks) was selected as the primary outcome in the ORATORIO trial.

A3. **Priority question:** Please provide baseline characteristics by arm for the subgroup of patients with T1 Gd-enhancing lesions at screening or baseline. If differences in baseline characteristics were noted, have the hazard ratios for CDP-12 and CDP-24 (reported in table 10 in the appendices) been adjusted for these differences? If not, please provide the adjusted hazard ratios for CDP-12 and CDP-24 in this subgroup.

A4. In section B.2.6.7 of document B of the company submission, the subgroup that most closely resembles the licensed indication is described as people with T1 Gd-enhancing lesions at screening or baseline, or new T2 lesions between screening and baseline (both of these defined as the 'MRI active' subgroup). However data for this subgroup were not reported in the CHMP report or EPAR. The SmPC makes reference to imaging features characteristic of inflammatory activity 'i.e. T1 Gd-enhancing lesions and/or active [new or enlarging] T2 lesions'. However, the 'MRI active' subgroup does not include people with enlarging T2 lesions between screening and baseline. Please clarify why:

a) the 'MRI active' subgroup does not comprise only of people with T1 Gd-enhancing lesions, as presented in the CHMP report; and

b) the 'MRI active' subgroup does not include enlarging T2 lesions.

A5. **Priority question:** Please provide baseline characteristics by arm for the subgroup of patients defined as 'MRI active' (with T1 Gd-enhancing lesions at screening or baseline or new T2 lesions between screening and baseline). If differences in baseline characteristics were noted, have the hazard ratios for CDP-12 and for CDP-24 (reported in tables 14 and 15 in document B of the company submission) been adjusted for these differences? If not, please provide adjusted hazard ratios for CDP-12 and CDP-24 in this subgroup.

A6. Please provide the hazard ratio for CDP-12 and CDP-24 from the extended controlled treatment period in the subgroup of patients with T1 Gd-enhancing lesions at screening or baseline.

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A7. Please provide plots for time to onset of CDP-12 during the extended controlled treatment period of ORATORIO for the following subgroups:

a) people with T1 Gd-enhancing lesions at screening or baseline

b) people with T1 Gd-enhancing lesions at screening or baseline or new T2 lesions between screening and baseline.

A8. Please provide the plots for time to onset of CDP-24 during the extended controlled treatment period of ORATORIO for the following subgroups:

a) people with T1 Gd-enhancing lesions at screening or baseline

b) people with T1 Gd-enhancing lesions at screening or baseline or new T2 lesions between screening and baseline.

A9. Please provide mean (SD) or median (range) expanded disability status scale (EDSS) at 120 weeks for each arm for the intention to treat (ITT) population, T1 Gd-enhancing lesions subgroup, and the MRI active subgroup.

A10. Please provide baseline and endpoint data for timed 25-ft walk for each arm for the ITT population, the T1 Gd-enhancing lesions subgroup, and the MRI active subgroup.

A11. Please provide CDP-12 and CDP-24 results without imputation of events that were not confirmed for the ITT population, the T1 Gd-enhancing lesions subgroup, and the MRI active subgroup.

A12. Please provide by study arm the number of CDP-12 events recorded in the graph depicted in figure 20 in document B of the company submission.

A13. In appendix F of the company submission reference is made to data from a meta-analysis of placebo arms from 10 MS RCTs and a Danish MS Registry. Please provide further details of:

a) the meta-analysis and the studies within it, and

b) the registry.

A14. Please provide underlying data for the patients in the plots shown in figure 21 in document B of the company submission. Please use the format below:

Weeks	event1cens0	control0intervention1
N	n	n
N	n	n

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A15. **Priority question:** The legend for figure 21 in document B of the company submission suggests that the data is for EDSS≥7, whereas for figure 22 the caption implies that the data is for EDSS greater than 7. Please clarify whether data source is the same for the 2 figures.

A16. Please provide the Weibull and exponential parameters for the extrapolations of time to onset of confirmed EDSS≥7 shown in figure 22, together with the format for the Weibull distribution used.

A17. Please clarify if the proportional hazards assumption was used to derive the Weibull extrapolations shown in figure 22, and if so please clarify how the assumption was tested.

A18. The ERG have digitised the Kaplan-Meier plots in figures 21 and 22 and have noted that the plots in the two figures do not correspond as they anticipated. The ERG suggest that if the plots use the same data, it appears that it has been assumed that there are 49.6 weeks in a year rather than 52.2 (365.25/7). Please clarify whether the same data is used in the 2 figures and, if so, provide an explanation for the discrepancy noted by the ERG.

A19. In figure 22 (document B, company submission) the primary progressive multiple sclerosis (PPMS) MSbase data reaches a maximum follow-up of approximately 25 years. However, this is inconsistent with appendix L (page 141) where it is stated that the registry has been initiated in 2004, leaving a maximum follow-up of only approximately 13 years. It is not clear if retrospective data was gathered for the registry included in the analysis shown in figure 22? Elsewhere in the company submission (document B, table 41, page 101) the registry median follow-up and quartiles are reported as 6.72 and 3.99 to 10.49 years, respectively. Please clarify these apparent inconsistences and provide full information about any retrospectively collected registry data included in the submission.

A20. Please provide the individual patient data for time to EDSS≥7 (or EDSS>7 as appropriate) in:

a) people with T1 Gd-enhancing lesions at screening or baseline

b) people with T1 Gd-enhancing lesions at screening or baseline or new T2 lesions between screening and baseline.

For both datasets, please use the format below:

Weeks	event1cens0	control0intervention1
N	n	n
N	n	n

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A21. If time to EDSS≥7 (or EDSS>7 as appropriate) confirmed at 24 weeks has been evaluated, please provide the individual patient data for this outcome (using the same dataset format as described in question A20) in:

a) the ITT population

b) people with T1 Gd-enhancing lesions at screening or baseline

c) people with T1 Gd-enhancing lesions at screening or baseline or new T2 lesions between screening and baseline.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** Please confirm if waning of the treatment effect can be implemented in the model by changing cells F55 to F62 in the 'Inputs – treatment effect' worksheet. If not, please provide a cost-effectiveness model that includes the the option to implement a waning of treatment efficacy as follows: 50% reduction in the hazard ratio for CDP-12 and CDP-24 from 10 years onwards; 25% reduction of the hazard ratio from three to five years of follow-up then a 50% reduction from 6 years onwards.

B2. **Priority question:** Section 3.3.2 of document B of the company submission (on page 104) describes the application of instantaneous hazard rate to obtain transition probabilities between EDSS health states for ocrelizumab-treated patients. However no resulting transition matrix is provided and the ERG are unclear precisely how the hazard ratio has been applied. Please provide worked examples showing how transition probabilities from the PPMS natural history dataset are modified (using hazard ratios) to obtain the corresponding transition probabilities for people treated with ocrelizumab.

B3. **Priority question:** Section B.3.3.5 of document B of the company submission presents a survival analysis of treatment withdrawal. Please provide the data used for this analysis (Kaplan-Meier plots and patient data in the format specified in clarification questions A14 and A20).

B4. On page 99 of document B of the company submission it is stated that the MSBase registry contains 2,074 patients with primary progressive MS. However, in table 12 of the same document the number of people with progressive MS in the MSBase is reported as 775 and in table 41, the number of people included in the PPMS analysis set is reported as 1,079:

a) please clarify who these 775 people represent

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b) please provide a flow diagram showing the process of patient selection with numbers and the reasons why some people were excluded from the analysis

c) please provide the number of people in the UK included in the sample of 1,079.

B5. In table 42 in document B of the company submission, 2 people transition from the health state EDSS 8 to EDSS 1, which seems an unlikely transition. Please confirm that this is correct.

B6. Table 58 in document B of the company submission reports the monitoring costs for ocrelizumab incurred in the first year as £558.58; however, the economic model uses monitoring costs of £509.62 for the first year. Additionally, monitoring costs for year 2+ in Table 58 states £293.86, but the model uses £214.04 ('Inputs – treatment costs' worksheet). Please clarify, which of these values are correct and should be used in the model.

B7. Some model parameters (incidence of adverse events, disutilities associated with adverse events, and management costs associated with treating adverse events) have not been included in the probabilistic sensitivity analysis. Please justify why these inputs were not varied in the PSA.

Section C: Textual clarifications and additional points

C1. Please provide a clinical rationale for including the subgroup analysis of people aged 50 years or younger. This should include reference to the natural history of PPMS and the biological rationale for a decreased treatment effect in older age groups.

Literature searching

C2. For the cost-effectiveness and HRQoL literature reviews, the PRISMA diagram (figure 4) and text in appendix G of the company submission refer to 55 full publications and 7 previous HTA submissions. A summary of the 7 previous NICE submissions is provided in in table 25 (appendix G of the company submission), but not for the 55 publications. Please provide a list and, if possible, PDFs of these publications. Similarly the PRISMA diagram and text in appendix H of the company submission refers to 51 included studies. A summary of 24 of these studies is provided in table 35, but not the 27 that were considered inconsistent with the NICE reference case or that only contained two EDSS data points. Please provide a list of the missing 27 publications and if possible PDFs of these publications. Please could these be sent as soon as possible?

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C3. In the clinical effectiveness literature review (page 13 of appendix D in the company submission) it states that 1 trial (16 records) met the eligibility criteria, but only 15 documents are listed in table 3. Please clarify whether this is an error or provide the missing publication.

C4. If possible please provide the PDF for reference 115 cited in document B of the company submission. Please could this be sent as soon as possible?

C5. If possible please provide the PDFs for references 16, 18, 29, 38 and 40 cited in the appendices document of the company submission. Please could these be sent as soon as possible?

ID938 Ocrelizumab in PPMS

Roche Response to ERG Clarification Questions

Contents

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Section A: Clarification on effectiveness data

A1. Please provide details of the reasons why participants 'withdrew consent' during the ORATORIO study (22 in the ocrelizumab arm and 21 in the placebo arm, as described in figure 2 in appendix D). Please also provide details of the 'other' reasons participants withdrew from the study (20 in the ocrelizumab arm and 13 in the placebo arm, as described in figure 2 in appendix D).

Response:

It was the responsibility of the treating investigator to complete the reason for withdrawal of a patient from treatment or study in the eCRF. All reasons for withdrawals were regularly reviewed by the Sponsor in a blinded fashion to determine whether the underlying cause was safety related (in which case the site was asked to consider changing the withdrawal reason to “adverse event”).

The category “Withdrew consent” (or otherwise referred to as “withdrawal by subject”) represents cases of patients withdrawing consent for further participation in the study; manual review of investigators’ comments in the CRF showed a mixture of reasons, such as, perceived lack of efficacy, disease progression, personal reasons, desire to receive a different treatment, relocation, and desire to have children.

Most of the withdrawals in the category “Other” were due to perceived lack of efficacy, disease progression, personal reasons, or the desire to receive an alternative treatment.

A2. Please explain why CDP-12 (confirmed disability progression for 12 weeks) rather than CDP-24 (confirmed disability progression for 24 weeks) was selected as the primary outcome in the ORATORIO trial.

Response:

In 2008, during a scientific advice meeting with CHMP (EMA), Roche laid out the rationale for selecting 12-week CDP as primary endpoint for the proposed (at the time) ORATORIO trial. Due to higher number of detected progressions, 12-week CDP has more power to detect treatment effect and is therefore generally preferred as primary endpoint by sponsors of clinical trials in MS. Roche discussed results from the OLYMPUS trial, which included PPMS patients, where consistent treatment effect was observed using either 12-week or 24-week CDP. Due to the fact that ORATORIO would only include PPMS patients, and therefore be less confounded by long relapses, the correlation was expected to be improved. After this meeting, CHMP confirmed that 12-weeks CDP would be accepted as a primary endpoint for the ORATORIO trial.

*A3. **Priority question**: Please provide baseline characteristics by arm for the subgroup of patients with T1 Gd-enhancing lesions at screening or baseline. If differences in baseline characteristics were noted, have the hazard ratios for CDP-12 and CDP-24 (reported in table 10 in the appendices) been adjusted for these differences? If not, please provide the adjusted hazard ratios for CDP-12 and CDP-24 in this subgroup.*

Response:

The baseline characteristics for ITT, MRI Active and T1 Gd subgroups are provided below. There appear no major imbalances between treatment arms in the subgroups for key characteristics. All hazard ratios are stratified by Region of World and age (<=45 vs >45) as was defined for the primary endpoint.

Table 1: Baseline characteristics for ITT and subgroups in ORATORIO

	ITT		MRI Active		T1 Gd	
Characteristic	**Placebo n=244**	**Ocrelizumab n=488**	**Placebo n=104**	**Ocrelizumab n=189**	**Placebo n=77**	**Ocrelizumab n=157**
Female n, (%)	124 (50.8)	237 (48.6)	[redacted]	[redacted]	[redacted]	[redacted]
Mean age, Years (SD)	44.4 (8.3)	44.7 (7.9)	[redacted]	[redacted]	[redacted]	[redacted]
Age <=45, n (%)	118 (48.4)	230 (47.1)	[redacted]	[redacted]	[redacted]	[redacted]
Age > 45, n (%)	126 (51.6)	258 (52.9)	[redacted]	[redacted]	[redacted]	[redacted]
United States n, (%)	34 (13.9)	67 (13.7)	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World n, (%)	210 (86.1)	421 (86.3)	[redacted]	[redacted]	[redacted]	[redacted]
Mean time since symptom onset, years (SD)	6.14 (3.59)	6.66 (4.01)	[redacted]	[redacted]	[redacted]	[redacted]
Mean time since diagnosis, years (SD)	2.75 (3.32)	2.85 (3.16)	[redacted]	[redacted]	[redacted]	[redacted]
No previous DMT n, (%)	214 (87.7)	433 (88.7)	[redacted]	[redacted]	[redacted]	[redacted]
Mean EDSS score (SD)	4.73 (1.17)	4.74 (1.17)	[redacted]	[redacted]	[redacted]	[redacted]
Mean no. of lesions on T2-weighted MRI, (SD)	48.15 (39.31)	48.71 (38.16)	[redacted]	[redacted]	[redacted]	[redacted]
Mean volume of lesions on T2-weighted MRI, cm3 (SD)	10.91 (12.95)	12.67 (15.11)	[redacted]	[redacted]	[redacted]	[redacted]
Normalised brain volume, cm3 (SD)	1469.86 (88.73)	1462.91 (83.95)	[redacted]	[redacted]	[redacted]	[redacted]
Any Baseline T1 Lesions n, (%)	60 (24.6)	133 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]
Any Screening T1 Lesions n, (%)	30 (12.3)	39 (8)	[redacted]	[redacted]	[redacted]	[redacted]
Any Baseline or Screening T1 Lesions n, (%)	77 (31.6)	157 (32.2)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline No. of Gd-enhancing lesions on T1-weighted MRI, n (%)	N = 243	N = 484	[redacted]	[redacted]	[redacted]	[redacted]
0	183 (75.3)	351 (72.5)	[redacted]	[redacted]	[redacted]	[redacted]
1	29 (11.9)	62 (12.8)	[redacted]	[redacted]	[redacted]	[redacted]
2	15 (6.2)	22 (4.5)	[redacted]	[redacted]	[redacted]	[redacted]

3	5 (2.1)	17 (3.5)	[redacted]	[redacted]	[redacted]	[redacted]
>=4	11 (4.5)	32 (6.6)	[redacted]	[redacted]	[redacted]	[redacted]

A4. In section B.2.6.7 of document B of the company submission, the subgroup that most closely resembles the licensed indication is described as people with T1 Gd-enhancing lesions at screening or baseline, or new T2 lesions between screening and baseline (both of these defined as the 'MRI active' subgroup). However data for this subgroup were not reported in the CHMP report or EPAR. The SmPC makes reference to imaging features characteristic of inflammatory activity 'i.e. T1 Gd-enhancing lesions and/or active [new or enlarging] T2 lesions'. However, the 'MRI active' subgroup does not include people with enlarging T2 lesions between screening and baseline. Please clarify why:

a) the 'MRI active' subgroup does not comprise only of people with T1 Gd-enhancing lesions, as presented in the CHMP report; and

Response:

The CHMP report and EPAR only include the pre-specified subgroup of patients with T1 Gd-enhancing lesions at baseline. No other data was requested by CHMP and these data were considered by CHMP to be generalizable to all patients with inflammatory activity as defined by T1 Gd enhancing lesions or new/enlarging T2 lesions.

The reasons for broadening the MRI active subgroup definition beyond the pre-specific subgroup of T1 Gd-enhancing lesions and performing post hoc subgroup analyses for the NICE submission are:

- Clinical practice is moving away from routine T1 Gd scanning due to safety concerns about the contrast agents used. Clinical opinion indicated that T2 scanning would more closely resemble future practice in the UK.
- Broadening the definition more closely resembles the EMA label which defines inflammatory activity as T1 Gd enhancing lesions or new/enlarging T2 lesions and allows for evidence-based decision making.

b) the 'MRI active' subgroup does not include enlarging T2 lesions.

Response:

The data captured on the screening CRF page did not allow a classification of enlarging T2 lesions to be made between screening and baseline.

Only new T2 lesions could be identified between screening and baseline as data captured on the CRFs included T2 lesion counts, hence numerical increases in T2 lesion counts could be derived.

*A5. **Priority question**: Please provide baseline characteristics by arm for the subgroup of patients defined as 'MRI active' (with T1 Gd-enhancing lesions at screening or baseline or new T2 lesions between screening and baseline). If differences in baseline characteristics were noted, have the hazard ratios for CDP-12 and for CDP-24 (reported in tables 14 and 15 in document B of the company submission) been adjusted for these differences? If not, please provide adjusted hazard ratios for CDP-12 and CDP-24 in this subgroup. (a) Please*

provide copies of all the references listed in company submission Appendix Tables 5-6, together with any supplementary appendices they contain. Please provide as a priority the references listed in the following table (these relate to non-open-access studies for which no references were provided in the submission and therefore the ERG cannot currently appraise these studies):

Response:

Please see response to question A3.

A6. Please provide the hazard ratio for CDP-12 and CDP-24 from the extended controlled treatment period in the subgroup of patients with T1 Gd-enhancing lesions at screening or baseline.

Response:

The table below shows the results from the extended controlled treatment period (CCOD 20 January 2016).

Table 2: Extended controlled treatment period CDP results in subgroups (with imputation)

		Placebo		Ocrelizumab		Stratified Analysis
Endpoint	**Population**	**Patients**	**Events n (%)**	**Patients**	**Events n (%)**	**Hazard Ratio (95% CI)**
CDP-12	ITT	244	106 (43.4)	487	177 (36.3)	0.74 (0.58, 0.94)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CDP-24	ITT	244	98 (40.2)	487	154 (31.6)	0.70 (0.54, 0.90)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The clinical cut-off datacut of 20 January 2016 is in line with the data submitted to EMA. The NICE submission contained extended controlled period data for a different datacut (15 September 2016), hence ITT and MRI active data are added here for reference and transparency.

A7. Please provide plots for time to onset of CDP-12 during the extended controlled treatment period of ORATORIO for the following subgroups:

a) people with T1 Gd-enhancing lesions at screening or baseline

Response:

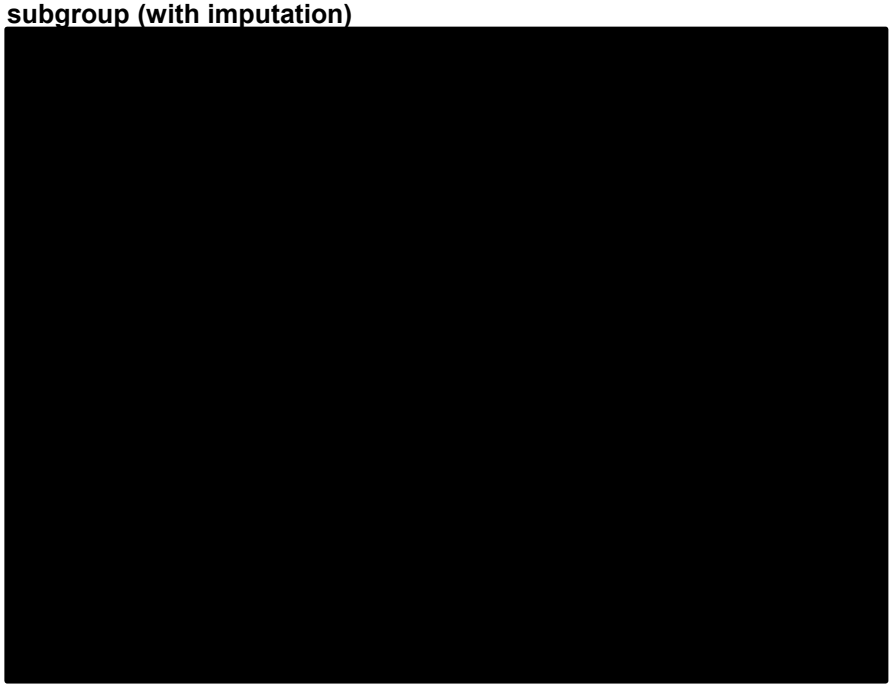
The figures below show the results from the extended controlled treatment period (CCOD 20 January 2016) for the subgroups.

Figure 1: Kaplan-Meier plot for CDP-12 in extended controlled treatment period in T1 Gd subgroup (with imputation)

b) people with T1 Gd-enhancing lesions at screening or baseline or new T2 lesions between screening and baseline.

Response:

Figure 2: Kaplan-Meier plot for CDP-12 in extended controlled treatment period in MRI active subgroup (with imputation)

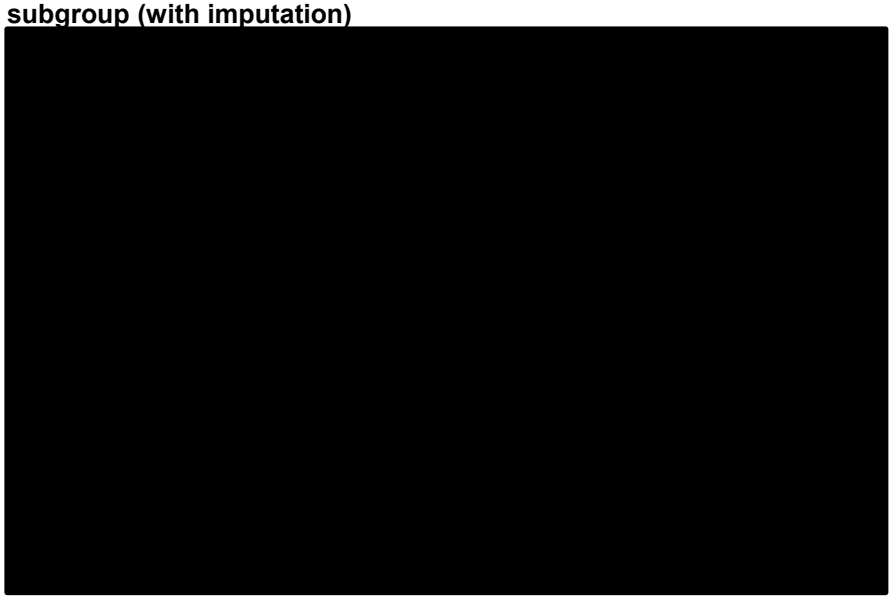


A8. Please provide the plots for time to onset of CDP-24 during the extended controlled treatment period of ORATORIO for the following subgroups:

a) people with T1 Gd-enhancing lesions at screening or baseline

Response:

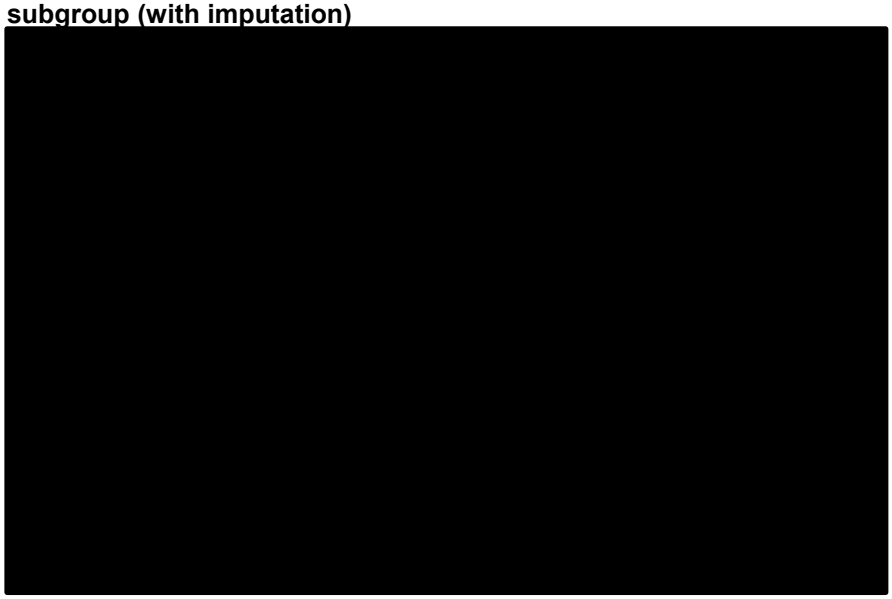
Figure 3: Kaplan-Meier plot for CDP-24 in extended controlled treatment period in T1 Gd subgroup (with imputation)



b) people with T1 Gd-enhancing lesions at screening or baseline or new T2 lesions between screening and baseline.

Response:

Figure 4: Kaplan-Meier plot for CDP-24 in extended controlled treatment period in MRI active subgroup (with imputation)



A9. Please provide mean (SD) or median (range) expanded disability status scale (EDSS) at 120 weeks for each arm for the intention to treat (ITT) population, T1 Gd-enhancing lesions subgroup, and the MRI active subgroup.

Response:

Summary statistics of EDSS by population are provided below at baseline and 120 weeks.

Table 3: Summary of EDSS statistics

		Placebo					Ocrelizumab				
Population	**Week**	**n**	**Mean**	**Median**	**Min**	**Max**	**n**	**Mean**	**Median**	**Min**	**Max**
ITT	0	242	4.69	4.5	2.5	6.5	474	4.69	4.5	2.5	6.75
	120	178	4.86	4.5	1.5	8	399	4.81	5	1.5	8
MRI Active	0	102	4.59	4.38	2.5	6.5	185	4.76	4.5	3	6.75
	120	76	4.74	4.5	1.5	8	159	4.86	5	1.5	8
Gd >= 1	0	75	4.63	4.5	2.5	6.5	153	4.85	5	3	6.75
	120	55	4.75	4.5	1.5	8	131	5.01	5.5	1.5	8

Although summary statistics of EDSS provide a descriptive overview of the average disease level of the population at specific time points, it does not provide any insight into the efficacy of treatments. Mean change in EDSS levels is not an appropriate efficacy parameter according to EMA guidelines, as it does not take into account confirmed changes in EDSS levels (1). Instead progression should be predefined, like sustained worsening of a relevant magnitude (e.g. 1 point on EDSS) over a confirmatory period.

A10. Please provide baseline and endpoint data for timed 25-ft walk for each arm for the ITT population, the T1 Gd-enhancing lesions subgroup, and the MRI active subgroup.

Response:

The table below provides a summary of T25FW data by population during the double blind controlled treatment period in ORATORIO.

Table 4: Summary results for T25FW

		Placebo		Ocrelizumab		
Population	**Week**	**n**	**Mean**	**n**	**Mean**	**Ratio of adjusted geometric means (95% CI)**
ITT	0	239	12.781	473	14.573	
	120*	174	1.551	397	1.389	0.896 (0.792-1.013)
MRI Active	0	100	14.334	185	15.858	
	120*	75	1.704	157	1.393	0.817 (0.677-0.987)
T1 Gd	0	74	16.169	152	16.680	
	120*	55	1.673	128	1.412	0.844 (0.672-1.060)

* Ratio relative to baseline

A11. Please provide CDP-12 and CDP-24 results without imputation of events that were not confirmed for the ITT population, the T1 Gd-enhancing lesions subgroup, and the MRI active subgroup.

Response:

The table below shows the results from the extended controlled treatment period (CCOD 20 January 2016)

Table 5: Summary results for CDP-12 and CDP-24 without imputation

		Placebo		Ocrelizumab		Stratified Analysis
Endpoint	**Population**	**Patients**	**Events n (%)**	**Patients**	**Events n (%)**	**Hazard Ratio (95% CI)**
CDP-12	ITT	244	94 (38.5)	487	168 (34.5)	0.80 (0.62, 1.03)
CDP-12	MRI Active	104	39 (37.5)	189	65 (34.4)	0.79 (0.53, 1.18)
CDP-12	T1 Gd	77	28 (36.4)	157	56 (35.7)	0.84 (0.53, 1.32)
CDP-24	ITT	244	82 (33.6)	487	139 (28.5)	0.76 (0.58, 1.00)
CDP-24	MRI Active	104	36 (34.6)	189	57 (30.2)	0.74 (0.49, 1.13)
CDP-24	T1 Gd	77	25 (32.5)	157	49 (31.2)	0.81 (0.50, 1.31)

There is no fully satisfactory approach to handling missing data because missingness usually is informative rather than random. The best approach is to avoid missing observations all together, and the ORATORIO trial achieved a relatively low level of missing data with 92% of EDSS initial progression events having enough follow-up to be confirmed (or not confirmed).

Censoring data without imputation (as is done in the table above) lacks validity as it ignores the insight that an initial assessment of progression is highly prognostic of later having a confirmed progression. In ORATORIO, approximately 80% of initial progressions were later confirmed. Thus, the most reasonable approach is to assume that the true confirmation rate in these patients would be between 80% and 100%. The pre-specified primary analysis, which imputed a 100% confirmation rate, yielded a hazard ratio of 0.76 (0.59-0.98), and sensitivity analysis that imputed a 80% confirmation rate yielded a hazard ratio of 0.77 (0.59-0.99), indicating minimal difference.

Thus, it demonstrates considerable robustness of estimates of treatment effect in the pre-specified analyses, which was also accepted by EMA.

A12. Please provide by study arm the number of CDP-12 events recorded in the graph depicted in figure 20 in document B of the company submission.

Response:

The number of events per study arm are described below.

Table 6: Number of events of CDP-12 in ORATORIO

n (%)	Placebo n=244	Ocrelizumab n=488
Pts included in analysis	244 (100)	487 (100)
Pts with event	96 (39.3)	160 (32.9)
Pts without event	148 (60.7)	327 (67.1)

A13. In appendix F of the company submission reference is made to data from a meta-analysis of placebo arms from 10 MS RCTs and a Danish MS Registry. Please provide further details of:

a) the meta-analysis and the studies within it, and

Response:

The meta-analysis was conducted in 2015 to identify clinical trials and observational studies with any information on the occurrence of malignancies in patients with MS, and to estimate exposure time and event rates based on the available information in the publications.

The overall objective of the meta-analysis was broader and included identifying information on occurrence of infections, depression, completed suicides, and autoimmune diseases in patients with MS. The results related to these other objectives are not reported here as they were not deemed relevant for the ocrelizumab submission.

A brief summary of the methodology and results are provided below. More detailed information can be found in the confidential meta-analysis report (2).

Search methodology

Two systematic literature searches were conducted, the first in 2012 and an update search with extensions in 2015. Table 7 describes the PICOS search terms.

Clinical trials and observational studies of all licensed or investigational (in phase III) pharmacological MS therapies were searched for. A search for systematic reviews, meta-analyses and HTA reports was added to hand-search bibliographies in order to identify any further relevant study not detected by the search

The following 9 databases were searched:

- Cochrane Central Register of Controlled Trials
- Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effectiveness
- HTA Database (INAHTA)
- Medline
- EMBASE
- BIOSIS Preview
- EMBASE Alert
- SciSearch

Additional data source:

In case a NCT number (clinicaltrials.gov identifier) was provided in a selected study publication the website of the study registry of the U.S. National Institutes of Health

(https://clinicaltrials.gov/ct2/home) was visited to check whether safety results are published for this study in which case these were used in addition.

The time frame of the search for original papers was restricted to studies published from 1990 to the present date. This was deemed appropriate to cover interferons that came on the market in the 1990s. The search for systematic reviews, meta-analyses and HTAs covered the last 8 years only (from 2007) as these were used for hand-searching of reference lists. The search was limited to evidence published in English, French or German language.

Table 7: PICOS search terms

	Inclusion criteria	Exclusion criteria
Population	Patients with any phenotype of multiple sclerosis	clinically isolated syndrome (CIS) was not included
Interventions	interferon beta-1a (e.g. Avonex, Rebif) • interferon beta-1b (e.g. Betaseron) • glatiramer acetate (Copaxone) • fingolimod hydrochloride (Gilenya) • natalizumab (Tysabri) • mitoxantrone • azathioprine • methotrexate • cyclophosphamide • intravenous immune globulin • dalfampridine/fampridine • ocrelizumab • alemtuzumab (Lemtrada, Campath) • dimethyl fumarate (BG-12) • teriflunomide (Aubagio) • laquinimod • daclizumab (Zenapax) • masitinib • PEG-interferon beta-1a / BIIB0176 • cladribine • rituximab	Corticosteroids and symptomatic therapies (with the exception of dalfampridine/fampridine) were not included.
Comparators	Any comparator was considered.	
Outcomes	any information on occurrence of (non)-serious infections, malignancies, depression, suicides or autoimmune diseases such as number of events, number of patients with events or rates of events	
Study / Publication type	• phase III and phase IV trials (randomized and non-randomized, blinded and unblinded) • observational trials such as cohort and case-control studies (no case reports) • minimum total sample size of 100 patients • full study publications (no conference abstracts, editorials, letters and comments) • Systematic reviews, meta analyses and HTAs (health technology assessments) (for cross checking of references) (no non-systematic reviews)	• Duplicate, reporting of preliminary data of an already included study • article could not be obtained • already found in search 2012

Study selection

The study selection was performed by two reviewers independently and discrepancies were resolved after discussion. The appliance of inclusion and exclusion criteria at all stages of the selection process was documented, detailing the rationale for exclusion in each case.

Information used for estimating exposure time and event rates was abstracted into an EXCEL file. A second reviewer independently reappraised the extracted data.

Statistical Methods

An algorithm was applied to calculate the event rates of episodes of diseases, i.e. number of events divided by the cumulative exposure (in person-years). The results are presented by 100 person-years (PY).

To this aim the exposure time was estimated based on an exponential time-to-event model with cut-offs (described in more details below). It was assumed that in each period the same percent of patients were dropping out.

Results

In total, the systematic literature search in 2012 and the update search with extensions in 2015 in bibliographic databases retrieved 3809 citations: 3493 hits for strategy 1 (clinical and observational studies) and 316 hits for strategy II (systematic reviews/meta-analyses/HTAs). After excluding duplicates (1195 [strategy I] plus 120 abstracts [strategy II]) and screening against inclusion/exclusion criteria 1983 plus 153 abstracts were excluded, and 315 citations were found eligible for the screening on full-text level and 43 systematic reviews/meta-analyses/HTAs for checking of reference lists. Of the 315 full-text articles 162 publications were excluded. Via cross-check of references, four relevant publications were included into the final study pool. In total, 158 publications (referring to 142 different studies) were included in this review and its extension.

b) the registry

Response:

The Danish Multiple Sclerosis Registry (DMSR) was formally established in 1956 but started operating in 1949 with a nationwide survey of prevalent cases of MS (3). It is the longest running population-based MS register in the world and is estimated to be more than 90% complete with a diagnostic validity of 94%.

The Danish Cancer Register is a population-based register containing data on incident cases of cancer throughout Denmark since 1943 (4). Details of individual cases of cancer are available according to the 7th revision of the international classification of diseases (ICD) for all years, and in addition according to the ICD-O since 1978.

The DMRS was linked with the Danish Cancer Register to identify all cases of cancer occurring in patients registered with MS. In the statistical analyses, the MS patients were followed for cancer occurrence from April 1, 1968, or MS diagnosis, whichever came later, until the date of death, emigration or December 31,1997, whichever came first. The ratio of the number of observed to the number of expected cancers, i.e., the standardized incidence ratio (SIR), served as measure of the relative risk of cancer in the cohort. The expected number of cancers in the cohort was calculated as the sum of the sex-, age- and period-

specific person years at risk in the cohort multiplied by correspondingly stratified national cancer incidence rates. Ninety-five percent confidence intervals (95% CIs) for the SIRs were estimated by means of Wald's test assuming a Poisson distribution of the observed cases (5).

Patient demographics and characteristics (6)

[redacted]

[redacted]

[redacted]

[redacted]

Age	Mean EDSS
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

A14. Please provide underlying data for the patients in the plots shown in figure 21 in document B of the company submission. Please use the format below:

Weeks	**event1cens0**	**control0intervention1**
N	n	n
N	n	n

Response:

The table below shows underlying data for Figure 21 in Document B (CCOD 20 January 2016).

Please note that the table provides survival proportion estimates, i.e. proportion of patients without event, while the figure depicts proportion of patients with event (1-survival).

Table 8: Patient data for time to EDSS ≥7 in extended controlled treatment period (ITT)

PLACEBO (N=244)				OCRELIZUMAB (N=487)			
WEEKS	Survival	Number Left	Failed	WEEKS	Survival	Number Left	Failed
0.0	1.00	244	0	0.0	1.00	487	0
12.4	1.00	236	1	10.4	1.00	472	1
15.6	0.99	233	2	11.0	1.00	471	2
24.1	0.99	231	3	24.3	0.99	463	4
25.1	0.98	228	4	36.3	0.99	456	5
35.9	0.97	224	6	48.1	0.99	451	6
36.7	0.97	218	7	48.4	0.98	445	7
39.1	0.97	216	8	60.1	0.98	437	8
48.4	0.96	214	9	61.0	0.98	435	9
60.1	0.96	208	10	62.3	0.98	434	10
60.6	0.95	205	11	72.1	0.97	429	12
84.1	0.95	196	12	72.4	0.97	426	13
90.4	0.94	191	13	73.1	0.97	425	14
96.3	0.94	189	14	74.1	0.97	424	15
100.1	0.93	186	15	88.3	0.96	415	16
110.4	0.93	179	16	96.0	0.96	413	17
120.1	0.92	174	17	96.7	0.96	411	18
132.1	0.91	164	19	109.1	0.96	400	19
133.4	0.90	160	20	109.4	0.96	399	20
180.1	0.89	67	21	132.0	0.95	391	21
180.7	0.88	56	22	132.1	0.95	390	22
193.0	0.85	39	23	144.3	0.95	378	23
203.4	0.83	30	24	145.3	0.95	374	24
228.3	0.83	0	24	153.0	0.94	372	25
				156.1	0.94	335	26
				175.3	0.94	222	27
				181.0	0.93	141	28
				192.1	0.92	118	29
				205.1	0.90	42	30
				240.4	0.90	0	30

A15. ***Priority question****: The legend for figure 21 in document B of the company submission suggests that the data is for EDSS≥7, whereas for figure 22 the caption implies that the data is for EDSS greater than 7. Please clarify whether data source is the same for the 2 figures.*

Response:

We can clarify that the data source is the same and that the caption for figure 22 is incorrect.

A16. Please provide the Weibull and exponential parameters for the extrapolations of time to onset of confirmed EDSS≥7 shown in figure 22, together with the format for the Weibull distribution used.

Response:

The parameters for the extrapolation are shown below. Note this is parameterized in terms of weeks and with Ocrelizumab considered as the reference treatment for treatment effect estimates.

Table 9: Parameters for extrapolation of time to EDSS ≥7

	Parameter Estimates			Covariance Matrix Estimate			
Model		**Estimate**	**Std Error**		**INTERCEPT**	**Treatment = PLACEBO (N=244)**	
Exponential	**INTERCEPT**	7.831	0.183	**INTERCEPT**	0.033	-0.033	
	Treatment = PLACEBO (N=244)	-0.582	0.274	**Treatment = PLACEBO (N=244)**	-0.033	0.075	
	Parameter Estimates			**Covariance Matrix Estimate**			
					INTERCEPT	**Treatment = PLACEBO (N=244)**	**SCALE**
Weibull	**INTERCEPT**	7.364	0.322	**INTERCEPT**	0.104	-0.038	0.030
	Treatment = PLACEBO (N=244)	-0.496	0.233	**Treatment = PLACEBO (N=244)**	-0.038	0.054	-0.006
	SCALE	0.826	0.106	**SCALE**	0.030	-0.006	0.011

To convert this to a survival function the following transformations are performed (similarly to treatment discontinuation extrapolations included in the model).

Table 10: Survival function transformations for time to EDSS ≥7

	Ocrelizumab	Placebo
Exponential (t weeks)	λ = exp(-Intercept) $S(t) = \exp(-\lambda t)$ S(t) = exp(-0.000397 * t)	λ= exp(-(intercept+treatment)) $S(t) = \exp(-\lambda t)$ S(t) = exp(-0.000711 * t)
Weibull (t weeks)	λ = exp(-intercept/scale) γ = 1/scale $S(t) = \exp(-\lambda t^{\gamma})$ S(t) = exp(-0.000134 * t ^1.21)	λ= exp(-(intercept+treatment)/scale) γ = 1/scale $S(t) = \exp(-\lambda t^{\gamma})$ S(t) = exp(-0.000245 * t ^1.21)

For these Weibull distribution parameterized as $S(t) = \exp(-\lambda t^{\gamma})$ the median time to event can be calculated as:

$$Median\ (weeks) = \left(\frac{\log 0.5}{-\lambda}\right)^{\frac{1}{\gamma}}$$

The parameters for Weibull models and estimated medians by population are shown below.

Table 11: Weibull model estimates for time to EDSS ≥7

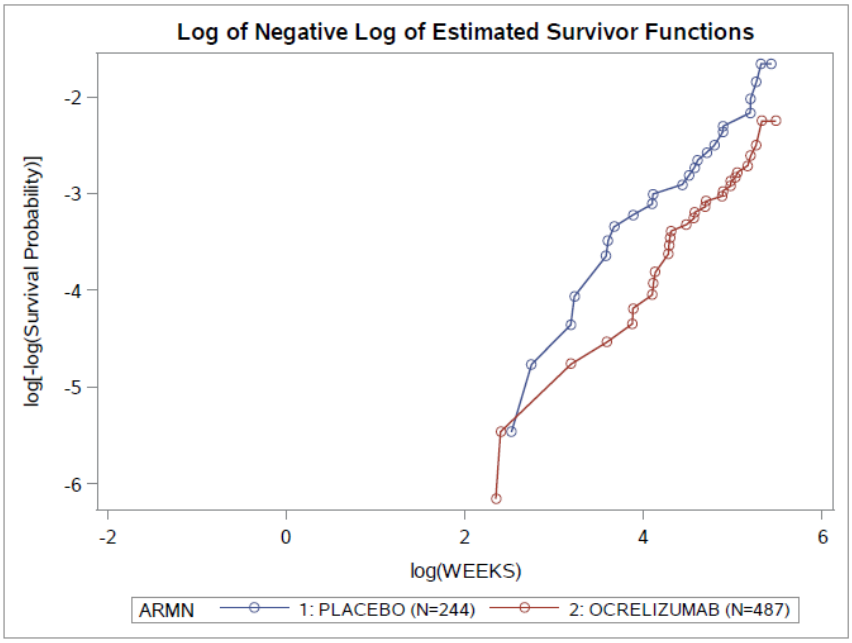
	Ocrelizumab			Placebo		
Population	**λ**	**γ**	**Median (years)**	**λ**	**γ**	**Median (years)**
ITT	0.000134	1.21	22.4	0.000245	1.21	13.6
MRI Active	0.000161	1.18	23.6	0.000399	1.18	10.9
T1 Gd	0.000125	1.24	19.6	0.000313	1.24	9.4

A17. Please clarify if the proportional hazards assumption was used to derive the Weibull extrapolations shown in figure 22, and if so please clarify how the assumption was tested.

Response:

A proportional hazards model was used. This assumption was tested based on plotting log of negative log of survival estimate vs log time as shown in figure below. This suggests the PH assumption is reasonable as the curves are parallel.

Figure 5: Proportional hazards plot for time to EDSS ≥7 in extended controlled treatment period (ITT, with imputation)



Excluding patient with missing baseline EDSS

A18. The ERG have digitised the Kaplan-Meier plots in figures 21 and 22 and have noted that the plots in the two figures do not correspond as they anticipated. The ERG suggest that if the plots use the same data, it appears that it has been assumed that there are 49.6 weeks in a year rather than 52.2 (365.25/7). Please clarify whether the same data is used in the 2 figures and, if so, provide an explanation for the discrepancy noted by the ERG.

Response:

The same data is presented in Figures 21 and 22. To avoid any potential issues with digitization we have provided the underlying KM data in response to question A14 and the related Weibull parametrization in response to question A16, to enable the ERG to recreate these graphs more easily. For presenting the Weibull extrapolated estimates of median time to EDSS ≥7 in years rather than weeks we have assumed 52 weeks in a year.

A19. In figure 22 (document B, company submission) the primary progressive multiple sclerosis (PPMS) MSbase data reaches a maximum follow-up of approximately 25 years. However, this is inconsistent with appendix L (page 141) where it is stated that the registry has been initiated in 2004, leaving a maximum follow-up of only approximately 13 years. It is not clear if retrospective data was gathered for the registry included in the analysis shown in figure 22? Elsewhere in the company submission (document B, table 41, page 101) the registry median follow-up and quartiles are reported as 6.72 and 3.99 to 10.49 years, respectively. Please clarify these apparent inconsistences and provide full information about any retrospectively collected registry data included in the submission.

Response:

As we state in appendix L (page 141), MSBase is an ongoing, longitudinal, strictly observational web-based registry collecting standardized outcomes in MS using an agreed minimum dataset. The Registry collects clinic-based and private practice based information on people with MS. From its inception in 2004 key data (including EDSS) are prospectively collected from patients and entered on to the Registry together with retrospective data derived from the patients' medical history, thereby enabling long term clinical follow up. Additionally, a number of MSBase centers transferred their already prospectively collected follow-up data from the previous EDMUS (European Database for Multiple Sclerosis) program to the MSBase system. The EDMUS project was created in Lyon in 1976 <https://www.edmus.org/en/proj/index.html>.

As such, the follow up period when we extracted the data for this analysis (10th December 2016), was more than 25 years [appendix L - Figure 13 page 140]. We have edited document B, table 41, page 101 below by adding minimum and maximum follow up period (highlighted in red).

Table 12: Population characteristics of MSBase PPMS analysis set

Characteristic	PPMS analysis set
Clinic or population-based cohort	Clinic
Data collection period (time period)	June 1976 to December 2016
Recording disability scores	Both prospective and retrospective
Number of patients	1079
Females: n (%)	596 (55.2)
Age at analysis baseline, years: mean (SD); median (quartiles)	51.0 (10.2); 51.3 (44.9, 58.4)
Age at onset of PPMS, years: mean (SD); median (quartiles)	42.9 (10.2); 43.5 (35.9, 50.2)
Age at diagnosis of PPMS, years: mean (SD); median (quartiles)	47.9 (10.1); 48.3 (41.6, 54.8)
Disease duration at analysis baseline, years: mean (SD); median (quartiles)*	8.2 (7.6); 5.7 (2.6, 11.3)
Patients who experienced a relapse in the analysis period: n (%)	88 (8.2)
First eligible EDSS: median (quartiles)	4 (3, 6)
Follow-up: mean (SD); median (quartiles) [min, max]	8.10 years (6.47) 6.72 (3.99, 10.49) [2.00 ; 25.08]
Time to reach EDSS 6, years: median	6.71

A20. Please provide the individual patient data for time to EDSS≥7 (or EDSS>7 as appropriate) in:

A summary of results by population is provided in Table 13. Plots and patient data for each population are provided below.

Table 13: Summary results for time to EDSS ≥7 in confirmed at 12 weeks in extended control period (with imputation)

	Placebo		Ocrelizumab		Stratified Analysis
Population	Patients	Events	Patients	Events	Hazard Ratio
		n (%)		n (%)	(95% CI)
ITT	244	24 (9.8)	487	30 (6.2)	0.55 (0.32, 0.94)
MRI Active	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T1 Gd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a) people with T1 Gd-enhancing lesions at screening or baseline

Response:

The figures below show the results while the tables provide underlying data (CCOD 20 January 2016). Please note that the tables provide survival proportion estimates, i.e. proportion of patients without event, while the figures depict proportion of patients with event (1-survival).

Figure 6: Kaplan-Meier plot for time to EDSS ≥7 confirmed at 12 weeks in T1 Gd subgroup (with imputation)

Table 14: Patient data for time to EDSS ≥7 confirmed at 12 weeks in T1 Gd subgroup (with imputation)

PLACEBO (n=77)				OCRELIZUMAB (n=157)			
WEEKS	**Survival**	**Number Left**	**Failed**	**WEEKS**	**Survival**	**Number Left**	**Failed**
0.00	1.00	77	0	0.00	1.00	157	0
12.43	0.99	72	1	24.29	0.99	150	1
24.14	0.97	71	2	48.14	0.99	148	2
25.14	0.96	70	3	48.43	0.98	145	3
36.71	0.94	66	4	72.43	0.97	139	4
39.14	0.93	64	5	73.14	0.97	138	5
60.14	0.91	60	6	109.14	0.96	130	6
100.14	0.90	56	7	132.00	0.95	127	7
132.14	0.88	47	8	132.14	0.94	126	8
180.14	0.84	23	9	144.29	0.94	122	9
180.71	0.81	21	10	181.00	0.92	54	10
203.43	0.73	10	11	205.14	0.87	19	11
228.14	0.73	0	11	231.29	0.87	0	11

b) people with T1 Gd-enhancing lesions at screening or baseline or new T2 lesions between screening and baseline.

Response:

Figure 7: Kaplan-Meier plot for time to EDSS ≥7 confirmed at 12 weeks in MRI active subgroup (with imputation)

Table 15: Patient data for time to EDSS ≥7 confirmed at 12 weeks in MRI active subgroup (with imputation)

PLACEBO (N=104)				OCRELIZUMAB (N=189)			
WEEKS	**Survival**	**Number Left**	**Failed**	**WEEKS**	**Survival**	**Number Left**	**Failed**
0.00	1.00	104	0	0.00	1.00	189	0
12.43	0.99	99	1	11.00	0.99	184	1
24.14	0.98	98	2	24.29	0.99	181	2
25.14	0.97	97	3	48.14	0.98	179	3
36.71	0.96	92	4	48.43	0.98	176	4
39.14	0.95	90	5	72.43	0.97	168	5
60.14	0.94	85	6	73.14	0.97	167	6
60.57	0.93	84	7	109.14	0.96	158	7
96.29	0.92	79	8	132.00	0.95	155	8
100.14	0.90	78	9	132.14	0.95	154	9
132.14	0.88	67	11	144.29	0.94	148	10
180.14	0.85	33	12	181.00	0.93	62	11
180.71	0.82	30	13	205.14	0.89	22	12
203.43	0.77	15	14	231.29	0.89	0	12
228.14	0.77	0	14				

For both datasets, please use the format below:

Weeks	event1cens0	control0intervention1
N	n	n
N	n	n

A21. If time to EDSS≥7 (or EDSS>7 as appropriate) confirmed at 24 weeks has been evaluated, please provide the individual patient data for this outcome (using the same dataset format as described in question A20) in:

A summary of results by population is provided in Table 16. Plots and patient data for each population are provided below.

Table 16: Summary results for time to EDSS ≥7 confirmed at 24 weeks in extended control period (with imputation)

	Placebo		Ocrelizumab		Stratified Analysis
Population	Patients	Events	Patients	Events	Hazard Ratio
		n (%)		n (%)	(95% CI)
ITT	244	23 (9.4)	487	28 (5.7)	0.53 (0.31, 0.93)
MRI Active	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T1 Gd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a) the ITT population

Response:

Figure 8, Figure 9, and Figure 10 show the results in ITT, T1 Gd, and MRI active subgroups, while Table 17, Table 18, and Table 19 provide underlying data (CCOD 20 January 2016).

Please note that the tables provide survival proportion estimates, i.e. proportion of patients without event, while the figures depict proportion of patients with event (1-survival).

Figure 8: Kaplan-Meier plot for time to EDSS ≥7 confirmed at 24 weeks (ITT, with imputation)

Table 17: Patient data for time to EDSS ≥7 confirmed at 24 weeks (ITT, with imputation)

PLACEBO (N=244)				OCRELIZUMAB (N=487)			
WEEKS	**Survival**	**Number Left**	**Failed**	**WEEKS**	**Survival**	**Number Left**	**Failed**
0.00	1.00	244	0	0.00	1.00	487	0
12.43	1.00	236	1	10.43	1.00	472	1
15.57	0.99	233	2	11.00	1.00	471	2
24.14	0.99	231	3	24.29	0.99	464	3
25.14	0.98	228	4	36.29	0.99	457	4
35.86	0.98	225	5	48.14	0.99	452	5
36.71	0.97	219	6	48.43	0.99	446	6
39.14	0.97	217	7	60.14	0.98	438	7
48.43	0.97	215	8	61.00	0.98	436	8
60.57	0.96	207	9	62.29	0.98	435	9
84.14	0.96	198	10	72.14	0.98	430	11
90.43	0.95	193	11	72.43	0.97	427	12
96.29	0.94	190	13	73.14	0.97	426	13
100.14	0.94	187	14	74.14	0.97	425	14
110.43	0.93	180	15	88.29	0.97	416	15
120.14	0.93	175	16	96.00	0.96	414	16

132.14	0.91	165	18	96.71	0.96	412	17
133.43	0.91	161	19	109.14	0.96	401	18
180.14	0.88	67	21	109.43	0.96	400	19
180.71	0.87	56	22	132.00	0.95	392	20
203.43	0.84	31	23	132.14	0.95	391	21
228.29	0.84	0	23	144.29	0.95	379	22
				145.29	0.95	375	23
				156.14	0.94	337	24
				175.29	0.94	224	25
				181.00	0.93	143	26
				192.14	0.93	120	27
				205.14	0.90	43	28
				240.43	0.90	0	28

b) people with T1 Gd-enhancing lesions at screening or baseline

Response:

Figure 9: Kaplan-Meier plot for time to EDSS ≥7 confirmed at 24 weeks in T1 Gd subgroup (with imputation)

Table 18: Patient data for time to EDSS ≥7 confirmed at 24 weeks in T1 Gd subgroup (with imputation)

PLACEBO (N=77)				OCRELIZUMAB (N=157)			
WEEKS	Survival	Number Left	Failed	WEEKS	Survival	Number Left	Failed
0.00	1.00	77	0	0.00	1.00	157	0
12.43	0.99	72	1	24.29	0.99	150	1
24.14	0.97	71	2	48.14	0.99	148	2
25.14	0.96	70	3	48.43	0.98	145	3
36.71	0.94	66	4	72.43	0.97	139	4
39.14	0.93	64	5	73.14	0.97	138	5
96.29	0.91	57	6	109.14	0.96	130	6
100.14	0.90	56	7	132.00	0.95	127	7
132.14	0.88	47	8	132.14	0.94	126	8
180.14	0.84	23	9	144.29	0.94	122	9
180.71	0.80	21	10	181.00	0.92	54	10
203.43	0.73	10	11	205.14	0.87	19	11
228.14	0.73	0	11	231.29	0.87	0	11

c) people with T1 Gd-enhancing lesions at screening or baseline or new T2 lesions between screening and baseline.

Response:

Figure 10: Kaplan-Meier plot for time to EDSS ≥7 confirmed at 24 weeks in MRI active subgroup (with imputation)

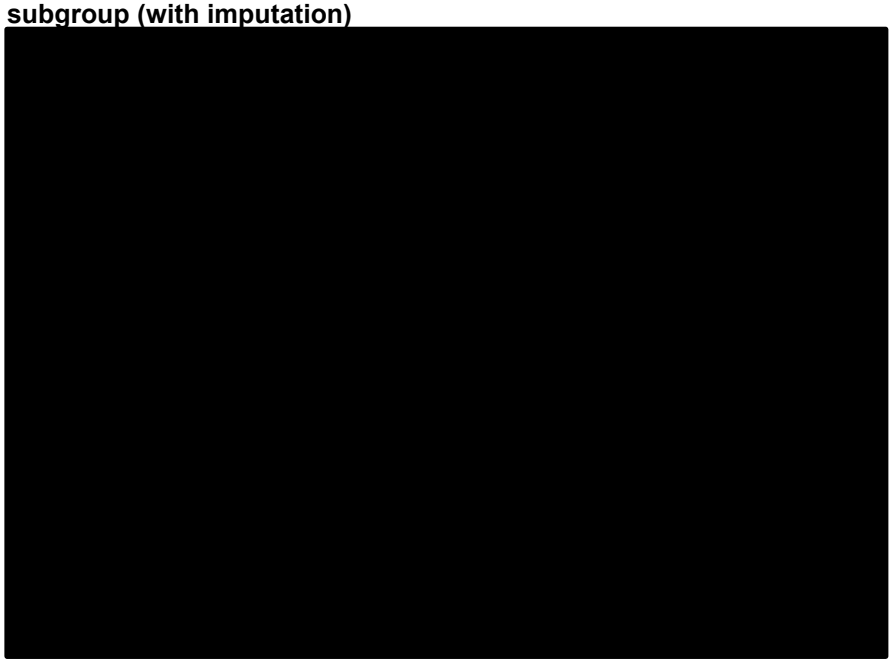


Table 19: Patient data for time to EDSS ≥7 confirmed at 24 weeks in MRI active subgroup (with imputation)

PLACEBO (N=104)				OCRELIZUMAB (N=189)			
WEEKS	Survival	Number Left	Failed	WEEKS	Survival	Number Left	Failed
0.00	1.00	104	0	0.00	1.00	189	0
12.43	0.99	99	1	11.00	0.99	184	1
24.14	0.98	98	2	24.29	0.99	181	2
25.14	0.97	97	3	48.14	0.98	179	3
36.71	0.96	92	4	48.43	0.98	176	4
39.14	0.95	90	5	72.43	0.97	168	5
60.57	0.94	85	6	73.14	0.97	167	6
96.29	0.91	79	8	109.14	0.96	158	7
100.14	0.90	78	9	132.00	0.95	155	8
132.14	0.88	67	11	132.14	0.95	154	9
180.14	0.85	33	12	144.29	0.94	148	10
180.71	0.82	30	13	181.00	0.93	62	11
203.43	0.77	15	14	205.14	0.89	22	12
228.14	0.77	0	14	231.29	0.89	0	12

Section B: Clarification on cost-effectiveness data

B1. ***Priority question****: Please confirm if waning of the treatment effect can be implemented in the model by changing cells F55 to F62 in the 'Inputs – treatment effect' worksheet. If not, please provide a cost-effectiveness model that includes the option to implement a waning of treatment efficacy as follows: 50% reduction in the hazard ratio for CDP-12 and CDP-24 from 10 years onwards; 25% reduction of the hazard ratio from three to five years of follow-up then a 50% reduction from 6 years onwards.*

Response:

We can confirm that assumptions around long-term waning of treatment effect can be implemented in the model by changing cells F55:F62 in 'Inputs – treatment effects'.

However, we would like to reiterate that we believe it to be unlikely that the effect of ocrelizumab wanes in the long term due to its unique immunogenicity profile. Ocrelizumab is a humanized antibody and negligible neutralizing anti-drug antibodies were detected in patients during the ORATORIO study (see document B, table 35, page 84). Presence of neutralizing anti-drug antibodies has been shown to be associated with diminishing efficacy in other DMTs in MS (7, 8).

In addition, preliminary analyses of long-term follow-up data in the Open Label Extension (OLE) period of ORATORIO demonstrates that there is no evidence of treatment waning with ocrelizumab in PPMS. Including data from the OLE period extends follow-up to 5.5 years. The analyses demonstrated that efficacy in the ITT population observed in the core phase of ORATORIO remained constant during the OLE phase for both 12-week confirmed disability progression as measured by EDSS and 9-HPT (Figure 11, Figure 12, and Table

20). This is despite crossover of patients from the placebo arm to ocrelizumab treatment during the OLE phase.

Thus, 5.5 years of follow-up data suggests that there is no evidence of any treatment waning occurring in patients treated with ocrelizumab in PPMS. The sustained effect of ocrelizumab demonstrated in PPMS is consistent with the OLE data of ocrelizumab in RRMS as presented in Appendix M, page 152.

Figure 11: Kaplan-Meier plot for CDP-12 including Open Label Extension period (ITT)

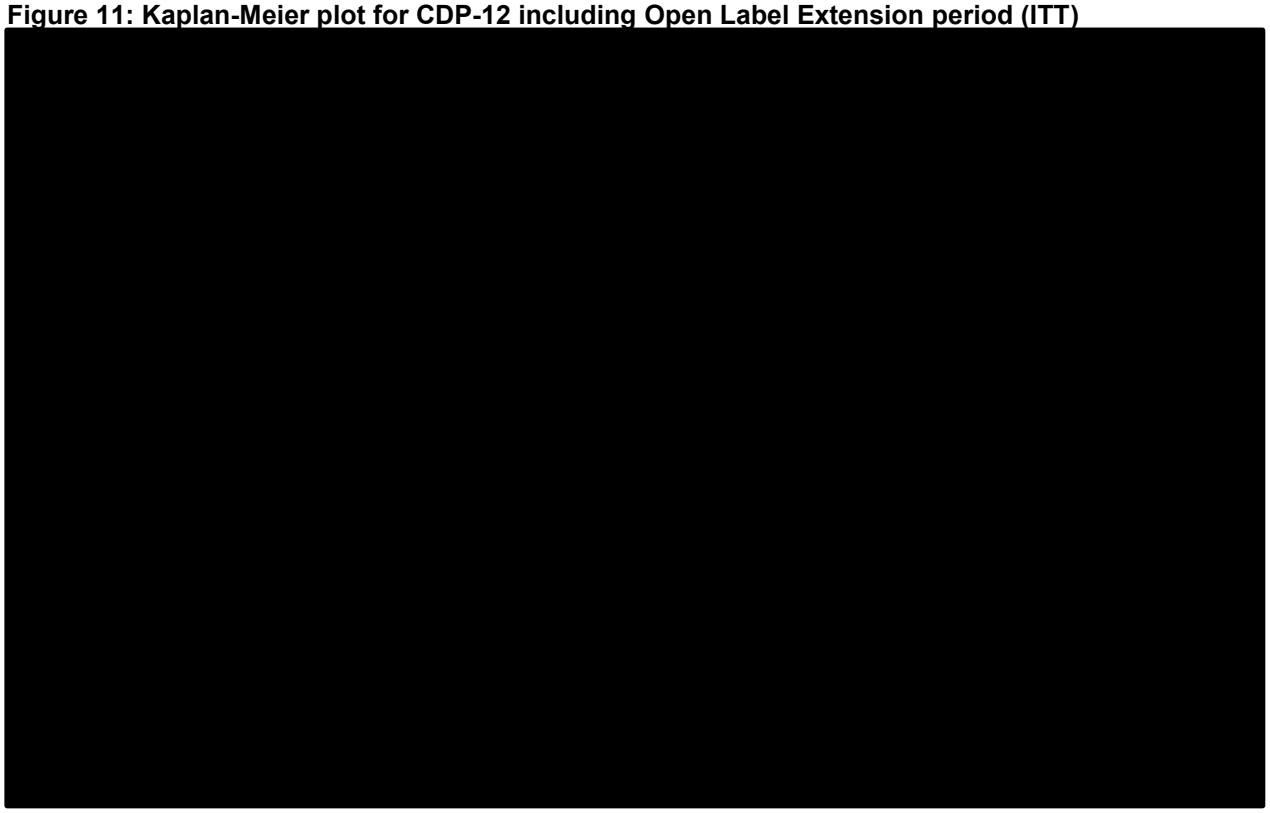


Figure 12: Kaplan-Meier plot of 9-HPT including Open Label Extension period (ITT)

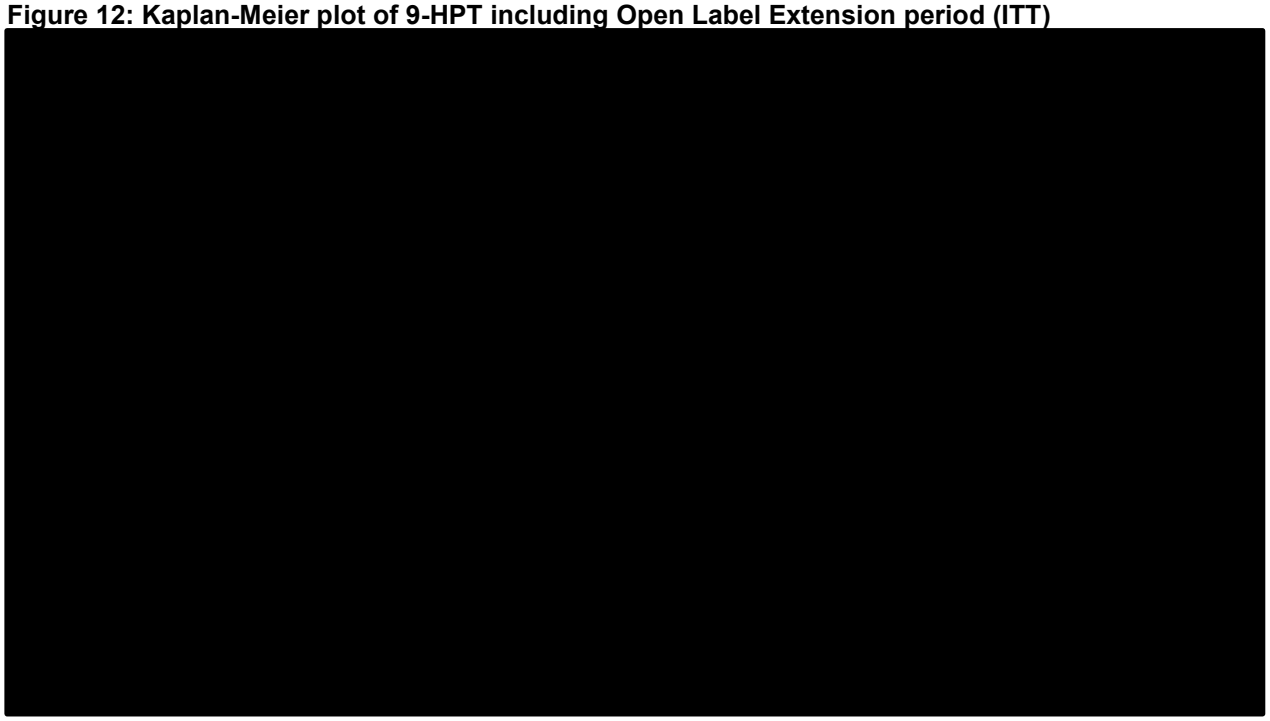


Table 20: Results for time to 12-week CDP and time to confirmed 20% increase in 9-HPT during the core, extended controlled and OLE periods of ORATORIO (ITT, with imputation)

	Placebo / OCR		OCR / OCR		
Outcome	**Patients, n**	**Events, n (%)**	**Patients, n**	**Events, n (%)**	**Hazard Ratio (95% CI)**
12-week CDP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-week 9-HPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B2. ***Priority question:*** *Section 3.3.2 of document B of the company submission (on page 104) describes the application of instantaneous hazard rate to obtain transition probabilities between EDSS health states for ocrelizumab-treated patients. However no resulting transition matrix is provided and the ERG are unclear precisely how the hazard ratio has been applied. Please provide worked examples showing how transition probabilities from the PPMS natural history dataset are modified (using hazard ratios) to obtain the corresponding transition probabilities for people treated with ocrelizumab.*

Response:

Natural history data has been adjusted using the commonly cited formulae that are used to convert a probability into a rate, apply a treatment effect, and then convert the rate back to a probability (9).

In brief, here are the steps which can all be found in the 'State transitions' sheet of the economic model.

1. Convert natural history transition probability matrix to rates ('State transitions' sheet columns C:L)

2. Multiply rates for progressions only (upper right triangle of matrix) by hazard ratio ('State transitions' sheet columns S:AB)
3. Then convert rates back to probabilities. As there are fewer progressions on treatment, the diagonals [probability of staying in the same state] are increased so that each row equals 1 ('State transitions' sheet columns AG:AP)
4. Final probabilities from step 3 are copied ('State transitions' sheet columns AW:BF) to be applied in the Markov trace

Please note that this is the same approach as used in previous MS models used in NICE appraisals.

B3. ***Priority question:*** *Section B.3.3.5 of document B of the company submission presents a survival analysis of treatment withdrawal. Please provide the data used for this analysis (Kaplan-Meier plots and patient data in the format specified in clarification questions A14 and A20).*

Response:

The requested information on all-cause discontinuation in ORATORIO is provided below (ITT).

Figure 13: Kaplan-Meier plot for survival analysis of all-cause discontinuation

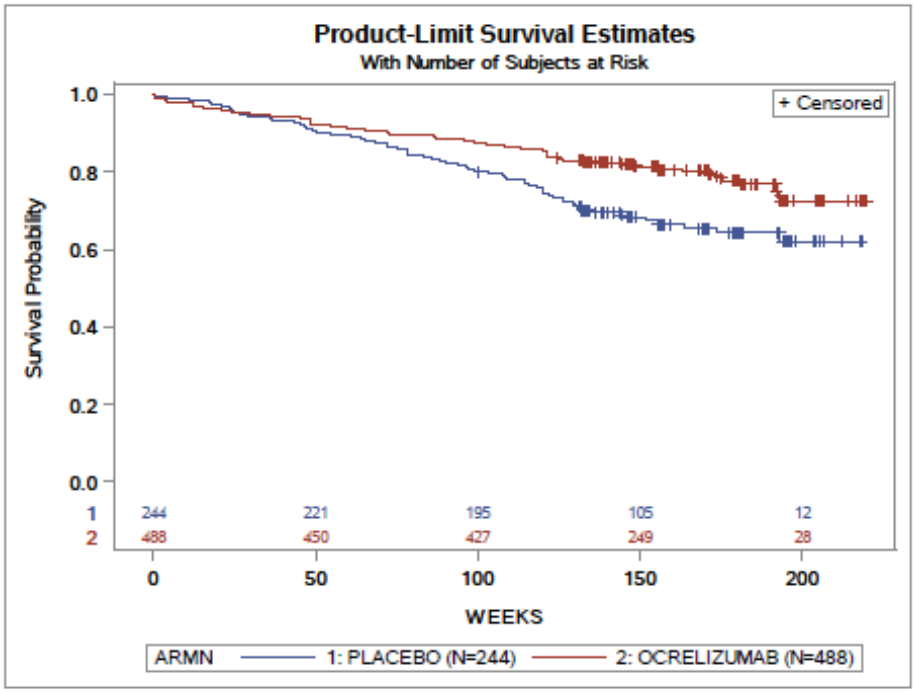


Table 21: Patient data for survival analysis of all-cause discontinuation

PLACEBO (N=244)				OCRELIZUMAB (N=488)			
WEEKS	**Survival**	**Number Left**	**Failed**	**WEEKS**	**Survival**	**Number Left**	**Failed**
0.00	1.00	244	0	0.00	1.00	488	0
0.29	1.00	243	1	0.14	1.00	486	2

4.14	0.99	242	2	0.29	0.99	485	3
6.14	0.99	241	3	0.43	0.99	484	4
11.14	0.98	240	4	2.14	0.99	483	5
17.29	0.98	239	5	3.29	0.99	481	7
18.00	0.98	238	6	4.00	0.98	480	8
20.86	0.97	237	7	4.29	0.98	479	9
23.14	0.97	236	8	8.43	0.98	478	10
23.71	0.96	235	9	9.71	0.98	477	11
24.29	0.96	234	10	12.14	0.97	474	14
24.43	0.95	233	11	12.29	0.97	473	15
26.43	0.95	232	12	12.86	0.97	472	16
26.57	0.95	231	13	15.14	0.97	471	17
28.86	0.94	230	14	17.00	0.96	470	18
36.14	0.94	229	15	19.71	0.96	469	19
36.43	0.93	228	16	21.14	0.96	468	20
42.29	0.93	227	17	23.86	0.96	467	21
43.71	0.93	226	18	24.29	0.95	465	23
45.29	0.92	225	19	25.00	0.95	464	24
46.71	0.92	224	20	30.00	0.95	463	25
46.86	0.91	223	21	35.14	0.95	462	26
48.14	0.91	222	22	36.14	0.94	461	27
49.00	0.91	221	23	36.29	0.94	460	28
50.00	0.90	220	24	38.43	0.94	459	29
54.86	0.90	219	25	45.00	0.94	458	30
56.00	0.89	218	26	48.00	0.94	457	31
60.57	0.89	217	27	48.14	0.93	456	32
64.29	0.89	216	28	48.29	0.93	453	35
65.00	0.88	215	29	48.43	0.92	451	37
68.29	0.88	214	30	49.00	0.92	450	38
72.14	0.87	212	32	51.14	0.92	449	39
72.29	0.86	211	33	54.43	0.92	448	40
75.00	0.86	210	34	57.71	0.92	447	41
76.29	0.86	209	35	59.71	0.91	446	42
78.29	0.85	208	36	60.43	0.91	445	43
78.43	0.85	207	37	62.14	0.91	444	44
78.57	0.84	206	38	65.00	0.91	443	45
83.43	0.84	205	39	71.86	0.91	442	46
84.14	0.84	204	40	72.14	0.90	440	48
85.57	0.83	203	41	72.29	0.90	439	49

88.43	0.83	202	42	72.71	0.90	438	50
90.43	0.82	201	43	78.14	0.90	437	51
94.14	0.82	200	44	82.57	0.89	436	52
95.71	0.82	199	45	86.43	0.89	435	53
96.57	0.81	198	46	86.86	0.89	434	54
96.86	0.81	197	47	87.29	0.89	433	55
99.14	0.80	196	48	89.43	0.89	432	56
99.57	0.80	195	49	94.29	0.88	431	57
103.00	0.80	193	50	95.86	0.88	430	58
107.86	0.79	192	51	96.14	0.88	429	59
108.29	0.79	191	52	98.57	0.88	428	60
109.14	0.78	190	53	99.14	0.88	427	61
110.14	0.78	189	54	101.14	0.87	426	62
114.29	0.77	188	55	102.86	0.87	425	63
114.43	0.77	187	56	104.86	0.87	424	64
115.71	0.77	186	57	108.14	0.87	423	65
118.29	0.76	185	58	108.43	0.86	422	66
119.29	0.76	184	59	110.00	0.86	421	67
120.14	0.75	182	61	113.14	0.86	420	68
120.29	0.75	181	62	118.29	0.86	419	69
121.71	0.74	180	63	118.86	0.86	418	70
122.29	0.74	179	64	120.29	0.85	417	71
123.43	0.73	178	65	120.86	0.85	416	72
126.00	0.73	177	66	121.00	0.85	415	73
126.14	0.73	176	67	121.14	0.85	414	74
128.43	0.72	175	68	121.29	0.85	413	75
129.57	0.72	174	69	121.57	0.84	410	78
130.29	0.71	173	70	122.71	0.84	409	79
132.00	0.71	168	71	125.00	0.84	407	80
132.14	0.70	164	73	125.29	0.83	405	82
135.86	0.69	131	74	126.29	0.83	404	83
144.14	0.69	124	75	132.71	0.83	343	84
145.86	0.68	117	76	136.57	0.82	318	85
151.71	0.68	104	77	144.14	0.82	304	86
155.29	0.66	102	79	146.14	0.82	284	87
163.86	0.66	77	80	148.14	0.82	252	88
173.43	0.64	56	81	149.14	0.81	249	89
193.14	0.62	27	82	155.71	0.81	242	90
218.29	0.62	0	82	155.86	0.81	241	91

				163.29	0.80	193	92
				171.00	0.80	139	93
				173.14	0.79	131	94
				174.86	0.78	129	95
				175.29	0.78	127	96
				181.29	0.77	85	97
				192.00	0.76	73	98
				192.14	0.75	72	99
				193.00	0.74	65	100
				193.14	0.73	63	101
				219.86	0.73	0	101

B4. On page 99 of document B of the company submission it is stated that the MSBase registry contains 2,074 patients with primary progressive MS. However, in table 12 of the same document the number of people with progressive MS in the MSBase is reported as 775 and in table 41, the number of people included in the PPMS analysis set is reported as 1,079:

a) please clarify who these 775 people represent

Response:

The 775 figure represents the 'ORATORIO-like' cohort of patients with EDSS 3.0 - 6.5 at baseline which were used for analysis of time to EDSS ≥7.0.

b) please provide a flow diagram showing the process of patient selection with numbers and the reasons why some people were excluded from the analysis

Response:

The requested flow diagram is described below showing the process of patient selection and reasons for exclusion.

Table 22: Flow diagram for MSBase registry analysis

Description	N
"Pure" primary progressive MS (PPMS) patients included in the MSBase registry (at the time of initial analysis), without application of inclusion of exclusion criteria of any type. *Note1: This excludes patients with a Progressive Relapsing MS (PRMS) diagnosis code. PRMS is a retrospective diagnosis assigned in MSBase database to those PPMS patients who experience a relapse after the initial diagnosis.*	2,074

Note2: This number changes frequently as the database is updated (i.e. it is not based on the specific data-cut for the natural history analysis) and is provided mainly for context. No analyses were conducted in this population		
Inclusion/Exclusion Criteria	**Rationale**	
1. PPMS diagnosis as per McDonald criteria 2005. This includes both PPMS and PRMS	Restrict to progressive MS patients	-
2. Age 18+	Restrict to adult patients	-
3. At least two EDSS measurements during follow-up	Allow for analysis of EDSS progression	-
Inclusion criteria 1-3		1,079
4. Baseline EDSS 3.0-6.5	Cohort with baseline EDSS matching the ORATORIO trial inclusion criteria to allow for more robust comparison of time to EDSS ≥7. *Note: Same analysis were also conducted in a cohort without these EDSS restrictions, with similar findings*	775

c) please provide the number of people in the UK included in the sample of 1,079..

Response:

27 patients (2.5%) of the 1079 cohort were UK patients

B5. In table 42 in document B of the company submission, 2 people transition from the health state EDSS 8 to EDSS 1, which seems an unlikely transition. Please confirm that this is correct.

Response:

We agree that transitions from EDSS 8 to 1 would seem improbable. However, it is important to note that the time between these observations are not visible in the matrix, i.e. the observations are not captured on a fixed cycle. As such the time between measurements could be multiple years apart.

The MSBase registry data was analyzed without making adjustments to the real world measurements. This is in line with the approach taken in RRMS where the London Ontario registry dataset has been criticized by previous NICE Committees due to removal of EDSS improvements.

However, based on clinical advice and similar to the approach taken by the Institute of Clinical and Economic Review in their cost-effectiveness analysis in PPMS (10), we explored scenario analysis in the submission which constrained the transition probability matrix to allow progression only in PPMS.

B6. Table 58 in document B of the company submission reports the monitoring costs for ocrelizumab incurred in the first year as £558.58; however, the economic model uses monitoring costs of £509.62 for the first year. Additionally, monitoring costs for year 2+ in

Table 58 states £293.86, but the model uses £214.04 ('Inputs – treatment costs' worksheet). Please clarify, which of these values are correct and should be used in the model.

Response:

Apologies for this inconsistency. The model contains the correct values. In table 58 in document B the breakdown of monitoring costs in year 1 is correct but the total is incorrect. The total is £509.62 which matches the model. The cost of full blood counts was not updated in the table for monitoring costs in year 2+ and the total is incorrect. The correct value for total monitoring costs in years 2+ is £214.04 which matches the model.

B7. Some model parameters (incidence of adverse events, disutilities associated with adverse events, and management costs associated with treating adverse events) have not been included in the probabilistic sensitivity analysis. Please justify why these inputs were not varied in the PSA.

Response:

Compared to previous MS models submitted to NICE we have added a considerable number of variables in the PSA (for example, not all previous submissions included the natural history transition matrices in the PSA). Balancing model complexity and the potential for inputs to impact the final probabilistic results we have included what we considered to be relevant parameters.

Section C: Textual clarifications and additional points

C1. Please provide a clinical rationale for including the subgroup analysis of people aged 50 years or younger. This should include reference to the natural history of PPMS and the biological rationale for a decreased treatment effect in older age groups.

Response:

In Europe, Ocrevus is indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity. Support for the indication was largely based on subgroup analyses of ORATORIO showing greater benefit in delaying confirmed disability progression as measured by EDSS in patients who were younger and had T1 Gd lesions at baseline (11) (additional analyses also demonstrated that the observation was seen when including new T2 lesions).

We recognise that this subgroup analysis based on age may raise equality concerns. The decision to present subgroup results in younger patients is informed by evidence from the pivotal Phase III ORATORIO study, and was the subject of extensive discussions with health regulatory authorities. The pre-specified analysis with age cut-off of 45 years was based on the expected median of the studied population. The post hoc analysis with age cut-off of 50 years was chosen to be as inclusive as possible, as treatment effect by age quartiles indicated that clinical benefit in patients over 50 years was uncertain.

The observed trend towards less benefit in older patients when considering confirmed worsening of EDSS may be consistent with the therapeutic reserve hypothesis (see document B, Figure 5, page 24) (12). The hypothesis suggests that neuronal domains may enter the clinically-apparent progressive phase of the disease at different rates depending on the length of the axons in the pathway and the reserve capacity of that pathway, i.e. its ability to compensate for ongoing or future damage. This hypothesis predicts that different neuronal domains will have different length-dependent therapeutic windows in which to respond to anti-inflammatory therapies that suppress ongoing inflammatory demyelinating lesions. The neuronal domains that have not entered the clinically-apparent progressive phase of the disease, due to preservation of functional reserve, may only respond to anti-inflammatory therapies with a delay in the effect due to the delayed onset of clinical expression of neurodegenerative axonal loss; the so-called therapeutic lag. In contrast, the neuronal domains that have already entered the clinically-apparent progressive phase of the disease, due to loss of functional reserve, may fail to respond to anti-inflammatory therapies.

The trend that older patients may exert lower benefit with respect to worsening of EDSS was also observed in a recent meta-regression of MS trials (13). The meta-regression predicted no therapeutic benefit in the average MS patient after 53 years of age. Although the authors did not explicitly examine the effect of age within a progressive population, it does lend some support to the therapeutic reserve hypothesis.

Analyses of other endpoints in ORATORIO lend support to the therapeutic reserve hypothesis (Table 23). Similar to EDSS worsening, ocrelizumab efficacy in delaying worsening of T25-FW (confirmed 20% increase in T25-FW for at least 12 weeks or 24-

weeks) was more pronounced in younger patients (stratified by pre-specified age subgroups), irrespective if they had Gd-T1 lesions at baseline or not. In contrast, analyses of worsening of 9-HPT (confirmed 20% increase in 9-HPT for at least 12 weeks or 24-weeks) indicated that clinically meaningful benefit was observed in patients treated with ocrelizumab irrespective if they were younger or older. Thus, the trend of lower benefit with respect to worsening of EDSS in older patients, but generally larger benefit in delaying upper limb worsening across all age groups may be explained by the fact that while older patients may have accumulated more permanent disability with respect to lower limb function (a major contributor to the EDSS score and therefore the confirmed EDSS worsening assessment), the shorter neuronal pathway for the arms may be less likely to have accumulated sufficient focal lesions and axonal loss to exhaust its reserve capacity.

Table 23: Effects of age and T1 Gd lesions at baseline on ocrelizumab efficacy (hazard ratios and 95% confidence intervals) on measures of disease progression in ORATORIO

	Gd-T1 Negative	Gd-T1 Positive	All patients
12-week confirmed EDSS disability progression			
All patients	0.84 (0.62-1.13)	0.65 (0.40-1.06)	
Pre-specified age subgroups			
Age at baseline ≤45	0.74 (0.48-1.15)	0.52 (0.27-1.00)	0.64 (0.45-0.92)
Age at baseline >45	0.93 (0.62–1.40)	0.85 (0.40-1.80)	0.88 (0.62-1.26)
12-week confirmed 20% increase in 9HPT			
All patients	[redacted]	[redacted]	
Pre-specified age subgroups			
Age at baseline ≤45	[redacted]	[redacted]	[redacted]
Age at baseline >45	[redacted]	[redacted]	[redacted]

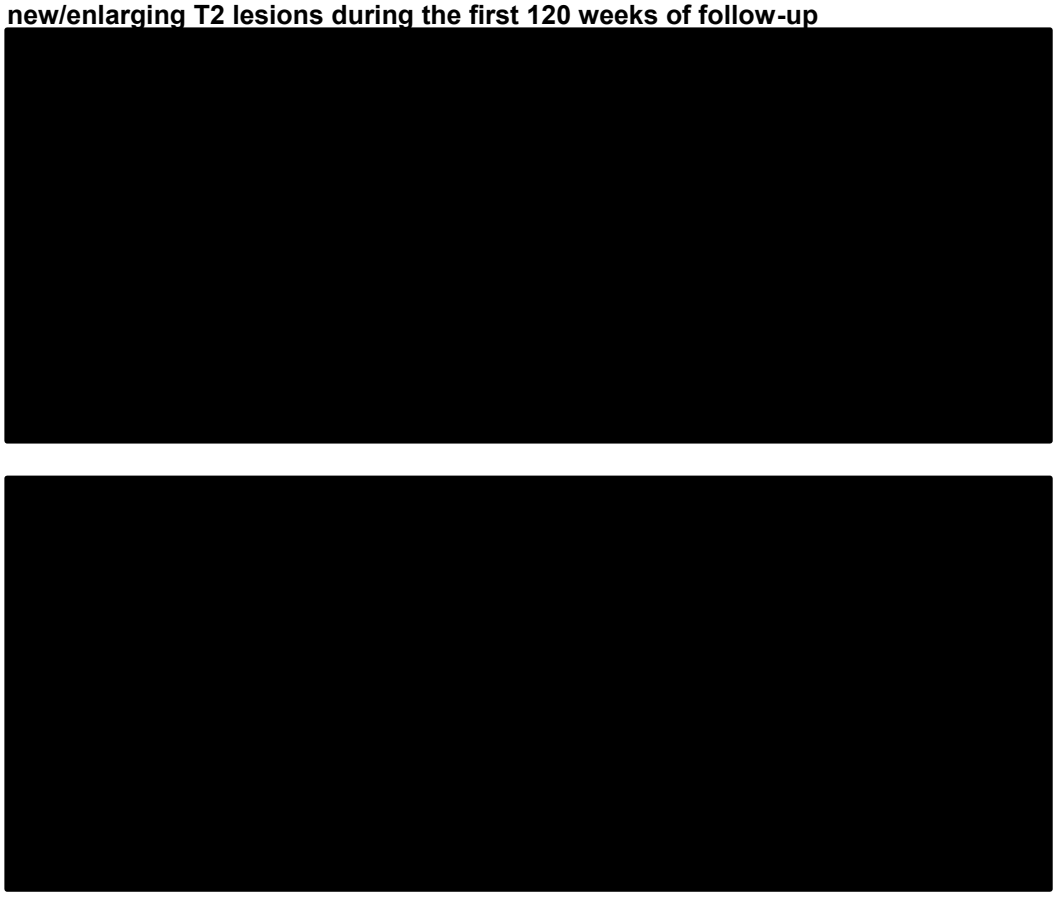
Although the observation that younger patients demonstrated increased benefit versus older patients indicates which patients can potentially obtain more benefit from treatment with ocrelizumab, the primary question is: what explains this observation?

A proxy for age was not identified in the ORATORIO data. Disease duration may intuitively be considered a proxy for age, but the baseline patient characteristic of 'duration since MS symptom onset (years)' did not correlate well with treatment effect. This is likely due to the subjective nature of this variable, as it may be impacted by recall bias and is likely complicated by the delayed diagnosis of PPMS.

Analyses of placebo patients to identify the proportion with acute MRI activity (Gd-T1 or new/enlarging T2 lesions) during follow-up (from baseline to Week 120) in the ORATORIO trial demonstrated that younger patients were more likely than older patients to have acute MRI activity (Figure 14). These longitudinal analyses provide further context of the effects of inflammation, as the MRI active subgroup only takes into account acute MRI activity during a much shorter time-window (between screening and baseline) and G-T1 lesions are transient. Thus, these analyses demonstrate that younger age is associated with higher acute MRI activity and therefore likely explain part of the increased efficacy of ocrelizumab in younger patients.

The intent of presenting the additional subgroup of patients aged 50 years or younger at baseline was not to propose a cut-off for reimbursement but rather to present more context to the efficacy of ocrelizumab in early PPMS patients with acute inflammatory activity, and thus the benefit expected in the label PPMS population for ocrelizumab. Both the pre-specified age subgroup (45 years) and the post-hoc subgroup (50 years) demonstrate that acute inflammatory activity is more prevalent in younger patients, and that the efficacy of ocrelizumab is higher in patients with acute inflammatory activity.

Figure 14: Proportion of placebo patients in ORATORIO with (a) Gd T1 lesions or (b) new/enlarging T2 lesions during the first 120 weeks of follow-up



Literature searching

C2. For the cost-effectiveness and HRQoL literature reviews, the PRISMA diagram (figure 4) and text in appendix G of the company submission refer to 55 full publications and 7 previous HTA submissions. A summary of the 7 previous NICE submissions is provided in in table 25 (appendix G of the company submission), but not for the 55 publications. Please provide a list and, if possible, PDFs of these publications. Similarly the PRISMA diagram and text in appendix H of the company submission refers to 51 included studies. A summary of 24 of these studies is provided in table 35, but not the 27 that were considered inconsistent with the NICE reference case or that only contained two EDSS data points. Please provide a

list of the missing 27 publications and if possible PDFs of these publications. Please could these be sent as soon as possible?

Response:

Apologies for not providing this information in the submission documents.

Here is the list of the 55 publications (referring to 53 unique economic studies) included in **the cost-effectiveness literature review**:

1. Agashivala N, Kim E. Cost-Effectiveness of Early Initiation of Fingolimod Versus Delayed Initiation After 1 Year of Intramuscular Interferon Beta-1a in Patients with Multiple Sclerosis. Clinical Therapeutics. 2012 July;34(7):1583-90.
2. Agashivala NV, Dastani HB, Carlton R, Sarnes E. Cost-effectiveness of fingolimod in treating patients with relapsing-remitting multiple sclerosis. American Journal of Pharmacy Benefits. 2011 November/December;3(6):320-8.
3. Bakhshai J, Bleu-Laine R, Jung M, Lim J, Reyes C, Sun L, et al. The cost effectiveness and budget impact of natalizumab for formulary inclusion. Journal of Medical Economics. 2010 March;13(1):63-9.
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relapsing-remitting multiple sclerosis: a Markov model based on data a Balkan country in socioeconomic transition. Vojnosanitetski Pregled. 2009 Jul;66(7):556-62.
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Here is the list of the 27 publications identified in the **HRQoL literature review** but that were not further described in the submission because they were not consistent with the NICE reference case:

1. Ahmad H, Taylor BV, van der Mei I, Colman S, O'Leary BA, Breslin M, et al. The impact of multiple sclerosis severity on health state utility values: Evidence from Australia. Mult Scler. 2016 Sep 01:1352458516672014.
2. Ahmad H, Van Der Mei I, Taylor B, Palmer AJ. Assessing health-state utility values in Australian people with multiple sclerosis. Value in Health. 2016 November;19 (7):A875.
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7. Daigl M, Jhuti GS, McDougall F, Bennett I. EDSS state and health utility measured by EQ5D in relapsing-remitting multiple sclerosis (RRMS). Value in Health.

2016;Conference: ISPOR 19th annual european congress. Austria. Conference start:. 20161029. Conference end: 20161102 19(7):A435.
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15. Kobelt G, Berg J, Gannedahl M, Eriksson J, Thompson A. Cognition, fatigue and health-related quality of life in patients with multiple sclerosis: Results from a european-wide study. Multiple Sclerosis. 2016 September;22:440.
16. Kobelt G, Berg J, Lindgren P, Fredrikson S, Jonsson B. Costs and quality of life of patients with multiple sclerosis in Europe. Journal of Neurology, Neurosurgery and Psychiatry. 2006 August;77(8):918-26.
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C3. In the clinical effectiveness literature review (page 13 of appendix D in the company submission) it states that 1 trial (16 records) met the eligibility criteria, but only 15 documents are listed in table 3. Please clarify whether this is an error or provide the missing publication.

Response:

Apologies for this mistake. There were indeed 16 records associated with the ORATORIO trial and 1 was accidentally omitted from the list provided on page 13 of appendix D:

Seze, J.; Montalban, X.; McDougall, F.; Sauter, A.; Deol-Bhullar, G.; Wolinsky, J. Patient-reported outcomes in the phase III double-blind, placebo-controlled ORATORIO study of ocrelizumab in primary progressive multiple sclerosis. Multiple Sclerosis. 2016; 22 (Suppl. 3): 677-678.

C4. If possible please provide the PDF for reference 115 cited in document B of the company submission. Please could this be sent as soon as possible?

Response:

Apologies for the omission, these references have now been uploaded to NICE Docs.

C5. If possible please provide the PDFs for references 16, 18, 29, 38 and 40 cited in the appendices document of the company submission. Please could these be sent as soon as possible?

Response:

Apologies for the omission, these references have now been uploaded to NICE Docs.

References

1. European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis. 2015.
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NICE National Institute for Health and Care Excellence

Patient organisation submission

Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	MS Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	We're the MS Society. Our community is here for people with MS through the highs, lows and everything in between. We understand what life's like with MS. Together, we are strong enough to stop MS. We have over 30,000 members and the vast majority of our income comes from voluntary donations and legacies.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have expertise from years of experience working alongside people with MS and their carers. For this submission we have engaged directly with people with MS, asking them to get in touch with us via online platforms as well as contacting neurologists who have been involved in the trials for ocrelizumab to ask them to put us in touch with people who are currently taking it. We specifically asked people who have experience of taking ocrelizumab or feel that ocrelizumab would benefit their MS to contact us and tell us about what it is like to live with primary progressive MS and their experiences of seeking care and treatment.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**Primary Progressive MS** As the name suggests, unlike relapsing forms of MS, primary progressive MS is a progressive form of MS where symptoms gradually worsen over time. This means rather than fluctuating symptoms experienced by people with relapsing MS, people's symptoms worsen from onset. Estimates suggest there are 10,000-15,000 people who have primary progressive MS in the UK and most are diagnosed when they are in their forties and fifties. Unlike relapsing MS where women are three times more likely to be diagnosed, primary progressive MS is only slightly more common in women than men.[1] Living with a chronic, disabling and degenerative condition such as primary progressive MS is hard. It is also expensive. There are often substantial extra costs, such as accessible transport, specialist equipment, medication and help with household activities – a neurological condition like MS can cost, on average, an additional £200 a week[2]. Research into the burden and cost of MS in the UK has found that this significantly increases with disability progression. One study has found that people at Expanded Disability Status Score (EDSS) 0-3 have related costs of £11,400 per year, while those at EDSS 7-9 have related costs of £36,500 per year (costs factored in all health care and resource utilisation related to MS).[3] MS is categorised into primary progressive, relapsing, and secondary progressive, however our understanding of MS is changing. Research now suggests it is a continuous condition with coexisting processes of inflammation and neurodegeneration. Because of this the MS categories are increasingly seen as inappropriate designations. The majority of people with relapsing MS will go on to develop secondary progressive MS (which like primary progressive MS currently has no disease modifying treatments available on the NHS). Studies have found that while disability progression in those diagnosed with primary progressive MS is faster than in people diagnosed with relapsing MS, the age where people reach particular EDSS points are largely similar. This is due to people usually being diagnosed with

[1] Rice CM, Cottrell D, Wilkins A, et al. J Neurol Neurosurg Psychiatry 2013; 84; 1100-1106
[2]Extra Costs Commission, Driving down the costs disabled people face : Final report, June 2015, pp. 13
[3] Thompson et al, Multiple Sclerosis Journal, 2017, Vol. 23 (28) 204-216.

relapsing MS at a younger age. The progression experienced by people who have gone on to develop secondary progressive MS is similar to that in primary progressive MS.[4]

A substantial minority of people with primary progressive MS will experience a relapse even years after their diagnosis.[5] This further highlights why categorising MS into relapsing MS and primary/secondary progressive is problematic.

Diagnosis

Due to the gradual progression of symptoms, it can often take a long time to diagnose someone with primary progressive MS. Diagnosis is done by identifying one year of disease progression (either determined by observing ongoing symptoms or looking at previous symptoms), plus any two of the following measures:

- One or more lesions detected by an MRI
- Two or more lesions in the spinal cord
- Positive tests on cerebrospinal fluid drawn off by lumbar puncture

Coming to terms with a diagnosis of relapsing MS is challenging enough for someone to deal with, but for people who are diagnosed with primary progressive MS it is made all the more difficult by the fact that no effective disease modifying treatments are available on the NHS. While there are a range of licensed options to treat different subgroups of relapsing MS, those with primary progressive MS are told that the best that can be done is to treat their symptoms which will gradually worsen over time. Many describe feeling that they are left 'thrown on the scrapheap', that they 'did not hit the brick wall, it hit me' when told by their neurologist that there is nothing that can be done to alter the course of their disease progression.

"I've been to the depths of despair coming to terms with my diagnosis, knowing the drugs I'm taking can only lessen the pain, discomfort and reduced mobility"

[4] Rice CM, Cottrell D, Wilkins A, et al. J Neurol Neurosurg Psychiatry 2013; 84:1100-1106
[5] Ibid

	Being given a primary progressive diagnosis makes planning for the future difficult as neurologists can't say for certain how MS will affect each person.[6] The symptoms and disability progression each person experience will vary, while some may experience only minor symptoms for years after diagnosis others experience a rapid progression which sees their lives radically altered within just a few short years. For example one study following the natural history of primary progressive MS found that 25% of people had reached EDSS 6.0 within 5 years, but after 17 years 25% still had not reached the same milestone (similar outcomes have been found in other studies).[7] For anyone facing such an uncertain and frightening future, treatments that can offer some amount of assurance are paramount. **Symptoms** In MS, the immune system attacks the nerve cells, resulting in different symptoms depending on which part of the central nervous system is affected. Common symptoms include fatigue, muscle weakness, difficulty walking, bladder problems, pins and needles, dizziness, muscle spasms, pain, visual disturbances and difficulties with memory. These symptoms gradually worsen over time, as they do so people find it harder to stay mobile, in employment and become more reliant on the support of carers. The degree to which each person experiences these symptoms varies but even experiencing one in isolation can be hugely disruptive and difficult to cope with. It is estimated that half of people with MS experience clinical depression. For someone who suddenly finds themselves with restricted mobility, with no hope of improvement, the impact on their life can be huge. The vast majority of people with primary progressive MS who wrote to us in support of this submission wanted to convey how much of an impact walking difficulties have had on their life. Dealing with symptoms such as walking difficulties can be distressing even when they first start to appear. Knowing that it will gradually worsen and that they may well require the use of a wheelchair in the future adds greater distress.

[6] Stellmann J, et al. Validating Predictors of Disease Progression in a Large Cohort of Primary-Progressive Multiple Sclerosis Based on a Systematic Literature Review. Villoslada P, ed. *PLoS ONE*. 2014;9(3):e92761. doi:10.1371/journal.pone.0092761.
[7] Harding KE, Wardle M, Moore P, et al. J Neurol Neurosurg Psychiatry. 2014

"I have been living with MS since 2013 and have gone from walking to needing a walking stick in 3 years. I am 35 years old and watching my prime years go by day by day."

The impact MS has on upper limb function is another symptom which people find incredibly challenging. For those who are dependent on a wheelchair, retaining their upper mobility means the difference between having a level of independence and being almost completely reliant on a carer. As one mother described her daughter's primary progressive MS:

"*Three limbs are totally lifeless and the fourth (her left arm/hand) is virtually useless. She has carers to get her up/wash/dress her, toilet her at lunch/teatime and undress/put her to bed daily. Without her electric bed hoist/electric wheelchair and electric transfer hoist life would stop."*

Impact on family

The impact that symptoms have on a person's ability to engage in everyday activities can be profound. Many people spoke of how their difficulties with walking mean they can no longer fully engage in everyday activities they would like to be doing. One of the most mentioned aspects highlighted by people in support to this submission was no longer being able to be active with their children. This can have a big impact on someone's mental wellbeing: "my heart breaks that I can't be a mum that can take them out and do all the things that mums should do with their children". Numerous parents of young children wrote to us to comment on their fears of the future and what role they will be able to play in their children's lives.

Activities which most would take for granted are affected by having primary progressive MS. Many people commented to us that they no longer take family holidays due to their symptoms and that they have had to move to smaller properties to cope with managing housework and the maintenance of their garden.

Impact on relationships

MS can also impact on people's relationships. For some couples, worries about MS and uncertainty about the future can cause a breakdown in communication and intimacy. MS can also directly cause sexual

	difficulties. Sexual arousal, response and orgasm require messages to be sent between the brain and sexual organs via the spinal cord. If there is nerve damage in the parts of the brain and spinal cord involved, this can cause problems for both men and women. **Impact on Employment** On average people with MS retire from work by the age of 42 due largely to symptoms such as walking difficulties, fatigue and cognitive issues.[8] Only 36% of people with MS are in employment compared with an employment rate of 75% amongst the general population.[9] Of the people who wrote in support of this submission, having to give up work or the fear that they will have to soon was one of the most distressing outcomes of dealing with MS. "To not go to work virtually every day and mix with other people on a day to day basis, has just knocked my for 6" It is clear that treatments are a factor in keeping people with MS in employment. The employment rate for people with primary progressive MS is 12% compare to 53% for relapsing MS.[10] Other research shows how much lower employment rates are for people with more severe MS - 37% for people with mild MS, and only 4% for people with severe MS.[11] Any treatments which delay the onset of more severe MS will have a positive impact on employment rates. **Welfare support**

[8] MS Society, Employment that works: Supporting people with MS in the workplace – APPG Report. 2017
[9] MS Society, Facing the future: Leaving work and MS report. 2018
[10] Data Source: Additional analysis of the MS Society, My MS My Needs Survey, a online and postal survey of 10,888 adults with MS in the U.K. Data was collected between February and April 2O16 by the MS Society. The final data set has been weighted to ensure it is representative of the MS Population, all analysis below excludes those who did not answer. Subgroup analysis of social care related to a sub sample who identified a social care need (n=6261). Full details of the survey are available at www.mssociety.org.uk.
[11] MS Society, Employment that works: Supportin people with MS in the workplace – APPG Report. 2017

	As of November 2016, 23,350 people with MS were in receipt of Employment and Support Allowance (ESA), and a further 1,100 were in the process of being assessed for eligibility for the benefit.[12] Generally the benefits that people receive mean that they have to adapt to live on a much lower income than they would if they had been able to remain in work. 88% of people with MS receiving ESA are on the highest rate of award –Support Group which can be up to £109 a week per person, this is for people who can't work and it is not expected that this will change. Those who are unable to work are also more likely to claim other benefits such as Personal Independence Payments (PIP), with 81% of those not working, and not looking for work claiming PIP.[13] **Impact on Carers** Primary progressive MS presents particular challenges to families and carers which can make balancing work, education and taking care of one's own health and wellbeing difficult. Our research also shows that 85% of people with MS who need care and support receive unpaid care, support or assistance from a friend or family member. This has increased from 71% in 2013, suggesting carers are taking on more of a role supporting people with MS relative to the state or paid support. In addition, 36% of people who need support told us they rely solely on unpaid care (2016). Based on the latest prevalence data and our research, there could be more than 54,000 people with MS in England who need care and support, indicating there are tens of thousands of carers supporting them.[14] Carers support people with MS with a wide variety of essential activities. Our research found 63% of people with MS who need support require help carrying out essential activities of daily living such as getting up in the morning, washing and eating. We found that severity of needs increase with age, as the disease progresses. Treatment's that slow the progression of disability therefore not only benefit the person with MS, but impact on their carer too.

[12] FOI 2590 – response from DWP to request by MS Society (2017
[13] MS Society, Exploring employment support needs, 2017.
[14] Wallace, L., Cavander- Attwood, F., Redfern-Todts, D. Social care and the MS community in England 2016.

	But too many carers tell us they don't get the support they need to continue caring, from respite care to social care for the person they care for, financial support and emotion support. Carers also often act as care coordinators for the person they support, overseeing complex treatment regimens and navigating disjointed health, care and welfare systems. In our survey of over 11,000 people with MS last year, 14% of people with MS consider a family member or carer their main contact for health care support[15]. One carer described just how complex this support network can be: "*Between the nurse, the speech and language therapist, the neurologist and various other specialists, there is roughly a team of twenty involved in my wife's care. She relies on me as a part of this team and to co-ordinate them. It's becomes a big 'project' to manage".* As primary progressive MS is typically diagnosed in people in their forties, many people have young children. We have heard from numerous people and their carers in support of this submission who speak of how difficult they find it to be dependent on their family to help care for both them and their children. *"Without the support (both from social services and our help) she would have to go into full-time care, her husband couldn't work, her daughters would grow up without their mum, with a stressed/heartbroken dad and totally burnt-out aged grandparents, and yet we aren't the only ones, watching, waiting..."*
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	*"Being diagnosed with primary progressive MS is devastating and is a life sentence where the future is uncertain"* While people access a range of symptom management treatments to help them manage primary progressive MS, as there are no disease modifying treatments currently available many people are despondent about their condition. With NHS services coping with financial pressures, specialist services for MS are increasing focused on delivering MS treatments with services less focused on helping people

[15] Redfern-Tofts, D., Wallace, L. and McDougal, A. (2016) My MS, My Needs 2: technical report

	with progressive forms of MS. Of the treatments accessed by people, physiotherapy and exercise regimes are often cited as the most effective ways of managing symptoms. One survey found that the most common treatments for primary progressive MS were home exercise programmes (86% of respondents), followed by physiotherapy (74%). Of the respondents, 70% reported that they felt physiotherapy was beneficial or very beneficial. 13% of respondents said that they could not access any physiotherapy. Treatments for dealing with mobility are predominantly focused on exercise regimes and physiotherapy and it is important that people are able to access services to support this. Our research suggests that 45% of people with progressive forms of MS are currently accessing a physiotherapist.[16] Many people find that fampridine significantly helps with their mobility but this treatment is not currently recommended as cost effective by NICE and is only available to those who are able to pay for a private prescription. Options for treating spasticity on the NHS include baclofen and gabapentin. While these and other treatments work for treating spasticity for some people with MS, our medical advisers have estimated that there is a sizeable portion of people with MS whose symptoms do not adequately respond to these options. They have suggested up to 10% of people with MS would be better treated with a cannabinoid based drug such as Sativex.[17] However this is another treatment which is currently recommended against by NICE for not being cost effective. The results of the MS Trust's 'Is MS Care Fair?' survey, conducted in 2016, found people with progressive MS are much less likely to have seen either a consultant neurologist (55% vs 79%) or an MS nurse (60% vs 79%) than people with relapsing MS in the previous 12 months. They were also less likely to have seen any MS specialist healthcare professionals. Some people with advanced MS who are not followed up by a neurologist may be discharged only to the care of their GP.[18] In our 2016 survey of people with MS we found that the amount of people with primary progressive MS who had had access to a neurologist within the last 12 months was 63%, with access to an MS specialist nurse at 68%.[19] This suggests that there are a large number of people with primary progressive MS who are no longer accessing the specialist services they are entitled to and should be receiving.

	While treatments such as physiotherapy help people to manage their symptoms they do nothing to slow the progression of MS. While many people with primary progressive MS manage their symptoms as best they can, the overwhelming response that we received when we asked people why they would like to try ocrelizumab was that there is an urgent need for disease modifying treatments for this condition.
8. Is there an unmet need for patients with this condition?	Primary progressive MS represents a huge unmet need in MS treatments. Currently there are 14 licensed disease modifying treatments for relapsing MS and 13 available through the NHS but ocrelizumab is the only licensed disease modifying treatment for primary progressive MS. People with primary progressive MS have watched and waited while licensed treatments for relapsing MS have increased and become more effective and easier to take. NICE should take into account the huge impact that this treatment will have in reducing disability progression and offering people a new hope.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	**Trial results** In a phase 3 trial, ocrelizumab reduced MS progression by 25% in people with primary progressive MS. This was compared with a placebo over the course of two years. The scientists focused on symptoms defined in the Expanded Disability Status Scale, these include problems with walking, thinking and swallowing.

[16] Data Source: Additional analysis of the MS Society, My MS My Needs Survey, a online and postal survey of 10,888 adults with MS in the U.K. Data was collected between February and April 2O16 by the MS Society. The final data set has been weighted to ensure it is representative of the MS Population, all analysis below excludes those who did not answer. Subgroup analysis of social care related to a sub sample who identified a social care need (n=6261). Full details of the survey are available at www.mssociety.org.uk.

[17] MS Society, Cannabis and MS, 2017

[18] MS Trust, Is care fair? 2016

[19] Data Source: Additional analysis of the MS Society, My MS My Needs Survey, a online and postal survey of 10,888 adults with MS in the U.K. Data was collected between February and April 2O16 by the MS Society. The final data set has been weighted to ensure it is representative of the MS Population, all analysis below excludes those who did not answer. Subgroup analysis of social care related to a sub sample who identified a social care need (n=6261). Full details of the survey are available at www.mssociety.org.uk

At 12 weeks the percentage of confirmed disability progression for the people on ocrelizumab was 32.9%, while it was 39.3% for those on placebo. At 24 weeks, the percentage of people with confirmed disability on ocrelizumab was 29.6% compared with 35.7% on those on the placebo. The difference from the beginning to week 120 in a timed 25 foot walk was 38.9% with ocrelizumab compared to 55.1% with placebo.

The team also found that treatment with ocrelizumab decreased the total volume of brain lesions seen on MRI, whereas lesion volume increased in those treated with placebo.

The benefits of hope

"Having access to a drug that could slow the progression is a dream, one which I now have a hope of becoming a reality"

As primary progressive MS treatments are currently an unmet need, one of the most important benefits that ocrelizumb offers people is hope for the future. The negative impact on mental health that being diagnosed with an untreatable progressive condition has cannot be overstated. Some people have commented to us that they hope ocrelizumab will help slow their progression until more effective treatments are established. Other people hope that ocrelizumab could be even more effective than the trials have indicated so far, giving them a chance to get some mobility back so that they can again engage in everyday activities, such as walking to the shops or even to the bathroom without difficulty. Others have more modest hopes that ocrelizumab will slow their disability progression allowing them to stay active for longer so that they can keep providing for their family. For many others the thought of being able to achieve important milestones in life that they currently feel will be impossible is inspiring. One person spoke of "maybe being able to walk my daughter down the aisle one day", another spoke about taking "my son to football matches without worrying how far I would have to walk".

Around 50% of people with MS will experience clinical depression at some point.[20] For people with primary progressive MS struggling to manage their physical symptoms clinical depression is common and

[20] Sadovnick,et al, Neurology Mar 1996, 46 (3) 628-632; DOI: 10.1212/WNL.46.3.628

	many people take medication to treat it. A number of people who experience mental health issues because of their MS have commented to us that ocrelizumab would have a positive impact on their mental wellbeing. **Helping people with MS to stay in work** *"Having to be interviewed/examined by the authorities continually just to get my NI stamp paid and PIP, when my condition is progressive is extremely frustrating, especially as I worked all my life and paid my taxes."* As previously stated the average retirement age for people with MS is much lower than the general population with the number of people requiring welfare support much higher. For those who are still in work the fear of having to retire early and to seek financial support is a particular worry. A point raised by many people with MS as to why they want ocrelizumab was to help keep them providing for themselves and their family. With many people specifically calling for NICE to take this into consideration. **Positive impact on lifestyle and carers** People with MS often need support from family and/or friends to help them to manage the impact of having MS, to help them remain independent and lead a fuller life. This includes support with everyday tasks like washing and dressing and getting out and about. As disability progresses the need for this support increases and the impact on carers can be greater. Recent research by the MS Society showed that the proportion of people with MS who received care, support or assistance from a friend or family member had increased from 71% to 85% from 2013 to 2016.[21] If people had access to ocrelizumab and were able to decrease the progression of disability there would be less need to rely on support from carers. This was brought up frequently by people who wrote to us in support of this submission, many of whom are concerned about the impact their MS has on their family.

[21] Wallace, L., Cavander- Attwood, F., Redfern-Todts, D. Social care and the MS community in England 2016

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The most commonly reported side effects within the clinical trials were infusion related reactions. 40% of people who received ocrelizumab reported at least one infusion related reaction compared to 26% of the placebo group. There were also more upper respiratory tract infections within the ocrelizumab group than in the placebo group.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The licence for ocrelizumab for primary progressive MS stipulates that inflammation must be identified through an MRI scan which means those who's MS is predominantly neurodegenerative are less likely to respond. As ocrelizumab has been shown to slow progression of disability it is important that people are diagnosed and treated as early as possible to get the best results from treatment. At the same time the importance of upper limb function for people whose disability as progressed to EDSS 7 is not captured as well in clinical trial data but is incredibly important in protecting.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The licence for ocrelizumab stipulates it is for 'early primary progressive MS' but other than stating that there must be disease activity identified by an MRI scan, what is classified as 'early' is not clarified. Any NICE decision to approve this treatment based on the age of a person or time since diagnosis would potentially lead to equality issues and needs to be considered carefully. Especially considering that these parameters do not clearly determine what each person's EDSS score would be.
Other issues	
13. Are there any other issues that you would like the committee to consider?	The majority of clinical trials for MS treatments have focused on relapsing MS, where people are diagnosed earlier and the effect of the treatment can be ascertained by the subsequent reduction of relapses, amongst other factors. Studying the effects of a drug on people with progressive forms of MS presents greater challenges. Those involved are likely to be at a higher EDSS score yet need to be assessed by the impact the treatment has on the disability progression alone. This means that longer trials are needed which take greater account of how upper limb function is impacted. When assessing the evidence NICE should consider that treatments for primary progressive MS are currently an unmet need with ocrelizumab the only licensed option. Therefore if the evidence is not considered cost effective it is vital that an agreement is agreed which facilitates access to ocrelizumab while more evidence is collected.
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission:	

- Primary progressive MS is currently an unmet treatment need
- Ocrelizumab has been shown to be effective at treating people with ‘early primary progressive MS’
- The first treatment for primary progressive MS available on the NHS would enable people to take control of their lives and maintain their independence, thereby reducing productivity and societal costs associated with living with MS.
- Ocrelizumab would have a positive impact on people’s mental wellbeing as it offers many people hope for the future.
- Ocrelizumab would have a positive impact on the carers and family members of people with primary progressive MS.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Ocrelizumab for treating primary progressive multiple sclerosis

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Multiple Sclerosis Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MS Trust is a UK charity dedicated to making life better for anyone affected by MS. The MS Trust is in contact with over 40,000 people affected by MS - that's people with MS, their families, friends and the health care professionals who help manage MS. Our core belief is that the best outcomes will come from well-informed people with MS making decisions in partnership with their specialist health professionals, and our aim is to support both sides of this partnership as much as we can. We provide expert information to help people with MS manage their own condition, and, uniquely, we inform and educate the health and social care professionals who work with them about best practice in MS treatment and care. We receive no government funding we are not a membership organisation. We rely on donations, fundraising and gifts in wills to fund our services.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have prepared this submission based on our experience of supporting people affected by MS at all stages of the condition. We speak daily to people who are dealing with issues relating to MS: coping with the impact of diagnosis, coping with physical, emotional and financial consequences of MS. Working with people with primary progressive MS (PPMS) and MS specialist health professionals, we have published a book which covers the physical and emotional aspects of living with PPMS and the ongoing management of the condition. The publication can be viewed on our website: Primary progressive multiple sclerosis

	To gain further insight into the views of those affected, we conducted an online survey of people with PPMS, their families and specialist MS health professionals, receiving nearly 500 responses (31 January – 14 February 2018). Their experiences provide a valuable personal perspective on living with PPMS, the impact it has on quality of life, and their perception of ocrelizumab. All of these sources have informed our submission.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Primary progressive MS (PPMS) is a complex and unpredictable condition which has an impact on all aspects of life - physical, emotional, social and economic. These are profoundly important not just for the person diagnosed with MS, but for their families as well. Approximately 10% of those with MS have PPMS; in England, of the 90,000 people, about 9,000 will have PPMS. PPMS is a form of MS in which disability increases from the outset. The rate of disability progression varies between individuals. For some, disability may progress very gradually, and may remain stable or even improve very slightly over a short period. For others the progression is more rapid and unrelenting. Although the degree of disability will vary, the uncertainty of prognosis is universal. From the early stages of PPMS, quality of life is markedly affected and deteriorates as the disease progresses. Common symptoms such as cognitive function, bladder and bowel issues, and fatigue impact on day-to-day activities and the ability to work, which in turn influence a person's mental state. Increased disability imposes a heavy burden on people with MS and on their extended families, who often act as informal carers. It also leads to substantial economic losses for society, owing to diminished work capacity for the person with PPMS as well as loss of employment for their partners who become full-time carers. **Diagnosis:** The majority of people with PPMS are diagnosed in their 40s and 50s[1] but can be diagnosed at a younger age; nearly 10% of our survey respondents were aged 25-44. Diagnosis can be slow as the initial

[1] Rice CM. et al. Primary progressive multiple sclerosis: progress and challenges. J Neurol Neurosurg Psychiatry. 2013 Oct;84(10):1100-6. https://www.ncbi.nlm.nih.gov/pubmed/23418213.

	symptoms, such as fatigue or difficulties with walking, can be dismissed or misdiagnosed by GPs leading to years of delay in referral to a neurologist. Indeed, several survey respondents commented that they had to see several neurologists before receiving a diagnosis. As a result of these delays, people may have already had PPMS for some time before being formally diagnosed. Since ocrelizumab is most effective in early active PPMS and cannot reverse disability already accrued, it is vital that delays in diagnosis are eliminated. At diagnosis, many respondents described a sense of relief at finally having an explanation for the health problems they had been experiencing followed by fear for the future knowing that PPMS is a deteriorating condition and desperation at being told there is no treatment available. **Physical impact:** In the majority of people with PPMS, the spine is predominantly affected by MS lesions, leading to symptoms which affect the lower part of the body. Our survey asked people with PPMS how the condition affected them physically; out of 231 responses to this question, the symptoms most frequently selected were mobility problems (95%), balance and posture (91%) and fatigue (89%). Response to the full list of symptoms is shown below – this clearly shows the range of symptoms affecting people with PPMS: • 95% Mobility problems • 91% Balance and posture • 89% Fatigue • 74% Bladder problems • 71% Spasticity and spasms • 57% Pain and sensory problems • 48% Bowel problems • 47% Sexual difficulties • 44% Depression and anxiety • 36% Cognitive problems • 18% Vision and hearing • 20% Speech and/or swallowing

People experience multiple symptoms; on average respondents selected 7 symptoms from this list. Secondary symptoms arise as a consequence of the problems that MS brings. These may include falls due to walking or balance problems, muscle pain as a result of added strain on the back or legs caused by changes to gait, weight problems if there are mobility or swallowing issues, or the development of pressure sores due to lack of mobility.

The effect of these symptoms is compounded, leading to increasing disability: survey respondents were asked to select their physical ability:

- 21% I can walk without help for at least 100 metres and largely look after myself
- 66% I need a stick, frame or wheelchair to get around and do need help with specific activities, but largely look after myself
- 13% I am dependent on a wheelchair or spend the majority of time in bed, and need a great deal of help with daily activities

- *I have difficulty preparing meals as I am naturally right handed and I no longer have any strength in my right hand or arm. Also very little strength in my right leg and foot as I have foot drop on that foot. Dressing is also a problem.*
- *Have had several bad falls which on a couple of occasions resulted in other injuries one in particular with a damaged knee which now further affects my mobility.*
- *Bowel problems were horrible. At times not only messing myself but also bedding. Taking showers at all times of night, not being able to leave home worried of accidents. Pain and spasticity an issue until my GP found correct mix of drugs to help.*

Emotional impact:

PPMS can take a heavy toll emotionally; many respondents reported anxiety, depression, frustration, anger, isolation/abandonment and struggled to come to terms with loss of the life they had planned for.

- *I am on antidepressants often very tearful as feel such a failure as a mum and wife. I hate the progression of this disease robbing me and my family of a quality life.*
- *I get anxious, and very low and take antidepressants to help me. I have bad mood swings.*
- *From being self-confidant and self-reliant I now have to rely on others. My relationship with my husband was always of equal partners and now I feel that balance has changed.*
- *Very frustrating that I have to rely on my husband in everything I do. I can't leave the house on my own. Can't go upstairs alone.*

- *It's been a bit of a rollercoaster. I get so angry it comes out as red rage. Other times I am so sad. I'm angry about all the time and money I spent on my education, all of the missed opportunities because of work, saving for a future that will never come etc etc I feel like I wasted half of my life preparing for something that can never happen now. The other half of my life is going to be spent in a wheelchair and eventually in bed. My friends have deserted me because I'm too slow or unreliable. PPMS makes me sad and lonely.*

Others work hard to maintain a positive mental attitude, often with the support of partners:

- *With my wife as my carer we have stayed strong and positive. Together we have kept going.*
- *I haven't time to feel sorry for myself. Don't get me wrong, frustration in not being able to do things for myself can lead to a wobble, then I give myself a shake and soldier on.*
- *Initially I was very sad. Once diagnosed, my neurologist recommended I take part in an NHS run Mindfulness course - this was extremely useful for learning to control my emotions*

People with PPMS and their families go to great lengths to remain active and independent and do whatever they can to stay in work. This often involves paying privately for treatments with limited availability through the NHS, such as physiotherapy, or treatments which are not available, such as Sativex and Fampyra.

- *At the moment I am paying £200 every 4 weeks for a drug for ppms.*
- *I am already paying for medication for ppms as there's not much else that helps*
- *Family support has been brilliant. Friends are very understanding and want to help with wheelchair or carrying things, though I can't go everywhere I would have done previously. I feel guilty that my husband is now my carer.*
- *Still positive, organised a weekly home visit physio, home carer three hours a week, gardener, chiropodist*
- *I have a PA weekly who can take me out in my converted car. I avoid crowded noisy places and parties as they stress me out. I have stopped distance travel and holidays. Fatigue is a major factor in my M.S. I do have a lovely big house and garden so these have become a reasonable alternative and I ask people to come to me. I enjoy shopping on Sundays (quieter). In the same way I have a list of restaurants and places to visit that can accommodate me in the wheelchair. M.S. has changed my social life but not ended it, I lived to work. I miss traveling outside U.K. the most.*
- *For the first year of my ill health retirement I was physically and emotionally exhausted and only went out once a week with my partner when she was on her days off. Most time was spent sleeping or watching television sadly. After reaching a particularly low spot for both of us, I agreed to support from a carer. This was organised through collaboration by health and social care. We also got involved with the local M S society on Wirral. Attendance at therapy classes eg. Tai Chi and Chair exercises along with psychological support from other service users and carers staff has been life saving for both of us.*

Social impact:

As PPMS progresses, people increasingly lose their independence and social activities require considerably more planning. Symptoms of PPMS, such as bladder and bowel incontinence can make activities particularly challenging; other aspects of PPMS can make people feel very self-conscious. For those who live alone, social isolation becomes a major concern.

- *I don't like being with people I don't know. I'm embarrassed because I can't use my hands properly so I have to have food cut up for me and I can't hold a glass or cup properly.*
- *I am totally isolated except for care givers visits*
- *I hardly go out socially in public as worry about falling and people looking at me*
- *It has made it impossible to go out alone and dramatically cut back on holiday and outing choices*

Economic impact:

Although NICE cost effectiveness calculations do not take account of the burden of loss of work, remaining in work is of critical importance to people with PPMS, not only for economic reasons but also for maintaining social contact and a sense of purpose. Survey respondents frequently mentioned their efforts to continue in paid employment (sometimes at the expense of social activities) or expressed regret at the loss of a working life and economic independence. Out of the 234 survey respondents, just 12% were in paid employment, a further 12% had had to reduce working hours since diagnosis, and 40% reporting that they had stopped work early or were unable to work due to ill health. A treatment which delays progression is seen as having the potential to help people with PPMS stay in work for longer.

The impact on work of the different types of MS have not been studied in the UK population but results from Scandinavian studies might be expected to apply to the UK. A Norwegian study conducted[2] in 2014 reported that just 14.8% of people with PPMS were employed full or part-time, compared with 66.1% with relapsing remitting MS and 24.3% with secondary progressive MS. Similarly, a Swedish study[3] reported that people with PPMS had significantly lower income than people with relapsing MS.

- *My son-in-law was just 34 when he was diagnosed, my daughter was expecting their first baby. Our world was shattered. We have seen him go from a walking stick to a frame to a wheel chair. He goes to work with great difficulty*

[2] Boe Lunde HM et al. Employment among patients with multiple sclerosis – a population study. PLoS One 2014; 9(7): e103317. https://www.ncbi.nlm.nih.gov/pubmed/25054972

[3] Kavaliunas A et al. Income in Multiple Sclerosis Patients with Different Disease Phenotypes. PLoS One. 2017;12(1): e0169460. https://www.ncbi.nlm.nih.gov/pubmed/28081163

	and the help of the people there to get him into the wheel chair and into the office and the same at home time. My husband follows him home to help him out the car and into the house. • *I am employed full time, so by the time I get through my work week, and the necessary household chores, I don't have much energy for much of a social life. Luckily I have an extremely supportive husband and family who understand my limitations. But I still have to be very conscious about what activities I take part in and it is a balancing act. Getting errands done requires careful planning due to my fatigue. Any decision to take part in social activities is a balancing act and something else has to be taken off of the list.* • *My position as a pharmacist was eliminated and I have been unable to find a job. My mind has not been affected, but confined to wheelchair so basically the only part of body that worked well is not being used. Loss of income, loss of motivation to keep going and reason to get up in the morning. Husband has become caregiver which has changed our relationship negatively.* • *I get so tired that I find it difficult to meet up with friends or go out socially. I use all my energy to continue in paid employment.* • *I have gone from running my own company employing over 20 people, to being unable to work and reliant on benefits within a few years. My wife has had to give up work (and a decent pension) to look after me.* • *Through losing ability to keep in employment, have struggled to have meaning in life, which leads to depressed state.* • *I stayed in employment, at a managerial level, for 5 years following diagnosis of PPMS. Thanks to the gradual erosion of abilities, particularly cognitive abilities, due to the disease, I have lost employment and cannot now even sustain employment at a junior level.* • *I want to be as active a member of society as I can be, to continue in employment and pay my taxes.* • *Through losing ability to keep in employment, have struggled to have meaning in life, which leads to depressed state.* **Caregiver impact:** PPMS does not only impact the person diagnosed with it, but also family and friends who may provide informal care. With increasing disability, people with PPMS become more and more dependent on carers for their personal care and in order to access activities outside the home. This can strain relationships, as family members may need to take on additional responsibilities. Caregiving partners may feel uncertainty about the future, financial difficulties, social disruption and isolation.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Management of PPMS focuses on four key areas: symptom management; prevention of complications; maintaining function and promoting general health and wellbeing. Given the wide range of symptoms that people with PPMS may experience, it is important that there is access to a range of therapies delivered by skilled allied health professionals, competent in MS care. These health professionals are generally engaged according to patient need for episodes of treatment focussed on individual problems and goals. In reality, access to NHS and social care interventions to support people living with PPMS such as physiotherapy or neurorehabilitation are limited, sporadic or even non-existent. The quality of and access to care is highly dependent on where someone lives. Calculation of the cost of providing "established clinical management" cannot assume an ideal situation where these services are readily available. Our survey asked people with PPMS about contact with MS specialist health professionals in the last 12 months. • 70% had seen a neurologist • 63% had seen an MS nurse • 9% had seen neither, but would have liked to • 5% had seen neither, but by choice We are aware that in some areas, people with PPMS have been effectively 'discharged' from MS services, either due to a perception that there is no 'treatment' available for PPMS or due to limitation in service capacity. Overwhelmingly, the message that people receive from MS health professionals is that there is no treatment available for PPMS. Our survey respondents also reported how often they had used other NHS services; those most frequently accessed include: • 17% A&E • 27% Continence advisor • 14% Community/district nurse

- 14% Other specialist nurse
- 10% Rehabilitation medicine team
- 73% Family doctor
- 45% Physiotherapist
- 32% Occupational therapist
- 12% Orthotist
- 15% Chiropodist

A number commented that access to care, particularly physiotherapy, was inadequate or they had to pay for private treatment.

- *I'm on so many waiting lists I've lost track (some have been months)*
- *Long waiting time if I need to see someone.*
- *Poor provision for services in the area. i see a physio privately, private hydrotherapy, private reflexology, private medication. Without this I feel I would definitely be more disabled.*
- *Access to physiotherapy, dietitian etc just doesn't happen on NHS. I have had to seek these privately. Or via the local MS Therapy Centre*

"Established clinical management" is not defined in the final scope, but it is clear from the data collected in our survey that people with PPMS have a high level of need for NHS care. There is currently no research or professional consensus on what "established clinical management" is or how much it costs; any definition will be idealistic. It is unrealistic to assume that all people with MS have access to high quality care that fully meets their needs. The reality is that people with MS often have very limited access to services. The quality of and access to care is highly dependent on where an individual lives. An MS Society report found that 40 per cent of MS specialist centres failed to offer people with MS a truly multi-disciplinary clinic[4]. This was also reflected in the Royal College of Physicians national audit of services for people with MS which found only 43% of people said they knew they had access to specialist neuro rehabilitation and 57% said that they had access to specialist MS physiotherapists.[5] In 2011 the National Audit Office report for services for people with neurological conditions found that the case loads of MS

[4] MS Society, MS 2015 Vision, (2011)
[5] RCP and MS Trust, National Audit of services for people with Multiple (2011)

	nurses varied extensively in each Strategic Health Authority[6]. A more recent survey[7] conducted by the MS Trust in 2016 found that on average, people with progressive MS are seeing MS specialists much less often than people with relapsing MS.
8. Is there an unmet need for patients with this condition?	Time and again respondents to our survey commented that there is currently no treatment to delay the progression of PPMS, nothing that can change the prognosis of their condition. Many people are doing all that they can to minimise the impact of PPMS, but they are all too aware that there is nothing that will slow down the progression of their disease. • *I was told a slow gradual decline towards a wheelchair with no drugs to help on the way* • *Took ages to get a diagnosis. Over 2 years. Then got told nothing could be done and likely to be in a wheelchair within 10 yrs. Thanks, bye, next! No support, no help.* • *My neurologist goes through the motions but there is nothing he can prescribe for PPMS* • *The NHS services can diagnose PPMS and inform you that you have a life changing incurable neurological condition that at present they have no treatment for. This is devastating. My daughter was diagnosed with MS over a year ago (she is 34 now). Although she was assessed by a very experienced neurologist he told us there was presently no licenced drug treatment for PPMS and therefore there was nothing he could do other than monitor her symptoms.* • *Very poor, my daughter has not seen a consultant for over two years, she has district nursing care and drugs to deal with symptoms but nothing to stop or slow down the deterioration* In the absence of a treatment that will stop or slow down deterioration, the biggest unmet need remains access to the full range of NHS services on demand and coordination of services to ensure rapid referrals at times of critical need. • *Until suitable drugs are available, I feel that REGULAR and adequate physiotherapy should be offered as a matter of course, along with counselling.*

[6] National Audit Office. Services for people with neurological conditions (HC 1586). TSO, 2011
[7] MS Trust. Is MS care fair? MS Trust; 2016

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The clinical trial data[8] have demonstrated the effectiveness of ocrelizumab at delaying progression in PPMS: • Fewer people taking ocrelizumab had an increase in disability, compared to placebo. An increase in disability which lasted 12 weeks was seen in 32.9% of those taking ocrelizumab and 39.3% of those taking placebo. In addition, increased disability which lasted at least 24 weeks was seen in 29.6% taking ocrelizumab and 35.7% taking placebo. Comparing the two groups, people taking ocrelizumab were 24% less likely to have an increase in their disability than those taking placebo. • After 120 weeks of treatment, walking speed over 25 feet was 39% slower for ocrelizumab compared to 55% slower for placebo. Brain lesion volume decreased by 3.4% with ocrelizumab and increased by 7.4% with placebo. Loss of brain volume was 0.9% for ocrelizumab and 1.09% for placebo. • Ocrelizumab treatment lowered the risk of progression of upper extremity disability, as measured by the 9 hole peg test, compared with placebo.[9] The overwhelming majority of people with PPMS are delighted that there is, at last, potential to slow down the progression of their condition; over the years as the number of treatments available for relapsing MS have grown, people with progressive MS have felt that their needs have been forgotten. Many respondents to our survey recognised that their PPMS may be too advanced to gain a benefit, but believed others should be given the opportunity to take a medication that would slow down progression. The benefits of slowing down progression are seen as maintaining mobility and independence for longer, allowing people to continue to work for longer, and saving costs for the NHS in the long term by preventing progression and the need for MS services and social care.

[8] Montalban X, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. New England Journal of Medicine 2017; 376: 209-220. https://www.ncbi.nlm.nih.gov/pubmed/28002688

[9] Fox EJ, et al. Effect of ocrelizumab on upper limb function in patients with primary progressive multiple sclerosis in the ORATORIO study. ECTRIMS Online Library. Fox E. Oct 27, 2017; 200891.

	While some have high expectations, anticipating improvement in mobility and other symptoms, others are more realistic about what it could offer them. There is a general recognition that ocrelizumab is not a cure for PPMS. • *if I could preserve my hand function it would mean I could remain mainly independent which would benefit everyone.* • *Although I have limited mobility it is my hands deteriorating that I would like to slow or stop* • *Ocrelizumab is the first treatment EVER for PPMS, I have done everything I can for myself, without this treatment, I will be accumulating disabilities much faster if I am not allowed to have this treatment.* • *Yes I think it should be prescribed by the NHS. Any hope of delaying the onset of worsening symptoms would improve not only my prospects but also of my wife and children - aged 11 & 14.* • *It should be prescribed by the NHS because it is the only current medication which has been shown to slow the progression of PPMS. Quite apart from the benefit to the patient, it would be cost-effective for the NHS, since it would lessen the chances of further treatment and/or social care being needed further down the line.* • *Ocrelizumab should definitely be prescribed on the NHS. The evidence to date indicates it can have an effect on slowing progression. Progression must be slowed to ensure individuals can remain active, can remain in employment and can remain as productive members of society. The existing bleak outlook of no treatment and no hope can be challenged by ocrelizumab as it is being challenged in other countries where ocrelizumab is now being used.* • *Even a marginal improvement in my mobility would have a significant impact on my QOL and ability to work & earn.* • *Could be life changing for me, may be able to stay in full time employment and still pay tax* • *As someone with very early stage PPMS i believe ocrelizumab should be prescribed by the NHS as studies have shown it can ease progression of MS. My neurologist tells me the earlier this treatment is available to people like me the better to delay any progression. It is very hard to be told you have a progressive illness where no treatment is currently available* • *I do think ocrelizumab should be prescribed on the NHS. I want the chance to have the progression of my MS slowed, this would enable me to continue in paid employment in a job I enjoy. I want to remain mobile and to be able to look after myself.* • *I of course think it should. I have no other drug available to me for PPMS to help slow progression. At this stage, I don't need support from health care providers (although I would like more). I can walk unaided and generally live a full life, with a positive attitude. However I am aware my symptoms are getting worse, my mobility and cognition are in decline, which in is increasing anxiety and depression. This will only get worse. If I am not able to access something to slow progression I would imagine I will require more medical intervention costing the NHS in the not too distant future. Whilst I still have some mobility it makes sense to help me to maintain it for as long as possible so it takes longer for me to become a burden on NHS resources. I would hope this alone would make the drug cost effective.*

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Very few people expressed reservations about ocrelizumab. One person expressed concerns about risk of cancer, another felt the treatment effect was small and not enough to consider taking the drug. Expectations of treatment will need to be managed; people will need to be counselled that ocrelizumab will not necessarily make them better, but will slow down the rate at which they get worse. Undoubtedly, there will be disappointment when some people learn that they are not eligible for ocrelizumab. Experieince gained from MS teams in the United States and other countries where ocrelizumab has been approved for PPMS will be invaluable to manage expectations and identify potential risks.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Ocrelizumab has been licensed by the EMA for early, active PPMS. Active PPMS is defined in terms of MRI evidence. However, “early” PPMS is not defined other than by reference to the ORATORIO inclusion criteria. We anticipate that the definitions of “active” and “early” will be further refined during the course of the appraisal. To ensure people have access to treatment early in the course of their PPMS, it is paramount that delays in diagnosis are minimised.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**None.**
Other issues	
13. Are there any other issues that you would like the committee to consider?	The dosing schedule consisting of two initial infusions, followed by infusions every six months offers a very practical regimen which will minimise the impact on family and work commitments, reduce the impact of side effects. Experience from treatments for relapsing remitting MS has shown that this type of treatment pattern is often preferred over more frequent dosing (such as taking tablets daily) and ensures a higher level of adherence. Side effects are limited to a day or two following an infusion (and became milder after the first infusion).
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission: • Primary progressive MS is a life-long condition which is characterised by increasing disability from the outset • Increasing disability has an impact on physical and emotional well-being for the individual and on family members who act as informal carers, causing anxiety, depression, and leading to breakdown in relationships	

- PPMS has significant social and economic impact as people are less able to work and contribute to society in a way that has meaning for them
- Current management of PPMS is inconsistent as access to appropriate therapies is difficult or only available through private healthcare – which for those unable to work or on low incomes is not an option
- Ocrelizumab is the first treatment which has been shown to slow down progression, which in turn improves health outcomes and thus alleviates the impact of PPMS

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Multiple sclerosis (primary progressive) – ocrelizumab

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Association of British Neurologists**

3. Job title or position	**Professor Neuroimmunology, [redacted]** **Consultant Neurologist, [redacted]**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The Association of British Neurologists is the professional society for neurologists and clinical neurology researchers in the United Kingdom; it has 800 members. The aim of the Association of British Neurologists is to promote excellent standards of care and champion high-quality education and world-class research in neurology. It is funded by member subscription.**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No.**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	**The aim of ocrelizumab is to reduce the accumulation of disability in people with primary progressive multiple sclerosis.** **It is unclear how ocrelizumab works to reduce disability accumulation. Its known effect (to deplete B cells) and the characteristics of patients who particularly benefit (see below) suggest that is anti-inflammatory. However, other effective immunotherapies have failed to impact progression in this**

or prevent progression or disability.)	**form of multiple sclerosis. Either the specificity of the drug for B cells is important (perhaps through acting indirectly on meningeal follicle formation) or it acts through another mechanism.**
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	**There is no precedent for a treatment of primary progressive multiple sclerosis, so there has been no opportunity to arrive at a consensus of a clinically significant treatment effect. We expect that this will be an important part of the discussions at the NICE appraisal.** **The primary endpoint of the ORATORIO trial was the % of patients with disability worsening (by one or 0.5 Kurtzke point over 3 months depending on the baseline EDSS score), which was 33% with ocrelizumab versus 39% with placebo (a 24% relative risk reduction) representing a hazard ratio of 0.76; 95% confidence interval 0.59 to 0.98; P = 0.03. The results of the analyses of the other end points were consistent with the primary results, with the exception of the physical component-related quality of life, which did not differ between treatment and placebo.**
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	**There is an overwhelming unmet need. There is no other treatment which is licensed to reduce disability progression in primary progressive disease.**
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	**Supportive care only, but which we mean attending to the symptoms of the disease and consequences of progressive neurological disability.**

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	**Multiple sclerosis. Management of multiple sclerosis in primary and secondary care** **Issued: November 2003, NICE clinical guideline 8** **For patients with relapsing remitting MS and for symptoms management:** **http://pathways.nice.org.uk/pathways/multiple-sclerosis** **NICE Pathway last updated: 05 December 2017**
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	**The diagnosis of primary progressive multiple sclerosis is made by a neurologist, but thereafter pathways of care differ, but often do not involve multiple sclerosis specialist neurologists. The MS Trust has documented that fewer people with primary progressive multiple sclerosis had seen either a consultant neurologist (55% vs 79%) or an MS nurse (60% vs 79%) compared to those with relapsing-remitting multiple sclerosis in the previous 12 months [MS Trust, Is care fair? 2016].** **In the best of centres, patients with an established diagnosis are managed in multidisciplinary clinics with an emphasis on rehabilitation and holistic care. In many centres, specialist nurses take over care, referring on to specialities as necessary. However, we recognise that significant numbers of people with primary progressive multiple sclerosis become disenchanted and disengage with medical services.** **As disability progresses, people with primary progressive multiple sclerosis increasingly require the support of social services.**
• What impact would the technology have on the current pathway of care?	**There are 10,000 to 15,000 people with primary progressive multiple sclerosis in the UK and all activity associated with this prevalent population, assessing the eligibility of these patients for**

	ocrelizumab and then administering it, would be a considerable <u>new</u> activity for MS therapy services. **The first impact will be on clinicians' definition of primary progressive multiple sclerosis. Varying definitions may explain the difference in prevalence of this type of MS between cross sectional (20% of all cases of MS) and prospective (10%) studies.** **Not all prevalent patients would be eligible for ocrelizumab. Its license (EMA) is for "adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity". These criteria are unclear, and need to be further defines, but would probably would include 25-50% of the prevalent population.** **We estimate that 6,000 to 8,000 of prevalent patients will be referred to disease-modifying therapy clinics, for assessment as to eligibility for ocrelizumab. Perhaps 2,000 will not meet the disability and disease duration criteria, meaning that 4,000 to 6,000 will undergo a brain MRI scan with gadolinium (which they otherwise would not have). Given that enhancement can be found in 40% of people with early primary progressive MS (Ingle 2005), between 1,6000 to 2,400 patients would be require ongoing monitoring, and administration of ocrelizumab every 6 months at infusion centres.** **Once the prevalent population has been assessed and treatment started, MS services would then have to contend with the lesser impact of the incident population which is around 500 patients/year.**
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	**There is no current care for the use of ocrelizumab, but its parent molecule, rituximab, is in wide use throughout secondary healthcare (although not in multiple sclerosis).**

• How does healthcare resource use differ between the technology and current care?	**As documented above, the use of ocrelizumab will:** • **Increase the number of patients needing to access specialist disease-modifying therapy clinics (perhaps 6000 people / UK in first instance for assessment, although subsequent incident cases will be much less)** • **Increase the requests for MRI scans with (and without) gadolinium** • **Increase the workload on infusion centres** • **Increase primary and secondary care workload managing adverse effects**
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	**We recommend ocrelizumab is used in the same settings as other high-efficacy multiple sclerosis therapies, namely managed by specialist multiple sclerosis neurologists and nurses in secondary care, supported by multidisciplinary teams.**
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	**Investment would be required to increase the capacity of specialist neurology and nursing time, disease-modifying therapy clinics, MRI units and infusion centres.**
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	**There is no doubt that ocrelizumab provides statistically significant benefits to the progression of disability for people with primary progressive multiple sclerosis. The magnitude of the benefit is only moderate but this should assessed sympathetically given the context of no other therapies.** **We anticipate that this moderate disability benefit may not meet cost-effectiveness criteria under current disability models.**

• Do you expect the technology to increase length of life more than current care?	**No, because no therapy in multiple sclerosis has been shown convincingly to increase length of life.**
• Do you expect the technology to increase health-related quality of life more than current care?	**Yes, marginally.**
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	**We note that the licensed indication for ocrelizumab is for patients with "early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability". We would be interested to explore with the manufacturer and NICE the subgroup analyses which led to this indication. Currently, it is too vague to be useful in clinical practice and this will lead to inconsistency in the way these criteria will be interpreted across centres.** **We note that the ORATORIO trial included patients aged 18-55 years with disability scores from EDSS of 3.0 to 6.5. Therefore the trial results cannot be extrapolated to people with primary progressive multiple sclerosis outside of these age and disability ranges. Additional criteria included disease duration of less than 10 years for EDSS of 5 or less, a score on the pyramidal functions component of the Functional Systems Scale of at least 2, and the presence of a positive CSF. It is unknown what it the effect of the medication if these criteria are not met.** **The 2016 NEJM publication of the ORATORIO trial provides a subgroup analysis of efficacy endpoints in gadolinium-positive and gadolinium-negative patients (as a supplementary Appendix). The Summary of Product Characteristics identifies subgroups in the trial who did benefit, based on younger age and evidence of gadolinium (Gd)-enhancement on their MRI brain scans.** **"Pre-specified non-powered subgroup analysis of the primary endpoint suggests that patients who are younger or those with T1 Gd-enhancing lesions at baseline receive a greater treatment benefit than patients who are older or without T1 Gd-enhancing lesions (≤ 45 years: HR 0.64 [0.45, 0.92],**

	>45 years: HR 0.88 [0.62, 1.26]; with T1 Gd-enhancing lesions at baseline: HR 0.65 [0.40-1.06], without T1 Gd-enhancing lesions at baseline: HR 0.84 [0.62-1.13]). **Moreover, post-hoc analyses suggested that younger patients with T1 Gd-enhancing lesions at baseline have the better treatment effect (≤ 45 years: HR 0.52 [0.27-1.00]; ≤ 46 years [median age of the WA25046 study]; HR 0.48 [0.25-0.92]; <51 years: HR 0.53 [0.31-0.89]).”** **We therefore expect that ocrelizumab will be most effective, and therefore most cost-effective, in younger patients, with limited disease duration, less disability and evidence of gadolinium-enhanced lesions on MRI scans. We cannot robustly define these features and specify the cut-offs without greater access to subgroup analyses of the ORATORIO data.**
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	**Ocrelizumab is more difficult to use than current clinical care of people with primary progressive multiple sclerosis, but is no more difficult to use than rituximab or any of the infusions licensed for relapsing-remitting multiple sclerosis.** **Testing eligibility for ocrelizumab requires visits in specialist clinics for disability assessment and additional MRI scans with (and without) gadolinium. Screening blood tests, for instance for hepatitis B serology, are required before treatment.** **To manage infusion reactions, all people receiving ocrelizumab should have intravenous methylprednisolone (100 mg) before infusion and, optionally, prophylaxis with analgesics or antipyretics and antihistamine.**

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	**We recommend that starting rules are discussed to identify the subgroup most likely to benefit from ocrelizumab (as discussed above).** **Stopping rules are more difficult. The NHS England stopping rules for current disease-modifying therapies in relapsing-remitting disease include a persistent inability to walk more than a few steps (corresponding to a disability score of EDSS 7.0 or greater). However, many ABN members argue for continued dosing in progressive multiple sclerosis beyond this disability score, in order to preserve upper limb function. In favour of this argument, ocrelizumab reduce the worsening of scores for the "nine hole peg test" (a test of arm and hand coordination) in the ORATORIO trial (supplementary appendix). Against this view is the fact that patients with an EDSS of greater than 6.5 were not included in the trial and therefore trial results cannot be extrapolated to them.** **Less controversial stopping criteria are: Intolerable adverse effects of the drug or plans for pregnancy or breastfeeding.**
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	**No. We consider that QALYs should appropriately capture health-related benefit.** **However, we anticipate that there will be discussion at the appraisal meeting on how to appropriately derive QALYs from current models of disability progression in multiple sclerosis.** **For instance, we are aware of one view that there should be an emphasis on preserving upper-limb function in primary progressive multiple sclerosis.** **In this unprecedented situation, of a licensed therapy of people with primary progressive multiple sclerosis, we are open to innovative ways of capturing meaningful benefit to patients.**
16. Do you consider the technology to be innovative in its potential to make a significant and substantial	**This technology is innovative and unprecedented in applying to people with primary progressive multiple sclerosis. We consider it may offer a significant and substantial benefit to a subgroup of these patients.**

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	**Yes.**
• Does the use of the technology address any particular unmet need of the patient population?	**Yes, it addresses the most important unmet need of this patient population: progression of disability.**
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	**The infusion-related side effects of ocrelizumab are common, mild and not significant in the long-term.** **No concerning adverse events emerged from the phase 3 trials of ocrelizumab in multiple sclerosis. There was a slight excess of malignancies (2.3% versus 0.8% on placebo) on ocrelizumab, not statistically significant.** **Although there was no excess of serious infections on ORATORIO, we note the unexpected infections on ocrelizumab which caused early termination of the phase 3 BELONG study in lupus nephritis.** **From our experience of the long-term use of rituximab in the treatment of neuromyelitis optica, we anticipate that a significant proportion of people treated with ocrelizumab will develop hypogammaglobulinaemia and a few of these would experience opportunistic infections.**

	One case of progressive multifocal leukoencephalopathy (PML) was described in a patient with relapsing remitting multiple sclerosis (MS) after treatment with ocrelizumab which was considered to be a "carryover" from treatment with natalizumab. Cases of PML have been described in association with rituximab in disorders other than MS. The SmPC for ocrelizumab states that PML has been observed in patients treated with anti-CD20 antibodies, so physicians should be vigilant For the early signs and symptoms of PML.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	**Yes.**
• If not, how could the results be extrapolated to the UK setting?	**N/A**
• What, in your view, are the most important outcomes, and were they measured in the trials?	**The most important outcome for people with primary progressive multiple sclerosis is accumulation of disability over the long term. This was captured in the ORATORIO trial by the conventional measure of Kurtzke EDSS. This is the "industry-standard" measure of disability which persists despite many failings and attempts to improve it. (For instance the "Multiple Sclerosis Composite Score" has been disappointingly unresponsive in treatment trials).** **A reasonable criticism of the EDSS, in the context of primary progressive multiple sclerosis, is that is biased towards ambulation and fails to sensitively capture hand and arm function. The 9-hole peg test does capture arm function; ocrelizumab reduces the risk of 12- and 24-week confirmed ≥20% progression on 9-hole peg test compared with placebo.**
• If surrogate outcome measures were used, do	**Ocrelizumab reduced the total volume of T2 MRI brain lesions by 3.4% whereas it increased by 7.4% with placebo (P<0.001); however, this reflects an anti-inflammatory effect, and it is unknown how**

they adequately predict long-term clinical outcomes?	**much this anti-inflammatory effect translates in neuroprotection, and therefore, reduced disability progression, in the longer term.** **Perhaps of more relevance is the rate of brain atrophy is marginally reduced by ocrelizumab, from 0.90% compared to 1.09% with placebo (P = 0.02) over two years. Intuitively, we feel this will translate into reduction of disability accumulation in the long term, although this has not been definitively shown, admittedly for the difficulties in carrying out long-term MRI studies in this relatively rare patient group.**
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	**Not that we are aware of.**
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	**No**.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s)	**No**

and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	**There are no such data for treatment of people with primary progressive multiple sclerosis.**
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	**No.**
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions	

will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- **Ocrelizumab is the first therapy to be licensed to reduce disability in people with primary progressive multiple sclerosis. This affects up to 15,000 people in the UK and their greatest unmet need is a drug to reduce progression of disability.**
- **Current standard of care for these people is symptomatic therapy only. Introduction of ocrelizumab will be a considerable challenge for the capacity of radiology departments and multiple sclerosis services.**
- **The mechanism of action of ocrelizumab in primary progressive multiple sclerosis is unclear, particularly as other immunotherapies have failed to impact this disease.**
- **The effect of ocrelizumab on disability progression in people with primary progressive multiple sclerosis is modest. There may be subgroups of patients who experience greater benefit from ocrelizumab: for instance, younger patients with less disability, shorter disease duration and enhancing lesions on a MRI. It is important that cost-effectiveness is explored for these subgroups and clear prescribing criteria defined.**
- **We recognise that assessing cost-effectiveness of a drug in people with primary progressive multiple sclerosis is unprecedented and may require innovative techniques.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NHS England**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ commissioning services for a CCG or NHS England in general? ☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NHS England**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	A NICE Clinical Guideline on MS, several TA's on the use of medicines in MS and a NHS England policy on the use of several medicines in MS including beta interferon and glatiramer acetate. The policy can be found at https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d04/
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is current variation in the approach to the treatment of multiple sclerosis with some clinicians taking an incremental approach, starting with drugs of lower toxicity and efficacy and escalating to more potent/toxic therapies if disease breaks through. Alternatively, advocates of "induction therapy" suggest early treatment with more potent/toxic treatments is favourable such as alemtuzumab. NHS England has recently introduced a prior approval system for MS drugs which requires Trusts to register patients on treatment which overtime should identify the level of variation in practice. The key aim will be to agree a national algorithm based on NICE guidance and this clinical practice. The algorithm is due to be published shortly.
8. What impact would the technology have on the current pathway of care?	There are few treatments available for primary progressive MS (biotin is currently undergoing a parallel TA). If approved it would likely have a significant budget impact whilst at the same time meeting a current unmet clinical need.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	It is not currently funded although some patients may be gaining access via eg clinical trials.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No as this is a different indication to current treatments that are indicated for eg RRMS and highly active MS. It would be delivered in the same way as other existing drugs such as natalizumab and alemtuzumab which are also intravenous drugs.
• How does healthcare resource use differ between the technology and current care?	As stated above this is likely to have a significant impact on both activity and direct cost of medicine as it will not be replacing any current therapy
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It should only be prescribed in settings where there is an appropriately constructed MS MDT. As it is IV it will need to be delivered in secondary care day case clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Facilities are already available although there is likely to be increased capacity requirements given there is no current treatment available for this indication. The main investment will be for the drug itself.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this	Unknown

include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	There have been no audits on the use of this technology
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not aware of any
12b. Consider whether these issues are different from issues with current care and why.	n/a

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Peter Brex**
2. Name of organisation	**King's College Hospital NHS Foundation Trust**

3. Job title or position	**Consultant Neurologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ √ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ √ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To slow down the rate of disability in people with Primary Progressive (PP) Multiple Sclerosis (MS)
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Increasing the number of years that the person can maintain independence
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	There are currently no available treatments proven to slow down progression in MS
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	• There has been a number of **NICE TA**s for treating relapsing-remitting (RR) MS but none for PP MS. • **NHS England** have recently put a document out for consultation to guide on the use of disease-modifying drugs in MS but this only covers RR and relapsing-progressive MS. It does not cover PP MS. • The **European Committee for the Treatment and Research in MS (ECTRIMS)** and the **European Association of Neurology (EAN)** jointly published guidelines on the pharmacological treatment of people with MS (European Journal of Neurology 2018;25:215-237). Recommendation 8 was to 'consider treatment with Ocrelizumab for patients with primary-progressive MS [weak]'. • The **American Academy of Neurology (AAN)** recently have published a practice guidelines recommendations summary for disease-modifying therapies for adults with MS (Neurology 2018;90:777-788). Statement 17 is that clinicians should offer Ocrelizumab to people with PPMS who are likely to benefit from this therapy unless the risks if treatment outweigh the benefits (Level B). • The **American Academy of Neurology (AAN)** recently have published a comprehensive systematic review summary of disease-modifying therapies for adults with MS (Neurology 2018;90:789-800) and in this states that Ocrelizumab and Mitoxantrone are probably more effective than placebo in reducing the risk of in-study disability progression in people with progressive MS.

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Given that there are no approved treatments for PP MS then the pathway of care is similar across the NHS. The focus is on symptom control in this patient population, i.e. management of spasticity, pain, neuropathic bladder, etc.
• What impact would the technology have on the current pathway of care?	All patients with PP MS would need to be identified to determine if they would be suitable for treatment and this may involve them having an additional out-patient review and / or further investigations, e.g. MRI, analysis of CSF. If suitable they will need to be admitted as a day-case every 6-months for a day-case to receive the treatment and will require regular clinical, laboratory and MRI monitoring whilst on treatment.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	MS centres are already delivering infusions for RR MS. Treating PP MS patients with Ocrelizumab will require additional resources but will be an expansion of existing services rather than a new resource.
• How does healthcare resource use differ between the technology and current care?	This will require additional medical and nursing time, increased capacity in infusion units and additional investigations (blood tests and MRI).
• In what clinical setting should the technology be used? (For example,	Specialist MS centres

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Increased access to MS specialists – neurologists and MS nurses. Increased capacity in infusion units Increased access to imaging
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Unknown
• Do you expect the technology to increase health-related quality of life more than current care?	Yes

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	In my opinion this technology would be most beneficial to people with PP MS (diagnosed using the McDonald criteria) who retain some independence, i.e. are mobile and / or retain good upper limb function. Clinical trial evidence has been shown in people who remain ambulatory (can walk at least 20m with support), have at least one oligoclonal band in the cerebrospinal fluid (CSF) and in whom the duration of MS symptoms was less than 15 years. There have not been any clinical trials of the technology in individuals who are non-ambulatory with respect to impact on vision, cognition or upper limb function.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	This will require additional resources as outlines above but regional neuroscience centres are set up to deliver and monitor this type of treatment

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I expect there will need to be starting and stopping criteria for this treatment. This will involve additional testing (clinical, blood, CSF, MRI).
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Not known
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	This technology is innovative in that it is the first proven treatment for delaying disability in PP MS

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Patients will need to be monitored for side-effects through regular clinical review and by blood tests and MRI scans
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	This technology is not available in the UK out-side of clinical trials

• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Delay in sustained disability
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Magnetic Resonance Imaging (MRI) is the most commonly used surrogate outcome measure in MS trials. New and enhancing lesion occur less frequently in PP MS than in RR MS. Brain volume may be a better measure in PP MS but don't often reflect the burden of spinal cord disease, which can have a major impact of disability in PP MS.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

21. How do data on real-world experience compare with the trial data?	Unknown
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
23. The marketing authorisation for ocrelizumab in this indication defines the population as “adult patients with early primary progressive multiple sclerosis in terms of	

disease duration and level of disability, and with imaging features characteristic of inflammatory activity." 23a. How would 'adult patients with early primary progressive multiple sclerosis in terms of disease duration and level of disability' be understood or interpreted in clinical practice? Are there any criteria that would be used to identify these patients? 23b. How is inflammatory activity usually assessed for people with primary progressive MS; for example, type of imaging (gadolinium-enhanced T1 weighted MRI,	Criteria would need to be defined based on disease duration, EDSS and MRI findings. These would all be routinely recorded in clinic. MRI scans are currently less frequently performed in PP MS than in RR MS. This would lead to increased imaging in this population.

T2 weighted MRI etc.) and frequency of repeat imaging? 23c. Would you expect there to be any treatment waning for people with primary progressive MS treated with ocrelizumab?	Unknown at present

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- This is a novel treatment; there is currently no other treatment shown to reduce the accrual of disability in PP MS
- Published European and American guidelines support the use of Ocrelizumab in PP MS
- Treatment with Ocrelizumab would be primarily to maintain an individual's independence, with current evidence supporting delaying worsening mobility
- Starting and stopping criteria will need to be agreed – likely to be based on disease duration, EDSS and MRI activity
- MS centres are set up to deliver and monitor this treatment but there will be an increase demand on neurologists and MS nurse time, more investigations and need for additional infusion space.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Prof Alasdair Coles**
2. Name of organisation	**Association of British Neurologists**
3. Job title or position	**Professor Neuroimmunology, University of Cambridge**

4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes

Alasdair Coles response to NICE

My apologies for missing these questions in my original submission.

23. The marketing authorisation for ocrelizumab in this indication defines the population as "adult patients with early primary progressive multiple sclerosis in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity."

23a. How would 'adult patients with early primary progressive multiple sclerosis in terms of disease duration and level of disability' be understood or interpreted in clinical practice? Are there any criteria that would be used to identify these patients?

There is no general understanding of a definition of this subgroup of patients in clinical practice. This is because there has never needed to be, as previously no disease-modifying therapy has been licensed for any type of PPMS. One of the challenges of this appraisal is the lack of a precedent, and no clear consensus on what constitutes a useful therapeutic effect in progressive multiple sclerosis.

The shape of the Kaplan-Meir curves for ocrelizumab's effect on disability progression in the ORATORIO study suggests to me that a subgroup of patients have responded to the drug. I expect this group to be patients with shorter disease duration, lowed disability and greater evidence for on-going inflammatory activity.

The inclusion criteria for the Oratorio study included two definitions of "early": disease duration of less than 10 years in patients with an EDSS at screening ≤5.0 or disease duration of less than 15 years in patients with an EDSS at screening >5.0. However, the actual recruited patients had a median disease duration of 6 years and median EDSS of 4.5. I would be interested to see an analysis of the efficacy data fractionated by disease duration and EDSS at baseline.

3b. How is inflammatory activity usually assessed for people with primary progressive MS; for example, type of imaging (gadolinium-enhanced T1 weighted MRI, T2 weighted MRI etc.) and frequency of repeat imaging?

In general neurological practice, there has been no need to assess inflammatory activity in people with primary progressive MS, because this has had no treatment consequence. So, as with the above comments, this appraisal has no precedent.

In relapsing-remitting multiple sclerosis, disease activity is assessed by relapse frequency and by the rate of new MRI lesion formation. As relapses are uncommon or absent in primary progressive multiple sclerosis, this appraisal should focus on MRI definitions of inflammatory activity. The most rational MRI assessment is the number of new MRI lesions which have appeared over a defined period of time: for instance two new T2 lesions over one year would be widely regarded as indicating a patient with "active" inflammation. This definition requires a baseline scan. An additional definition would include the appearance on a current scan of one or more gadolinium-enhancing lesions. Where these are present, the patient undoubtedly has active inflammation. The disadvantages of this approach is that gadolinium enhancing lesions persist only for one month, so an active patient may be miscategorised as inactive if the scan happens to be done inbetween the appearance of new

lesions, and there is a growing desire to reduce exposure to gadolinium as it appears to accumulate in human brains.

A close analysis of the efficacy data by baseline MRI features, in the ORATORIO study, would be really helpful (partially done in the supplementary data).

23c. Would you expect there to be any treatment waning for people with primary progressive MS treated with ocrelizumab

I would expect treatment waning. This is not because the B cell depletion induced by ocrelizumab is likely to reduce over time (although that may happen through neutralising antibodies). Rather, it is clear from trials of anti-inflammatory drugs (including from the ORATORIO trial), that they are less efficacious as disease duration increases and progressive disability increases.

The natural history of multiple sclerosis is that markers of inflammation (relapses, MRI new lesions) diminish over time, and are rare in established progressive disease.

NICE National Institute for Health and Care Excellence

Patient expert statement

Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 10 pages.

About you	
1.Your name	CRAIG MILVERTON
2. Are you (please tick all that apply):	a patient with the condition? ✓ a carer of a patient with the condition? a patient organisation employee or volunteer? other (please specify):
3. Name of your nominating organisation	M.S. SOCIETY
4. Did your nominating organisation submit a submission?	yes, they did ✓ no, they didn't I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	yes, I agree with it ✓ no, I disagree with it I agree with some of it, but disagree with some of it other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	yes ✓
7. How did you gather the information included in your statement? (please tick all that apply)	I have personal experience of the condition ✓ I have personal experience of the technology being appraised ✓ I have other relevant personal experience. Please specify what other experience: I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	DIFFICULT. MUSCLE SPASM, TIREDNESS, NERVE PAIN, CAN'T WALK TO FAR, NUMBNESS.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and	THIS IS THE ONLY TREATMENT I WAS OFFERED FOR MY P.P.M.S.

care available on the NHS?	THERE WAS NOTHING ELSE AVAILABLE OTHER THAN MEDS FOR PAIN & SPASMS
10. Is there an unmet need for patients with this condition?	YES, THIS DRUG HAS KEPT ME WORKING AND WILL OTHERS.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	I THINK ITS SAVED MY LIFE, ALLOWING ME TO CONTINUE WORKING & HAVING A FULFILLING LIFE WITH MY FAMILY.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	CAN'T THINK OF ANY
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	I THINK ALL PEOPLE WITH M.S. WILL BENEFIT.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	CAN'T THINK OF ANY
Other issues	
15. Are there any other issues that you would like the committee to consider?	KEEPING PEOPLE AS WELL AS POSSIBLE WITH M.S. BENEFITS EVERYONE.
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • HAS STOPPED THE PROGRESSION OF MY M.S. • ALLOWS ME TO KEEP WORKING. • KEEPS ME INVOLVED IN FAMILY LIFE • IM NOT A BURDEN TO FAMILY & FRIENDS • 100K M.S. SUFFERERS IN THE U.K. WOULD HAVE THERE LIVES AND OUTLOOK VASTLY IMPROVED	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Patient expert statement

Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Yvonne Pettigrew**
2. Are you (please tick all that apply):	**X** a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	MS Trust
4. Did your nominating organisation submit a submission?	**X** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	**X** I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	My symptoms at the moment are, for the most part, invisible to others. They include constant increased tone and changed sensation with reduced proprioception in both of my legs and bladder and bowel dysfunction. I also have intermittent changed sensation throughout my body; vibration and buzzing which are aggravated by walking and cause me to feel nauseous and exhausted. My balance is vulnerable especially amongst people moving around me or when I'm trying to change direction especially in confined spaces, and I have a tendency to tip forwards, all of which can be

	debilitating and embarrassing. Uneven surfaces and steps increase my unsteadiness and I have occasionally fallen. A stick does not help. My bowel control is impaired and aggravated by walking, so access to toilet facilities are often needed at very short notice to avoid incontinence. At the moment I can usually manage this using douches and suppositories. I can manage my bladder by regular toileting but I'm aware that this control is weakening and I am likely to need to move to self-catheterisation in the near future. My abilities are variable from day to day but I always fatigue easily, disproportionally to the effort outlay, and my gait then becomes increasingly rigid and awkward. I have been advised my condition will not improve and is expected to deteriorate. My nerve pain and functional control is slightly worse year on year, which is both frightening and depressing. I retired earlier than I had planned from a senior manager full time role in the NHS as I no longer had the energy reserves to function at the level required. I have been supported to continue working part-time but anticipate this too will be constrained by my gradual deterioration. I currently hold a full driving licence under a 3 year review, but anticipate that my reducing sensory abilities will limit the duration of this. I do not require care at this stage but am very fortunate to receive full emotional support and practical assistance in managing my incontinence from my husband. I know he is disappointed we can no longer pursue some of our shared hobbies such as hill walking, but equally I know I can rely on him to provide care if and as I need it which is very reassuring. I do recognise however that this will be limited as we both move into our later years.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	There is no current treatment for PPMS available on the NHS which is very disheartening for both patients and carers. I am aware that access to symptom management is very variable across the country. I have been fortunate to have been very well supported in both.
10. Is there an unmet need for patients with this condition?	Absolutely. Patients will continue to deteriorate.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	To slow or halt the disease progression to enable sustained function and independence for as long as is possible.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Very few. There have been low risks associated with the treatment.
Patient population	
13. Are there any groups of patients who might benefit	I understand patients with a history of breast cancer may be identified as high risk for the treatment. I also understand patients who have had the disease for a long time may not be eligible.

more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Appropriate access based on clinical evidence without a 'postcode lottery'
Other issues	
15. Are there any other issues that you would like the committee to consider?	No
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • This technology offers the first opportunity for patients with PPMS to receive treatment • The treatment has the potential to slow or halt PPMS disease progression	

- The sooner disease progression can be halted the less costs will be incurred for disability associated care.
- The treatment can potentially enable patients will PPMS to lead fulfilling and purposeful lives
- The impairments caused by PPMS are often, especially in the early stages, invisible to others but their impact is significant to the patient and their family.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Ocrelizumab for treating primary progressive multiple sclerosis [ID 938]

Produced by: Warwick Evidence

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Declared competing interests of the authors

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows

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Contributions of authors:

Peter Auguste (Research Fellow) reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses; Jill Colquitt (Senior Researcher) co-ordinated and conducted the critique of the clinical effectiveness evidence; Martin Connock (Senior Research Fellow) reviewed and critiqued the survival analysis and cost-effectiveness evidence and undertook additional analyses; Emma Loveman (Senior Researcher) conducted the critique of clinical effectiveness evidence; Rachel Court (Information Specialist) critiqued the company searches and undertook additional searches; Olga Ciccarelli (Clinical Professor) provided expert clinical advice; Carl Counsell (Reader) provided expert clinical advice; Xavier Armoiry (Senior Research Fellow) co-ordinated the project and the report, and reviewed and critiqued the clinical effectiveness evidence.

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

9-HPT	9-hole peg test
ABN	Association of British Neurologists
AE	Adverse events
AIC	Akaike information criterion
ARR	Annualised relapse rate
BSC	Best supportive care
CDP	Confirmed disability progression
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CS	Company submission
CSR	Complete study report
DMTs	Disease modifying therapies
EDSS	Expanded disability status scale
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	Euro QoL 5 dimensions questionnaire
ERG	Evidence Review Group
Gd	Gadolinium
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
LYG	Life years gained
MFIS	Modified fatigue impact scale
MFSC	Multiple sclerosis functional composite measure
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Multiple Sclerosis
MRI	Magnetic Resonance Imaging
MTA	Multiple Technology Appraisal
NEP	No evidence of progression

NEPAD	No evidence of progression and active disease
NHS	National Health System
NICE	The National Institute for Health and Care Excellence
NNT	Number needed to treat
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PML	Progressive multifocal leukoencephalopathy
PPMS	Primary progressive multiple sclerosis
PSA	Probabilistic sensitivity analysis
QALYs	Quality Adjusted Life Years
RCT	Randomised controlled trial
ROW	Rest of world
RRMS	Relapsing remitting multiple sclerosis
SPC	Summary of product characteristics
URTIs	Upper respiratory tract infection
WTP	Willingness-to-pay

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company submission (CS) decision problem matches the intervention and the comparator described in the final NICE scope, as seen in Box 1.

The outcomes reported in the CS generally matched the final scope with the exception of visual disturbance. Although visual function is one of the eight functional systems measured in the expanded disability status scale (EDSS), no separate measures of visual disturbance were reported.

The CS decision problem also differs from the NICE scope on the population. This has been restricted to people with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity. This is for consistency with the label indication of the marketing authorisation that was granted by the European Medicines Agency (EMA) for ocrelizumab in January 2018.

The ERG has found the marketing authorisation criteria of "early disease in terms of disease duration and level of disability" and "with imaging features characteristic of inflammatory activity" to be vague and subjective, in the absence of more precise eligibility criteria for ocrelizumab, these criteria are at risk of being interpreted differently across the NHS.

For example, the ERG's clinical experts disagree with the definition of early course of disease provided by the company and they have indicated that early PPMS pertains more to a time variable rather than a level of disability and that early PPMS would be better defined as PPMS within five years from symptoms onset.

Most importantly, the company has defined inflammatory activity according to the presence of T1 gadolinium (Gd) enhancing lesions and/or active (new or enlarging) T2 lesions. Applying the criteria of new or enlarging T2 lesions to assess eligibility for ocrelizumab treatment would involve repeated magnetic resonance imaging (MRI), which is currently not common practice in

the UK for patients with PPMS. Similarly, it appears that many centres do not routinely undertake brain imaging with gadolinium at present. This means that eligibility to ocrelizumab treatment may not be uniformly applicable across centres to patients within the NHS.

The ERG considers these aspects of the CS decision problem do not reflect NHS practice.

In order to provide evidence for the population with imaging features characteristic of inflammatory activity, the company presented results for a post-hoc subgroup of patients with T1 Gd enhancing lesions and/or new T2 lesions at baseline (enlarging T2 lesions were not assessed), referred to as the 'MRI active' subgroup.

Box 1: NICE final scope

Population	People with primary progressive multiple sclerosis
Intervention	Ocrelizumab
Comparator	Established clinical management without ocrelizumab
Outcomes	- disability (for example, expanded disability status scale [EDSS], or time to walk 25 feet) - disease activity - patient-reported outcomes including fatigue, - cognition and visual disturbance - mortality - adverse effects of treatment - health-related quality of life.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidence in the CS comes from a single randomised controlled trial (RCT), the ORATORIO trial of ocrelizumab versus placebo in people with PPMS.

The main results are reported following a minimum of 120 weeks of double-blind controlled follow-up: 1) from the intention to treat (ITT) population of the ORATORIO trial; 2) from the post-hoc MRI active subgroup.

ITT population (pre-specified analyses):

- The risk of confirmed disability progression (CDP) was significantly delayed in the ocrelizumab group compared to the placebo group, irrespective of whether CDP was sustained for 12 weeks (primary endpoint) (hazard ratio [HR], 0.76; 95% confidence interval [CI]: 0.59 to 0.98; p = 0.0321) or 24 weeks (HR 0.75; 95% CI: 0.58 to 0.98; p = 0.0365).
- Change in timed 25-foot walk (T25FW) from baseline to week 120 showed a relative reduction of percent progression in T25FW of 29.3% (95% CI –1.6 to 51.5; p=0.0404) with ocrelizumab compared with placebo. The absolute difference was not reported.
- The benefit of ocrelizumab on Health-related quality of life (HRQoL) was not consistent across the different components of the tools which were used:
    - There was no statistically significant difference between ocrelizumab and placebo using the physical component score of the SF36 (SF-36 PCS) (pre-specified secondary endpoint).
    - There was a statistically significant improvement using the mental component score of the SF36 (SF-36 MCS) score with ocrelizumab versus placebo (exploratory endpoint).
    - Change in EuroQoL 5 dimensions (EQ-5D) (listed as an exploratory endpoint) was not reported.

- The benefit of ocrelizumab on functional outcomes (all exploratory) was unclear:
    - There was a statistically significant impact of ocrelizumab over placebo on upper limb function measured with the proportion of patients with ≥20% increase of the 9 Hole Peg Test (9-HPT) sustained for 12 weeks.
    - There was no statistically significant difference between ocrelizumab and placebo in the mean change from baseline on the Multiple Sclerosis Functional Composite Score (MSFC) which measures the leg function/ambulation (using T25FW), arm/hand function (using the 9-HPT), and cognitive function (using the paced Auditory Serial Addition Test [PASAT]).

- There was no statistically significant difference in the change from baseline to week 120 in the PASAT score (measure of cognitive impairment).

- Based on the Modified Fatigue Impact Scale (MFIS, scored 0-84), the total score of fatigue decreased at week 120 by 0.462 (95% CI: -2.145 to 1.222) with ocrelizumab while it increased by 2.994 (95% CI: 0.658 to 5.330) with placebo (difference in adjusted means not statistically significant: -3.456 [95% CI: -6.048 to 0.863]).

Post-hoc MRI active subgroup (matching the label indication):

- The risk of disability progression, with progression confirmed for 12 or 24 weeks, was delayed in the ocrelizumab group compared to the placebo group: with the less relevant endpoint, namely 12-week CDP, the benefit reached statistical significance (HR for 12-week CDP, 0.68; 95% CI: 0.46 to 0.99; p = 0.0448) while with the most relevant endpoint, namely 24-week CDP, it did not (HR for 24-week CDP, 0.71; 95% CI: 0.47 to 1.06; p = 0.0917).
- The change in T25FW from baseline to week 120 was not reported in the CS so the relative effect in reducing progression in T25FW is not known.
- No results for HRQoL were presented
- The benefit of ocrelizumab on functional outcomes (all exploratory) was unclear:
    - There was a positive impact of ocrelizumab over placebo: the HR for the risk of 20% increase in 9-HPT (sustained for 12 weeks) was 0.52 (95% CI 0.32-0.85).
    - No results on the MSFC were reported
    - No results measuring the PASAT score were reported
- Figures provided by the company suggest that ocrelizumab had no impact on fatigue compared to placebo based on the mean changes on the MFIS.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

As noted above, the key concern regarding the ORATORIO trial is the difference between the ITT population and the marketing authorisation indication, and the selection of a post-hoc subgroup in an attempt to match the indication. The ERG is unable to verify the data presented

for this subgroup as it has not been published elsewhere. The evidence is largely based on patients from outside the UK and the generalisability to the UK population is unclear.

The CS selectively reports outcomes, placing greater emphasis on statistically significant exploratory outcomes in the main submission. Several pre-defined exploratory outcomes measured in the ORATORIO trial were not presented in the main CS or its appendices. Limited endpoint or change data are reported in the CS, with results mainly presented in figures and as hazard ratios between groups.

There was some imbalance between groups in withdrawals from the trial; reasons may be linked to perceived lack of efficacy, but it is not possible to determine this as the overall number withdrawing for this reason is unclear. A small proportion of patients were unblinded during the trial, the impact of this is unclear.

The primary outcome of the trial was time to CDP sustained for 12 weeks, however the ERG considers the secondary endpoint CDP sustained for 24 weeks to be more clinically meaningful. Statistical analysis of CDP involved imputation of events in which initial progression was not confirmed due to early discontinuation. Analysis without imputation of events resulted in a reduced treatment effect for both the ITT population and the MRI active subgroup that was no longer statistically significant.

1.4 Summary of cost effectiveness submitted evidence by the company

The submission received by the ERG included: a systematic review of the economic evidence related to the treatment of people with multiple sclerosis, a review of the evidence on resource and costs and a separate review to identify studies that measure the HRQoL for people with multiple sclerosis, more specifically people with PPMS, and an electronic version of a Markov model built in Microsoft Excel.

The search of the cost-effectiveness literature showed that there is a paucity of studies undertaken in people with PPMS, with majority of the research undertaken in comparing disease modifying treatments (DMTs) for people with RRMS. One economic analysis was identified that compared

ocrelizumab with best supportive care (BSC) but the results were not presented in the form of an incremental cost-effectiveness ratio (ICER), due to lack of ocrelizumab price information. Further searching identified key studies that provide health state utility values for people with MS. Very few studies reported utility values by EDSS level for people with PPMS. Results from the study undertaken by Orme et al. [1] were used in the company scenario analysis.

The company's *de novo* Markov model depicts the natural history of a cohort of people with PPMS who may undergo treatment with ocrelizumab or BSC. The model defined health states by EDSS ranging from 0-10 (dead). The disability progression in the model was based on the MSBase natural history cohort which showed disease progression in the absence of disease modifying treatment. The model starts from a hypothetical cohort of people with PPMS. Treatment with ocrelizumab delayed disability progression. Evidence for the clinical effectiveness of ocrelizumab relied on the ORATORIO trial. In the base-case, treatment effect in the form of a hazard ratio is based on the 12-week CDP (CDP-12) was applied to the forward transitions. Annual cycles were used to show the movement of people through the model. In each cycle, people transitioned between EDSS levels, withdrew from treatment, or transition to the dead state. In EDSS states 0-9, people incurred costs and accrued benefits [quality adjusted life-years (QALYs)].

In the base-case, utility values for EDSS 0-1 and 8-9, were obtained from Orme et al.[1] and all other values were based on health-related quality of life information collected using the EQ-5D-3L in the ORATORIO trial. Any disutilities associated with adverse events were obtained from recent technology appraisals and published sources. Utility decrements for upper limb impairment and fatigue were based on a regression analysis. Carer disutilities by EDSS state were obtained from TA127, which were derived from the UK MS survey.

The model estimated the resource use and treatment costs (drug acquisition, administration and monitoring costs) associated with ocrelizumab. Other costs included state-dependency costs and adverse event management costs. Treatment costs for ocrelizumab were applied until people discontinued treatment (due to adverse events or progressing to EDSS ≥8), after which it was assumed that people would not switch to any other DMT; thus receiving BSC.

The analysis was undertaken from the NHS and PSS perspective, and the outcomes are reported in terms of life years gained (LYG) and QALYs, with the overall cost-effectiveness results reported in terms of an ICER, expressed as cost per QALY gained over a 50-year time horizon. Both costs and effects were discounted at 3.5% per annum. A number of deterministic one-way sensitivity analyses and scenario analyses were undertaken, as well as probabilistic sensitivity analysis (PSA) based on the outcome cost per QALY.

The company's base-case results showed that the ICER for the strategy ocrelizumab compared to BSC was approximately [redacted] per QALY gained in the MRI active population, using the list price. Under the approved PAS, the ICER reduced to approximately £88,200 per QALY. Sensitivity analysis results showed that the treatment effect on CDP-12 had the greatest impact on the ICER, suggesting that the results are sensitive to this parameter. Results for the PSA showed that at a willingness-to-pay (WTP) threshold of £30,000 per QALY gained, ocrelizumab had a zero probability of being cost-effective.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG has a series of concerns regarding values and assumptions in the company base-case model. With that there would be no waning of the treatment effect in the base-case and the inclusion of utility decrements in the model for upper limb impairment and fatigue. With respect to the inclusion of utility decrements:

1. There is a lack of transparency on the choice of outcomes that were incorporated to measure disutilities:

• The company chose to incorporate utilities to reflect upper limb function using outcomes from the 9-HPT. In the ORATORIO trial, the 9-HPT was included in two outcomes: 20% increase in 9-HPT sustained over 12 weeks and the MSFC (composite endpoint). The company chose results for a 20% increase in 9-HPT to reflect upper limb function impairment indicating this corresponds to clinically meaningful upper limb impairment but made no statement on 1) the fact that MSFC is a composite outcome that includes the 9-HPT; 2) why MSFC outcomes showed no differences between treatments arms.

• The company incorporated disutilities to reflect fatigue and cognitive impairment as assessed by using MFIS ≥38. Our understanding is that MFIS denotes how fatigue impacts patients' lives, but

does not measure cognitive impairment. Cognitive impairment was measured in ORATORIO using the PASAT, and the results showed that there was no statistically significant difference between the treatment arms.

2. The company incorporated disutilities related to upper limb and fatigue using the 9-HPT and the MFIS, respectively, which were measured only as part of exploratory analyses in the trial. The ERG is concerned about the selective use of outcomes from exploratory analyses in the base case of an economic model.

3. There is the potential for double counting of utilities since the EQ-5D adequately captures overall HRQoL for people with MS. The inspection of the MFIS and EQ-5D questionnaires shows a number of similarities in the questions. For example, questions pertaining to "self-care" or "usual activities" are captured in the physical subscale of the MFIS as well as EQ-5D. There is also the potential for double counting of utilities using outcomes from the 9-HPT and MFIS. For example, item 4 from the MFIS examines whether patients report "they have been clumsy and uncoordinated". A patient rating "almost always" for this item is also likely to have a poorer score on the 9-HPT. Lastly, some of the MFIS items appear to be linked to progression through the EDSS. As an illustration, a patient responding "almost always on the MFIS item 13 "my muscles have felt weak" is likely to experience ambulation impairment.

4. In addition to utility decrements associated with upper limb, and fatigue and cognitive impairment, the company included carers' disutilities for all EDSS states. Given that the company included utility decrements for caregivers' burden, we consider these additional decrements for upper limb impairment and fatigue to be double counting the impact on QALYs.

5. To our knowledge, utility decrements for upper limb, and fatigue and cognitive impairment have not been used in other MS technology appraisals. It was emphasised that upper limb function is an important outcome for people with PPMS but it is unclear why this should be a more so for PPMS than RRMS. The ERG is not convinced that the 9-HPT should receive greater emphasis in PPMS compared to RRMS. Moreover, the ERG has noted that this outcome was not incorporated in the submission by the company for ocrelizumab in RRMS.

6. Regarding the hazard ratio and disutilities derived from 20% increase in the 9-HPT:

• A hazard ratio of 0.52 is presented based on the 12-week 9-HPT: as noted, the hazard ratio should be better based on 24-week sustained 20% increase in 9-HPT (this was not provided by the company);

• It appears the hazard ratio was derived from people with EDSS 2 to 6 but was applied to people with EDSS ≥7: it is unclear whether this hazard ratio generalises to people in lower (0-1) and higher (≥7) EDSS states;

• There is a lack of transparency about the number of people randomised to ocrelizumab who experienced a 12-week sustained 20% increase in 9-HPT. Results are presented for each EDSS level for the placebo group;

• For time to 20% increase in 9-HPT, it appears that the hazard ratio was used in the model as a relative risk;

• Should utility decrements based on 20% increase in 9-HPT be incorporated in the model, the ERG believes that the model should include a feature to allow a waning of the benefit consistent with that using CDP, which is not currently the case.

7. Regarding the relative risk and disutilities derived for fatigue

• MFIS was used to measure fatigue, with a score ≥38 representing clinically meaningful fatigue. The company noted that 'cut-offs are not commonly used with fatigue scales and have not been extensively researched in PPMS.' The ERG note that the baseline mean score for fatigue was 41.6 (17.2), suggesting that the majority people were already fatigued upon entering the trial. Figures provided by the company suggest that ocrelizumab had no significant impact on fatigue compared to placebo based on MFIS mean changes;

• The proportion of people who are likely to experience upper limb, and fatigue and cognitive impairment at each EDSS level was based solely on the company's clinical expert opinion.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Clinical effectiveness

Overall the quality of the systematic review of clinical effectiveness was reasonable and the single relevant RCT had a low risk of bias. The trial met its primary endpoint, demonstrating a reduction in time to CDP sustained for 12-weeks.

Cost-effectiveness

The company's model is logical and appears to depict the natural history for people living with PPMS and the cycle length is appropriate to capture any changes in the disease progress. In general, the process of identifying and justifying the choice of key model inputs were transparent and robust. The economic analysis conforms to the NICE reference case in that the perspective, discount and the lifetime horizon was considered to be long enough to capture the costs and benefits of ocrelizumab. The majority of the assumptions made in order to have a workable model appears to be appropriate. We noted that there was consistency in the inputs and the results reported in the main report with those in the company's model.

1.6.2 Weaknesses and areas of uncertainty

Clinical effectiveness

The population of the trial is broader than the marketing authorisation indication. Evidence for the clinical and cost-effectiveness of ocrelizumab is based on a post-hoc subgroup ('MRI active' subgroup) that does not fully meet the marketing authorisation indication in terms of 'early disease' and omits people with enlarging T2 lesions between screening and baseline. The trial population was limited to age 18 to 55 years, therefore there is no direct evidence for the effectiveness of ocrelizumab over the age of 55 years. The representativeness of the trial population and the MRI active subgroup to the UK population eligible for ocrelizumab is uncertain. The outcome measures selected by the company have uncertain clinical relevance, and the ERG preferred to use 24-week rather than 12-week confirmed disease progression in the economic model. There was potential bias in the selective reporting of exploratory outcomes in

the CS. The primary endpoint was not robust to sensitivity analysis without imputation of unconfirmed disease progression events.

Cost-effectiveness

To our knowledge, the MSBase registry appears to be the most appropriate natural history cohort of people with PPMS. However, the population modelled included people with and without characteristics of inflammatory disease and included less than 3% of people from the UK. Hence, it was not practicable to estimate the impact of ocrelizumab compared to best supportive care solely in UK adults with early PPMS and characteristics of inflammatory disease; this should be borne in mind when interpreting results. Other concerns included assumptions that there would be no waning of the treatment effect in the base-case and the inclusion of utility decrements in the model for upper limb impairment and fatigue.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Exploratory analyses related to clinical effectiveness

The ERG has undertaken exploratory analyses to assess time to reach EDSS ≥ 7 which presents a tangible and interpretable indicator of treatment effect.

For the ITT population the analysis delivers gains from ocrelizumab treatment that depend heavily on the models used for extrapolation beyond the observed data:

- using a Weibull model (as in the CS), the delay in median time to EDSS ≥ 7 is 8.64 years in favour of ocrelizumab compared to placebo
- using a Gompertz model (ERG's preferred model), the delay in median time to EDSS ≥ 7 falls to 3.06 years in favour of ocrelizumab compared to placebo.

An exploratory analyses of the MRI active subgroup similarly estimated delay in median time to EDSS ≥ 7 was 2.88 years in favour of ocrelizumab using a Gompertz model and 9.24 years using a Weibull model.

Exploratory analyses related to cost-effectiveness

The ERG identified a series of modifications to the company's base-case economic model. Making each individual change while holding all other input parameters constant caused small to moderate changes to the company's base-case ICER. The ERG's preferred base-case consists of the following combination of changes:

- Efficacy set to CDP-24 for the unextended treatment controlled period (minimum of 120 weeks of double-blinded controlled period)
- 50% decrease in treatment efficacy from 5 years onwards and an increase in the annual rate of discontinuation from active treatment from 5 years onwards such that the average time spent in treatment beyond 5 years was reduced to 50%
- Excluding utility decrements for upper limb impairment
- Excluding utility decrements for fatigue
- Using an imputed relative risk for a 20% increase in 9-HPT sustained for 12 weeks (explored in a scenario analysis)
- Including costs, disutilities, and treatment effect associated with relapses

Using the list price, the results of our preferred analysis indicate that ocrelizumab is expected to yield [redacted] QALYs at a cost of approximately [redacted], equating to an ICER of approximately [redacted] per QALY gained. Applying the approved PAS discount to the cost of ocrelizumab resulted in a reduction of the ICER (approximately £145,700 per QALY). Results (using the list price or PAS) from the PSA showed that at a WTP threshold of £30,000 per QALY, there was zero probability that ocrelizumab was cost-effective when compared to BSC.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem.

On pages 14 to 18, the company presents an overview on the disease including its clinical presentation and characteristics.

Multiple sclerosis (MS) is a progressive, degenerative disease affecting the central nervous system which is characterised by inflammation and demyelination of the neurons, mediated by an autoimmune response by T-cells to white matter.[2]

The disease can develop and progress in four major forms: (i) relapsing remitting (RRMS); (ii) Primary progressive (PPMS); (iii) Secondary progressive (SPMS) and (iv) progressive relapsing (PRMS).[3]

In 80% of cases, RRMS is the form of MS at time of diagnosis. In RRMS patients experience an exacerbation of symptoms followed by periods of remission.

PPMS has an older age of onset, with greater susceptibility in men,[4] and is typically characterised by occasional plateaus in disease progression, with temporary minor improvements from onset.[5]

The company has stated that PPMS represents around 14% of cases of MS in the UK which the ERG confirms is accurate.

The company has indicated on page 16 of the CS that the focus of new treatment for PPMS should be the preservation of patient independence (upper limb function) rather than just patient mobility referring to a review by Lamers et al. [6]. While this review highlights the need to fully assess upper limb function, this is not be specific to PPMS being equally applicable to RRMS.

On pages 18 to 21, the company provides a very detailed critique of the EDSS which is a well-known and accepted tool used in clinical research that has mainly been used for drugs developed in RRMS. The rationale for the critique is that, according to the company, the EDSS is a tool more relevant to capture walking disability, making it less relevant to PPMS, since preserving upper limb function is deemed by the company more important than lower limb function in PPMS.

The limitations that the EDSS does not adequately assess upper limb function and cognitive impairment have been emphasised within the EMA guidelines on clinical investigation of drugs for MS, although guidelines have not been especially focused on this concern in PPMS [7]. On that

basis, the EMA advocates the use of additional rating scales and quantitative neurological performance tests (such as the multiple sclerosis functional composite measure [MSFC]) as secondary measurements of disability[7].

The emphasis by the company on upper limb function outcomes as opposed to lower limb function outcomes contradicts the choice made by the company to use confirmed disability progression through EDSS levels (denoting lower limb function worsening) as the primary endpoint of the ORATORIO trial [8] while the 9-HPT, which is specific to upper limb function, was only an exploratory endpoint of this trial.

On page 22 of the CS, the company has highlighted fatigue as one of the most debilitating patient reported symptom that occur in MS. While the ERG agrees that fatigue is a very commonly reported symptom in MS patients, the ERG would underline that fatigue, measured through MFIS, was an exploratory outcome assessed as part of exploratory objectives.

On page 23, the company has presented composite endpoints which have been proposed in PPMS as a way to develop meaningful measures of disability progression, this includes No Evidence of Progression (NEP) and No Evidence of Progression and Active Disease (NEPAD). These outcomes will be reviewed in section 4.3.

On pages 24 and 25, the company has presented a section describing the hypothesis of functional reserve but the clinical relevance of this is a matter of debate.

2.2 Critique of company's overview of current service provision

The company has described the current treatment for PPMS in the UK indicating that no treatment has been approved in this indication. High-dose biotin was examined by the EMA within the scope of an application for marketing authorisation in people with progressive MS but the company withdrew its application in November 2017 [9].

On CS Table 5 page 31, the company has reported results from different RCTs that have tested DMTs for PPMS and failed to demonstrate significant impact on clinical progression and/or did meet their primary endpoints. Of these, the OLYMPUS trial has tested the effectiveness of rituximab, which has exactly the same mechanism of action as ocrelizumab: in the ITT population the authors have concluded there was no evidence of significant difference (p=0.1442) in time to 12-week CDP between rituximab and placebo after 96 weeks of follow-up [10]. Interestingly, the

proportion of patients with CDP at week 96 with rituximab was very similar to that with ocrelizumab in the ORATORIO trial [8] at week 120 (respectively 30.2% vs 32.9%).

In Table 4 (page 30 of the CS), the company has presented symptomatic treatments recommended for use in MS, referring to Spanish guidelines published in 2012[11].

The NICE Clinical Guideline on the management of MS in primary and secondary care published in 2014 [12] has not been cited by the company. The ERG has noted several differences between currently recommended symptomatic treatments in the UK and those listed by the company based on the Spanish guidelines (Table 1).

Table 1: Comparison of pharmacological options for the management of MS

Symptom	Pharmacological Options listed by the company	Pharmacological options based on NICE clinical guideline [12]
Relapses	• Methylprednisolone • Adrenocorticotrophin hormone is an option where there is no administration route for methylprednisolone	• Oral methylprednisolone • IV methylprednisolone as an alternative
Fatigue	• Amantadine	• Amantadine • Vitamin B12 not recommended
Spasticity	• Baclofen • Tizandine (second line; added to or instead of baclofen) • Diazepam (third line) • Gabapentin • Nabiximols (where no clinical improvement is seen with other treatments or they are poorly tolerated) • Local application of botulinum toxin A (focal spasticity)	• Baclofen or gabapentin as first-line • Possible combination of baclofen and gabapentin • Tizanidine or dantrolene as second-line • Benzodiazepines as a third line option • Nabiximols not recommended (not cost-effective)
Impaired mobility	• Dalfampridine	• Fampridine not recommended (not cost-effective)

3 Critique of company's definition of decision problem

3.1 Population

Compared to the population described in the NICE final scope, namely people with PPMS, the population defined in the decision problem of the company submission (CS) has been restricted to people with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity. This has been done for consistency with the label indication of the marketing authorisation that was granted by the EMA for ocrelizumab in January 2018.

In their original submission to the EMA, the company applied for marketing authorisation in the treatment of adult patients with PPMS [13] using the evidence from the ITT population of the ORATORIO trial [8]. During the scientific assessment, the company modified the indication to early PPMS on the grounds that subgroup analyses showed more favourable results in younger patients (aged ≤45 years) as well as in those presenting with T1-gadolinium (Gd) enhancing lesions at baseline[13]. The decision made by the CHMP (Committee for Medicinal Products for Human Use) pertaining to the choice of the label indication appeared to be difficult since it relied only on subgroup analyses for which the study was not powered. Eventually, the CHMP limited the indication to early PPMS, which the company defined in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

The ERG notes that the definition of these criteria are crucial in determining the population eligible for this drug, and would like to discuss how these criteria may be applied in routine practice within the NHS.

Overall, the ERG has found the criteria of "early disease in terms of disease duration and level of disability" and "with imaging features characteristic of inflammatory activity" to be vague and subjective. This was highlighted by the ERG's two clinical experts who work in different hospital settings. The experts consider that, in the absence of more precise eligibility criteria for ocrelizumab, should this drug be recommended, these criteria would be at risk of being interpreted differently across centres, thereby creating inequalities in the access to the treatment within the NHS.

The company have stated (CS page 62) that the ITT population of the ORATORIO trial was early in their disease course and level of disability (given the inclusion/exclusion criteria of EDSS ≤6.5 and disease duration from MS symptoms onset of <15 years [EDSS at screening >5.0] or 10 years

[EDSS at screening ≤5.0]). The ERG's clinical experts have disagreed with this statement and consider that these inclusion criteria do not indicate early disease. They have indicated that early PPMS pertains more to a time variable rather than a level of disability and that early PPMS would be better defined as PPMS within five years from symptoms onset. In the ORATORIO trial, only [redacted]% of patients in the placebo arm and [redacted]% in the ocrelizumab correspond to this definition (CSR).

With respect to inflammatory activity, the summary of product characteristics (SPC) clarifies that this refers to T1 Gd enhancing lesions and/or active (new or enlarging) T2 lesions. While the European Public Assessment Report (EPAR) refers on several occasions to subgroup analyses in patients with T1 Gd enhancing lesions to define the population that is most likely to benefit from ocrelizumab, the ERG has noted that very little was stated in the EPAR regarding the subgroup of patients with "active (new or enlarging) T2 lesions". The definition of the criteria seems based upon discussions between the company, the CHMP, and clinical experts (EPAR page 176[13]) but not based on subgroup analyses (whether pre-specified or post-hoc) that were presented to the CHMP.

In response to clarifications question A4, the company has explained that the reasons for broadening the MRI active subgroup beyond the pre-specified T1Gd-enhancing lesions subgroup were that clinical practice is moving away from routine T1 Gd scanning due to safety concerns about the contrast agents used, and that the broadened definition more closely resembles the EMA label (which defines inflammatory activity as T1 Gd enhancing lesions or new/enlarging T2 lesions). Yet, it is still unclear why the label indication was broadened in the absence of specific evidence based on a population matching this label indication. The ERG has also noted that some members of the CHMP expressed divergent position on the positive opinion for marketing authorisation of ocrelizumab in early PPMS with inflammatory activity indicating that: 1) the demonstrated efficacy was not compelling from a statistical and clinical point of view; 2) the exploratory subgroup analyses, eventually used to support the clinical effectiveness and marketing authorization, were hypotheses generating and did not identify a patient population where efficacy has been sufficiently[13].

Furthermore, the post-hoc analyses presented in the CS as pertaining to the label, referred to as the "MRI active" subgroup are based on data from patients with gadolinium-enhancing lesions or new T2 lesions but not those with enlarging lesions since these data were not captured in the trial between screening and baseline, meaning that the clinical effectiveness of ocrelizumab in the population strictly matching the label indication is not known.

Most importantly, the ERG's clinical experts have indicated that applying the criteria of new or enlarging T2 lesions to assess eligibility for ocrelizumab treatment would involve repeated imaging, which is currently not common practice in the UK for patients with PPMS. This, together with the lack of standardisation for timing of repeated imaging in MS patients, could translate into situations where some patients may benefit from more frequent brain MRI scans compared to others, thereby creating potential inequalities in the access to ocrelizumab therapy within the NHS should this drug be recommended by NICE. Additionally, scoring enlarging lesions on MRI scans is more challenging that scoring new lesions, and is affected by technical issues such as suboptimal repositioning of the patients in the scanner and (low) agreement between observers in visually scoring lesion enlargement in the clinical setting.

Therefore, the ERG would like to emphasise that, based on current practice, the criteria of new or enlarging T2 lesions to assess eligibility to ocrelizumab treatment may not be uniformly applicable across centres to patients within the NHS. Should this drug be recommended, this eligibility criteria could only be consistently implemented based on recommendations specifying when MRIs should be done (how far apart and how often), and how an enlarging lesion should be defined.

The criterion "presence of T1 Gd enhancing lesions" to assess eligibility for ocrelizumab relies on the evidence provided by the company based on pre-specified subgroup analyses of improved confirmed disability progression at 12 or 24 weeks.

One of the ERG's clinical experts has indicated that many centres would currently not routinely undertake brain imaging with gadolinium. The Association of British Neurologists (ABN) has also commented that eligibility to ocrelizumab would necessitate PPMS patients undergoing a brain MRI with gadolinium which they otherwise would not have. The implementation of this criteria in routine practice may also be problematic given the current general debate pertaining to the use of gadolinium-containing contrast agents. Gadolinium-based MRI scans may be phased out in the future. There has been recent removal and/or restriction on the use of several gadolinium-containing contrast agents by the Medicines and Healthcare products Regulatory Agency (MHRA): from February 2018, OMNISCAN and MAGNEVIST have been removed from the market while MULTIHANCE and PRIMOVIST have been restricted to liver imaging only [14].

As of April 2018, PROHANCE, GADOVIST and DOTAREM are still available in the UK [15].

One of the ERG's clinical experts has indicated that the specialist MS group of the Association of British Neurologists (ABN) has been asked to develop a definition of disease activity; the publication date for this is not yet known.

One of the ERG's clinical experts, involved in the specialist MS group of the ABN, has suggested that an option could be to implement a step-wise approach: the first indication could be for patients presenting gadolinium-enhancing lesions on the brain MRI; in the absence of gadolinium-enhancing lesions or in the event the gadolinium scan is unavailable, a second eligibility criterion could be based on the presence of a new or enlarging T2 lesion.

A final issue regarding the population eligible for ocrelizumab relates to the age of patients. While PPMS can occur in older age, the ORATORIO trial has only included people aged 18-55 years[8]. As noted above, subgroup analyses of ORATORIO have suggested a more favourable results in younger patients (aged ≤45 years).

Given that the label indication of ocrelizumab has no restriction on age, the ERG would like to emphasise that there is no evidence regarding the benefit/risk balance of ocrelizumab in PPMS patients aged >55 years. The company have indicated (CS page 85) that a phase IIIb RCT study is planned and will include patients in later disease course (EDSS 3 to 8, age 18-65) with results anticipated in 2024.

Overall, the ERG has concerns about the definition of the population eligible to ocrelizumab in practice should this agent be recommended by NICE.

Recommendations by the ABN that could be endorsed by NICE are expected. This appears to be important to avoid different interpretation across centres likely to generate inequalities in the access to treatment.

3.2 Intervention

The intervention in the decision problem is ocrelizumab as monotherapy, which matches the NICE final scope. The company provides a description of the technology and the mechanism of action of ocrelizumab (CS p17) which the ERG's clinical advisors have confirmed is an accurate description.

Ocrelizumab is an intravenously administered medication that has been authorised for use in relapsing forms of multiple sclerosis with active disease defined by clinical or imaging features: this indication is subject to an ongoing separate appraisal by NICE (ID937).

Ocrelizumab is a monoclonal antibody that selectively binds to and depletes CD20-expressing B cells. The SPC of ocrelizumab indicates that the exact mechanisms by which this agent exerts its clinical effects in MS is not fully known [13]: it is thought that the effect involves immunomodulation through the reduction in the number and function of CD20-expressing B cells. While the mechanism of action of ocrelizumab used in MS is original compared to other DMTs licensed in MS (irrespective of the type of MS), the selective binding to CD20+ B cells is not innovative. Indeed, as noted above, another monoclonal antibody rituximab is also available and currently licensed for the treatment of some hematologic malignancies and specific autoimmune disorders. Ocrelizumab and rituximab are owned by the same company, Roche Products limited. While the company has cited rituximab in the submission to indicate that this drug was unsuccessfully tested in PPMS, the company has not emphasised the substantial similarity between these two agents. Ocrelizumab and rituximab are both monoclonal antibodies, rituximab being chimeric while ocrelizumab is humanized [16]. Both chimeric and humanized antibodies contain murine sequences which are known to increase their immunogenicity [16]. Based on the humanized nature of ocrelizumab, the company claims that the immunogenicity is reduced compared to other DMTs, providing the rationale for reduced probability of long-term treatment waning effect due to the formation of neutralising and inhibitory anti-drug antibodies (CS p87). The ERG review this statement in the cost-effectiveness section (section 5.2.6) of the report.

In the clinical trial report of ocrelizumab (ORATORIO[8]), the authors suggest that rituximab (in the OLYMPUS trial) in failing to reach the primary efficacy endpoint provided the rationale to restrict inclusion to people below the age of 55 years. Indeed, subgroup analyses from the OLYMPUS trial suggested some benefit in younger patients with evidence of increased inflammatory activity [10].

Ocrelizumab is given intravenously at the initial dose of 600mg administered as two separate intravenous infusions (first as a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion). Subsequent doses of ocrelizumab are administered as a single 600 mg intravenous infusion every 6 months.

3.3 Comparators

The comparator described in the decision problem is established clinical management without ocrelizumab, consistent with the NICE final scope. There are no DMTs licensed in people with PPMS. The ERG's clinical advisors have confirmed that there are no other agents are used off-label in the UK.

3.4 Outcomes

The outcome measures listed in the NICE scope have generally been reported in the decision problem. They are disability, disease activity, patient-reported outcomes including fatigue, cognition impairment, mortality, adverse effects (AE) and HRQoL.

Although visual function is one of the eight functional systems measured within the EDSS, no separate measures of visual disturbance were reported.

The ERG provide a critique of these outcomes in the relevant section of the clinical effectiveness review (section 4.3).

3.5 Other relevant factors

As part of equity considerations, the ERG has raised several issues regarding the applicability of eligibility criteria to ocrelizumab based on current practices (section 3.1).

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The ERG's appraisal of the CS systematic review of clinical effectiveness is summarised in Table 2. Overall, the systematic review process is considered to be reasonable. Although limitations with the searches were noted (section 4.1.1), only one trial of ocrelizumab in PPMS was eligible for inclusion and it is unlikely any relevant studies were missed. The company assessed the quality of the included trial; the ERG generally agreed with the company's assessment although there were some differences in judgements (section 4.1.4). The ERG also had concerns regarding selective reporting of outcomes (section 4.3). The submitted evidence is generally consistent with the decision problem defined in the CS and there is a low chance of systematic error.

Table 2: Quality assessment of the CS systematic review of clinical effectiveness

CRD Quality Item	Yes/No/Uncertain
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all relevant research?	No, but unlikely to have missed any relevant publications (see section 4.1.1)
3. Is the validity of included studies adequately assessed?	Yes, but ERG judgements differ for some items (see section 4.1.4)
4. Is sufficient detail of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Uncertain, the single trial is appropriately summarised in a narrative synthesis, but the ERG has concerns regarding the selection of reported outcomes (see section 4.3)

4.1.1 Searches

A search of one database (CENTRAL) was undertaken on 14 November 2017. The choice of search terms was appropriate to the company's broad aim to identify any trial relating to PPMS, regardless of intervention. However, no other sources were searched and no supplementary search methods were used.

It is therefore possible that some, particularly recent trials, have been missed for this broad aim. The ERG has searched the WHO trials register portal and can confirm there are no other trials of ocrelizumab in PPMS listed. For the narrower scope of this submission the ERG consider it reasonable for the company not to have undertaken a full systematic review using an adequate range of sources and methods because the NICE 2015 user guide states that "in exceptional

circumstances, such as when all published or unpublished clinical data are within the company's possession, custody or control the company do not have to do a systematic review".[17]

The ERG has searched the WHO trials register portal and can confirm there are no other registered trials of ocrelizumab in PPMS.

4.1.2 Inclusion criteria

The systematic review is described in CS Appendix D. The review aimed to identify studies of comparators that are used off-licence as part of standard of care for PPMS in some other countries (likely for other submissions) but are outside the NICE scope. The tabulated eligibility criteria are therefore broader than the NICE scope and licensed indication, however further criteria were then applied to exclude studies not meeting the NICE scope (not stated how this was applied).

The eligible population for the company's systematic review is adults with PPMS. This is in line with the NICE scope but is broader than the marketing authorisation which limits to early disease and imaging features characteristic of inflammatory activity (see section 3.1 'decision problem'). The ERG considers this reasonable. Mixed populations were eligible under specific conditions but no studies of these were included. Eligible outcomes were broad and the ERG consider would capture all relevant studies. Study designs were limited to RCTs with a minimum duration of 12 weeks and there were no limits relating to quality, these were also considered appropriate criteria by the ERG.

A flow diagram as per the PRISMA statement is reported and a list of excluded studies with reasons is provided. One trial with 16 records was included, however only 15 records are listed in CS Appendix D Table 3; the missing reference was provided by the company in response to clarification question C3.

4.1.3 Critique of data extraction

Study selection was undertaken by two reviewers (unclear if independently but a third reviewer was used for any disagreements over eligibility): there was no description of the data extraction process.

4.1.4 Quality assessment

The company provided a quality assessment of the ORATORIO RCT using the NICE criteria. The ERG largely agrees with the company's assessment (**Table *3***) and notes the imbalances in dropouts as described by the company (the ERG assesses this as a risk of bias, CS does not). The ERG also notes that a proportion of patients were unblinded during the trial: this occurred in 19 patents due to suspected unexpected serious adverse reactions, in a further seven whose suspected unexpected serious adverse reactions were subsequently downgraded, and in 13 upon investigator request (mainly due to alternative treatment decision, worsening MS symptoms and safety concerns). The impact of this is unclear. The company states that not all outcomes are presented (but their comment suggests they believe there was no risk of selective outcome reporting). The ERG agrees that selected exploratory measures were presented in the CS and that there is some risk of bias due to selective outcome reporting in the CS. Those not presented include (clinical study report [CSR] p.74):

- Proportion of patients with confirmed disability progression at Week 120
- Change from baseline in EDSS score
- Cortical grey matter brain volume and white matter volume (presented in subgroup analyses only)
- MFIS subscale scores from baseline to Week 120.
- Change from baseline in total non-enhancing T1 lesion volume.

EQ-5D is listed as an outcome of ORATORIO in CS Tables 6 and 9, and CS p.100 states EQ-5D data were collected in the ORATORIO study; but it is not listed in the CSR and no data are presented.

In addition, The CS is not clear that the outcomes ‘20% increase in 9-HPT’ (CS B.2.6.4 p 48, Table 16 p. 67 and Table 22 p. 72) and ‘20% increase in T25FW’ (Appendix K p.132) were not defined as a pre-planned exploratory endpoint in the statistical analysis plan (CSR p. 74), despite the emphasis placed on the former outcome by listing it as the second bullet point under CS B.2.6.1 Overview of efficacy.

Table 3: Company and ERG assessment of trial quality

NICE Checklist Item	CS judgement [a]	ERG judgement
Was randomisation carried out appropriately?	Yes (randomisation was performed via an independent IVRS provider).	Yes
Was the concealment of treatment allocation adequate?	Yes (concealment was adequate as randomisation was performed using an IVRS).	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Baseline disease characteristics for MS were similar across both treatment groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. (Investigators, patients and sponsor personnel were blinded to treatment assignment. Blinding was achieved by receiving either ocrelizumab or matching ocrelizumab placebo by IV infusion every 24 weeks. Further details regarding the blinding of the study are given in section 3.6.5 of the Clinical Study Report.)	Yes (although a small proportion of patients were unblinded)
Were there any unexpected imbalances in drop-outs between groups?	No major imbalances. A higher proportion of patients in the placebo group (34%) withdrew prematurely from treatment during the double-blind treatment period compared to the OCR group (21%). The difference was mainly due to higher incidences of withdrawals due to lack of efficacy (11% versus 4%) and withdrawal by subject (9% versus 5%) in the placebo group versus the OCR group, respectively.	Yes. Imbalances noted as described, clarification on reasons requested (A1) but numbers not provided.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No (all the outcomes mentioned in the study protocol were reported in the manuscript and study report; however, only those relevant for modelling cost-effectiveness are included in this dossier)	Yes. Selected outcomes are reported in the CS and trial publication.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes (ITT analysis was used for efficacy and safety outcomes. Appropriate methods for accounting for missing data were employed; refer to section B.2.4)	Yes (but see section 4.5.1 for implications of imputation)

[a] *CS Appendix D1.3*

4.1.5 Evidence Synthesis

A narrative review of the single included trial was provided. The tabulated data and narrative reflect the data in the trial publication and CSR, although some measured outcomes were not reported (see section 4.3). Additional outcomes were requested from the company (clarification questions A9-A10) and are summarised by the ERG in sections 4.5.

There are no licensed or off-label products used in the UK for PPMS therefore it is appropriate that an indirect comparison was not performed. Limited endpoint or change data are reported in the CS, with results mainly presented in figures and as hazard ratios between groups (clarification questions A9-A10.

For adverse events, including malignancies, the CS pooled data from four ocrelizumab trials (CS Appendix F):

- ORATORIO: Phase III placebo-controlled trial in PPMS (main study in the CS)
- OPERA 1 and 2: Two phase III trials (ocrelizumab versus interferon Beta-1a) in RRMS
- A Phase II study in RRMS:
    - Ocrelizumab, first dose of two infusions of 300mg followed by 600mg as a single infusion in cycles 2-4
    - Ocrelizumab, first dose of two infusions of 1000mg followed by 1000 mg as a single infusion in cycles 2-3 and 600mg in cycle 4
    - Interferon Beta-1a followed by two infusions of ocrelizumab 300 mg in cycles 2 and a single infusion of 600mg in cycles 3-4
    - Placebo followed by two infusions of ocrelizumab 300mg in cycles 2 and a single infusion of 600mg in cycles 3-4

Data were included from the open label extension (OLE) periods from the trials; the CS notes the bias due to the open label design and non-random drop-outs. All patients who received any part of an ocrelizumab dose were pooled, including patients who switched to ocrelizumab from comparators. Comparator data were pooled from patients receiving interferon Beta-1a and placebo. It appears that simple pooling of data was used and analysis did not account for initial randomisation or trial allocation. Exposure (patient-years of observation) and mean number of doses received were reported, but not the range of doses. Results from two data-cuts are reported

but the reasoning for this is not justified, although rates at the latest data cut were lower. An explanation for this is not provided.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

Evidence for the clinical effectiveness on ocrelizumab is presented from a single pivotal RCT. The ORATORIO (WA25046) trial was a phase III double-blind, multi-centre, placebo controlled RCT sponsored by the company. The results were reviewed by the EMA and the FDA as part of the process aimed to grant marketing authorisation. Summary details of the trial were provided in the CS and in CS Appendices D, E F, K. In addition the trial is reported in a number of peer review publications (main publication Montalban et al. 2017[8]) and a confidential CSR which have been submitted to the ERG.

The trial was designed to investigate the use of ocrelizumab in people with PPMS. Intravenous ocrelizumab 600mg (by infusion) or placebo was assigned randomly in a 2:1 ratio for a double-blind controlled period of at least 120 weeks. Participants, investigators and outcome assessors were blinded to treatment allocations (intravenous infusion of placebo was administered to participants), although see Section 4.1.4 re un-blinding of some participants and risk of bias assessment of the blinding. Treatments were given every 24 weeks (at least 5 doses). Ocrelizumab was given as two infusions of 300mg, 14 days apart (placebo administration followed the same treatment cycles). Patients were randomised between 3 March 2011 and 27 December 2012 and the clinical cut-off was 24 July 2015 (it was noted as 24 July 2014 on page 45 of CS which appears to be a typographical error).

The key inclusion criteria are reported in CS Table 8 (p39), in summary these were age 18-55 years, PPMS diagnosis by 2005 revised McDonald criteria, EDSS score 3.0-6.5 at screening, duration of MS symptoms <15 years if EDSS score >5.0 at screening or <10 years if EDSS score ≤5.0 at screening. A history of RRMS, secondary progressive MS (SPMS) or progressive relapsing MS (PRMS), contraindications to MRI and previous treatment with B-cell–targeted therapies and other medications for MS were key exclusion criteria. The CS states that systemic corticosteroid use within 4 weeks of screening was a reason for exclusion; the trial publication states that contraindications to or unacceptable side effects from oral or intravenous

glucocorticoids was an exclusion criteria. The ERG considers that these criteria are generally appropriate. In the ocrelizumab group at least one participant had a higher than 6.5 score on the EDSS at baseline (range was 2.5 – 7.0). This may be related to the time between screening and baseline which was between 4-8 weeks.

A flow-chart of participants through the ORATORIO trial was presented in CS Appendix D: 732 were randomised, 725 received at least one dose of the assigned treatment (99%, see below), 576 completed to week 120 (78.7%) and 549 (75%) were ongoing at the clinical cut-off date. The numbers receiving treatment are difficult to follow as it suggests that 6 in each arm did not receive treatment, however, according to CSR p.85 there were [redacted] in the ocrelizumab arm and [redacted] in the placebo arm who did not receive at least 1 dose of the assigned treatment. Four of those in the placebo group were given ocrelizumab incorrectly and for the safety analysis were included in the ocrelizumab group. In the ocrelizumab arm 488 were randomised, 482 (98.8%) received at least one dose, 402 (82.4%) completed to week 120 and 387 (79.3%) were ongoing at the clinical cut-off. Numbers and reasons for withdrawals were reported combined for the 6 who did not receive treatment and the 95 who had at least one treatment and withdrew at any point prior to the cut-off date. The most common reasons for withdrawal in the ocrelizumab group were withdrawal of consent (4.5%); lack of efficacy (4.3%) adverse events (3.7%) and 'other' (4.1%). 61 of those withdrawing were included in the safety follow-up. In the placebo group 244 were randomised, 243 (99.6%) received at least one dose (although note above inconsistency as the figure incorrectly states 6 were not treated with placebo), 174 (71.3%) completed to week 120 and 162 (66.4%) were ongoing at the clinical cut-off. The most common reasons for withdrawal at any time point, including those not treated was withdrawal of consent (8.6%), lack of efficacy (11.1%), adverse event (4.9%) and 'other' (5.3%). 45 of those withdrawing were included in the safety follow-up. Therefore the proportions receiving at least one treatment were similar between groups but the withdrawals prior to week 120 and to clinical cut-off date were higher in the placebo group. Further details of the reasons why participants 'withdrew consent' and details of 'other' reasons for withdrawal were requested by the ERG (clarification question A1). The company provided a narrative description of the categories but did not provide numbers. Both 'withdrew consent' and 'other' categories included the reasons perceived lack of efficacy, disease progression, personal reasons, and desire to receive a different treatment. The ERG notes that lack of efficacy was also a distinct category, therefore the overall number of participants in each arm withdrawing for this reason is unclear.

CS Table 34 provides details of treatment exposure which shows that 83% of ocrelizumab participants and 71% of placebo participants received at least 6 doses. This difference between groups was apparent between 2 and 5 doses (rates higher in the placebo group) and 7 and 10 doses where rates were all lower in the placebo group than the ocrelizumab group (although the mean number of doses was similar (6.6 ocrelizumab versus 6.1 placebo)).

Follow-up visits occurred every 12 weeks from the date of last visit until 48 weeks had elapsed since the last treatment. Outcomes reported were time to CDP-12 (primary outcome); CDP-24 weeks, 25-foot walk, change in T2 brain lesions on MRI, percentage change in total brain volume, change in physical component summary score of the SF-36 (all secondary outcomes) and time to sustained increase in 9-HPT, fatigue as measured by the MFIS and other imaging assessments (all exploratory endpoints), see CS Table 8 and CS B.2.6. For further description and ERG assessment see Section 4.3.

Statistical analyses are summarised in CS Table 10 (for ERG assessment see Section 4.4 trial statistics). Data from the trial are reported for the ITT population, a safety population, and a post-hoc subgroup population according to active disease on MRI (those with T1 Gd-enhancing or new T2 lesions between screening and baseline) to meet the CS's base-case to match the marketing authorisation of 'early and active' disease (post hoc analyses, see Section 4.5.1.2 for further details).

The CS states that pre-planned subgroup analyses were undertaken on the primary outcome and the 24-week CDP, the change in time to 25-foot walk and total volume of T2 lesions. These are listed in CS Table 8 and 10 and B.2.7 as by age (≤45 vs >45 yrs), sex (male vs female), baseline EDSS (≤5.5 vs >5.5), region (USA or rest of world), Gd-enhancing T1 lesions at baseline (yes vs no), prior disease modifying treatments for MS (yes vs no), duration of symptoms (≤3 yrs, 3 to ≤5 yrs, 5 to ≤10 yrs, >10 yrs), weight at baseline(≤75 vs >75 kg, BMI (<25 vs ≥25 kg/m^2) at baseline. However, only results for sex, age and T1 Gd-enhancing lesions at baseline are presented for outcomes other than the primary outcome, including several secondary and exploratory endpoints (Appendix E). Post-hoc subgroup analyses in people meeting the company's definition of the marketing authorisation label ('MRI active') in people with inflammatory activity and aged 50 years or younger were presented in sections B.2.6.7 and

B2.7.2, respectively. See Section 3.1 for ERG assessment of the subgroups and ERG Section 4.5.1.3 for results of the subgroups.

Table 4 summarises the key baseline characteristics of the trial ITT population and the MRI active subgroup. There were no meaningful differences at baseline in demographic or disease characteristics between ocrelizumab or placebo groups in the ITT population. The CS (p41) reports that more patients in the ocrelizumab group reported active comorbidities than patients in the placebo group (81% versus 75% respectively). The most commonly reported current diseases listed in the CS were psychiatric disorders, musculoskeletal and connective tissue disorders and nervous system disorders. The rates for each of these were very slightly higher in the placebo group than the ocrelizumab group (rates provided on CS p41). From the CSR it can be seen that although less frequently reported overall [redacted] were reported slightly more often in participants in the ocrelizumab group than the placebo group. Baseline characteristics for MRI active subgroup were not reported in the CS; these were provided by the company in response to clarification question A5. No major imbalances were apparent (Table 4).

There were 29 patients from the UK in the trial (5% ocrelizumab, 2% placebo), CS Table 7. The ERG's clinical experts do not consider the population of the ORATORIO trial to be generalizable to the UK population of 'early' PPMS (see critique of the decision problem in section 3.1).

No non-RCTs of relevance were identified. Data from an extended controlled treatment period from the ORATORIO trial were also included in the CS p57-60. These analyses were presented to the EMA. This is unpublished, post-hoc analyses, and provides approximately 3 months longer blinded follow-up and approximately 3 months follow-up during which time participants were un-blinded and switched to open-label treatment.

The ORATORIO open label extension study is ongoing; the expected publication date was not reported. In addition, the CS reports that a new phase IIIb study is under development to respond to the EMA risk management plan for ocrelizumab (detailed on CS p85): this trial will include PPMS patients aged up to 65 years.

Neither the company nor the ERG identified any other relevant RCTs that meet the NICE scope.

Table 4: Baseline characteristics: ITT and MRI active subgroup

Characteristic	ITT		MRI active subgroup	
	Ocrelizumab n=488	**Placebo n=244**	**Ocrelizumab n=189**	**Placebo n=104**
Age, mean (SD)	44.7 (7.9)	44.4 (8.3)	[redacted]	[redacted]
Sex, % male	51.4	49.2	[redacted]	[redacted]
Race, % White	93.0	96.3	NR	NR
Time since onset of MS symptoms, mean (SD) median (range)	n=474 6.7 (4.0) 6.0 (1.1 to 32.9)	n=237 6.1 (3.6) 5.5 (1.1 to 32.9)	[redacted] NR	[redacted] NR
Time since diagnosis, mean (SD) median (range)	n=486 2.9 (3.2) 1.6 (0.1 to 16.8)	n=243 2.8 (3.3) 1.3 (0.1 to 23.8)	[redacted] NR	[redacted] NR
No previous use of DMT, %	88.7	87.7	[redacted]	[redacted]
EDSS mean (SD) median (range)	N=487 4.7 (1.2) 4.5 (2.5-7.0)	 4.7 (1.2) 4.5 (2.5-6.5)	[redacted] NR	[redacted] NR
Gd-enhancing lesions on T1 at baseline, %	27.5	24.7	[redacted]	[redacted]
Gd-enhancing lesions on T1 at screening or baseline, %	32.2	31.6	[redacted]	[redacted]
No. of lesions on T2 mean (SD) Median (range)	N=486 48.7 (38.2) 42 (0-249)	N=243 48.2 (39.3) 43 (0-208)	NR	NR

NR; not reported

4.3 Description and critique of company's outcome selection

The outcomes reported in the CS generally matched the final scope with the exception of visual disturbance. Although visual function is one of the eight functional systems measured in the EDSS, no separate measures of visual disturbance were reported. Table 5 summarises the outcomes reported in the CS and the ERGs comments.

Table 5: CS reported outcomes and ERG comments

CS outcome	In line with NICE Scope	ERG comments
Primary outcome:		
12-week confirmed disability progression (CDP) (an increase in the EDSS sustained for at least 12 weeks, referred to as time to onset of 12-week CDP in the CS) with ≥1.0 /≥0.5 point change if the baseline score is ≤5.5/>5.5 points, respectively. Primary trial outcome. EDSS scores range from 0 to 10, with 0.5 unit increments representing increasing levels of disability (ranges from 0 (normal neurological function) to 10 (death). Scored by neurologists. Scores up to 5-6 are based on 8 functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder function, visual function, cerebral functions, and 'other'. Scores 5-9.5 are defined by level of impairment to walking, with EDSS 7 considered clinically important as this is when people become restricted to a wheelchair.	Yes (disability)	In clarification response A2, the company argued that 12-week CPD has more power to detect a treatment effect due to a higher number of detected progressions, and that the inclusion of only PPMS patients in ORATORIO would mean less confounding by relapses than in RRMS. The ERG believe the primary outcome should be CDP-24 weeks as this is a more clinically relevant and meaningful outcome of a sustained effect on disease progression. In PPMS EDSS can be affected temporarily by factors other than disease progression including variations due to relapses (relatively rare in PPMS, ~5% pts) or deterioration due to intercurrent illnesses (e.g. infections) or psychological factors. While these periods of deterioration can last for months they would generally be expected to have improved back to baseline by 6 months. The CS acknowledges shortcomings of the EDSS including its subjective nature, poor reliability, non-linear ordinal scale, its reliance on walking as the main measure of disability and poor capture of cognitive impairment (CS p19). Despite documented deficiencies in reliability and sensitivity to change in the EDSS it is used widely in clinical studies as an outcome measure.[18, 19] The definition for CDP (thresholds of required change in EDSS according to baseline score) was predefined and is in line with recommendations from the EMA.[7] The ORATORIO trial protocol listed change in EDSS score as an exploratory endpoint, however, these data were not presented in the CS. The data were provided by the company in response to clarification question A9 (see section 4.5.1 results).
Secondary outcomes:		
24-week CDP	Yes (disability)	As above

Timed 25-foot walk (T25FW) change from baseline	Yes (disability)	The T25FW is a widely used measure of disability,[20] although the ERG's clinical experts consider its lacks clinical relevance as it does not measure function (activity limitation). Baseline and endpoint data were not presented in the CS; these were requested by the ERG (clarification question A10), but only the ratio of change was provided (see section 4.5.1).
Total volume in T2 hyperintense brain lesions on MRI (change from baseline)	Yes (disease activity)	A surrogate outcome monitoring CNS lesions. Imaging outcomes are currently not clearly demonstrated to be validated surrogates of patient outcome but are appropriate as secondary outcomes. As per EMA recommendations[7] the reading of images were centralised and blinded in the ORATORIO trial.
Total brain volume (percentage change from week 24)	Yes (disease activity)	A surrogate outcome monitoring CNS atrophy. As above
Physical Component Summary score of the SF-36, change from baseline (Mental Component Summary score specified as an exploratory outcome)	Yes (HRQoL)	The SF-36 is a reliable and validated generic measure of HRQoL and has been used widely in MS. It consists of 8 domains which can be presented individually and two component scores can be generated. The PCS was a secondary outcome in the pivotal trial included in the CS. The MCS was an exploratory outcome (presented in CS Appendix K only). It is not clear to the ERG why the PCS was a secondary outcome but the MCS was exploratory. The CS does not discuss what constitutes a clinically meaningful change in the PCS.
Exploratory outcomes:		
Time to increase (≥20%) in the 9-hole peg test that is sustained for at least 12 weeks (or 24 weeks). 9-HPT assesses upper extremity function, scored by the time taken to repeat 4 trials of selecting 9 pegs, one at a time, and placing them in to holes in a block, and then removing them one at a time. Reproducibility is high and changes have been associated with greater long-term disability levels.	Yes (disability)	The 9-HPT is widely used and a validated outcome measure in MS, although the ERG's clinical expert considers it to be a poor surrogate measure of disability. The threshold of ≥20% increase has been used in previous studies in MS although this definition is not fully validated in all stages of the disease.[21] The CS is correct that the EDSS does not adequately assess upper limb function and cognitive impairment. It has been suggested that the 9-HPT 20% outcome may be less suitable than EDSS and T25FW when used alone due to minimal changes observed in the PROMISE trial, but it may still have validity as part of a composite measure (see below).[20] However, it does not test the ability of upper limbs to do meaningful tasks which would cause loss of independence

		(feeding, dressing etc). The CS is unclear in places as to what is being reported, for example using the terms 'at 12 weeks' or 'at 24 weeks'. The ERG considers that a ≥20% increase in 9-HPT sustained for 24 weeks would be more appropriate than sustained for 12 weeks
EQ5D change from baseline	Yes (HRQoL)	The EQ-5D is an appropriate measure of HRQoL. However, the CS and CSR do not report the baseline findings or any results.
Modified Fatigue Impact Scale (MFIS), change from baseline in total score and subscale scores. MFIS total scores range from 0 to 84, with higher scores indicating greater fatigue; scores ≥38 indicate a clinically important level of fatigue.[22] Subscale components for physical, cognitive and psychosocial impact. CS p.112 says that the MFIS is reliable to assess the burden of fatigue in MS, but does not provide evidence to support this. The CS also notes that cut-offs are not commonly used with fatigue scales and have not been extensively researched in PPMS.	Yes (Fatigue)	The ERG has concerns regarding the reliability and validity of the MFIS. A 2013 review reports that the reliability and validity of the MFIS has not been adequately assessed and there are problems with interpretation.[23] The threshold of ≥38 is from one correlation study and while this has been used as a cut-off in other studies, Larson argues that this is not a clear rationale and verification of the figure has not been adequate. It is therefore unclear if the cut-off score of 38 is able to discriminate fatigued from non-fatigued people.
Imaging outcomes, change from baseline in: New or enlarging T2 hyperintense lesions Cortical grey matter volume, % change White matter volume, % change Total non-enhancing T1 lesion volume	Yes (disease activity)	Surrogate outcomes, as above
No Evidence of Progression (NEP) – composite outcome, combines EDSS, 9-HPT and T25FW. CS p52 states that thresholds were: No 12-week CDP No 12-week ≥ 20% progression on 9-HPT No 12-week ≥ 20% progression on T25FW CS p21 states has greater sensitivity to clinical progression than the EDSS alone. CS p23 states a limitation is that it doesn't account for relapse or MRI activity.	Yes (disability)	Stated in CS page 52 that this was a pre-specified exploratory endpoints, however, not referred to in CS Table 8. The composite has been tested in a recent analysis of PPMS participants in the placebo arm of the PROMiSe study. Results suggest that the composite (including the thresholds used) are an appropriate measure of disability progression in MS.[20] It was also used as the primary outcome in the INFORMS trial of fingolimod in PPMS. [24]
No evidence of progression or active disease (NEPAD) – composite outcome, combines NEP and brain MRI disease activity	Yes (disability)	This was a post-hoc exploratory analysis (not referred to in CS Table 8). The ERG has been unable to identify any references critiquing this composite measure.

including no new or enlarging T2 lesions and no T1 gadolinium-enhancing (Gd+) lesions and no protocol-defined relapses.		
Multiple Sclerosis Functional Composite Score (MSFC) – a composite of the 9-HPT, T25FW and PASAT (see below), reported as an exploratory endpoint in CS Appendix K. CS does not describe the characteristics of the MSFC, or that its components include the 9-HPT and T25FW, which are also reported separately.	Yes (disability)	A valid measure of disability / progression of MS that has been used in some previous trials of MS treatments.[18]. The sensitivity of the MSFC to measure treatment effects is unclear, with some studies reporting reduced sensitivity and others improved sensitivity compared with the EDSS.[25] There can be difficulties with the scores used to calculate the summary score from the three components and evidence suggests it has low acceptance by patients. A 20% threshold for changes in the individual components are considered to be clinically relevant.[18]
Paced Auditory Serial Addition Test (PASAT), a test of cognitive impairment. Reported as an exploratory endpoint in CS Appendix K. CS does not describe the characteristics of the PASAT.	Yes (cognitive impairment)	As indicated, this is a component of the MSFC and it is a measure of cognitive impairment, a NICE scoped outcome. The test assesses the speed of information processing and calculation ability.[25] Weaknesses are that there can be a learning effect (patients can improve with practice); it can be stressful and patients do not like to undertake the test, and it correlates poorly with the EDSS.[18, 25] A recent SR notes that it does not reflect disease progression well in PPMS.[18]

4.4 Description and critique of the company's approach to trial statistics

The pre-specified primary end point in the trial was defined as: A time-to-event analysis of the proportion of patients with baseline score of ≤ 5.5 exhibiting a disability progression of ≥ 1.0 point from baseline confirmed at subsequent visits for at least 12 weeks, and the proportion of patients with baseline score of > 5.5 having disability progression of ≥ 0.5 points from baseline confirmed at subsequent visits for at least 12 weeks. At baseline for both arms the mean EDSS was 4.7 (±1.2) and median 4.5.

The Kaplan Meier (KM) plot for the primary outcome in the ORATORIO trial is shown in CS Figure 10 (the controlled double blind period). CS Figure 20 shows this outcome when the controlled extension period is also included in the analysis.

The null and alternative hypotheses respectively (CS Table 10) were: there was no difference in the time to CDP between the ocrelizumab and placebo groups, and there was a difference in the time to CDP between the ocrelizumab and placebo groups. The null hypothesis was tested at $\alpha = 0.05$ level (two-sided test) stratifying by geographic region (USA versus rest of world [ROW]) and age (≤45 versus >45 years). If the test result was statistically significant at $\alpha < 0.05$ level, it was concluded that the ocrelizumab group demonstrated a superior effect of increasing time to CDP, when compared with the placebo arm. The primary end point analysis reached statistical significance (HR = 0.76, 95% CI: 0.59-0.98; p = 0.0352 by log rank test) and the CS states the effectiveness of ocrelizumab at slowing progression was thereby demonstrated.

The following section discusses/ considers potential shortcomings in estimating the primary outcome.

The CS (page 19) acknowledges that "the [EDSS] scale has poor reliability within and between raters thereby creating considerable "noise" in real world measurements". The poor rater-reliability has been described by some as "jaw dropping" [26]. Nevertheless according to the EPAR "The Applicant argued that EDSS progression (of 1.0 or 0.5 EDSS points depending on baseline score), and consequently any measurable delay in progression, is clinically relevant".

The analysis (to ~216 weeks; 256 events: placebo 96, ocrelizumab 160) included imputed events in which initial EDSS progression of disability was not confirmed. The definitions of events and of censorings are summarised in Table 6.

Table 6: Definitions of censorings and events; based on the FDA statistical report[27]

No initial progression event at CCOD, or at TX discontinuation, or before LTFU	Initial progression event but no confirmation while on TX at CCOD	Initial progression event but discontinued TX before confirmation	Initial progression event with confirmation of EDSS change at 12 weeks.
CENSORED at last EDSS assessment	**CENSORED** at last EDSS assessment	**IMPUTED EVENT** at time of initial event	**EVENT** at time of initial event
CCOD = clinical cut-off date; LTFU = loss to follow up; TX = treatment			

Because treatment withdrawal was more common in the placebo arm so also was the number of imputed events. Of 21 imputations there were 12 in the placebo arm and 9 in the ocrelizumab arm, representing 12.5% and 5.6% of 12-week CDP events respectively. These data are shown in the Table 7, based on the FDA statistical report.[27]

Table 7: Primary outcome events; based on the FDA statistical report[27]

	OCRELIZUMAB	PLACEBO
Total number of patients	487	244
Number with 12-week CDP with NO imputation	151 (31.0%)	84 (34.4%)
Number with 12-week CDP WITH imputation	160 (32.9%)	96 (39.3%)
Total number that withdrew	101 (20.7%)	82 (33.6%)
Number of progressions without confirmation due to withdrawal	9	12
% of withdrawals that were unconfirmed progressions	8.9 (9/101)	14.6 (12/82)
% of all progressions that were unconfirmed progressions	5.6 (9/160)	12.5 (12/96)

A pre-specified sensitivity analysis of 12-week CDP based only on un-imputed events reduced the HR to 0.82 and increased the p-value to 0.1477 and a similar effect was found for the 24-week CDP outcome. According to the FDA review "*The results from these sensitivity analyses casted a question of whether the withdrawal had contributed to the size and significance of the treatment difference*".[27]

In addition to the 256 CDP events (of which 21 were imputed), 76 patients had an initial onset event that was not confirmed at a 12-week assessment after the initial onset. The likelihood that an initial event remained unconfirmed was 22.89% (76/(256+76)), and consequently this

proportion of the 21 imputed events (representing 5 events) may not have been confirmed at 12 weeks if they had been checked. The FDA statistical review therefore undertook analyses in which 5 randomly selected imputed events were treated as censorings, 500 iterations were performed; the resulting in a mean log-rank p value of 0.050 (range 0.0177 to 0.0931).

The FDA statistical review conclusion was expressed as follows: "*Study WA25046 [ORATORIO] provided data that were indicative of efficacy in the treatment of ocrelizumab in delaying the disability progression in patients with PPMS. The evidence of the effectiveness was weakened by the failure of the study to withstand an important sensitivity analysis on un-imputed data, which is commonly used as the standard primary data for disability progression endpoint*".

The above implies that the inclusion of imputed ("unconfirmed events") in 12-week CDP analyses is uncommon. The ERG therefore looked at the OLYMPUS RCT of rituximab in PPMS[10]. The published OLYMPUS report states *"There was no imputation of missing data for assessment of time to CDP";* however then goes on as follows: *"Patients with an initial disease progression who subsequently discontinued the study treatment before a subsequent confirmatory assessment could be obtained were considered to have CDP".* The use of imputed events in these trials appears relevant since in attempting to define a PPMS population most likely benefit from ocrelizumab the EPAR states (page 176) *"some supportive reasoning about the identification of a sub-population of PPMS patients that can benefit more from ocrelizumab, can be derived from the exploratory subgroup analysis of the findings from a similar trial performed with another monoclonal antibody (Olympus)"*; this indicated that patients with early PPMS might benefit from CD20-directed "mabs" (see ERG discussion of the Decision Problem section 3.2). Rituximab has a similar mode of action to ocrelizumab and is also owned by Roche (see section 3.2).

4.5 Summary and critique of the results

4.5.1 Effectiveness

In this section, the ERG has summarised and critiqued the results from the ORATORIO trial considering two populations: 1) The ITT population; and 2) the post-hoc subgroup of the patients with MRI-active disease defined by the company.

The key results are summarised in Table 8 and discussed in the following sections.

On page 57 of the CS, the company has referred to post-hoc analyses based on an extended controlled treatment period that added approximately 3 months of controlled follow-up. These analyses were provided to the EMA. The additional period went from the clinical cut-off date (24 July 2015) to 20 January 2016 or the time when the patient received their first open-label dose of ocrelizumab, whichever came first. During this time, patients were gradually unblinded and switched to open-label extension.

In Clarification question A6, the ERG asked the company to provide hazard ratios (HR) for CDP-12 and CDP-24 from the extended controlled treatment period in the subgroup of patients with T1 Gd-enhancing lesions at screening/baseline. The ERG has noted a discrepancy on the actual date of clinical cut-off between the CS and the clarification response to question A6. Based on the most updated information provided by the company, it is thought that the CS has provided on page 57 outcomes obtained from a clinical cut-off date of 20 September 2016 and this is those the ERG has chosen to report in Table 8.

Although the ERG was interested in results reporting slightly more mature data, the ERG is cautious regarding these additional results given that some patients were unblinded over the extended controlled treatment period, meaning results are more at risk of performance bias.

The following sections also summarizes results of secondary and exploratory outcomes from the ORATORIO trial. The ERG notes that exploratory analyses are intended to generate hypotheses for further prospective research which means that overall no formal conclusions should be drawn from these analyses. Similarly, the ERG indicate in the cost-effectiveness section that the incorporation of outcomes from these analyses into the cost-effectiveness model should be viewed cautiously (see section 5.2.9).

Table 8: summary of results from the ORATORIO trial on the main endpoints related to disability progression

Description of the population	**ITT population**		**MRI active patients (T1 Gd-enhancing at screening/baseline or new T2 lesions between screening and baseline)**	
Matching with the label indication at baseline	NO (only partial)		YES (as defined by the Company)	
Type of analysis with regards to the population	Pre-specified / powered		Post-hoc analysis / unpowered	
Arms (number of patients)	Ocrelizumab (n=488)	Placebo (n=244)	Ocrelizumab (n=189)	Placebo (n=104)
Pre-specified primary analysis (clinical cut-off date after a minimum of 120 weeks of double-blind controlled follow-up)				
Patients with 12-week CDP	32.9%	39.3%	32.8%	43.3%
HR for 12-week CDP (95% CI); p-value (log-rank)	0.76 (0.59, 0.98); p=0.0321		0.68 (0.46,0.99); p=0.0448	
Patients with 24-week CDP	29.6%	35.7%	30.7%	38.5%
HR for 24-week CDP (95% CI); p-value (log-rank)	0.75 (0.58, 0.98); p=0.0365		0.71 (0.47,1.06); p=0.0917	
Extended controlled treatment period (post-hoc analysis) [a]				
Patients with 12-week CDP	36.3%[b]	43.4%[b]	NR	NR
HR for 12-week CDP (95% CI); p-value (log-rank)	0.74 (0.58, 0.95) [c] p=0.0151		0.69 (0.47, 1.00); p=NR	
Patients with 24-week CDP	31.6%[b]	40.2%[b]	NR	NR
HR for 24-week CDP (95% CI); p-value (log-rank)	0.70 (0.54, 0.90)[d]; p=0.0056		0.68 (0.46,0.99); p=NR	

[a] Data from CS Table 17 and 18, this appears to be from clinical cut-off date of 15 September 2016 as stated in the footnote of clarification A6 Table 2 (although on CS p.57 it is stated the clinical cut-off date is 20 January 2016); AIC data from the 20 January data-cut can be seen in clarification A6 Table 2. [b] Data from EMA CHMP report, 20 January data-cut.[13]; [c] the value was extracted from CS page 57 as reported in EMA CHMP report[13], the ERG has noted a discrepancy between this value and that reported in CS Table 18 which is 0.75 (0.59, 0.96); [d] extracted from CS page 57 as reported in EMA CHMP report,[13] but the lower CI in CS Table 18 is 0.55. NR = not reported

4.5.1.1 Intention to treat population

The analyses based on the ITT population were those originally submitted by the company to regulatory authorities to support the marketing authorisation of ocrelizumab in PPMS. Although at baseline the majority of the ITT population does not match with the label indication eventually granted to ocrelizumab, the ERG has chosen to summarise the corresponding results as they were appropriately powered.

- **Confirmed disability progression (CDP) (Table *8*)**

Following a minimum of 120 weeks of double-blind controlled follow-up, the risk of CDP was significantly delayed in the ocrelizumab group compared to the placebo group, irrespective of whether CDP was sustained for 12 weeks (primary endpoint) (hazard ratio [HR], 0.76; 95% confidence interval [CI]: 0.59 to 0.98; p = 0.0321) or 24 weeks (HR 0.75; 95% CI: 0.58 to 0.98; p = 0.0365).

In the EPAR, comments were made that, although the study met its primary endpoint (12 week-CDP), the p-value was not compelling to provide strong statistical evidence based on a single RCT [13]. Moreover, while sensitivity analyses of the primary endpoint showed robustness of the treatment effect, it was noted that one of the methods of imputation of initial disability progression events for patients with early treatment discontinuation led to a reduced treatment effect (Section 4.4). The lack of statistical persuasiveness was also highlighted in the review by the FDA on the ground of the loss of significance without imputation of disability events.[27] The ERG requested the results for CDP-12 and CPD-24 without imputation of events that were not confirmed; these were provided by the company for the extended controlled period only and can be seen in clarification response A11.

The analyses based on extended controlled treatment period did confirm the treatment effect observed with the original follow-up duration (Table 8) but with the limitations indicated previously pertaining to the risk of performance bias (see page 53).

- **25-foot walk:**

The change in timed 25-foot walk (T25FW) from baseline to week 120 was reported in CS Appendix K.1.1.1: there was a relative reduction of percent progression in T25FW of 29.3% (95% CI –1.6 to 51.5; p=0.0404) with ocrelizumab (mean change in the percent progression 38.9%) compared with placebo (mean change in the percent progression 55.1%). The ERG believes the clinical relevance of these results are questionable (see section 4.3). Absolute differences were not presented. The adjusted geometric means at week 120 were provided by the company in clarification response A10; the ratio of adjusted geometric means was not statistically significant (0.896, 95% CI 0.792, 1.013).

- **Other pre-specified secondary outcomes**

Other pre-specified secondary endpoints, namely change in total volume of T2 hyperintense lesions, change in total brain volume were presented in the CS Appendix K.1.2.1 and K.1.2.2.

These are not summarised in the ERG report because these outcomes were deemed to be irrelevant to clinical practice by the ERG's clinical experts.

- **Health related quality of life**

As indicated in the section 4.3, a pre-specified secondary endpoint related to HRQoL was assessed in the ORATORIO trial, namely change in the physical component score of the SF36 (SF-36 PCS) questionnaire from baseline to week 120. In the ITT population, results presented in CS Appendix K.1.3 showed minimal changes between baseline to week 120 and no statistically significant difference between ocrelizumab and placebo.

The mental component score of the SF36 (SF-36 MCS) was an exploratory endpoint and was reported in CS Appendix K.1.5.1. There was a statistically significant improvement in SF-36 MCS score with ocrelizumab versus placebo (difference in adjusted means 3.318, 95% CI: 1.414 to 5.221, p=0.0007), but the clinical importance of this is unclear.

Change in EQ-5D score from baseline to week 120 was also listed as an exploratory endpoint (CS Table 8), but was not reported in the CS, appendix or in the CSR.

- **Other functional outcomes (all exploratory endpoints)**

9-HPT (20%-increase):

The results of the 9 Hole Peg Test (9-HPT) measuring the proportion of patients with ≥20% increase of the 9-HPT sustained for 12 week were reported in CS Appendix B.2.6.4 and found a positive impact of ocrelizumab over placebo. The positive finding from this exploratory analysis with the 9-HPT in the ORATORIO trial might explain why the company has chosen the 9-HPT as the primary endpoint of the planned phase IIIb in PPMS patients aged up to 65 years (CS p.86).

The clinical relevance of this outcome has been questioned (see section 4.3).

Multiple Sclerosis Functional Composite score (MSFC):

Results on the MSFC were reported in CS Appendix K.1.6.1 on the CS: there was no statistically significant difference in the mean change from baseline in MSFC score between treatment arms suggesting ocrelizumab had no impact on functional impairment compared with placebo. As previously indicated, the MSFC is a composite endpoint that includes the 9-HPT. The company has made no statement on why the MSFC endpoints showed no differences while a difference was shown on the proportion of patients with 20%-increase in the 9-HPT.

Cognitive impairment:

Results on the paced Auditory Serial Addition Test (PASAT) were reported in CS Appendix K.1.7.1 on the CS: no statistically significant difference was observed in the change from baseline to Week 120 in the PASAT score between ocrelizumab and placebo (mean change from baseline of 4.74 [95% CI: 3.78, 5.70] for ocrelizumab group versus 4.72 [95% CI: 3.42, 6.02] for the placebo group (difference in adjusted means 0.02 [95% CI: -1.45,1.49], p=0.9788).

EDSS (exploratory outcome, not reported in CS):

The change in EDSS score was an exploratory outcome but was not mentioned in the CS. Data were requested by the ERG and were provided in clarification response A9. [redacted]

- **Other exploratory endpoints**

Modified Fatigue Impact Scale:

In the ITT population, compared to a baseline mean total score of 41.6 based on the modified fatigue impact scale (MFIS), the total score of fatigue decreased to week 120 by 0.462 (95% CI: -2.145 to 1.222) with ocrelizumab while it increased by 2.994 (95% CI: 0.658 to 5.330) with placebo (difference in adjusted means: -3.456 [95% CI: -6.048 to 0.863], CS page 50-51), i.e. no statistical difference was observed between the two arms.

On CS p.112, the company has stated that the MFIS is a reliable measure to assess the burden of fatigue in people with MS and that clinically meaningful fatigue was defined as a total score ≥ 38 (section 4.3 for ERG's review of this). In the cost-effectiveness model, the company has used the proportion of patients experiencing clinically meaningful fatigue accordingly.

The ERG has made two comments with regards to this statement:

- The relative changes compared to baseline appear very small given that the MFIS is a scale that goes from 0 to 84; similarly, on average the MFIS total score remained above 38 in both arms and the change was small and potentially clinically unimportant.
- The proportion of patients with MFIS score >38 was not an outcome measure defined in the study protocol and was not reported in the CSR; indeed, the protocol only planned to measure change in MFIS between baseline and week 120. Therefore, the ERG believes there is a lack of transparency concerning the use of fatigue-related outcomes in the cost-effectiveness model (see section 5.2.9).

No Evidence of Progression

Based on the composite endpoint defined as NEP, which combines disability (as measured by EDSS), upper limb function (9-HPT), and ambulation (T25FW) components, ocrelizumab reached better outcomes compared with placebo (42.7% having NEP with ocrelizumab at week 120 vs 29.1% with placebo; Relative Risk [RR] 1.47, 95% CI 1.17, 1.84). Given the composite nature of NEP as an outcome, the ERG believes the suggested benefit of ocrelizumab on NEP is hard to interpret.

The company has also presented another composite endpoint called NEPAD (CS p.53-55) which was deemed to lack clinical relevance (see section 4.3 outcomes) and therefore was not reported here.

- **Relapses (specified as adverse events by the company but considered to be a clinical effectiveness endpoint)**

On page 104 of CS, the company has presented relapses, reported as adverse events in the ORATORIO trial rather than clinical effectiveness-related events. These were also presented in the CSR. Consistent with appraisals related to RRMS drugs, the ERG considers that relapses are more appropriately reported within the clinical effectiveness section.

The proportions of patients with relapses in the ocrelizumab and the placebo groups were 4.9% (95% CI 3.2%, 7.3%) and 11.3% (95% CI 7.6%, 16.0%) respectively.

In the CS, post-hoc analysis was conducted to derive annualised relapse rates (ARR). The adjusted ARRs were 0.011 (95% CI 0.005, 0.025) with ocrelizumab and 0.021 (95% CI 0.014, 0.071) with placebo leading to an adjusted ARR ratio of 0.350 (95% CI 0.190, 0.645).

This suggests a very small but plausible benefit of ocrelizumab in reducing onset of relapses in PPMS patients: the ERG has chosen to incorporate a treatment effect of ocrelizumab in its base-case accordingly (see section 5.3.2).

4.5.1.2 MRI-active disease subgroup (post-hoc analyses)

This subgroup was identified by the company in an attempt to meet the marketing authorisation, and is preferred by the ERG for the cost-effectiveness analysis (See section 5.3.2), however the limitations of the subgroup are noted in section 3.1.

- **Confirmed disability progression (CDP) (Table *8*)**

Following a minimum of 120 weeks of controlled follow-up of patients with MRI activity, as defined by the company, the risk of disability progression, with both progression confirmed for 12 or 24 weeks, was delayed in the ocrelizumab group compared to the placebo group: with the less relevant endpoint, namely 12-week CDP, this reached statistical significance (HR for 12-week CDP, 0.68; 95% CI: 0.46 to 0.99; p = 0.0448) while with the most relevant endpoint, namely 24-week CDP, it did not (HR for 24-week CDP, 0.71; 95% CI: 0.47 to 1.06; p = 0.0917). The absence of statistical significance might be explained by the lack of power of the post-hoc analysis based on MRI activity given that these patients represented around 40% of those enrolled in the ORATORIO trial.

The company has provided results based on extended controlled treatment period on page 57 of the CS: the HR for 24-week CDP was reported at 0.68 (95% CI 0.46, 0.99).

Again, the ERG views with cautious the results based on additional follow-up given that patients were progressively unblinded during this period of additional follow-up. Accordingly, the ERG's preferred cost-effectiveness base case uses inputs from the unextended controlled treatment period (minimum of 120 weeks of double-blind controlled follow-up) (see section 5.3.2).

- **25-foot walk:**

Change in T25FW from baseline to week 120 was not reported in the CS despite being a secondary outcome. Data for T25FW in the MRI active subgroup were provided by the company in response to clarification question A10. The ratio of adjusted geometric means reached statistical significance (0.817, 95% CI 0.677, 0.987).

Health related quality of life

No results were presented for SF-36 PCS or SF-36 MCS based on the MRI active population.

- **Other functional outcomes (all exploratory)**

9-HPT (20% increase)

The results of the 9-HPT were reported in the CS and found positive impact of ocrelizumab over placebo: the HR for the risk of 20% increase in 9-HPT (sustained for 12 weeks) in MRI active population was 0.52 (95% CI 0.32-0.85).

It is unclear if the 20% increase in 9-HPT sustained for 24 weeks was also measured. In line with the ERG's comment on CDP which is more relevant when the outcome is confirmed for 24 weeks as opposed to 12 weeks, the ERG would be more interested in results on 20% increase in 9-HPT sustained for 24 weeks. However the ERG also has concerns regarding the clinical relevance of this outcome as a measure of upper limb function.

Multiple Sclerosis Functional composite score (MSFC): No results were reported.

Cognitive impairment: No results were reported.

EDSS (exploratory outcome, not reported in CS)

As for the ITT population, the change in EDSS score was not mentioned in the CS. Data were requested by the ERG and were provided in clarification response A9, although no statistical analysis was provided. The mean change from baseline was similar between groups (crude difference in mean change calculated by ERG: -0.05).

- **Other exploratory endpoints**

Modified Fatigue Impact Scale:

Figure 24 on the CS reported change in fatigue for the MRI active subgroup as well as for patients not meeting the criteria of active disease. A comment was made by the company on page 65 that the impact of ocrelizumab relative to placebo on change in fatigue was less pronounced in these subgroups.

The ERG would phrase this more strongly: CS Figure 24A which relates to MRI active patients shows that ocrelizumab had no impact on fatigue compared to placebo. The mean changes for both treatment arms are not reported numerically but Figure 24A suggests that mean change at 120 weeks was around +2 points with placebo and around +1.1 with ocrelizumab with substantially overlapped 95% CIs.

In the cost-effectiveness section, the company has considered an effect of ocrelizumab on fatigue as measured by the proportion of people with MFIS>38 and applied a relative risk of [redacted]. It is unclear how this relative risk was derived but it is at odds with the mean change in fatigue score (a pre-specified exploratory endpoint) showing no impact from ocrelizumab (see section 5.2.9).

- **Relapses (specified as AE by the company but considered to be a clinical effectiveness endpoint)**

No results on relapses were reported specifically for the MRI-active subgroup.

4.5.1.3 Effectiveness in further subgroup analyses

Patients with T1 Gd-enhancing lesions (pre-specified subgroup analysis)

Following a minimum of 120 weeks of controlled follow-up of patients with T1 Gd-enhancing lesions at baseline, the risk of disability progression, with both progression confirmed for 12 or 24 weeks, was delayed in the ocrelizumab group compared to the placebo group but the suggested benefit did not reach statistical significance (hazard ratio [HR] for 12-week CDP, 0.65; 95% confidence interval [CI]: 0.40 to 1.06; p = 0.0826 / HR for 24-week CDP, 0.67; 95% CI: 0.40 to 1.14; p = 0.142). Although the analysis was pre-specified, the trial was not powered to demonstrate a benefit in patients with Gd-enhancing lesions at baseline. Because patients with Gd-enhancing lesions at baseline represented around 25% of patients enrolled in the ORATORIO trial, the number of events may have been insufficient to demonstrate a statistically significant delay in CDP with ocrelizumab.

Similar trends were observed based on extended controlled treatment period.

Other pre-specified subgroup analyses

The company has presented a number of analyses by predefined subgroups in CS Appendix E for the primary endpoint, 12-week CDP (see section 4.5.1). Other than "presence of gadolinium-enhancing T1 lesions at baseline MRI scan", these subgroups were:

- Age (≤45 vs >45 yrs)
- Sex (male vs female)
- Baseline EDSS (≤5.5 vs >5.5)
- Region (USA vs ROW)
- Prior MS DMTs with the exception of corticosteroids
- Duration since onset of MS symptoms (≤3 yrs, 3 to ≤5 yrs, 5 to ≤10 yrs, >10 yrs)
- Weight (≤75 vs >75 kg at baseline)
- BMI (<25 vs ≥25 kg/m^2 at baseline)

As stated by the company, the study was not powered to demonstrate efficacy differences for any of these subgroups. The interaction test results by subgroup presented in CS Appendix E Figure 3 showed no subgroup with a statistical significant interaction.

Analyses suggested better outcomes with ocrelizumab compared to placebo for patients aged ≤45 years, male patients, and those with BMI <25.

Analyses by the same predefined subgroups were reported in the CSR for 24-week CDP and showed similar trends.

The influence of patient age has been extensively discussed at the EMA level as part the process of drug approval. As discussed in the critique of the decision problem (section 3.1), the company has presented to the CHMP analyses suggesting a greater effect of ocrelizumab in younger patients (aged ≤ 45 years) and those presenting T1-Gd enhancing lesions at baseline. However, the CHMP highlighted that it was "*difficult to draw conclusions on whether age is the variable that drives an increase of the effect size independent of the presence of T1-Gd enhancing lesions (or vice versa) and, in addition, on whether there is an interaction effect or independence between these two variables (at least as a trend)*" [13].

On CS page 70, the company has presented a post hoc subgroup analysis of patients with imaging features of inflammatory activities aged ≤ 50 years at baseline. The ERG notes the cut-off differs from that for the pre-planned subgroup analyses (namely 45years). The company has justified the choice of 50 years cut-off, stating that the age-dependent effect on disease progression was assessed by age quartiles which showed efficacy was fairly stable in patients ages 50 or under while those aged >50 years did not derive benefit.

While the analysis accounting for patients with MRI active disease is already a post-hoc analysis that was not presented to the EMA, the company has added a cut-off for age which also differs from the pre-specified cut-off defined in the ORATORIO trial. The ERG believes that this further post-hoc analysis is methodologically questionable as it lacks transparency.

Given this, together with the potential implications of analyses by age which could lead to major equality issues should the drug be recommended according to patients' age, the ERG is concerned by the analyses presented by the company in patients with MRI activity and aged ≤50 years.

4.5.2 Safety

Adverse events (AEs) experienced by patients during the ORATORIO trial are reported in the CS (Section B.2.10.1). The CS also provides supportive evidence for the safety of ocrelizumab from the OPERA I and OPERA II trials in RRMS in CS Appendix F1. The ERG focuses the discussion of adverse events on the data from the ORATORIO trial as these are used to populate the economic model (see also Section 5.2.7). Information on adverse events from the supportive evidence in RRMS and from the use of ocrelizumab in other populations (rheumatoid arthritis and lupus nephritis, albeit different doses of 400mg or 1000mg) have been checked by the ERG to see if there are any major differences between these and the key adverse events reported in the ORATORIO trial.

The adverse event data presented in the main CS are from the safety population of the ORATORIO trial, all those who received at least one dose of any study treatment. Where patients received the incorrect therapy these were summarised in the group according to the therapy actually received. There were 486 participants in the ocrelizumab safety population and 239 in the placebo safety population.

Table 9 summarises the safety data from the ORATORIO trial. Treatment discontinuations due to adverse events were experienced by 4.1% in the ocrelizumab arm and 3.3% in the placebo arm. Any adverse events were experienced in 95.1% of patients in the ocrelizumab arm and 90% in the placebo arm and any serious adverse events (SAEs) by 20.4% and 22.2% for the two groups respectively. Rates of death were low in both groups. Limited details of specific AEs and SAEs were presented in the CS, but where reported they were generally similar to placebo, as were events grouped by system organ class (see CS Tables 27 and 28).

Rates of treatment discontinuations due to AEs were similar in the ocrelizumab treated participants in the ORATORIO trial and the trials in RRMS and in lupus; in the trials in rheumatoid arthritis the rates of withdrawals due to AEs were lower (~1.6%, the doses were 400mg or 1000mg).[28] Rates of any AEs appear to be higher than reported in the other ocrelizumab trials (which were around 80-86%) and rates of serious AEs were higher than seen in the RRMS trial populations and the rheumatoid arthritis studies (around 7-11%), but lower than seen in the lupus populations (around 22-36%; doses were 400mg or 1000mg).[29]

Adverse events of special interest include infusion related reactions, infections, malignancies and anti-drug antibodies. A higher proportion of patients treated with ocrelizumab reported infusion related reactions than placebo (39.9% ocrelizumab versus 25.5% placebo reported at least one). The CS states

on p78 that most were mild to moderate (grade 1 or 2) with 1.2% treated with ocrelizumab and 1.7% treated with placebo experiencing grade 3 reactions. The CS also states that none were fatal or life-threatening, that rates and severity decreased with subsequent dosing and that all were manageable through premedication, adjustments to the infusion and symptomatic treatments The ERG's clinical expert agreed with this statement. The ocrelizumab infusion related reactions were included in the economic model (see CS Section B.3.3.7).

Overall the proportion reporting an infection was similar between groups (69.8% versus 67.8% in the ocrelizumab versus placebo groups respectively). The CS states that most infections were mild to moderate in severity and that no opportunistic infections were reported in the trial (CS p81). Treatment-related infections that were reported in at least 2% of participants receiving ocrelizumab can be seen in Table 9. The CS reports (p.76) that these were included in the economic model. However, of the infections, only upper respiratory tract infections (URTI) were included in the economic model and the data used were not the "treatment-related" URTI events but 'any' URTI events (Table 9, 10.9% ocrelizumab and 5.9% placebo). The CS clarifies in section B.3.3.7 that only AEs occurring more frequently in the ocrelizumab arm with a difference more than 3% were included in the model (hence the inclusion of URTI). It is not stated why a difference of more than 3% was used as a threshold for inclusion in the model and the ERG notes that there may be other events that have a >3% higher rate in the ocrelizumab arm that are not included in the model, but that details are limited by the presentation by system organ class (e.g. 'any respiratory, thoracic and mediastinal disorders' CS Table 27). The ERG has checked and agrees that there are no other specific adverse events with a difference >3% between arms.

Rates of any malignancies (defined in the CSR as 'malignant tumours (narrow)') and treatment-related neoplasms (benign, malignant and unspecified) are presented in Table 9. The higher rate of 'any malignancies' is used in the economic model (see CS Section B.3.3.7). The rate of malignancies was higher in the ocrelizumab treated participants than the placebo treated participants (Table 9). The CS has undertaken additional analyses to investigate this apparent imbalance, which may be related to a cluster of breast cancer cases (n=4) in the ocrelizumab arm (the ERG also notes that 2 cases of breast cancer occurred in the ocrelizumab arm in the OPERA I trial (0 in the placebo arm), but none occurred in the OPERA II trial). The CS pools data from the wider ocrelizumab clinical trial programme and contextualises these data with a meta-analysis of placebo-treated patients from 10 clinical studies in MS and from MS registries. The company provided summary details of the meta-analysis methods and details of Danish MS registry in clarification A13. The methods of the systematic review, which is part of a larger review updated in 2015, appear appropriate. Details of the studies included in the systematic review are provided in a confidential report which is over 600 pages

and includes 142 studies for the wider questions. The CS reported that malignancy rates from placebo arms of 10 studies were meta-analysed. [redacted] The company clarification describes how the Danish MS registry was linked with the Danish Cancer registry to identify all malignancies in MS registrants and provides confidential patient demographics and characteristics. Both registries are large and well established and the ERG consider are reliable sources of epidemiological data, not discounting known limitations with this type of data. The proportion of participants with PPMS in the registry was [redacted] The CS concludes that the imbalance observed in the incidence of malignancies is within the expected epidemiological range in MS (CS Appendix F). The ERG notes that the EMA CHMP assessment report notes that *the available data do not allow to definitely establish nor rule out a clear causality to ocrelizumab treatment*, and that the post-marketing study should be able to clarify this in due course.[13]

The incidence of anti-drug antibodies was 1.9% in those treated with ocrelizumab and 3.8% in those treated with placebo in the trial (CS Table 35).

Table 9: Adverse event summary data from ORATORIO

Event, % (treatment related events reported in >2% in the ocrelizumab arm)[a]	**Ocrelizumab, n=486**	**Placebo, n=239**
Any AE leading to treatment discontinuation	4.1%	3.3%
Any AE	95.1%	90.0%
Serious AE	20.4%	22.2%
Death	0.8%	0.4%
Infusion-related reactions (≥1)	**39.9%**	25.5%
Total number of reactions	485	145
Serious infusion related reactions[b]	1.0%	0
Serious infections	6.2%[c]	5.9%[c]
Malignancy (any)	**2.3%**	**0.8%**
Treatment-related neoplasms (benign, malignant and unspecified)	1.2%	0.8%
Urinary tract infection	19.8%	22.6%
Treatment-related urinary tract infection	6.2%	5.0%
Nasopharyngitis	22.6%	27.2%
Treatment-related nasopharyngitis	4.3%	5.0%
Upper respiratory tract infection	**10.9%**	**5.9%**
Treatment-related upper respiratory tract infection	3.1%	2.1%
Bronchitis	6.2%	5.0%
Treatment-related bronchitis	2.5%	0.8%
Headache	13.4%[d]	13.8%[d]
Treatment-related headache	2.7%	4.2%

[a]Neoplasms included in the CS despite occurring <2% in ocrelizumab arm. The CS does not describe how 'treatment-related' was defined or assessed.
[b]trial publication reports severe reactions as 1.2% ocrelizumab and 1.7% placebo
[c]CS Table 28 reports these rates as 7.0 and 8.4 respectively which the ERG notes is from the CSR 'Serious infections including non-serious infections requiring IV anti-infective treatment'
[d]rate from CSR
Bold = CS used in economic model, Section B.3.3.7.

ERG comments

The rates of events appear to be similar between ocrelizumab and placebo in general. There were more infusion-related reactions with ocrelizumab, these have been included in the economic model. There were also more malignancies and URTIs and rates for both arms have been included in the economic model. The CS is unclear whether any other specific adverse events meet the CS threshold for more than a 3% difference between ocrelizumab and placebo because of the way the rates are

presented in system organ classes, however the ERG has checked these in the CSR and confirms there are no other events.

The analysis of safety from ORATORIO was undertaken after a mean follow-up of 140 weeks and the adverse event profile from long-term use of ocrelizumab is not established. In Appendix F.1.2 the CS present pooled analysis from the ocrelizumab MS trial programme, including open-label extension periods of the ORATORIO (in PPMS) and OPERA I and OPERA II trials and a Phase II study (in RRMS) and including 7748 patient-years of observation at their latest data cut. The rate of any AE was 226 per 100 person years (CS Appendix F.1.2 Table 13). These extension studies are ongoing.

The EMA CHMP states that no opportunistic infections in MS patients treated with ocrelizumab, including hepatitis B reactivation, have been reported[13]. They discuss one case of progressive multifocal leukoencephalopathy (PML; also reported with rituximab) but note that this patient had switched to ocrelizumab from natalizumab. It is currently unclear if the PML was linked to ocrelizumab. CS Appendix F.1.2 states that as of February 2017, no serious confirmed opportunistic infections have been reported.

4.6 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect or multiple treatment comparison was undertaken given that there was only one possible comparator which was established clinical management without ocrelizumab.

4.7 Critique of the indirect comparison and/or multiple treatment comparison

No indirect or multiple treatment comparison was undertaken given that there was only one possible comparator which was established clinical management without ocrelizumab.

4.8 Additional work on clinical effectiveness undertaken by the ERG

CS section 2.6.5 presents the results of a *post hoc* analysis of 12-week CDP using the extended controlled period of ORATORIO. CS Figure 20 (Figure 1) shows the 12-week CDP KM plots.

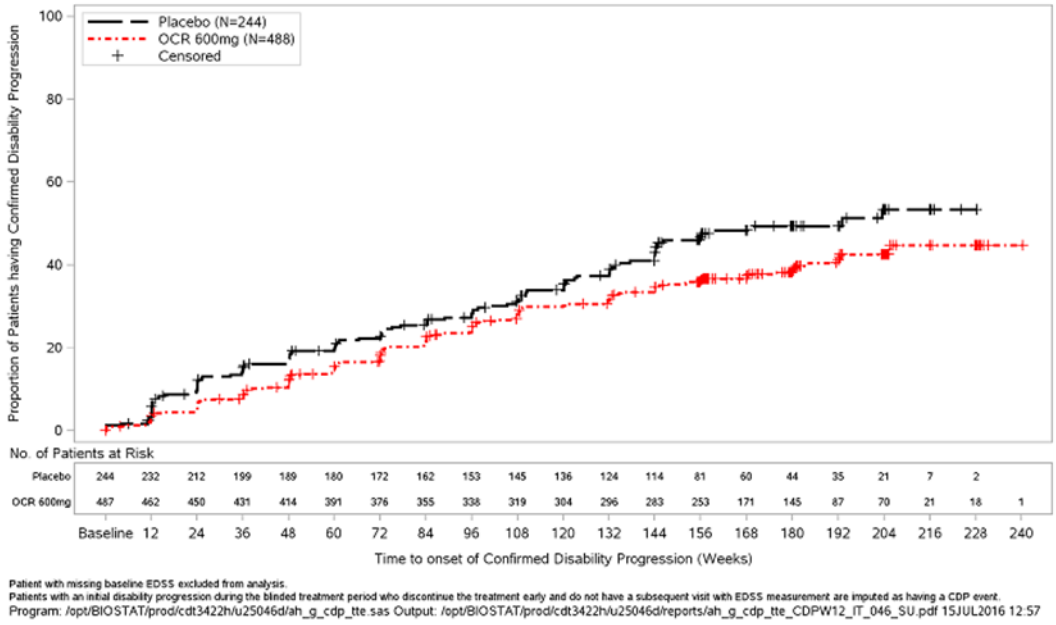

Figure 1: KM plots for 12-week CDP (extracted for the CS fig 20)

Imputed events were included. There were 283 events (placebo 106, ocrelizumab 177) compared to 256 in the pre-specified analysis. With addition of these 27 events (placebo 10, ocrelizumab 17) the log rank test p value decreased to p=0.0151 (from 0.032) and the stratified HR to 0.74 (95% CI: 0.58 - 0.95) from 0.76 (95% CI: 0.59-0.98).

The "average" HR from similar plots for various subgroup populations are taken as the "treatment effect" (CS Table 47) and used in the economic model for estimating transition probabilities between

EDSS states in the ocrelizumab arm. CS Figure 32 suggests that treatment effect size is a major driver of the economic model. The EDSS transition events in CS Figure 20 are unspecified. It is unlikely the same transitions are being compared across time points. If this is the case, and different EDSS transitions are not equally effected by treatment, then the hazard / risk of events will vary across arms with follow up time, as also will the ratio of hazards. Conversely should all EDSS events be equally effected by treatment with ocrelizumab, as is assumed in the economic model (e.g. the effect of ocrelizumab on the transition between EDSS scores 1 and 2 is taken to be the same as that for the transition between score 2 and 8), then types of event will be immaterial and their relative frequency (between arms), and therefore the HR, would be expected to be fairly stable across the time span of the plots. Thus for this assumption to hold and for the "average" HR to be a good estimate of treatment effect we would hope the hazards for each arm in Figure 20 would bear a reasonably constant relationship to each other (irrespective of the specific transitions taking place). However in CS Figure 20 the plots for each arm first separate, then converge (around 84 to 120 weeks) and then separate again indicating that the hazard ratio is changing through time.

To examine this more closely the ERG modelled the hazard in each arm of Figure 20 using flexible parametric models. Figure 2 shows the resulting modelled survival superimposed on CS Figure 20 and indicates a reasonable visual fit.

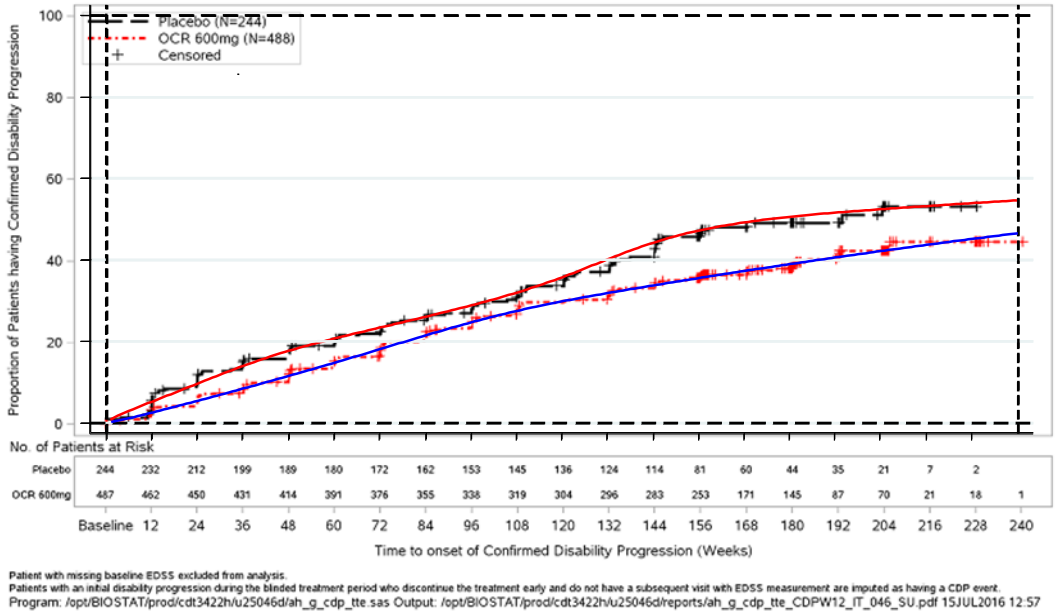

Figure 2: ERG flexible parametric models superimposed on the treatment arms of CS Figure 20.

Figure 3 shows the modelled hazard in each arm and the resulting HR changing with follow up.

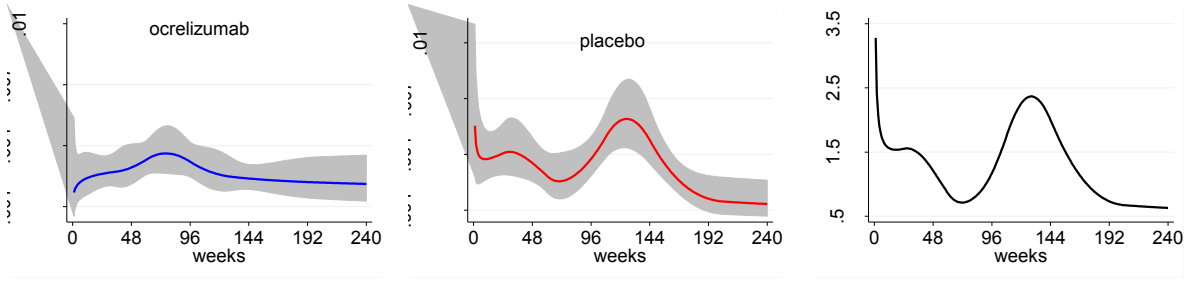

Figure 3: Modelled hazards and ratio of hazards for 12-week CDP

Although this analysis is imperfect it does suggests that HR changes with follow up duration and that the "average" HR is a function of length of follow up as well as of treatment effect. Other flexible parametric models and conventional parametric models lead to the same conclusion. Similarly shaped KM plots for the double blind period also suggest this conclusion.

The ERG suggests that the use of a single effect size value for all EDSS transitions is likely a considerable oversimplification and is potentially misleading. The average HR does not reflect the changing hazards in the data and appears influenced by length of follow up; follow up in ORATORIO was short even with the extended data set so that most patients (61%) had not yet experienced a 12-week CDP event. Although the EPAR states that, relative to numbers needed to treat (NNT), "*The hazard ratio as a weighted relative risk over the entire duration of the study provides a more comprehensive summary of the overall treatment benefit"* the use of an average HR makes the CS "treatment effect" difficult to interpret [13]. It appears to represent an average of the ratio between arms of unspecified increases in disability. The EPAR refers to the companies' extrapolated analysis of the extended controlled period data that suggested a delay in median time to progression of 1.3 years. This analysis was not presented in the CS. The ERG experience difficulty in interpreting this progression delay since no start or finish EDSS scores are specified.

The CS refers to the presentation by Giovannoni et al. 2017 [30] which reports various treatment effect size HRs for the whole population based on analyses of the double blind controlled data set. Although analysis is underpowered for the baseline <6.0 group the differing HRs imply that the average HR is unlikely to apply for all EDSS transitions.

Table 10: ONTARIO hazard ratios reported by Giovannoni et al. 2017

HR type	12 week CDP (95% CI)	24 week CDP (95% CI)
Average	0.76 (0.59-0.98)	0.75 (0.58-0.98)
Baseline EDSS <6.0 to ≥ 7.0	0.28 (0.04-2.18)	0.28 (0.04-2.18)
Baseline EDSS 6.0+6.5 to ≥ 7.0	0.57 (0.30-1.09)	0.59 (0.31-1.09)

The EPAR report also refers to submitted extrapolation analyses indicating a delay of 8.8 years in the median time to reach the EDSS 7 milestone [13]. A similar analysis has been presented in CS section B 2.6.5 and estimates a 8.7 year delay using Weibull models. Like the CS the ERG finds time to sustained EDSS ≥ 7 a more interpretable and tangible "treatment effect" since this final EDSS is specified; furthermore, reaching wheelchair status (EDSS ≥ 7) would appear to be less susceptible to within- and inter-rater variability than most other EDSS transitions. The EPAR was critical of the extrapolations from the observed data in estimation of this CDP delay, stating "*such extrapolations should be interpreted with caution. ....Moreover, these extrapolations incorporate the terminal part of the KM curve, including the extended controlled period, which represents an area of statistical uncertainties"*[13]. However, it appears that in defining the licensed indication for ocrelizumab the EMA have referred to *post hoc* 12 week-CDP analyses for *post hoc* subgroups that almost certainly suffer from similar areas of statistical uncertainty. Equally or more extensive extrapolations are necessary for a life time economic analysis.

CS section B 2.6.5 uses the extended data set to generate KM plots for the time to reach EDSS ≥ 7 (CS Figure 21). EDSS ≥ 7 was selected because it represents a particularly meaningful milestone for patients, indicating the time taken to the state of being restricted to a wheel chair. Parametric models were then fit and extrapolated so as to obtain estimates of median time to onset of EDSS ≥ 7; the model extrapolations were compared with a similar analysis of the MSBase PPMS cohort (CS Figure 22) (Figure 4 and Figure 5).

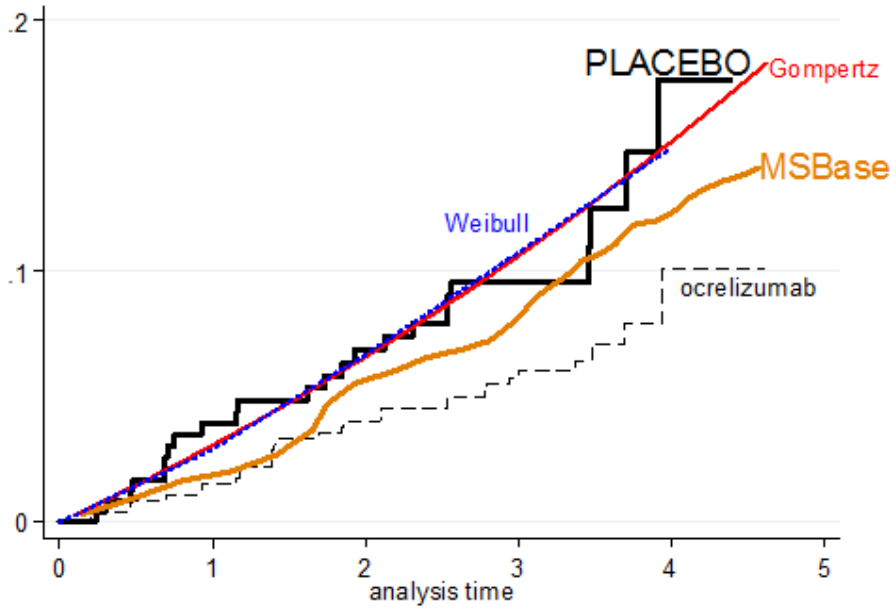

Figure 4: Observed time to EDSS>=7 in the ORATORIO placebo arm compared to MSBase patients over the same period. Note the relatively inferior performance of trial placebo patients.

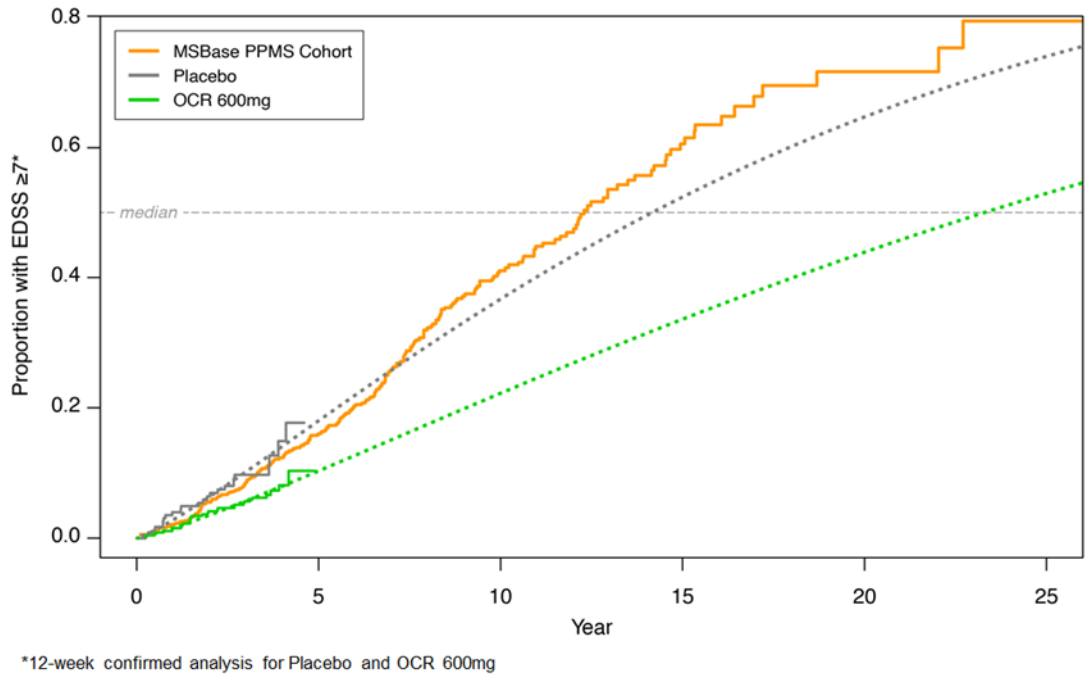

Figure 5: Extrapolation of time to onset of confirmed EDSS ≥7.0 for at least 12 weeks during the extended controlled treatment period of ORATORIO using a Weibull regression model

The ERG is interested in comparing the economic model output for reaching EDSS ≥ 7 with these results presented in the clinical effectiveness section of the submission (see section 5.3.3). Figure 6 shows a comparison between Weibull and Gompertz proportional hazards models for progression to EDSS ≥ 7 for the whole population (ITT population) and for the MRI-active population (data supplied at clarification stage). These are not stratified models and so the Weibull model for the ITT population predicts slightly different delay in median (8.64 years) compared to the company submission (8.8 years). There is little to choose between models on the basis of information criteria; Gompertz models give a slightly better visual fit to the KM plots. The placebo Gompertz model (whole population) conforms in shape to MSBase data (i.e. an initial increase in slope followed by decreasing slope) whereas for the Weibull models the slope of the extrapolation continuously decreases into the future. On balance the ERG favour the Gompertz model which predicts substantially less delay in progression of disability than the Weibull models. The EPAR advocated caution interpreting the very extensive extrapolations involved; however these are in fact similar to those necessary for the life time economic model.

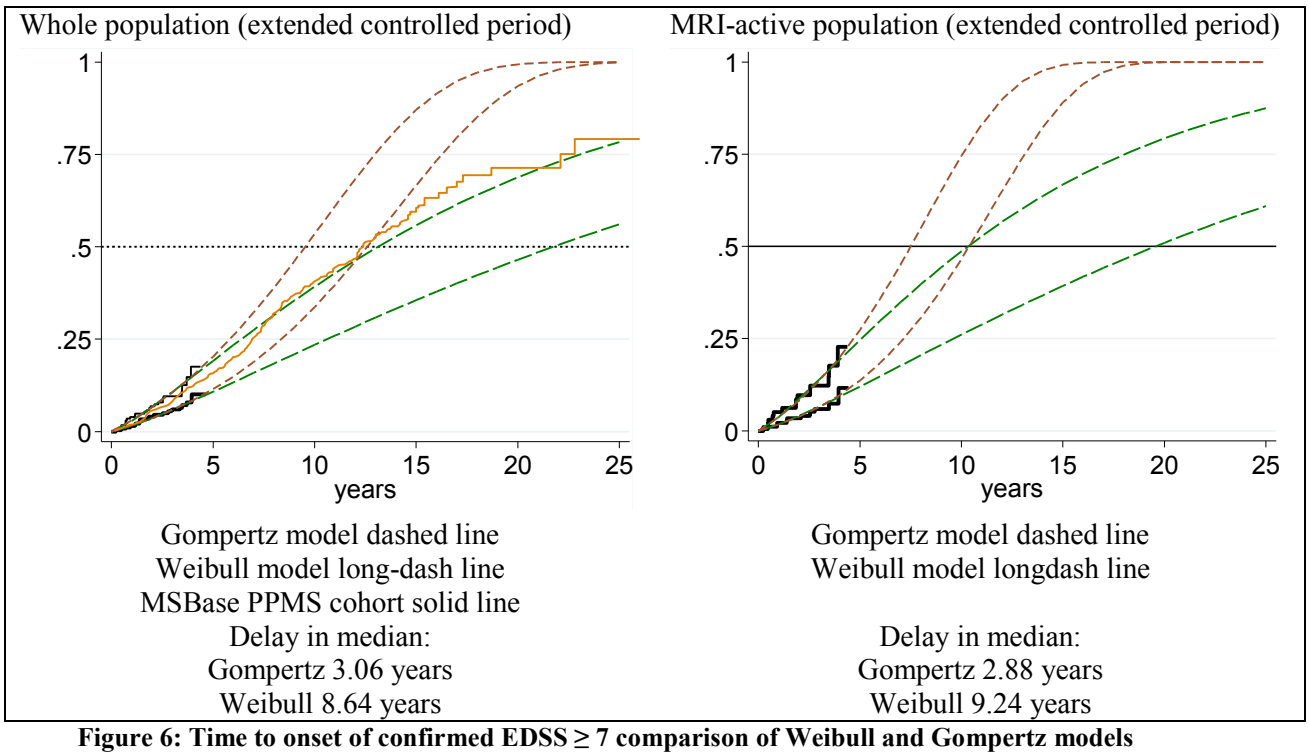

Figure 6: Time to onset of confirmed EDSS ≥ 7 comparison of Weibull and Gompertz models

In summary: The ERG has seen no evidence presented, and is unaware of relevant external evidence, that indicates or demonstrates that treatment effect size is the same for all EDSS transitions; the ERG is aware that this assumption has been previously adopted for economic models of various treatments for RRMS submitted to NICE and that such models have been considered fit for purpose; however

RRMS models have an important additional element that takes into account reduction of relapses - a minor feature of the CS PPMS model.

The 12-week CDP KM plots by arm clearly suggest that ocrelizumab is an effective treatment for PPMS, however the effect size is difficult to gauge because of the use of imputed events, and because the EDSS transition events are unspecified and unlikely to be comparable across study arms. The use of the average HR from such plots as an estimate of effect size is difficult to interpret and the estimate appears to depend on duration of follow up which was immature as reported in the ORATORIO trial.

The analysis of time to reach EDSS ≥ 7 presents a tangible and interpretable indicator of treatment effect. For the whole population this analysis delivers gains from ocrelizumab treatment that depend heavily on which models are used for extrapolation beyond the observed data; for the MRI-active population the estimates are associated with substantial uncertainty because of the small numbers of participants.

4.9 Conclusions of the clinical effectiveness section

The CS conducted a reasonable quality systematic review and included the single relevant trial of ocrelizumab for PPMS. No other trials of ocrelizumab in PPMS were identified by the ERG, and as no other DMTs for ocrelizumab are used in the UK, a network meta-analysis could not be undertaken. Overall, the trial had a low risk of bias. A statistically significant reduction in the trial's primary endpoint, time to CDP sustained for 12-weeks, was found, however there was a loss of statistical significance in sensitivity analysis without imputation of unconfirmed disability events. The trial population was broader than the marketing authorisation label, which specifies 'early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity'. The ERG's clinical experts did not consider the trial population to represent 'early PPMS'. The post hoc subgroup, selected by the company to meet the criteria 'imaging features characteristic of inflammatory activity' defined by the SPC as 'T1 Gd enhancing lesions and/or active (new or enlarging) T2 lesions', did not include patients with enlarging T2 lesions between screening and baseline. Moreover, the ERG has highlighted concerns regarding the application of these criteria in UK clinical practice. The outcomes listed in the NICE scope have generally been addressed by the CS, however there is concern regarding the clinical relevance of the measures selected. Visual disturbance was not measured as a separate outcome.

5 COST EFFECTIVENESS

This chapter focuses on the economic analysis submitted by Roche, and additional information received in response to the ERG's clarification questions. We critically appraised the evidence used in the analysis and examined the company's electronic model.

The chapter starts with a summary of the company's economic analysis, then in detail the systematic review, methods, and results (base-case, sensitivity and scenario analyses and budget impact model) as reported in the submission. We then compare the economic analysis to the NICE reference case, then provide a critique using frameworks on best practices for reporting economic evaluation and economic modelling to assess the overall quality and validity of these analyses (see Appendix 1 for checklists). In the subsequent chapter, where possible, we have addressed our concerns in the form of additional analyses undertaken by the ERG.

The submission received by the ERG included:

- A systematic review of the economic evidence for the management of people living with PPMS;
- Methods used to undertake the economic analysis, and the company's base-case and sensitivity analysis results;
- Electronic version of the *de novo* Markov model built in Microsoft Excel.

The company undertook a systematic review of the cost-effectiveness literature to identify studies reporting the results of economic analyses for people who received disease modifying treatment for the management of PPMS. This search was also used to identify resource use information and studies reporting HRQoL for people PPMS. In brief, the company searched MEDLINE, EMBASE, the Cochrane library, EconLit and the NHS Economic Evaluation Database for potentially relevant studies and selected studies based on pre-defined inclusion/exclusion criteria. Additional searches of conference proceedings and grey literature were undertaken to identify potentially relevant studies. The systematic review did not identify any published studies; however, their website search identified a report of an economic analysis that compared ocrelizumab with BSC in people with MS, but the results were not presented as an ICER as the price of ocrelizumab was not available at the time of analysis.

The company used a *de novo* Markov model to depict the natural history of a cohort of people with PPMS who may undergo treatment with ocrelizumab or BSC over a 50-year time horizon. The model defined health states by EDSS, which ranged from 0-10 (dead). The disability progression in the model was based on the MSBase natural history cohort which showed disease progression in the absence of disease modifying treatment. The model starts from a hypothetical cohort of people,

distributed across EDSS 3-7 to reflect the starting proportion in the ORATORIO trial. People remained in these health states, after which they can progress to more severe EDSS states. Treatment with ocrelizumab was assumed to delay disability progression. Evidence for the clinical effectiveness of ocrelizumab in this model relied solely on the ORATORIO trial [8]; hence the company did not undertake a network meta-analysis. In the company's base-case, the treatment effect in the form of an 'instantaneous hazard ratio' based on the CDP-12 was applied to the progression health states of the natural history cohort. Annual cycles were used to show the movement of people through the model. In each cycle, people transitioned between EDSS levels, withdrew from treatment, or transitioned to the dead state. People incurred costs and benefits [quality adjusted life-years (QALYs))] as a function of their current EDS health state 0-9.

In the base-case, utility values for EDSS 0-1 and 8-9, were obtained from Orme et al.[1] and all other values were based on HRQoL information collected using the EQ-5D-3L in the ORATORIO trial (the changes in HRQoL between baseline and week 120 were not reported by the company see section 4.5.1). Health-state utility values depended on each health state and thus, were not treatment related. Any disutilities associated with adverse events were obtained from recent technology appraisals and published sources.[31-33] Carer disutilities by EDSS state were obtained from TA127, which were derived from the UK MS survey.

Costs included in the analysis were those directly related to the NHS. The model estimated the resource use and treatment costs (drug acquisition, administration and monitoring costs) associated with ocrelizumab. Costs of treatment with ocrelizumab were based on the dose regimen used in the ORATORIO trial, using the list price to the NHS (£4,790 per vial). Management costs associated with state-dependency were obtained from Tyas et al. [34] and were inflated to current prices. Adverse events management costs were obtained from recent technology appraisals.[32] Treatment costs for ocrelizumab were applied until people discontinued treatment (due to adverse events or progressing to EDSS ≥8), after which it was assumed that people would not switch to any other DMT, instead receiving BSC.

The analysis was undertaken from the NHS and PSS perspective, the outcomes are reported in terms of life years gained (LYG) and QALYs, and the results were reported in terms of an ICER, expressed as cost per QALY gained. Both costs and effects were discounted at 3.5% per annum. A number of deterministic one-way sensitivity analyses and scenario analyses were undertaken, as well as probabilistic sensitivity analysis (PSA) based on the outcome cost per QALY. The company provided results using an agreed patient access scheme (PAS) based on a discounted price of [redacted] per vial.

The company's base-case results showed that the ICER for ocrelizumab compared to BSC was estimated at [redacted] per QALY gained in the MRI active population, using the list price. Under the approved PAS, the ICER was estimated at £88,214 per QALY. Company sensitivity analyses results

showed that the treatment effect upon CDP-12 had the greatest impact on the ICER. Discounts applied to costs and effects also had some impact on the ICER; all other company input parameters varied in one-way sensitivity analyses were robust to changes. Results for the company PSA showed that at a WTP threshold of £30,000 per QALY gained, ocrelizumab had a zero probability of being cost-effective.

5.1 ERG comment on company's review of cost-effectiveness evidence

The company undertook a systematic review in order to identify cost-effectiveness studies in people with MS.

5.1.1 Search strategy

Database searches combining terms for MS, DMTs and cost-effectiveness were undertaken on 23 March 2016 and updated on 24 March 2017. A range of appropriate sources were searched. A variety of suitable thesaurus and free-text terms were used for MS and cost-effectiveness. However, the inclusion of specific intervention terms in the search may have resulted in some MS cost-effectiveness studies with a broader scope being missed. The ERG also note that terms for ocrelizumab are not included in either the searches or the eligibility criteria and therefore specific studies on this intervention may have been missed. A good range of supplementary sources and search methods are utilised, but no details are reported of the methods used to search them, such as dates, search terms and numbers retrieved. The ERG also conducted targeted searches to check for cost-effectiveness studies specifically on Ocrelizumab in PPMS and updated the company's search to identify additional studies post March 2017.

5.1.2 Inclusion criteria

The company provided an appropriate description of the cost-effectiveness systematic review, which includes the search strategy, the inclusion/exclusion criteria, and a description of included and excluded studies.

Table 11: Eligibility criteria for cost-effectiveness searches

Category	Definition
Patient population	Participants ≥18 years with a diagnosis of MS (classified using an accepted diagnostic technique e.g. Poser or McDonald criteria) regardless of age, sex, degree of disability, and duration of the disease. The primary focus is on the following clinical phenotypes: -relapsing-remitting MS (RRMS) -secondary progressive MS (SPMS) -primary-progressive MS (PPMS)
Interventions	The following interventions were of primary interest for the economic evaluation review (irrespective of dose [provided within therapeutic range] or mode of administration): IFN-β1b, IFN-β1a (Rebif, Avonex), glatiramer acetate, Natalizumab, Fingolimod, Teriflunomide, Alemtuzumab and dimethylfumerate
Comparator	Placebo or any active treatment
Outcomes	Range of ICERs as per sensitivity analyses (and key drivers of reported ICERs), assumptions underpinning model structures, key costs drivers, sources of clinical, cost and quality of life inputs, discounting applied to costs and health outcomes, and model summary and structure
Indication	PPMS
Study type	Full economic evaluations: cost utility analyses (CUAs), cost-effectiveness analyses (CEAs), cost-benefit analyses (CBAs) and cost-minimisation analyses (CMAs)
Language of publication	No restriction
Limitations	English language studies pertaining to humans

5.1.3 Included studies

Through sifting, 33 potentially relevant studies were identified as well as seven technology appraisals, but none were specific to people with PPMS; all studies investigated the cost-effectiveness of DMTs for treating people with RRMS. These studies were excluded at the full-text stage. Through further searching, one report was identified that assessed the clinical effectiveness and the comparative value of using DMTs for treating people RRMS and those with PPMS.[35] Briefly, the authors used a Markov model to depict the natural history of a cohort of people with PPMS who may undergo treatment with ocrelizumab or BSC over a life-time horizon. The model defined health states by EDSS, which ranged from 1-9 and death. The disability progression in the model was based on the London Ontario natural history cohort which showed disease progression in the absence of disease modifying treatment. The model starts from a hypothetical cohort of people with mean age of 42 years, distributed across EDSS to reflect the starting proportion in the ORATORIO trial. People remained in these health states, after which they can progress to more severe EDSS states. It was assumed that people could not regress to less severe EDSS states. Due to the paucity of information, transition probabilities for people with

PPMS were the same as those for SPMS transitions, and were obtained from the London Oratorio dataset. Treatment with ocrelizumab was assumed to delay disability progression to higher EDSS levels. Evidence for the clinical effectiveness of ocrelizumab in this model relied on the ORATORIO trial together with the strong assumption of a constant rate of transition over the range of EDSS derived from the trial. The effect of treatment was modelled to show the impact to EDSS progression and health state costs and utilities. Annual cycles were used to show the movement of people through the model, whereby people transitioned to more severe EDSS levels, withdrew from treatment, or transition to the dead state. In EDSS states 1-9, people incurred costs and accrue benefits (QALYs).

In the model it was assumed that utility values for people with SPMS are the same as those for people with PPMS. These were obtained from Orme et al.[1]. Any disutilities associated with adverse events were obtained from published sources. Background mortality rates were obtained from age and gender-specific US life-tables and weighted by gender distributions for people with PPMS. These mortality rates were adjusted using MS-specific mortality multipliers derived from information reported by Pokorski et al.[36]

Direct costs were included in the analysis. Direct costs included inpatient and outpatient admissions, visits to healthcare professionals, examinations, medical devices, and non-DMT and over-the-counter medications. Indirect costs were considered in scenario analyses and included productivity losses and changes to working situations. The drug acquisition cost for ocrelizumab was not reported. Management costs associated with state-dependency were derived based on interpolation of information reported in Kobelt et al.[37] and were inflated to current prices. The outcomes were reported in terms of life years gained (LYG) and QALYs, but not in terms of an ICER. A number of deterministic one-way sensitivity analyses and scenario analyses were undertaken. The model estimated an expected mean cost of approximately US$164,800 for BSC and expected to yield 2.75 QALYs. Ocrelizumab was expected to yield 3.33 QALYs. Table 12 provides a summary of the key characteristics and results from this study.

Through searching (MEDLINE and Google) the ERG identified an abstract where the authors estimated the cost-effectiveness of ocrelizumab in people with PPMS compared to no active treatment[38]. Briefly, the authors used a Markov structure with quarterly cycles to model the natural history of a cohort of people with PPMS over a life-time horizon. The model defined health states by EDSS. Information used to populate the model were obtained from the trial (CDP-12) and the literature. The authors stated that ocrelizumab is not on the market, the price was benchmarked and evaluated in threshold analysis. Results were presented reported as an ICER, expressed as cost per QALY gained. The model estimated that Ocrelizumab was approximately US$1.35 million more costly than no active treatment and expected to yield 8.97 more QALYs, equating to an ICER of

approximately $US 150,500 per QALY gained. With WTP thresholds between US$50,000 and US$100,000 per QALY, the annual cost of ocrelizumab is likely to be between US$18,348 and US$33,840. One-way sensitivity analysis results showed that varying the cost of ocrelizumab had the greatest impact to the ICER. The authors further concluded that ocrelizumab may be cost-effective depending on the price and WTP threshold and could be a meaningful option for treating people with PPMS.

This abstract provides little detail on the economic analysis. Key information on the starting age of the population, assumptions, natural history cohort based on those included in the trial or from a registry and costs and utility values used in the model is missing. Hence, these results should be interpreted with caution.

Table 12: Summary of the key characteristics of the cost-effectiveness study identified

Author, year and country	Population	Intervention and comparator	Perspective and time horizon	Model type and cycle length	Health states	Evidence synthesis	Source of preference data	Outcomes	Results
ICER 2017; USA	People with RRMS and, people with PPMS. Mean age at baseline is 42 years and assumed that 47% are male	Ocrelizumab (300mg twice 14 days apart) versus BSC	US payers' perspective; lifetime horizon	Markov model with annual cycle lengths	EDSS 1-9 and dead	Results based on the ORATORIO trial.	Assumed that utility values for PPMS EDSS states were the same as for SPMS states. Unclear of the source of the preference data	QALYs gained	Expected mean costs for ocrelizumab not reported. Mean costs for BSC was approximately US$264,800 Ocrelizumab and BSC expected to yield 3.33 and 2.75 QALYs, respectively.
Suh et al., 2017	People with PPMS similar to those in the ORATORIO trial	Ocrelizumab versus no treatment	US payers' perspective; lifetime horizon	Markov model with quarterly cycles	Unclear	Results based on the ORATORIO trial.	Unclear	QALYs gained	Ocrelizumab was approximately US$1.35 million more costly than no treatment and expected to yield 8.97 more QALYs, equating to an ICER of approximately $US150,150 per QALY
BSC, best supportive care; EDSS, expanded disability status scale; ICER, Institute for clinical and economic review; QALY, quality adjusted life years; USA, United States of America									

5.1.4 Systematic review of studies reporting resource use and costs

Separate searches for cost and resource use for MS, restricted to the UK, were undertaken on 7-8 February 2017. An appropriate range of sources were searched. Several terms for the UK were included. Since this search was undertaken, a tested and validated UK geographic search filter for Medline has been published.[39]

5.1.5 Systematic review for HRQoL studies

Broad database searches for HRQoL studies, were performed separately from the cost-effectiveness searches on 23 March 2016 and updated on 24 March 2017. Sources and search terms appear to be appropriate. Search terms combine MS terms with HRQoL terms. As in the systematic review of cost-effectiveness, a good range of supplementary sources and search methods are used, but sufficient detail is not given for the methods used to search them. A summary of the PICO framework is shown in Table 13.

Table 13: Eligibility criteria for inclusion in the utility review (Table obtained from the CS, Appendix G)

Criteria	***Include***
Population	*Participants ≥18 years with a diagnosis of MS (classified using an accepted diagnostic technique e.g. Poser or McDonald criteria) regardless of age, sex, degree of disability, and duration of the disease. The primary focus is on the following clinical phenotypes:* • *relapsing-remitting MS (RRMS)* • *secondary progressive MS (SPMS)* • *primary-progressive MS (PPMS)*
Interventions and comparators	*No restriction*

Outcomes	*The following outcomes were of interest:*
	• *Utility values elicited directly using the following techniques:*
	  ○ *TTO*
	  ○ *SG*
	• *Utility values derived from generic preference-based instruments for relevant health states (e.g. baseline utility, disutilities associated with AEs)*
	• *Mapping studies that would allow disease-specific measures to be mapped to preference-based utilities*
	• *Key drivers of utilities*

Setting/study design	*No restriction and to include:* • *HSUV elicitation studies*

	• *Interventional studies* • *Observational study designs (e.g. cohort studies)*
Language of publication	*No restriction*
Date of publication	*Original review (March 2016): no restriction* *Update (March 2017): post-March 2016*
Country/global reach	*No restriction*

5.1.6 Results

The company identified 51 studies reporting health state utility values for people with MS according to EDSS levels. A further 23 studies were excluded because they were not consistent with the NICE reference case; four were further excluded because results were presented for two EDSS levels. The company also provided a list of all studies excluded, with reason for exclusion. Studies identified were quality appraised and useful information for the cost-effectiveness analysis was extracted. Detailed results by EDSS were reported for the remaining 24 studies.

5.1.7 Conclusions

In the reviews undertaken, the search strategy appeared to have some minor issues. However, targeted searches undertaken by the ERG were unable to identify any relevant studies that might have been missed by the company. There is scant evidence on the cost-effectiveness of DMTs used for treating people with PPMS; majority of the research has been undertaken in people with RRMS.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

In this section, we present in Table 14 the ERG's assessment of the company's economic analysis against the NICE reference case for technology assessment.[40] We provide details of the illustrative model structure, as well as the clinical (e.g. survival analysis and treatment effect) and economic (e.g. cost of ocrelizumab, treatment costs and adverse events management costs) evidence used; then we present a critical assessment.

5.2.1 NICE reference case checklist

Table 14: NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Defining the decision problem	The scope developed by NICE	People with PPMS
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice for this population	Ocrelizumab is being compared to best supportive care (clinical management)
Patient group	As per NICE final scope, the population refers to: People living with PPMS	Patient population in the ORATORIO trial included people without imaging features characteristic of inflammatory activity
Perspective costs	NHS & Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-effectiveness analysis	Cost-effectiveness analysis
Time horizon	Sufficient to capture differences in costs and outcomes between the technologies being compared	Lifetime horizon The model assumed a starting age of 44.
Synthesis of evidence on outcomes	Systematic review	Outcomes were obtained from the ORATORIO trial
Outcome measure	Quality adjusted life-years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes; Utility values are dependent on the health state occupied
Benefit valuation	Time-trade off or standard gamble	The standard UK EQ-5D-3L tariff is used, which is based upon time-trade off
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the	Yes

	individuals receiving the health benefit	
Probabilistic modelling	Probabilistic modelling	Yes
Sensitivity analysis		Number of sensitivity analyses were conducted on the base-case
BSC, best supportive care; HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PPMS, primary progressive multiple sclerosis; QALY, quality adjusted life-years;		

5.2.2 Model structure

The company used a *de novo* Markov model to depict the natural history of people with PPMS. The natural history of PPMS is characterised by a series of progressive health states representing the increasing levels of disability resulting from progressive loss of neurological function. The Kurtzke EDSS is commonly used to measure neurological disability and its progression overtime, and is used in this submission. The model defined health states by EDSS, which ranged from 0-9 and dead. The disability progression in the model was based on the MSBase natural history cohort which showed disease progression in the absence of disease modifying treatment. The model predicts how the distribution of people will progress over the model time horizon, starting with a baseline distribution reflecting the ORATORIO trial population at recruitment. People remained in these health states, after which they can progress to more severe EDSS states or death. For people who discontinued treatment (due to adverse events or progressing to EDSS ≥ 8), it was assumed that they would not switch to another DMT but would receive BSC and experience the same rate of disease progression from that point onwards as someone who had the same EDSS and had not received ocrelizumab. To reflect the observations in the MSBase registry, there is the possibility in the model for people to regress to less severe health states. However, it was assumed that the treatment effect did not directly impact on regression.

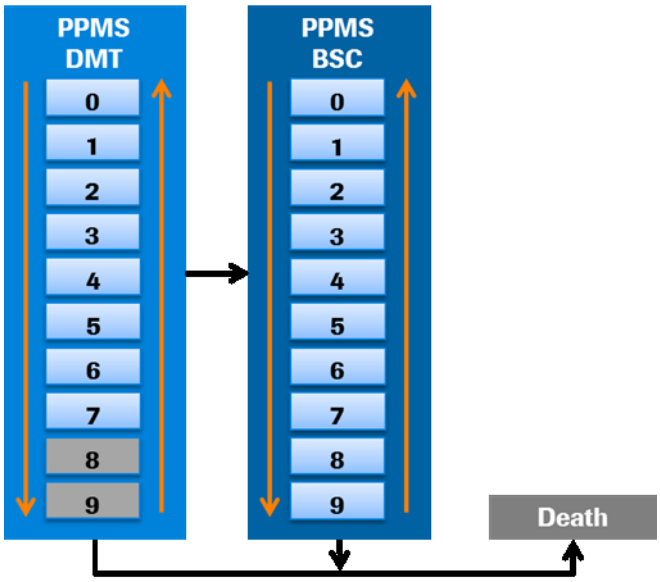

Figure 7: Illustrative model structure (obtained from the company submission)

ERG summary

The *de novo* model developed appears to capture the key important features of PPMS. The annual cycle length is adequate to capture the changes of the disease over time, and the time horizon is long enough to capture longer-term consequences (costs and benefits) associated with ocrelizumab.

5.2.3 Population

The indication for ocrelizumab is for the treatment of adults with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity. The population modelled was based on people with PPMS in the MSBase registry, comprising a broader cohort of people with PPMS who had not received DMT (i.e. including those without inflammatory activity), when compared to the ORATORIO trial population. The company states that the MSBase registry is made up of 352 members, 240 clinics across 73 countries and contains information for 2786 people with progressive MS (primary progressive and progressive relapsing). At the clarification stage, the ERG queried the inconsistency in the submission of the number of people with PPMS included from the MSBase registry and, the proportion of people from the UK included in the analysis. In the submission, Table 12 suggests that 775 people were included from the MSBase registry while on page 99, suggested 1076. The company clarified that the 775 represented an 'ORATORIO-like' cohort of people with EDSS 3.0-6.5 at baseline, that was then used for the analysis of

time to progression to EDSS ≥7. Also it should be noted that of the 1079 people included from the MSBase registry, 27 (2.5%) people were from the UK.

People entered the model in one of the EDSS levels ranging from 3 to 7 to reflect the starting distribution in the ORATORIO trial.

ERG summary

It was not quantitatively possible to estimate the impact of ocrelizumab compared to BSC solely in adults with early PPMS and characteristics of inflammatory disease. The population modelled was based on people from the MSBase registry. It should be borne in mind when interpreting these results that the MSBase registry included people with and without characteristics of inflammatory disease and included less than 3% of people from the UK.

5.2.4 Interventions and comparators

The company's base-case compares ocrelizumab with BSC. In the ORATORIO trial, people randomised to the intervention received 600mg of ocrelizumab by intravenous infusion, administered as two 300-mg infusions 14 days apart, in keeping with its marketing authorisation. Ocrelizumab treatment is assumed to continue until disease progresses to EDSS 8, tolerability or drug-related adverse events, lack of efficacy or other reasons.

People randomised to the BSC received matching placebo every 24 weeks in addition to symptom control, physical therapy, psychiatric and social support. The model assumed that the treatment effect was sustained for the model time horizon for people still on treatment.

ERG summary

BSC in the form of clinical management is an appropriate comparator in this analysis. As indicated in section 3.3, our clinical advisors have indicated that to the best of their knowledge no DMT is used off-label in the UK in patients with PPMS. The ERG has concerns (see Section 5.2.6) regarding the assumption that the treatment effect remains constant over the model time horizon.

5.2.5 Perspective, time horizon and discounting

The analysis was conducted from the NHS/PSS perspective, in line with the NICE 2013 Guide to Methods of Technology Appraisal.[41] The time horizon of the model was 50 years,

which is assumed to be lifetime given that the mean age of the starting population was 44 years, and is long enough to capture the long-term costs and benefits of ocrelizumab. In the base-case, costs and benefits were discounted at 3.5% per annum and varied in one-way sensitivity analysis.

ERG Summary

The perspective, time horizon and discount rates chosen by the company are in line with the NICE 2013 recommendations,[41] and are appropriate to the decision problem.

5.2.6 Treatment effectiveness and extrapolation

The effect of ocrelizumab treatment was included in the base-case model in three ways: confirmed disability progression, upper limb impairment and fatigue. The effect of treatment associated with relapses was considered in scenario analysis.

- **Confirmed disability progression (EDSS progression)**

With observed data from the MSBase registry, the company used multi-level modelling to generate annual transition probabilities to reflect disease progression in the absence of DMTs for people randomised to placebo. Table 15 shows the observed data obtained from the MSBase registry.

Table 15 : Number of observed transitions between EDSS scores in PPMS

From EDSS		To EDSS									
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
	0	10	7	3	4	2	0	1	0	0	0
	1	3	61	50	13	9	1	4	1	1	0
	2	7	28	358	115	64	16	11	1	0	0
	3	1	6	62	593	212	48	32	4	2	0
	4	0	3	28	84	1056	229	141	3	2	0
	5	0	2	2	10	101	641	279	8	2	0
	6	3	1	1	7	30	93	2142	231	27	1
	7	0	0	0	0	3	0	69	854	115	6
	8	0	2	0	0	0	0	2	31	376	22
	9	0	0	0	0	0	0	0	0	8	56

Source: Company submission page 102

From the observed data points, it appears that improvements may occur in people with PPMS. At the clarification stage, the company suggested that this may be implausible, and further stated that *'the time between these observations are not visible in the matrix, i.e. the observations are not captured on a fixed cycle. As such the time between measurements could*

be multiple years apart.' The company further clarified that no adjustments were made to the data by removing any EDSS improvements, which is in line with other submissions in MS. In a scenario analysis, the company derived transition probabilities based on observed data that only allows disease progression.

To the observed data, the company used similar methods to those reported by Palace et al. [42] and derived transition probabilities. The company has not provided any details of this method; therefore, no critique/commentary could be provided. Table 16 shows the transition matrix. The company stated that adjusting for age and/or sex did not lead to a better model. Hence, this transition matrix represents the unadjusted model.

The company highlights that due to the limited information collected on MRI in the MSBase registry, a transition matrix could not be generated solely on a population with imaging features characteristic of inflammatory activity.

Table 16: Transition probability matrix in PPMS

		To EDSS									
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
From EDSS	**0**	0.4068	0.2929	0.2242	0.0611	0.0132	0.0016	0.0002	0.0000	0.0000	0.0000
	1	0.0842	0.2617	0.4204	0.1735	0.0512	0.0076	0.0012	0.0000	0.0000	0.0000
	2	0.0138	0.0903	0.4409	0.2998	0.1264	0.0238	0.0048	0.0002	0.0000	0.0000
	3	0.0017	0.0164	0.1318	0.4008	0.3326	0.0905	0.0252	0.0010	0.0000	0.0000
	4	0.0001	0.0016	0.0182	0.1088	0.5181	0.2429	0.1046	0.0054	0.0002	0.0000
	5	0.0000	0.0002	0.0024	0.0209	0.1718	0.3922	0.3807	0.0299	0.0018	0.0000
	6	0.0000	0.0000	0.0001	0.0010	0.0127	0.0653	0.8011	0.1103	0.0093	0.0002
	7	0.0000	0.0000	0.0000	0.0000	0.0005	0.0038	0.0813	0.7766	0.1335	0.0043
	8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0042	0.0817	0.8599	0.0541
	9	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002	0.0046	0.0955	0.8998

Source: Company submission page 102

Treatment effect

Table 17 shows the hazard ratio used in the company's analyses. The base-case model uses the CDP-12 hazard ratio to model the treatment effect on disability progression for people (MRI active group) randomised to ocrelizumab. This treatment effect is applied to the forward transitions only. A critique of using a constant hazard ratio over the EDSS range is provided in section 4.8.

Table 17: Treatment effects applied in the model

	'MRI active' subgroup	'MRI active ≤50' subgroup	'MRI active' subgroup – extended control period	'MRI active ≤50' subgroup – extended control period
CDP-12	0.68 (0.46 – 0.99)	0.55 (0.36 – 0.85)	0.69 (0.47 – 1.00)	0.56 (0.37 – 0.85)
CDP-24	0.71 (0.47 – 1.06)	0.54 (0.35 – 0.85)	0.68 (0.46 – 0.99)	0.53 (0.35 – 0.81)

Source: Company submission page 104

- **Upper limb dysfunction and fatigue**

Upper limb dysfunction and fatigue were considered by the company to be important factors in PPMS that, in addition to EDSS, will impact on HRQoL; these are factors which have not been measured or included in other recent technology appraisals.[31, 43-45] For upper limb impairment, as measured by the 9-HPT, the company reported a hazard ratio of 0.52 (95%CI: 0.32, 0.85) for the MRI active population. This HR represents the results of a 20% increase in the 9-HPT sustained over 12 weeks as seen in the trial (see section 4.3 for ERG's critique). It appears to the ERG that this hazard ratio was derived from the number of people across all EDSS levels with a 20% increase in the 9-HPT sustained over 12 weeks, but is applied only to a proportion of people with EDSS ≥5. Also, the ERG considers there to be a lack of transparency in the number of people randomised to ocrelizumab who experience clinically meaning upper limb impairment. Table 18 shows these proportions for people randomised to BSC. However, a similar table was not provided by the company for ocrelizumab.

Table 18: Proportion of people experiencing clinically meaningful upper limb impairment (placebo)

Health state		**20% increase in 9-HPT sustained for 12 weeks**	**20% increase in 9-HPT sustained for 12 weeks (with imputation)**
	N (%)	**N (%)**	**N (%)**
EDSS 2	1(0.4)	1(100)	1(100)
EDSS 3	65(26.6)	11(16.9)	12(18.5)
EDSS 4	68(27.9)	14(20.6)	16(23.5)
EDSS 5	29(11.9)	3(10.3)	3(10.3)
EDSS 6	81(33.2)	29(35.8)	34(42.0)
Total	**244(100)**	**58(23.8)**	**66(27.0)**
9-HPT; nine-hole peg test, EDSS; expanded disability status score			

- **Relapses**

The company submission stated that relapses can occur in people with PPMS but these events are rare. In the ORATORIO trial 11% of people randomised to placebo experienced a relapse. From the MSBase registry, 8% of people experienced a relapse. As noted in section 4.5.1.1, post hoc analysis was conducted to derive an annualised relapse ratio based on the ITT population. Results from the post hoc analysis indicated a 65% reduction in relapses with ocrelizumab compared to placebo, with an adjusted annualised relapse risk ratio of 0.35 (95% CI: 0.190, 0.645). This treatment benefit for reducing relapses was not applied in the base-case analysis. The model uses an annual relapse rate of 0.015 which was derived based on the observed MSBase data, and is assumed to be constant over time. Using this annual relapse rate also assumes that the rate of relapses are the same for people in early EDSS and late EDSS levels. Additionally, it assumes that the relapse rate is the same for the ITT and an MRI active population.

ERG summary

The ERG notes that relapse was not pre-specified in the scope and thus not discussed in the clinical effectiveness section or included in the company's base-case model.

- **Treatment withdrawal**

The model allows for discontinuation of treatment. The company suggests that annual transition probabilities for treatment withdrawal were based on fitting different parametric models to the observed data for all-cause discontinuation (Kaplan-Meier plots along with parametric models were not presented in the main report). Based on the Akaike information criterion (AIC) and clinical opinion the Gompertz parametric model was considered to be the most appropriate because the annual transition probabilities for withdrawal are expected to increase over time. The company further stated that *'This was thought to be driven by the perception of relatively limited tangible benefits to patients of slowing down disability progression, as opposed to the benefits derived from high-efficacy DMTs in RRMS which can reverse disability.'* (CS page 107) Including the stopping rule at EDSS ≥8 and all-cause discontinuation, the company's clinical expert considered that the model overestimates the average treatment duration (approximately seven years). Treatment withdrawal was varied in sensitivity analysis. An annual discontinuation rate of 17%, as observed in a real-world setting for people who received rituximab for rheumatoid arthritis, was considered to be a proxy for discontinuation of ocrelizumab. Using this proxy, the model predicted that the

average treatment duration is approximately 4.5 years, which is in line with the company's clinical experts' opinion. It is unclear what information guided the expert estimation of average treatment duration given that no active treatment has ever been routinely used for PPMS patients. In the model, all-cause discontinuation was applied to the MRI active population as well as the MRI active ≤50 years of age subgroup, since the discontinuation rates were similar.

ERG summary

There were some concerns related to discontinuation. First, the KM plots along with the parametric fits were not presented by the company, so the ERG could not provide a critique. Second, we noted that the generalised-gamma parametric model was not fitted to the observed data. Third, the company suggested that all-cause discontinuation rates from the ITT population were applied to the MRI active and MRI active ≤ 50 years subgroup because they were similar; however, no supporting information was provided. Fourth, it was unclear to the ERG if people could discontinue treatment between infusions. Additionally, the ERG noted that the stopping rule applied in this model is later than stopping rules applied in other MS submissions.[31, 43-45]

- **Waning**

In the submission the company assumed no waning of long-term treatment effect in the base-case model for ocrelizumab, and have not explored the impact of treatment waning in a scenario analysis. The company stated that ocrelizumab is a humanised antibody that generates a negligible risk of neutralising antibodies thought to contribute to drug resistance.

While the ERG acknowledges that ocrelizumab appears to be at low risk of inducing neutralising antibodies, the relation between onset of neutralising antibodies and drug resistance is not clearly demonstrated. People may develop drug resistance in the absence of neutralising antibodies while people with neutralising antibodies may experience no reduction of treatment benefit. It is accepted that the rate of neutralising antibody formation alone is not a meaningful endpoint because of its limited clinical relevance in practice. To the best of the ERG's knowledge, the occurrence of neutralising antibodies in patients treated with DMT is not routinely monitored in the UK. As part of the recent MS multiple technology appraisal (MTA) on beta-interferon and glatiramer acetate, Melendez-Torres et al. [2] explored the evidence on discontinuation due to loss of effectiveness attributed to neutralising antibody formation for the above cited drugs and found no data on this specific outcome. Therefore, the

ERG believes that the statement about the humanised nature of ocrelizumab inducing fewer neutralising antibodies is not a valid reason to exclude a waning of the treatment effect of ocrelizumab used in PPMS. The same conclusion was reached by the Appraisal Committee on the ongoing appraisal on ocrelizumab used in RRMS.[46]

Second, the company stated that there is sustained effect across different time points in the open label extension study of ocrelizumab in RRMS (CS Appendix M). The ERG noted that the additional follow-up period provided in the open-label extension study is only two years which is insufficient to demonstrate that a long-term effect is sustained. Third, the company suggested that ocrelizumab decreases inflammation of the innate immune system and impact upon the adaptive immune system deemed by the ERG as poorly supported by clinical relevance.

ERG summary

The ERG considers the assumption of no treatment waning effect to be implausible for the following reasons:

1. The Kaplan-Meier plots show fluctuations in the treatment effect between 0 and 120 weeks.
2. There is an absence of evidence for long-term sustained effectiveness.

As a result, the ERG implemented treatment waning in the ERG base-case, and in scenario analysis excluded the waning effect.

Treatment waning effect could be implemented in the model in different ways.

In the original submission, the company has chosen a Gompertz function to describe change in treatment withdrawal over time. This denotes a probability of withdrawal increasing over time to reflect that patients may perceive relatively limited tangible benefits in the long-term. While this may be seen as a way to implement a waning of treatment effect, the ERG believes this would not translate an objective reduction of the treatment effect. Conversely, the ERG considers that applying a waning effect by increasing the HR for CDP without changing the rate of treatment withdrawal would not faithfully reflect the statement made by the company about people discontinuing more over time because the lack of perceived effectiveness in the long term. This option was tested in a scenario analysis. In our view, the most relevant way to apply a waning of treatment effect is to increase the HR for CDP over time while increasing the rate of discontinuation to treatment as a consequence of an objective loss of effectiveness.

The ERG has examined recent technology appraisals (TA) on DMTs to provide perspective of the extent to which a waning of treatment effect has been applied, this includes the current MTA on beta-interferon and glatiramer acetate. This is summarised as follows:

- Reduction in the treatment effect by 50% either from the end of the observation period (which is usually 2 to 3 years) onwards (option 1), from 5 years onwards (option 2), or from 10 years onwards (option 3)
- Reduction in the treatment effect by 25% from the end of the observation period (again 2 to 3 years), then a reduction by 50% from 5 years onwards (option 4)

Options 1 and 4 were deemed too pessimistic to be used here in the base case. Option 3 was preferred by the committee for the MTA on beta-interferon and glatiramer acetate used for RRMS, was deemed too optimistic because unlike RRMS, no other active treatment is available for PPMS which means that a loss of treatment effect is not likely to be offset by the use of subsequent treatments. Therefore, option 2 was chosen in the ERG's base-case model, reflecting a 50% increase of the HR for CDP from year 5 onwards. As indicated above, an increase of the rate of treatment withdrawal was also applied as a result of the waning of treatment effect from year 5 onwards.

5.2.7 Adverse events

Table 19 shows the adverse events included in the model. These adverse events relate to those that occurred more frequently with ocrelizumab compared to BSC, with a difference of >3%. The company reported the 3-year probability of adverse events, then converted these to annual probabilities to be used in the model. Using this method assumes that the risk of adverse events is constant over time. These probabilities were assumed to be applicable to the MRI active population and MRI active ≤50 subgroup.

Table 19: Adverse events with a > 3% difference from the ORATORIO trial

Adverse events	Ocrelizumab		Placebo	
	3-year probability	Annual probability	3-year probability	Annual probability
Infusion related reaction	39.9	15.6	0.0	0.0
Malignancies	2.3	0.8	0.8	0.3
Upper respiratory tract infection	10.9	3.8	5.9	2.0

ERG summary

The ERG considers the assumption of constant rate of adverse events to be appropriate.

5.2.8 Mortality

To reflect the increased risk of mortality in people living with PPMS the company used mortality multipliers estimated from Pokorski et al.[36] and applied these to a weighted average of the background mortality rates for the general population. Pokorski et al.[36] reported mortality multipliers of 1.60 for mild (EDSS ≤ 3.5), 1.84 for moderate (EDSS 4-7) and 4.44 for severe (EDSS ≥7.5) disease. However, no further information is provided in the report on the function used to derive mortality multipliers for this submission. In Table 20 we report the mortality multipliers at health states prior to EDSS 10.

Table 20: Mortality multipliers by EDSS level

EDSS	0	1	2	3	4	5	6	7	8	9
Mortality multiplier	1.00	1.43	1.60	1.64	1.67	1.84	2.27	3.10	4.45	6.45

As noted in the submission, these mortality multipliers are based on people with MS and not specifically to people with PPMS. The submission highlights that there is no direct treatment benefit on mortality. However, there is indirect benefit due to delaying/avoiding disability progression.

ERG summary

An increased risk of mortality for people living with PPMS is represented by a mortality multiplier applied to a non-MS related general population mortality.

5.2.9 Health related quality of life

Utility values included in the CS economic analysis were those associated with EDSS health states and, decrements associated with upper limb function and fatigue, adverse events and carers' disutility. The utility weights for EDSS health states were based on HRQoL data collected using the EQ-5D and utility values obtained from the literature.[1] HRQoL data collected in the ORATORIO trial for EDSS 2-7 were valued using the UK-specific general population value set by Dolan et al. [47]. The company suggested that the utility estimates for the MRI active and MRI active ≤ 50 subgroup were similar to the ITT population. Table 21 shows the utility values used in the base-case and scenario analysis.

Upper limb function and fatigue were considered to be factors that impacts on the HRQoL in addition to EDSS. Upper limb function, as measured by the 9-HPT was considered to be

clinically meaningful if there was a 20% increase sustained over 12 weeks. A disutility of -0.0641 is applied to EDSS states ≥5 to the proportion of people who experience upper limb impairment.

Based on CS clinical expert opinion, upper limb dysfunction on at least one side is assumed to affect approximately 30% of people with EDSS 0-4, 50% of people with EDSS 5-6 and 70% of people with EDSS ≥7 randomised to BSC. A relative risk reduction of 48% and 55% was applied to the MRI active population and MRI active ≤50 subgroup, respectively, for ocrelizumab. Due to the low numbers of people in the ORATORIO trial who had upper limb impairment at some EDSS levels, proportions based on clinical opinion were considered to be more credible.

The condition-specific measure, the MFIS was used to assess the burden of fatigue in people with MS, with a score of ≥38 being clinically meaningful. A disutility of -0.1502 for fatigue was applied to a proportion of people who are likely to experience fatigue. In the base-case it was assumed that fatigue affected approximately 10% of people in EDSS 0 increasing to 70% in people with EDSS 9 randomised to BSC, and a relative risk reduction of [redacted] and [redacted] was applied to the MRI active and MRI active ≤ 50 subgroup, respectively for people randomised to ocrelizumab. Due to the low numbers of people in the ORATORIO trial who were fatigued at some EDSS, the clinical expert's proportions were considered to be more credible. These proportions were varied in scenario analysis.

Table 21: Utility values used in the models

Health state	Base-case analysis		Scenario analysis	
	Utility value	Source	Utility value	Source
EDSS 0	0.837	Orme et al [1]	0.837	Orme et al [1]
EDSS 1	0.766		0.766	
EDSS 2	0.791	ORATORIO trial [8]	0.672	
EDSS 3	0.738		0.541	
EDSS 4	0.678		0.577	
EDSS 5	0.665		0.485	
EDSS 6	0.605		0.425	
EDSS 7	0.428		0.264	
EDSS 8	-0.082	Orme et al [1]	-0.082	
EDSS 9	-0.228		-0.228	
Upper limb impairment	-0.064	ORATORIO trial [8]	-0.064	ORATORIO trial [8]
Fatigue and cognitive impairment	-0.150		-0.150	

The ERG has concerns regarding the inclusion of utility decrements in the model for upper limb impairment and fatigue in addition to utility values for each EDSS level.

1. There is a lack of transparency on the choice of outcomes that were incorporated to measure disutilities:

The company chose to incorporate utilities to reflect upper limb function using outcomes from the 9-HPT. In the ORATORIO trial, the 9-HPT was included in two outcomes: 20% increase in 9-HPT sustained over 12 weeks and MSFC (composite endpoint). The company chose results for a 20% increase in 9-HPT to reflect upper limb function impairment indicating this corresponds to clinically meaningful upper limb impairment but neglected to note that: MSFC is a composite outcome that includes the 9-HPT (see section 4.3); and, that MSFC outcomes showed no differences between treatments arms (see section 4.5.1). However, MSFC is a listed outcome within the most recent EMA guidelines on clinical investigations for MS drugs [7].

The company incorporated disutilities to reflect fatigue and cognitive impairment as assessed, according to the company (Table 52 on page 111) by MFIS ≥38. We understand that MFIS is a tool denoting how fatigue impacts patients' lives, but does not measure cognitive impairment. Cognitive impairment was measured in ORATORIO using the PASAT, which found no statistically significant difference between the treatment arms. The company has not explained why disutilities related to cognitive impairment were not incorporated despite the cognitive impairment being measured, and EMA emphasis that EDSS does not adequately assess cognitive impairment.

2. The company incorporated disutilities related to upper limb impairment and fatigue using the 9-HPT and the MFIS, respectively, measured as exploratory analyses in the trial. As previously emphasised (see section 4.5.1), the ERG is concerned at the use of post-hoc selected outcomes from exploratory analyses, designed to generate hypotheses rather than provide formal conclusions by their use in the company base case model.
3. There is the potential for double counting of utilities since the EQ-5D may adequately capture HRQoL for people with MS.[48] The inspection of the MFIS and EQ-5D questionnaires show a number of similarities in the questions. Examples are questions pertaining to "self-care" or "usual activities" which appear in the EQ-5D and several questions related to physical subscale of the MFIS. There is also the potential for doubling of utilities using outcomes from the 9-HPT and MFIS. For example, the item 4 from the MFIS examines whether patients report "they have been clumsy and uncoordinated". A patient rating "almost always" to this item is also likely to have a

poorer score on the 9-HPT. Lastly, some of the MFIS items appear to be linked to progression through EDSS. As an illustration, a patient responding "almost always on the MFIS item 13 "my muscles have felt weak" is likely to experience ambulation impairment.

4. In addition to utility decrements associated with upper limb, and fatigue and cognitive impairment, the company included carers' disutilities for all EDSS states. Given that the company included utility decrements for caregivers' burden, we consider additional decrements for upper limb impairment and fatigue to be double counting the impact on QALYs.
5. To our knowledge, utility decrements for upper limb impairment, fatigue and cognitive impairment have not been used in other MS technology appraisals. As stated in section 2.1, the company emphasised that upper limb function is an important outcome for people with PPMS and, it is unclear why upper limb function should be a more important outcome in PPMS patients as opposed to RRMS patients. The ERG is not convinced that the 9-HPT should get greater emphasis in PPMS compared to RRMS. Moreover, the ERG has noted that this outcome was not incorporated in the submission by the company for ocrelizumab in RRMS.
6. Regarding the hazard ratio and disutilities derived from 20% increase in the 9-HPT:

- A hazard ratio of 0.52 is presented based on the 12-week 9-HPT: consistent with our previous comment that 24-week CDP should be preferred over 12-week CDP, the hazard ratio should be better based on 24-week sustained 20% increase in 9-HPT.
- It appears to the ERG that the hazard ratio was derived based on information from people with EDSS 2 to 6 but was applied to people with EDSS ≥7: it is unclear whether this hazard ratio should be applied or seen as generalizable to people in lower EDSS states (0-1) and higher EDSS states (EDSS ≥7).
- Results are presented for each EDSS level for the placebo group but not for ocrelizumab (Appendix H: Table 38): there is a lack of transparency on the number of people randomised to ocrelizumab who experienced a 12-week sustained 20% increase in 9-HPT.
- We examined the hazard ratio that was applied in the model for time to 20% increase in 9-HPT, and it appears that the hazard ratio was used as a relative risk. That is, the treatment effect was a reduction to the proportion of people with upper limb impairment in ocrelizumab compared to BSC. Based on the information provided in Tables 53 of the CS, the appropriate relative risk to be used in the model for the MRI active group is 0.656. Additionally, we consider it to be misleading that there appears to be treatment benefit from ocrelizumab for EDSS levels 8 and 9, as shown in Table

53 of the CS and in the economic model (worksheet 'inputs-utilities' cells N22 and O22). On further investigating of the Markov trace, it appears that this treatment benefit was not implemented in the analysis.

- Should disutilities based on 20% increase in 9-HPT be incorporated in the model, the ERG believes that the model should include a feature to allow a waning of the benefit consistent with that using CDP, which is not currently the case

7. Regarding the relative risk and disutilities derived for fatigue
    - MFIS was used to measure fatigue, with a score ≥38 representing clinically meaningful fatigue. The company further stated that *'cut-offs are not commonly used with fatigue scales and have not been extensively researched in PPMS.'* We further noted that the baseline mean score for fatigue was 41.6 (17.2), suggesting that on average people were already fatigued in the trial. Critically, as previously stated (see section 4.5.1.2), ocrelizumab had no impact on fatigue compared to placebo based on the mean changes on the MFIS.
    - A relative risk of [redacted] is reported for the treatment benefit of ocrelizumab for reducing fatigue. However, there was lack of transparency on the proportion of people randomised to ocrelizumab that experienced fatigue. These proportions were presented for people randomised to BSC. Similarly to upper limb impairment, there appears to be treatment benefit from ocrelizumab for EDSS levels 8 and 9, as shown in Table 54 of the CS and in the economic model (worksheet 'inputs-utilities' cells N35 and O35), but on further inspection these relative risks were not applied in the analysis.

Disutilities (Table 22) associated with adverse events were included in the base-case analysis, and were categorised as non-serious or serious. Adverse event disutilities were obtained from technology appraisals (alemtuzumab and daclizumab) in people with RRMS or from the literature. Disutilities associated with malignancies were based on a proxy of people with breast cancer in a recurrence free health state. In the model it was assumed that these decrements were a 'one-off' adjustment over a year. These adjustments were applied to a proportion of people with non-serious (20.4%) and serious (79.6%) adverse events as seen in the ORATORIO trial. The model uses average disutilities based on these proportions and duration (in days) of the adverse event. These decrements were applied to both BSC and ocrelizumab.

Table 22: Disutilities associated with adverse events

Adverse event (AE)	Non-serious AE	Serious AE	Average disutility	Source
Infusion related reaction	-0.011	-0.011	-0.0002	Alemtuzumab technology appraisal
Malignancies	-0.176	-0.284	-0.1986	Ward et al (2013)[33]
Upper respiratory tract infection	-0.200	-0.200	-0.0046	Daclizumab technology appraisal
AE, adverse event				

The base-case analysis included carers' disutility by EDSS health state. Table 23 shows the disutility values used in the model. These values were obtained from TA127 and were derived from a population of carers providing care for people with Alzheimer's disease (Acaster et al., 2013)[49] and adjusted to reflect the time spent providing care for people with multiple sclerosis, as seen in the UK MS survey.

Table 23: Carers' disutility by EDSS

Health state	Carers' disutility	Source
EDSS 0	0.000	TA127 manufacturer's submission[50]
EDSS 1	-0.001	
EDSS 2	-0.003	
EDSS 3	-0.009	
EDSS 4	-0.009	
EDSS 5	-0.020	
EDSS 6	-0.027	
EDSS 7	-0.053	
EDSS 8	-0.107	
EDSS 9	-0.140	
EDSS, Expanded disability status score		

ERG summary

The ERG has concerns with the utilities used in the model. The inclusion of a number of additional disutilities appear selective and opportunistic rather than scientific and robust. First, we consider there to be double counting by including utility decrements for upper limb and fatigue impairment, in addition to utility values for each EDSS level. Second, the proportion of people in each EDSS health state with upper limb impairment or fatigue and cognitive impairment were solely based on clinical expert opinion. Third, we note that hazard ratio for ocrelizumab treatment effect (20% increase in the 9-HPT sustained for 12 weeks) for upper limb impairment was used as a relative risk. Based on the information provided in

Table 16 of the CS, the ERG derived a relative risk of 0.656 (95%CI: 0.413, 1.042). However, it should be noted that this is based on the results for a 20% increase in 9-HPT sustained for 12 weeks. Results are not available for a 20% increase in the 9-HPT sustained for 24 weeks. Fourth, we note that relapses were considered to be an adverse event but a disutility (and costs associated with treatment) was not included in the base-case model.

5.2.10 Resources and costs

Total costs estimated in the model comprised of cost of DMT (drug acquisition, administration and monitoring costs associated with ocrelizumab), cost for the management of adverse events related to treatment and costs for BSC (healthcare, personal and social services costs for each EDSS level).

In the model, the estimated total cost for ocrelizumab is based on treatment, administration, monitoring and treatment of adverse events until people discontinue treatment, after which people are assumed to receive BSC. The estimated total cost for BSC is based on costs associated with EDSS state management and adverse events. The difference in costs between ocrelizumab and BSC is driven by the treatment effect on delaying disability progression to more severe health states between strategies.

- **Ocrelizumab costs**

The drug regimen for ocrelizumab was based on the dosing schedule within the ORATORIO protocol. People randomised to the intervention received 600mg of ocrelizumab by intravenous infusion, administered as two 300-mg infusions 14 days apart. The company presented drug acquisition costs based on a list price of £4,790/vial (leading to a yearly cost of £19,160) and a discounted price of [redacted]/vial (leading to a yearly cost of [redacted]) under the patient access scheme (PAS) approved by the Department of Health. Resource use associated with administration and monitoring was based on the summary of product characteristics and clinical expert opinion, and were valued using unit costs from the National schedule of reference costs [51] and personal and social services research unit costs.[52] Table 24 shows the resource use and costs used to derive unit costs for administration and monitoring. In the first year, ocrelizumab is administered in two separate infusions, over three days. People are assumed to require a MRI scan and a second MRI for 70% of people to identify active T2 lesions. Additionally in the first year, it was assumed that people would require one neurologist and MS nurse visit and needed two full blood count tests, one HBV test and varicella zoster virus test, totalling £1615.18 for drug administration and £509.62 for

monitoring in the first year. In the second year onwards, annual costs for administration and monitoring reduced to £1081.19 and £214.04, respectively because of the assumption that ocrelizumab would be administered over two infusions, but over two days and, no further MRI scans would be required.

Table 24: Cost of drug administration and monitoring associated with ocrelizumab

Cost item	Cost (year 1)	Resource use (year 1)	Cost (year 2+)	Resource use (year 2+)	Source (year 2016/17)
Administration costs	£1,595.67	3x day case (£531.89 each)	£1,061.78	2x day case (£531.89 each)	AA30F. Medical care of patients with multiple sclerosis, with CC score 0-1. Day case.
	£19.41	Methylprednisolone for 1st 3 vials (£17.30) Chlorphenamine 10 mg QD (£1.95) Paracetamol 2x500 mg QD (£0.16)	£19.41	Methylprednisolone for 1st 3 vials (£17.30) Chlorphenamine 10 mg QD (£1.95) Paracetamol 2x500 mg QD (£0.16)	British National Formulary. MIMS.
	£1,615.08	Total	£1,081.19	Total	
Monitoring costs	£236.28	1 MRI for all patients, second MRI needed for 70% of patients to identify active T2 lesions (£146.03 per MRI)	-	-	Weighted average of RD01A and RD04Z. MRI Scan of one area, without contrast, 19 years and over and MRI scan of two or three areas, without contrast. Market research indicated that 30% of patients with PPMS have a recent MRI available (within last 12 months).
	£204.86	1 neurology visit	£152.30	1 neurology visit	WF01B and WF01A. Non-admitted Face to face attendance, first and follow up. 400 Neurology. Consultant led outpatient attendance.
	£55.00	1 MS nurse visit (£110 per hour, half hour visit)	£55.00	1 MS nurse visit (£110 per hour, half hour visit)	Hospital based nurse band 6.
	£6.74	2 full blood counts (£3.37 each)	£6.74	2 full blood counts	DAPS08. Phlebotomy
	£3.37	1 HBV test	-	-	
	£3.37	1 varicella zoster virus test	-	-	
	£509.62	Total	£214.04	Total	

- **Health state costs**

The company undertook a systematic review to identify studies which reported resource use and costs associated with the management and treatment of people with MS. Four studies were identified as potentially relevant,[34, 37, 48, 53] with one being considered appropriate for this submission.[34] Briefly, Tyas et al.[34] undertook a cost analysis to assess the costs associated with treating people with MS. The authors used a survey to capture the resource use information, and assigned unit costs to derive the cost per person per year from payer and societal perspectives. The survey collected information on age, sex, marital status, education, disease status (RRMS, PPMS or SPMS), relapse status within three months of the survey, number of years since diagnosis, disability level (EDSS 0 to 9) and DMTs. The authors conducted an independent multivariate linear regression of the cost categories by using a step-down approach until only statistical significant ($p < 0.05$) covariates remained. These cost categories were stratified by direct government-funded costs (direct annual medical/non-medical cost coefficients funded by UK government) and direct out-of-pocket (direct annual medical and non-medical cost coefficients funded out-of-pocket) and indirect costs. From the 12,698 surveys mailed, 2508 (19.3%) MS patients responded, of which 2,048 (15.8%) were included in the analysis. Results showed that for direct medical costs funded by the government for levels up to EDSS 4 were not statistically significant from zero, but from EDSS ≥5 reached statistical significance. All non-medical costs funded by the government reached statistical significance for all EDSS levels except EDSS zero. Table 25 shows the direct costs obtained from Tyas et al. The company further adjusted these costs and assumed that 25% of direct non-medical costs are funded by the NHS and PSS. All costs were inflated to current prices using the hospital and community health pay and price index.[54]

Table 25: Summary of costs reported in Tyas et al. and inflated to current prices

EDSS levels	Annual cost (£, 2005)		Annual cost (£, 2016/17)		
	Direct medical costs	Direct non-medical costs	Direct medical costs	Direct non-medical costs a	Total costs
EDSS 0	250	2536	313.72	795.59	1109.31
EDSS 1	85	3462	106.66	1086.10	1192.76
EDSS 2	213	4414	267.29	1384.76	1652.05
EDSS 3	850	6212	1066.65	1948.82	3015.47
EDSS 4	806	4028	1011.43	1263.66	2275.09
EDSS 5	1419	6333	1780.67	1986.78	3767.46
EDSS 6	2162	6580	2713.05	2064.27	4777.32
EDSS 7	6583	10,808	8260.86	3390.68	11, 651.54
EDSS 8	10,761	15,339	13,503.74	4812.14	18, 315.88
EDSS 9	15,121	10,161	18,975.00	3187.70	22, 162.71
a Assumed that 25% of direct non-medical costs are borne by the PSS and inflated using PSSRU (Curtis and Burns 2017)[52]					

- **Cost for treating adverse events**

Costs for the treatment of adverse events were included in the model. Adverse event management costs were included for infusion related reactions, malignancies and upper respiratory tract infections, categorised as non-serious and serious events. Details of the resource use and costs for treatment are presented in Table 26. Resource and costs for infusion related reaction and upper respiratory tract infection were obtained from the alemtuzumab and daclizumab appraisals undertaken in people with relapsing remitting multiple sclerosis, and malignancies were obtained from the literature using breast cancer as a proxy. Though not explicitly stated by the company it was assumed that there were no resource use and costs related to the treatment of people who experience non-serious infusion related reactions. It was also assumed that people with non-serious malignancies did not receive chemotherapy treatment. The company derived an average cost for the treatment for each adverse event based on a proportion of 79.6% of people with non-serious and 20.4% of people experiencing serious adverse events as seen in the ORATORIO trial. These weights were applied to the costs obtained from the appraisals and literature, but were not inflated to current prices. The company assumed that inflating these costs would have a negligible impact on the results.

Table 26: Costs associated with treating adverse events

Adverse event	Non-serious		Serious		Average cost
	Cost (£)	Resource use	Cost (£)	Resource use	
Infusion related reaction	0	None	65.00	1 GP consultation	13.26
Malignancies	10,768	GP, nurse, hospitalisation and radiotherapy	22,980	GP, nurse, hospitalisation, chemotherapy, radiotherapy	13,328
Upper respiratory tract infection	65.00	1 GP consultation	65.00	1 GP consultation	65.00

ERG summary

The company provided details on the resource use and costs associated with treating adverse events. Costs associated with treating adverse events were obtained from recent submissions and the literature, but these were not inflated to current prices as it was assumed that uprating costs would have little impact on the results. The ERG has no concerns relating to the unit costs and the assumptions made.

5.2.11 Overview of model assumptions and ERG critique

In Table 27 we present the company's key modelling assumptions with comments from the ERG.

Table 27: Model assumptions with ERG's comments

Assumption	Justification	ERG's comments
The population in ORATORIO is representative of UK population with early and active PPMS	The ORATORIO studies included 5 UK trial sites across the country. The randomised control period of the ORATORIO study ran from 2011 - 2015. It is therefore considered reflective of patients with early PPMS with inflammatory activity in the UK today.	The ERG's clinical experts do not consider the population of the ORATORIO trial to be generalizable to the UK population of 'early' PPMS (see critique of the decision problem in section 3.1). Moreover, the treatment effect is applied to a proportion of people with PPMS in the MSBase natural history cohort, of which 27 people were from the UK.

Treatments effect is applied to EDSS progression but not regression	Treatment effect is only applied to EDSS progression; i.e. active treatment slows disease progression. This is in line with previous appraisals in RRMS.	The ERG considers this to be a reasonable assumption.
Patients with PPMS can improve EDSS (backward transitions)	EDSS improvements are observed in the raw data from the MSBase registry. Clinical opinion suggests that small improvements may occur at the lower end of the EDSS scale, but large improvements or improvements at the higher end of the scale would not be plausible in PPMS. Scenario analysis is included with the MSBase transition matrices constrained to allow progression only. No treatment effect is applied to EDSS improvements.	There were some large improvements at the higher end on the EDSS, which the ERG queried (see section 5.2.6), which gives rise to the plausibility. The ERG agree that the treatment effect should only be applied to forward transitions.
Upper limb function is not adequately captured by EDSS	Upper limb function is increasingly recognized as an important disease facet and component of disability in MS [21, 55]. Regression analysis of EQ-5D data in the ORATORIO study indicated that clinically meaningful upper limb dysfunction (as measured by 20% increase in 9-HPT sustained for 12 weeks) impacted EQ-5D independent of EDSS. It was therefore considered valid to apply disutilities and treatment effect of ocrelizumab on slowing of upper limb impairment. Upper limb impairment could have implications for the cost of disease management, but no data is available in the literature. The full benefits of preserving upper limb function in terms of utilities and costs are therefore likely under-estimated in the economic analysis.	There were some concerns regarding the choice of outcomes, the use of post-hoc selected outcomes from exploratory analyses, potential of double counting of utilities, and the hazard ratio used to show the treatment effect of a reduction in the proportion of people with upper limb impairment in ocrelizumab compared to BSC. See section 5.2.9
Impact of fatigue on functioning is not adequately captured by EDSS	Fatigue is a common symptom of MS and its impact on physical, cognitive, and psychosocial functioning is increasingly recognized [56]. Regression analysis of EQ-5D data in the ORATORIO study indicated that clinically meaningful fatigue (as measured by MFIS score >38)	As acknowledged by the company, cut-offs are not commonly used with fatigue scales and have not been extensively researched in PPMS. We note that the baseline mean score for fatigue

	impacted EQ-5D independent of EDSS. It was therefore considered valid to apply disutilities and treatment effect of ocrelizumab on reducing fatigue.	was 41.6, indicating people were fatigued in the trial. See section 5.2.9
No direct treatment effect on mortality	Literature has demonstrated that the risk of death is primarily dependent on the level of disability (EDSS). The duration of clinical trials in MS is not long enough to detect a direct impact of treatment on mortality. Instead, treatment influences mortality indirectly by slowing of disability progression. This approach is in line with previous RRMS appraisals.	Whilst the ERG consider there to be no direct benefit on mortality, there is some impact indirectly as a result of delaying disability progression.
Increasing rate of all-cause treatment withdrawal	Extrapolating an increasing rate of long-term all-cause discontinuation was supported by model fit statistics for the Gompertz function, and by clinical opinion. Clinical opinion considered patient expectations to play a key role in treatment withdrawal. The benefits of slowing disability progression may not appear immediately tangible to patients as the natural history of PPMS is highly variable on an individual patient level. Therefore, the real world treatment withdrawal rates are assumed to be higher than those observed during the trial.	The ERG agrees that it is reasonable to assume that treatment withdrawal rates may be higher than observed in the clinical trial.
No treatment waning for ocrelizumab	Long-term waning of treatment effect with DMTs has not been definitively proven nor disproven, and remains an area of debate. Open label extension data of up to four years is available for ocrelizumab in RRMS and demonstrates sustained treatment effect across CDP and MRI outcomes (see Appendix M). Open label extension data from ORATORIO in PPMS is yet to read out but there is no reason to believe the results are different from RRMS. Treatment waning is biologically implausible with ocrelizumab as it generates negligible neutralising	See Section 5.2.6. The ERG's base-case analysis includes a treatment waning effect for ocrelizumab.

	antibodies, unlike other DMTs used in RRMS (see Section B.2.10.8).	
Cost of disease management by health state	The cost of disease management per EDSS health state was based on estimates derived from RRMS patients. This was considered appropriate as application of the reported PPMS decrement would have resulted in negative costs for EDSS 0-5, which clinical experts deemed implausible. Clinical opinion supported the assumption that disease management costs are driven by level of disability (EDSS) and not by disease type.	Reasonable assumption
Drug related AEs	Many of the reported AEs in ORATORIO occurred at similar or higher frequency in the placebo arm than ocrelizumab arm, and were considered to be disease-related symptoms. In order to avoid double-counting of costs and disutilities already accounted for in the EDSS health states, only AEs with considerably higher frequency in the ocrelizumab arm were included in the model. AEs were assumed to be similar in the ITT, MRI active, and MRI active ≤50 populations.	Reasonable assumption

5.2.12 Cost effectiveness results

The company reports deterministic base-case and probabilistic results, as well as sensitivity analysis results for the comparison between ocrelizumab and BSC. Results are presented for the MRI active (base-case), and MRI active ≤ 50 years subgroup, based on the list price and the approved discounted price of ocrelizumab (approved PAS). Outcomes are reported in terms of LYG and QALYs and the results reported in the form of an ICER expressed as cost per QALY. Below we present the results (deterministic, probabilistic and sensitivity analysis) for the MRI active and MRI active ≤ 50 subgroups (as presented by the company) using the list price and the approved PAS.

5.2.12.1 Company's base case and probabilistic results

- **MRI active patients with list price for ocrelizumab**

Table 28: Deterministic results, company base case using the list price

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Cost per QALY probabilistic sensitivity analysis (PSA) results were higher than those of the deterministic analysis, which suggests that the deterministic results may not be robust to uncertainty in model input parameters. It should be noted that the company has not provided any comments on the discrepancy between deterministic and PSA values.

Table 29: Probabilistic sensitivity analysis, company base case using the list price

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Probabilistic sensitivity analysis was undertaken for the outcome cost per QALY only. For each simulation for the incremental costs and incremental QALYs for ocrelizumab and BSC was graphed/plotted on a cost-effectiveness plane (Figure 8), along with the respective cost-effectiveness acceptability curve (Figure 9). For the 1000 runs of the Monte Carlo simulation, the scatterplot shows considerable uncertainty around the incremental QALYs, and less so for the incremental costs. This may be a result of the company assuming some costs, or resource use estimates used to derive costs, to be constant/fixed. In Figure 8, it can be seen that majority of the simulations are in the north-east quadrant suggesting that ocrelizumab is more costly and effective than BSC. However, some of the simulations are in the north-west quadrant, signifying that BSC dominated ocrelizumab.

Figure 8: Cost-effectiveness plane, company base case using the list price

Figure 9 shows the probabilistic sensitivity analysis and the results are presented in the form of a cost-effectiveness acceptability curve. The curve shows the proportion of simulations in which ocrelizumab is cost-effective at different WTP thresholds for a QALY. At a WTP threshold of £30,000 per QALY there is a zero probability of ocrelizumab being cost-effective when compared to BSC.

Figure 9: Cost-effectiveness acceptability curve, company base case using the list price

- **MRI active patients with discounted price of ocrelizumab (approved PAS)**

Applying the agreed discount to the list price of ocrelizumab leads to a reduction in the expected mean costs. Results in Table 30 showed that the ICER is approximately £88,000. Results generated from the PSA showed that the ICER is approximately £93,900 (Table 31).

Table 30: Deterministic results, company base case under the approved PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	88,214
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Table 31: Probabilistic sensitivity analysis, company base case under the approved PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	93,949
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Figure 10 shows that majority of the simulations are in the north-east quadrant suggesting that ocrelizumab is more costly and effective than BSC but, some simulations suggest that BSC dominated ocrelizumab. In Figure 11, at a WTP threshold of £30,000 per QALY there is a zero probability of ocrelizumab being cost-effective when compared to BSC.

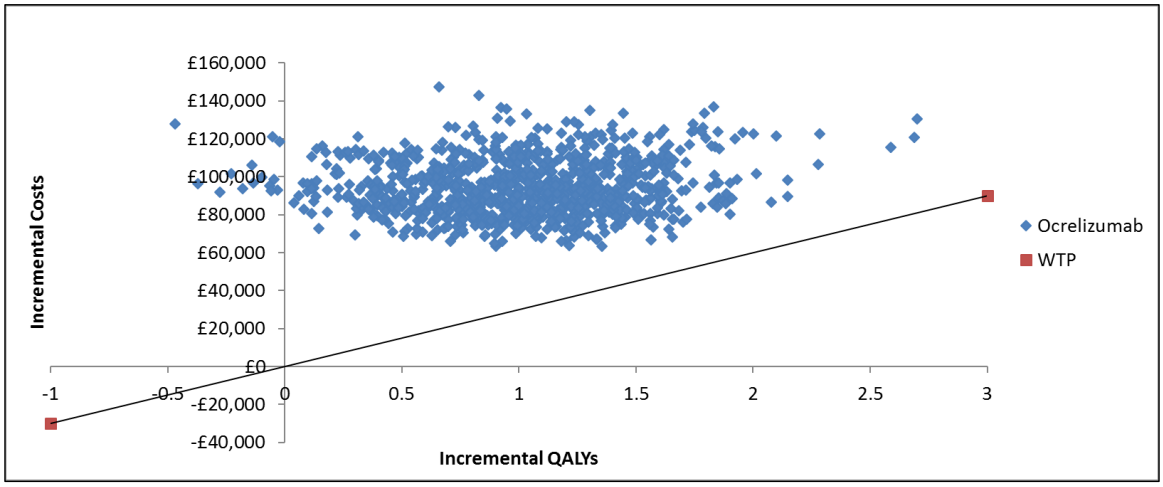

Figure 10: Cost-effectiveness plane, company base case under the approved PAS

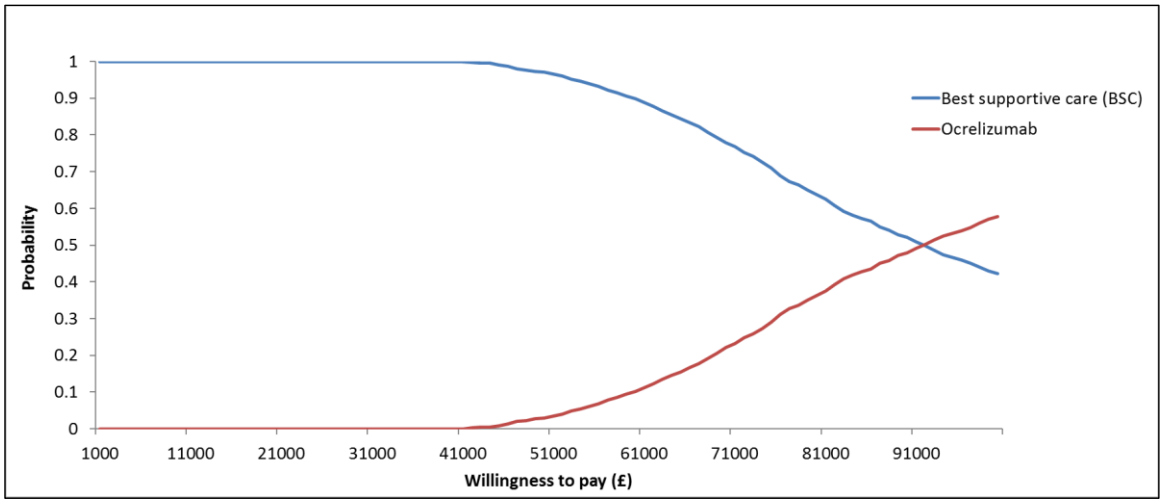

Figure 11: Cost-effectiveness acceptability curve, company base case under the approved PAS

Subgroup analysis

The company provided results for a subgroup analysis based on the MRI active ≤ 50 years. The ERG has critiqued this subgroup analysis in section 4.5.1.3. Estimating the cost-effectiveness in this subgroup involved deriving a separate transition probability matrix based on transitions observed in people from the MSBase registry with baseline age of ≤ 50 years and using CDP-12 hazard ratio 0.55 (95%CI: 0.36, 0.85) specific to this subgroup. All other inputs are assumed to apply to this subgroup.

- **MRI active ≤ 50 years subgroup, with list price for ocrelizumab**

Table 32 and Table 33 show the deterministic and probabilistic results, respectively, for the subgroup of adults with MRI activity aged ≤ 50 years. Deterministic results shows that ocrelizumab is approximately [redacted] more costly and expected to yield [redacted] more QALYs than BSC, equating to an ICER of approximately [redacted] per QALY.

Table 32: Deterministic results, MRI active ≤ 50 years using the list price

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Incorporating joint parameter uncertainty in the form of a probabilistic analysis showed that the ICER is higher than reported in the deterministic results. The results showed that ocrelizumab is approximately [redacted] and expected to yield [redacted] more QALYs, with an ICER of approximately [redacted] per QALY.

Table 33: Probabilistic sensitivity analysis, MRI active ≤ 50 years using the list price

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Figure 12 and Figure 13 show the scatterplot and the cost-effectiveness acceptability curve for ocrelizumab compared to BSC for the MRI active ≤50 years subgroup, with the list price. In Figure 12, it can be seen that majority of the simulations are in the north-east quadrant suggesting that ocrelizumab is more costly and effective than BSC. In Figure 13, at a WTP threshold of £30,000 per QALY there is zero probability of ocrelizumab being cost-effective when compared to BSC.

Figure 12: Cost-effectiveness plane, MRI active ≤ 50 years using the list price

Figure 13: Cost-effectiveness acceptability curve, MRI active ≤ 50 years using the list price

- **MRI active ≤ 50 years subgroup, with discounted price for ocrelizumab (approved PAS)**

Table 34 and Table 35 show the deterministic and probabilistic results, respectively, for the subgroup of adults less than or equal to 50 years with MRI activity, with discounted price for ocrelizumab. Deterministic results shows that ocrelizumab is approximately [redacted] more costly and expected to yield [redacted] more QALYs than BSC, equating to an ICER of approximately [redacted] per QALY.

Table 34: Deterministic results, MRI active ≤ 50 years under the approved PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]		-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	54,486
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Incorporating joint parameter uncertainty in the form of a probabilistic analysis showed that the ICER is higher than reported in the deterministic results. The results showed that ocrelizumab is approximately [redacted] and expected to yield [redacted] more QALYs, with an ICER of approximately [redacted] per QALY.

Table 35: Probabilistic sensitivity analysis, MRI active ≤ 50 years under the approved PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	61,241
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Figure 14 and Figure 15 show the scatterplot and the cost-effectiveness acceptability curve for ocrelizumab compared to BSC for the MRI active ≤50 years subgroup, with the PAS. In Figure 14, it can be seen that majority of the simulations are in the north-east quadrant suggesting that ocrelizumab is more costly and effective than BSC. In Figure 15, at a WTP threshold of £30,000 per QALY there is zero probability of ocrelizumab being cost-effective when compared to BSC.

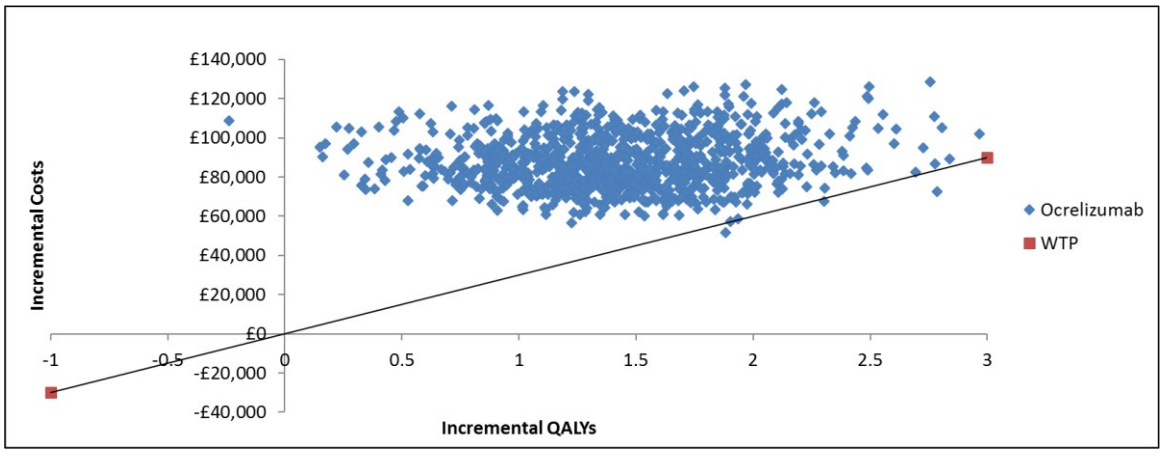

Figure 14: Cost-effectiveness plane, MRI active ≤ 50 years under the approved PAS

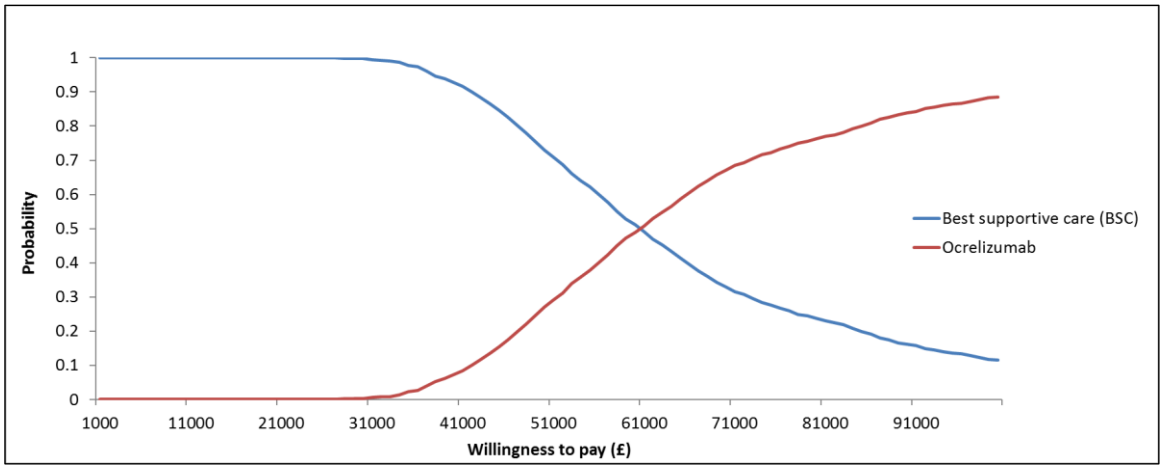

Figure 15: Cost-effectiveness acceptability curve, MRI active ≤ 50 years under the approved PAS

5.2.12.2 Sensitivity analyses

The company undertook deterministic one-way sensitivity analyses by varying inputs it identified as important using 95% confidence limits or by assuming a ±20% of the mean where confidence intervals were unavailable. The inputs with the most impact on the net monetary benefit were plotted on a tornado diagram. Figure 16 and Figure 17 shows the results using the list price and the discounted price under the PAS in the MRI active group.

Figure 16: One-way sensitivity analysis for ocrelizumab versus best supportive care, using the list price

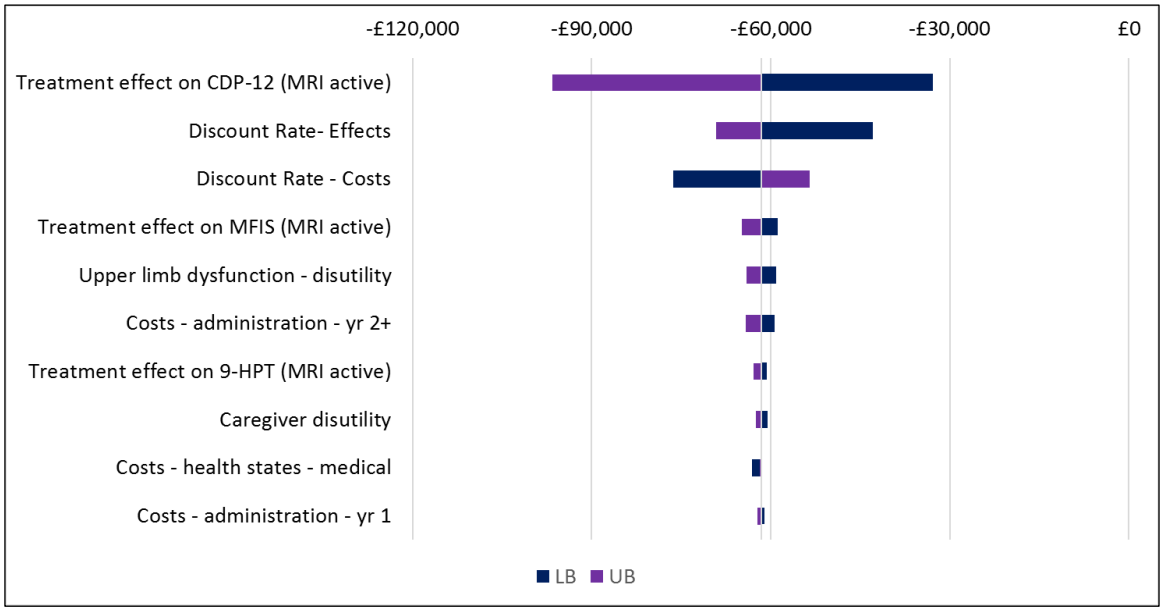

Figure 17: One-way sensitivity analysis for ocrelizumab versus best supportive care, using approved PAS price

Both figures show that varying the treatment effect of CDP-12 had the greatest impact. Results were also sensitive to variation in the annual discounting rate for costs and effects.

5.2.12.3Model validation and face validity check

The company stated that two validity checks (implementation of calculations and testing of extreme values) of the economic model were performed externally.

Face validity checks of model structure, inputs and results were tested by an advisory board consisting of clinical and health economic experts from the UK. The submission further compared the results from an ITT population with those reported by the Institute for Clinical and Economic Review and also highlighted the differences between these two analyses:

- *It utilises ITT data from the ORATORIO study*
- *It applies natural history based on SPMS patients from the London Ontario registry which does not allow EDSS improvements*
- *It does not incorporate upper limb and fatigue, and*
- *It applies utilities based on SPMS sourced from literature and US specific costs*

Table 36 shows the comparison of the company's results, presented in terms of expected mean QALYs and those presented by the Institute for Clinical and Economic Review.[35]

Table 36: Comparison of the QALYs generated by each model

Strategy	**Company submission, expected mean QALYs**	**US model, expected mean QALYs**
BSC	[redacted]	2.75
Ocrelizumab	[redacted]	3.33
Incremental QALYs	[redacted]	0.58
BSC, best supportive care; QALYs, quality adjusted life years; United States		

The company's results presented here are based on:

- ITT data
- MSBase registry
- Utility values from Orme et al. (2007)[1]
- Excludes utility decrements for upper limb impairment and fatigue

5.3 Exploratory and sensitivity analyses undertaken by the ERG

5.3.1 ERG's individual parameter changes to the Company's case base

Based on the ERG's concerns, we have used a modified version of the company's base-case model to undertake exploratory analyses, by incorporating the following changes/assumptions:

- SA1: Efficacy set to CDP-24 for the unextended treatment controlled period (minimum of 120 weeks of double-blinded controlled period)
- SA2: 50% decrease in the effectiveness from 5 years onwards
- SA3: Increase in annual discontinuation rate from 5 years onwards such that the average time spent in treatment beyond 5 years was reduced to 50%
- SA4 (SA2+SA3): 50% decrease in the effectiveness from 5 years onwards and an increase in annual discontinuation rate from 5 years onwards such that the average time spent in treatment beyond 5 years was reduced to 50%
- SA5: Excluding utility decrements for upper limb impairment
- SA6: Excluding utility decrements for fatigue and cognitive impairment
- SA7: Relative risk for 20% increase in 9-HPT sustained for 12 weeks
- SA8: Including costs, disutilities and treatment effect associated with relapses

In our exploratory analyses we present the results based on each change made. Deterministic analysis results are presented for the MRI active group, using the list price as well as the discounted price for ocrelizumab under the approved patient access scheme. Details of changes made to the Excel model are presented in appendix 1.

- **SA1: Efficacy set to CDP-24 for un-extended treatment controlled period (minimum of 120 weeks of double-blinded controlled period)**

The base-case model uses transition probabilities to show the transitions between EDSS states, which are based on the MSBase natural history cohort. In the base-case, the company uses a hazard ratio based on CDP-12 to reflect the treatment effect of ocrelizumab on disease progression. Our clinical experts suggested that a hazard ratio based on CDP-24 is of more clinical relevance. Therefore, in these analyses, we used the hazard ratio of 0.71 (95%CI: 0.47, 1.06) to estimate the impact on the company's base-case results. Results in Table 37 and Table 38

show a marginal increase in the incremental costs and a reduction in the incremental QALYs, with both ICERs increasing.

Table 37: Deterministic results, SA1 using the list price

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Table 38: Deterministic results, SA1 under the approved PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	97,625
ICER, incremental life years gained; QALY, quality adjusted life years gained					

- **SA2: 50% decrease in the effectiveness (by changing the HR from 0.71 to 0.86) from 5 years onwards**

We have undertaken a scenario analysis that assumes a 50% reduction in the treatment efficacy (by changing the HR from 0.71 to 0.86) from five years onwards, as a sustained treatment benefit is unlikely. This reduction resulted in a reduction in the expected mean QALYs gained, thus leading to an increase in the ICER (see Table 39 and Table 40).

Table 39: Deterministic results, SA2 using the list price

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Table 40: Deterministic results, SA2 under the approved PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	116,550
ICER, incremental life years gained; QALY, quality adjusted life years gained					

- **SA3: Increase in annual discontinuation rate**

The ERG undertook a scenario analysis assuming an increase in the annual discontinuation rate such that the average time spent in treatment beyond 5 years was reduced to 50%. The effect of applying this correction in discontinuation trajectory is illustrated in Figure 18.

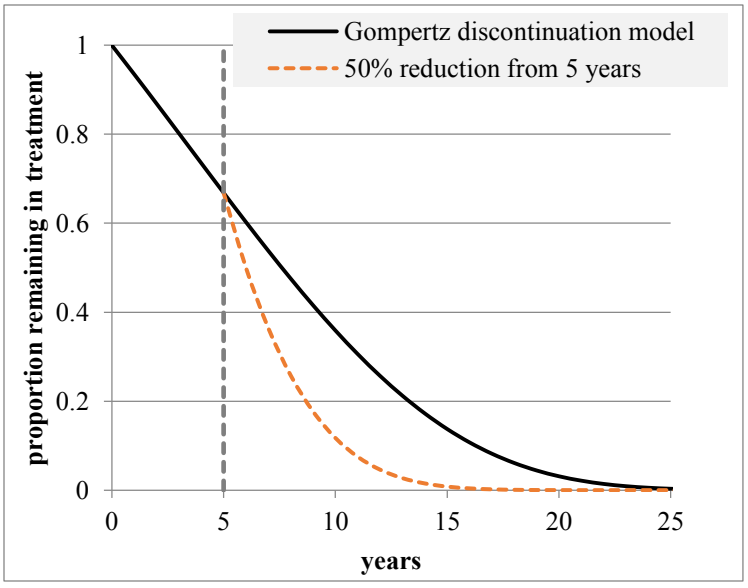

Figure 18: Illustration of the scenario assuming an increase in the annual discontinuation rate such that the average time spent in treatment beyond 5 years is reduced to 50%

As expected, this increase resulted in a decrease in the expected mean costs and a reduction in QALYs, with ICERs lower than seen in the base-case (see Table 41 and Table 42).

Table 41: Deterministic results, SA3 using the list price

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Table 42: Deterministic results, SA3 under the approved PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	84,239
ICER, incremental life years gained; QALY, quality adjusted life years gained					

- **SA4 (SA2+SA3): 50% decrease in the effectiveness from 5 years onwards and an increase in annual discontinuation rate**

This analysis assumes that from year 5 onwards, treatment efficacy reduces by 50%; that is ocrelizumab becomes less effective in delaying progression. Additionally, we assumed that as the treatment effect decreases, more people are likely to discontinue treatment. Including treatment waning has been applied in recent MS-drug appraisals.

Table 43: Deterministic results, SA4 using the list price

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Table 44: Deterministic results, SA4 under the approved PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	104,697
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Applying a treatment waning effect and an increase in annual discontinuation resulted in an ICER of approximately [redacted] per QALY gained (see Table 43). The PAS-adjusted finding was similarly increased above the company baseline PAS-adjusted model (see Table 44).

- **SA5: Excluding utility decrements for upper limb impairment**

Details of our concerns relating to utility decrement for upper limb impairment as well as utility decrements for fatigue are presented in section 5.2.9. Excluding these decrements individually resulted in an increase to the ICERs (Table 45 and Table 46 for SA5 and Table 47 and Table 48 for SA6).

Table 45: Deterministic results, SA5 using the list price

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Table 46: Deterministic results, SA5 under the approved PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	98,038
ICER, incremental life years gained; QALY, quality adjusted life years gained					

- **SA6: Excluding utility decrements for fatigue**

Table 47: Deterministic results, SA6 using the list price

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Table 48: Deterministic results, SA6 under the approved PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	95,696
ICER, incremental life years gained; QALY, quality adjusted life years gained					

- **SA7: Relative risk for 20% increase in 9-HPT sustained for 12 weeks**

In the company base-case a hazard ratio of 0.52 is used as though it is a relative risk. The hazard ratio of the two hazard rates, where the hazard rates are the transition probabilities and not a proportion of people in a health state. Hence, the treatment effect in their base case is likely exaggerated for upper limb deterioration. We derived a relative risk of 0.656 (95% CI: 0.413, 1.042) for upper limb impairment. Based on this changed resulted in an ICER of approximately [redacted] and [redacted] per QALY gained, using the list price and PAS, respectively. It should be noted that the ERG would have preferred to undertake an analysis that is based on a relative risk for 20% increase in 9-HPT sustained for 24 weeks but these data were not available.

Table 49: Deterministic results, SA7 using the list price

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Table 50: Deterministic results, SA7 under the approved PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	89,827
ICER, incremental life years gained; QALY, quality adjusted life years gained					

- **SA8: Including costs and disutilities associated with relapses**

This analysis includes the costs incurred for treatment and disutilities associated with relapses. The inclusion of outcomes related to relapses better reflects the events that may occur. Given that

the occurrence of relapses is rare in people living with PPMS, there is a negligible change to the ICERs (Table 51 and Table 52).

Table 51: Deterministic results, SA8 using the list price

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Table 52: Deterministic results, SA8 under the approved PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	88,047
ICER, incremental life years gained; QALY, quality adjusted life years gained					

ERG summary

We have outlined our concerns that relate to the inputs/assumptions used in the company's base-case and have addressed them. In these analyses, we explored the impact of each change to company's deterministic base-case ICER while all other inputs/assumptions remained constant. Results are presented for using the list price for ocrelizumab as well as the approved PAS.

5.3.2 ERG's preferred base case and sensitivity analyses

The ERG preferred base-case includes the following changes:

- Efficacy set to CDP-24 for un-extended treatment controlled period (minimum of 120 weeks of double-blinded controlled period)
- 50% decrease in treatment efficacy from 5 years onwards and an increase in annual discontinuation rate from active treatment such that the average time spent in treatment beyond 5 years was reduced to 50%
- Excluding utility decrements for upper limb impairment
- Excluding utility decrements for fatigue
- Including costs, disutilities, and treatment effect associated with relapses

The summary of the ERG's base case and scenario analyses with justifications to changes made to the company's base-case is provided in Table 53.

Deterministic and probabilistic sensitivity analysis results are presented for the MRI active population using the list price and under the approved PAS. Deterministic one-way sensitivity analysis was performed using the 95% confidence estimates to explore the effect of this variability on the ICER. We further undertook scenario analyses using our base-case model:

- Efficacy set to CDP-12 for un-extended treatment controlled period (minimum of 120 weeks of double-blinded controlled period)
- Efficacy set to CDP-12 for extended treatment controlled period
- No waning
- 50% decrease in treatment efficacy from year 5 onwards
- Increase in annual discontinuation rate such that the average time spent in treatment beyond 5 years was reduced to 50%
- MRI active ≤50 years subgroup
- Using utility values reported by Orme et al. (2007)[1]
- Inclusion of utility decrements for upper limb function
- Inclusion of utility decrements for fatigue
- Inclusion of utility decrements for upper limb function and fatigue
- Exclusion of costs and disutilities associated with relapses

Table 53: ERG base-case and scenario analyses with justifications

Model inputs	Options for inputs	Company's base case	ERG's preferred base case	*ERG's scenario analyses*	ERG's justification
Cost of ocrelizumab	List price	✓	✓		-
	Approved PAS	✓	✓		
Disability progression endpoint	CDP-12	✓		✓	24-CDP has more clinical relevance (see section 4.3)
	CDP-24		✓		
Time point for disability progression	Un-extended (120 weeks)	✓	✓		The extended controlled treatment period is at risk of bias (patients were progressively un-blinded) – see section 4.4
	Extended			✓	
Inclusion of waning effect	Yes		✓		Sustained treatment benefit is unlikely, base case used in MS related STA including ocrelizumab in RRMS – See section 5.2.6
	No	✓		✓	
Modality of waning effect	50% decrease in the effectiveness from 5 years + increase of discontinuation rate such that the average time spent in treatment beyond 5 years is reduced to 50%	NR	✓		
	50% decrease in the effectiveness from 5 years			✓	
	Increase of discontinuation rate such that the average time spent in treatment beyond 5 years is reduced to 50%			✓	
Population	MRI active	✓	✓		Most of the ITT population does not match with the label indication (see section 3.1)
	MRI active ≤ 50 years			✓	Raises major equality issues, moreover the respective role of MRI activity and younger age in inducing a greater benefit is unclear (see sections 3.1 and 4.5.1.3)

Model inputs	Options for inputs	Company's base case	ERG's preferred base case	*ERG's scenario analyses*	ERG's justification
EDSS utilities	ORATORIO trial	✓	✓		See section 5.2.9 for justifications
	Orme et al. (2007)[1]			✓	
Inclusion of disutilities for fatigue	Yes	✓		✓	
	No		✓		
Inclusion of disutilities for reduction in increase of 9-HPT (upper limb function)	Yes	✓		✓*	
	No		✓		
Include costs, disutilities and treatment effect associated with relapses	Yes		✓		
	No	✓		✓	

9-HPT, nine-hole peg test; CDP, confirmed disability progression; EDSS, expanded disability status score; EQ-5D, euroQol five dimensions; ERG, evidence review group; Gd, gadolinium; HR, hazard ratio; ITT, intention-to-treat; MRI, magnetic resonance imagining; MS, multiple sclerosis; PAS, patient access scheme; RRMS, relapsing remitting multiple sclerosis; STA, single technology assessment;
* this scenario analysis also includes the use of an imputed relative risk for 20% increase in 9-HPT

- **Base case deterministic results and probabilistic sensitivity analysis (list price):**

Results in Table 54 show that ocrelizumab is expected to cost approximately [redacted] more than BSC and expected to yield [redacted] QALYs, with an ICER of approximately [redacted] per QALY gained. The ICER based on the probabilistic results (Table 55) is higher than the ICER based on the deterministic results. The discrepancy arises as the PSA provides a lower average incremental QALY estimate, although the cause of this is uncertain.

Table 54: Deterministic results, ERG base case using the list price

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Table 55: Probabilistic sensitivity analysis, ERG base case using the list price

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Results for 1000 runs of the Monte Carlo simulation (see Figure 19) show considerable uncertainty about the incremental QALYs, and less so for the incremental costs. Figure 20 shows the results of the probabilistic sensitivity analysis presented in the form of cost-effectiveness acceptability curve for the comparison between ocrelizumab and BSC. At a WTP threshold of £30,000 per QALY, 0% of the simulations were below this threshold. It should also be noted that a proportion of simulations are in the north-west quadrant, which signifies that BSC dominated treatment with ocrelizumab.

Figure 19: Cost-effectiveness plane, ERG base case using the list price

Figure 20: Cost-effectiveness acceptability curve, ERG base case using the list price

- **<u>One-way sensitivity analysis (list price):</u>**

Results for the one-way sensitivity analysis are presented in Figure 21. These results are based on a net-monetary benefit (NMB) approach, with a WTP of £30,000. These results show that CDP-24 had the greatest impact on the ICER.

Figure 21: One-way deterministic results on the ERG base-case, using list price

- **Base case deterministic results and probabilistic sensitivity analysis (approved PAS price):**

Under the approved PAS, results in Table 56 show that ocrelizumab is expected to cost approximately [redacted] more than BSC and expected to yield [redacted] QALYs, with an ICER of approximately [redacted] per QALY gained.

Table 56: Deterministic results, ERG base case under the approved PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	145,717
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Table 57: Probabilistic sensitivity analysis, ERG base case under the approved PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	157,164
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Similar results are seen in Figure 22 and Figure 23, when applying the discounted price for ocrelizumab. Results show that there is some uncertainty about the incremental QALYs, and less so for the incremental costs. In Figure 23, at a WTP threshold of £30,000 per QALY, 0% of the simulations were below this threshold. It should also be noted that a proportion of simulations are in the north-west quadrant, which signifies that BSC dominated treatment with ocrelizumab.

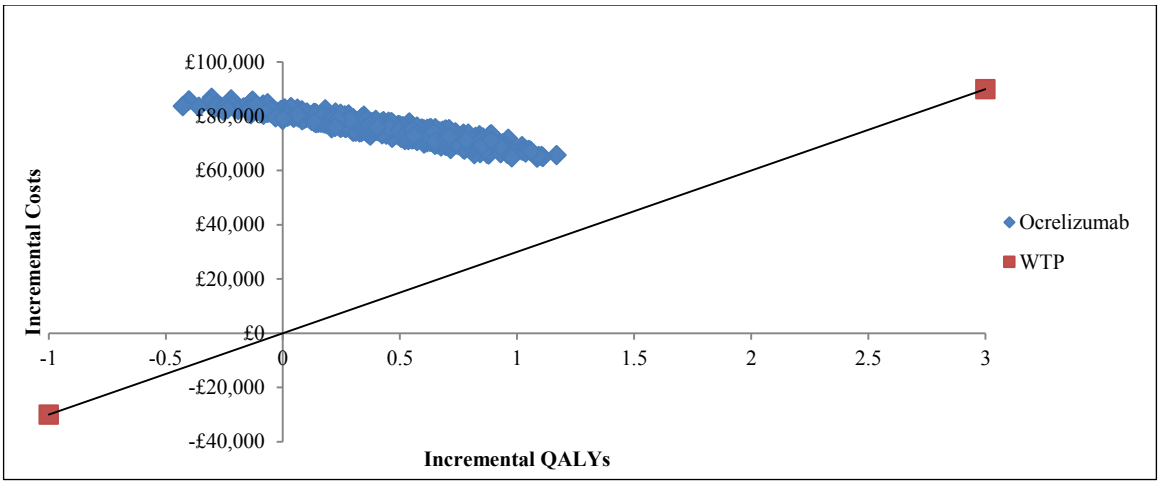

Figure 22: Cost-effectiveness plane, ERG base case under the approved PAS

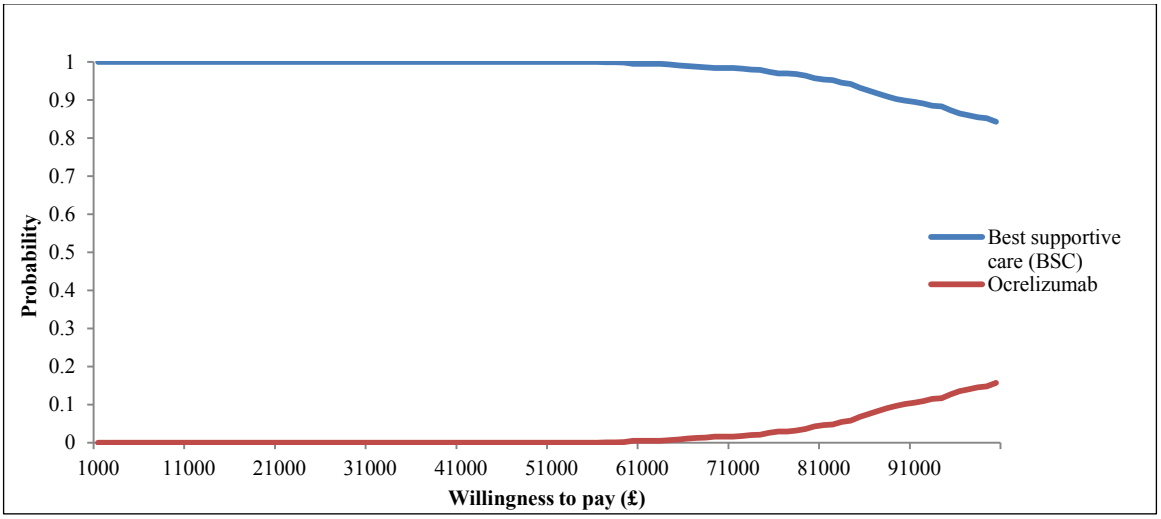

Figure 23: Cost-effectiveness acceptability curve, ERG base case under the approved PAS

- **One-way sensitivity analysis (approved PAS price):**

Results for the one-way sensitivity analysis are presented in Figure 24. These results show that CDP-24 had the greatest impact on the ICER.

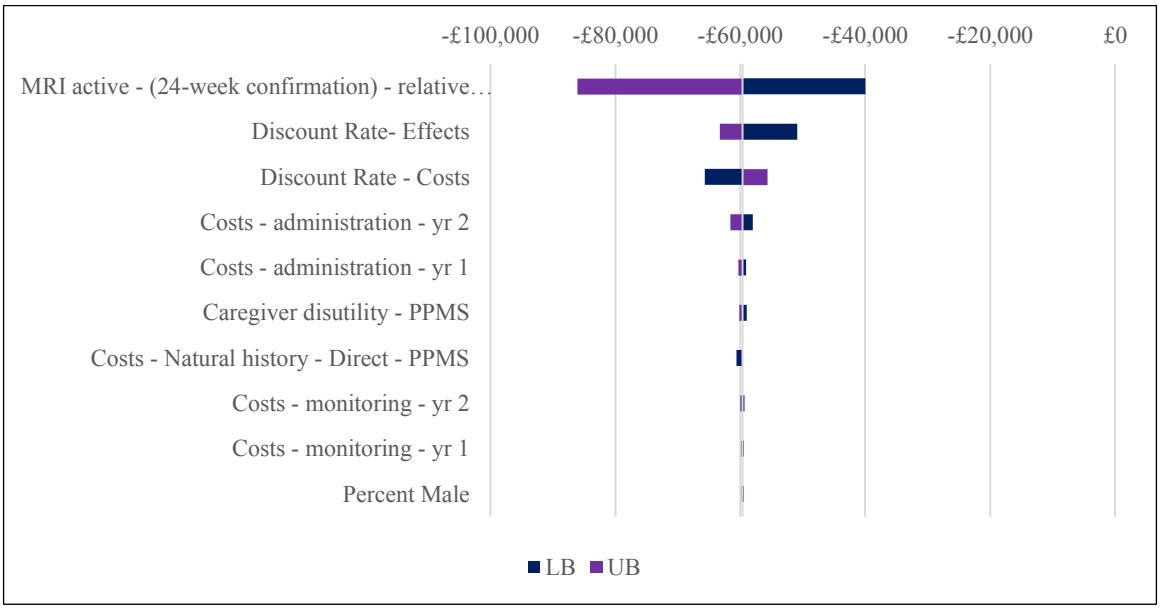

Figure 24: One-way deterministic results on the ERG base-case, under the approved PAS

- **Scenario analysis results (with list and approved PAS prices)**

In Table 58 and Table 59, we present the scenario analysis results undertaken on our preferred base-case, using the list price and the PAS, respectively. These results show the impact of each change to our preferred base-case ICER while all other inputs/assumptions remain constant. Using the list price, and changing the subgroup to MRI active ≤ 50 years had the greatest impact to our ICER, with a reduction from approximately [redacted] to [redacted] per QALY gained. Likewise, in Table 59, using the PAS and changing the subgroup to MRI active ≤ 50 years lead to a reduction of the ICER.

Table 58: Scenario analysis results based on individual changes made to ERG base-case, using the list price

Model inputs	Incremental costs	Incremental QALYs	Incremental LYGs	ICER (cost per QALY)	Impact on the ICER
ERG base-case results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analyses undertaken by the ERG					
Efficacy set to CDP-12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No waning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50% decrease in effectiveness from 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increase in annual discontinuation rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRI active ≤50 years subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility values from Orme et al. (2007)[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including utility decrements for upper limb impairment*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including utility decrements for fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including utility decrements for limb impairment and fatigue*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding costs and disutility for relapses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CDP, confirmed disability progression; CS, company submission; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life years gained

* this scenario analysis also includes the use of an imputed relative risk for 20% increase in 9-HPT

Table 59: Scenario analysis results based on individual changes made to ERG base-case, under the approved PAS

Model inputs	Incremental costs	Incremental QALYs	Incremental LYGs	ICER (cost per QALY)	Impact on the ICER
ERG base-case results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exploratory analyses undertaken by the ERG					
Efficacy set to CDP-12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No waning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50% decrease in effectiveness from 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increase in annual discontinuation rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRI active ≤50 years subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility values from Orme et al. (2007)[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including utility decrements for upper limb impairment*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including utility decrements for fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including utility decrements for limb impairment and fatigue*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding costs and disutility for relapses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CDP, confirmed disability progression; CS, company submission; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life years gained

Model inputs	Incremental costs	Incremental QALYs	Incremental LYGs	ICER (cost per QALY)	Impact on the ICER
* this scenario analysis also includes the use of an imputed relative risk for 20% increase in 9-HPT					

ERG summary

We have used modified values within the company's base-case model to undertake exploratory analyses for our preferred base-case. Collectively making these changes to the inputs and assumptions resulted in an increase to the ICER. Additionally, our sensitivity analysis strongly suggests that confirmed disability progression at 24-weeks had the greatest impact on the cost-effectiveness, with other inputs having a negligible impact.

5.3.3 ERG's model validation and face validity check

The ERG undertook further validity checks, mainly to test the consistency between the clinical benefit of ocrelizumab to that shown in the economic model, by comparing the Markov trace from the economic model to the clinically meaningful end-point (time to confirmed EDSS ≥ 7 see section 4.8). At the clarification stage, the company provided information on the time-to-progression to EDSS ≥ 7 for the MRI active group. In the model, we estimated the median time-to-progression to EDSS ≥ 7 for ocrelizumab and BSC. From our investigation, the median time-to-progression to EDSS ≥ 7 for BSC and ocrelizumab was approximately 13 years and 15 years (see Figure 25), respectively in the MRI active group. There appears to be some benefit in delaying the progression to EDSS ≥ 7.

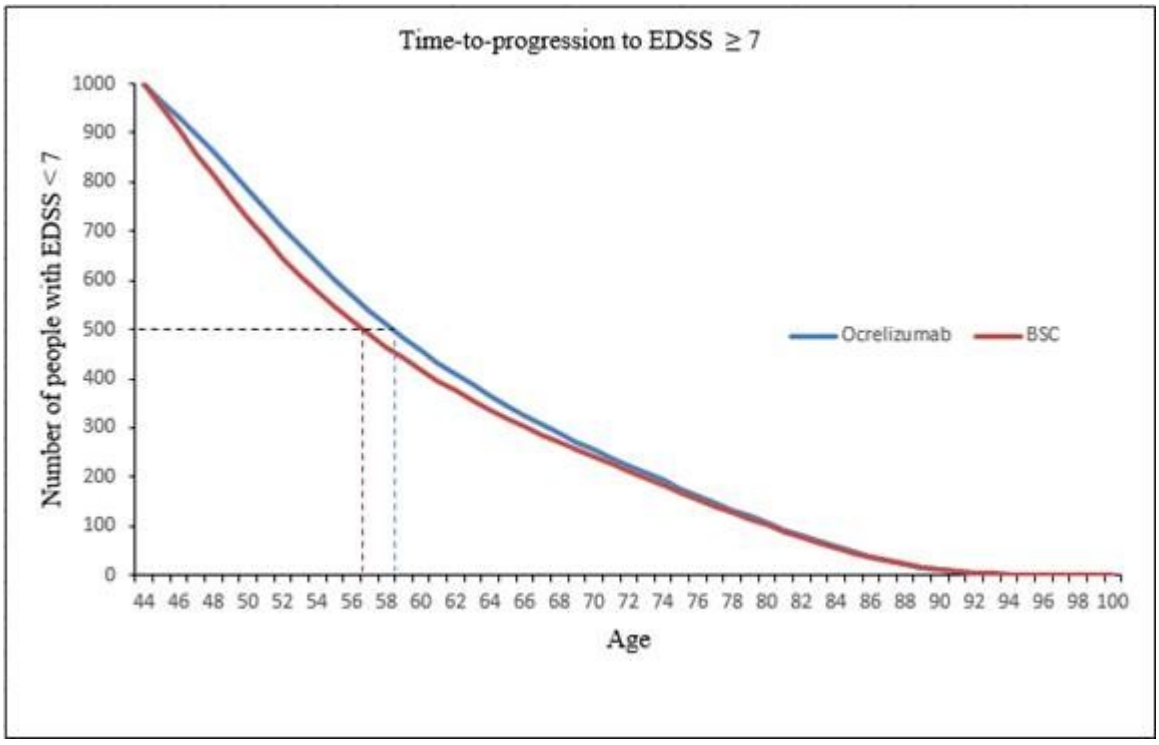

Figure 25: Markov trace on the time-to-progression to EDSS ≥ 7

There were some differences noted between Figure 25 and Figure 6. In the model the hazard ratio is applied to BSC, which is based on MSBase transitions. While in Figure 6, the BSC group is based on the trial observed data as also is the ocrelizumab arm (independent of applying the hazard ratio).

In Figure 25, time-to-progression to EDSS ≥ 7 is greater than observed in the BSC group of the ORATORIO trial. Therefore, we would not expect the two figures to be similar when the model output is compared to placebo; but we would expect the difference between groups from the model output and the Gompertz models to be similar if there is some coherence between the model and trial data and, if the Gompertz models are reasonable reflection of the trial data (which we think they are).

5.4 Conclusions of the cost effectiveness section

The company submission is based on an economic analysis of ocrelizumab compared to BSC, with clinical effectiveness inputs based on the ORATORIO trial, and applied to a natural history cohort from the MSBase registry. While the model captures the key features of the natural history of PPMS, under the company assumptions the base-case results are likely to be higher than that presented. Changes to some of the company's assumptions resulted in an increase to the ICER. In the base-case, the clinical effectiveness of ocrelizumab was based on an MRI active population. However, the population, reflected in the company model, representing the natural history of PPMS included people without characteristics of inflammatory activity.

Here we summarise our key concerns. First, the company included utility decrements for upper limb impairment and fatigue. The company undertook scenario analyses to estimate the impact of excluding each from the analysis; however, an analysis excluding both decrements was not undertaken. Second, the company assumed no waning of the treatment effect of ocrelizumab in the base-case and have not explored the impact of treatment waning in a scenario analysis. Third, the company's treatment effect is presented in the form of a hazard ratio based on confirmed disability progression sustained for 12 weeks (base-case). The company undertook a scenario analysis based on confirmed disability progression sustained for 24 weeks to show the impact to the ICER, whilst other inputs remained fixed. The ERG clinical experts stated that confirmed disability progression at 24 weeks is more robust measure of progression compared to 12 weeks. The impact of making each change leads to an increase to the company's base-case ICER.

In addition to the results for an MRI active population, results are presented for an MRI active ≤ 50 years subgroup. The company makes some acknowledgements relating to this subgroup. First,

the company highlighted that the clinical effectiveness information is based on a post hoc analysis. Second, the license indication for ocrelizumab is not restricted to a specific age group. Hence, we consider these analyses to be exploratory.

Due to the paucity of a longer-term epidemiology for people with PPMS, the company identified and used available information from the MSBase registry in their economic analysis. When assessing the cost-effectiveness, it is important to consider the collective uncertainty of model inputs and assumptions when interpreting model findings.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

Table 60 and Table 61 present the deterministic results for each change and its impact on the company's base-results, using the list price and PAS, respectively.

Table 60: Deterministic results based on individual changes made to inputs, using the list price

Model inputs	Incremental costs	Incremental QALYs	Incremental LYGs	ICER (cost per QALY)	Impact on the ICER
CS base-case results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exploratory analyses undertaken by the ERG					
Efficacy set to CDP-24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50% decrease in effectiveness from 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50% decrease in effectiveness from 5 years + increase of discontinuation rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding utility decrements for upper limb impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding utility decrements for fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Model inputs	Incremental costs	Incremental QALYs	Incremental LYGs	ICER (cost per QALY)	Impact on the ICER
Relative risk for 9-HPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs and disutility for relapses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CDP, confirmed disability progression; CS, company submission; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life years gained					

Table 61: Deterministic results based on individual changes made to inputs, under the approved PAS

Model inputs	Incremental costs	Incremental QALYs	Incremental LYGs	ICER (cost per QALY)	Impact on ICER
CS base-case results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exploratory analyses undertaken by the ERG					
Efficacy set to CDP-24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50% decrease in effectiveness from 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50% decrease in effectiveness from 5 years + increase of discontinuation rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding utility decrements for upper limb impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding utility decrements for fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative risk for 9-HPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs and disutility for relapses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CDP, confirmed disability progression; CS, company submission; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life years gained					

ERG summary

Across all ERG scenario analyses, the impact of the changes leads to an increase to the ICER based on cost per QALY. The assumption of a 50% reduction in the treatment effect from five years onwards had the greatest impact. Inclusion of costs and disutilities related to relapses were considered to be negligible.

7 END OF LIFE

No end of life considerations have been discussed in the CS.

8 OVERALL CONCLUSION

Regarding the clinical effectiveness analyses, the main differences of opinion between the company and the ERG are:

- Is the MRI active population, which was defined from the ORATORIO trial, representative to the UK?
- Are eligibility criteria to ocrelizumab treatment defined by the company, which are based on MRI scans, currently applicable and relevant to the clinical practice in the UK?
- Is there reasonable evidence suggesting that treatment effect varies by age?
- Should clinical effectiveness analyses be based upon confirmed disability progression for 12 weeks or upon confirmed disability progression for 24 weeks?
- What is the impact of ocrelizumab in improving HRQoL?
- What is the impact of ocrelizumab in reducing functional impairment using outcomes other than those related to progression through EDSS?
- What is the impact of ocrelizumab in reducing fatigue?
- What is the impact of ocrelizumab in delaying time to EDSS 7?

Regarding the cost-effectiveness analyses, the main differences of opinion between the company and the ERG are:

- Is it likely that the treatment effect of ocrelizumab wanes over time?

- Should the treatment effect wane over time, how does this affect treatment withdrawal?
- Should disutilities related fatigue and upper limb impairment be incorporated in the analyses?
- Should costs and utilities associated with relapses be included in the model?
- Are cost-effectiveness analyses by patient age relevant?

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10 Appendix: Detailed changes made to the Excel model

Table 62: Details of each change made to the company's base-case model

Reference	Changes made in each analysis	Changes made in Excel spreadsheet
Exploratory scenario analysis on the company's base-case		
Treatment effect based on CDP-12	Treatment effect based on CDP-24	"Main screen" sheet: cell F33
50% decrease in effectiveness from 5 years	No treatment waning	"Inputs-treatment effect": cells F57 – F62, changed to 50%
50% decrease in effectiveness from 5 years + increase of discontinuation rate	No treatment waning; Discontinuation rate based on the Gompertz model	Waning: "Inputs-treatment effect" sheet: cells F57 – F62, changed to 50% Discontinuation: "Main screen" sheet: cell F72 changed to 'User inputs' "Inputs-treatment effect" sheet: cells G57 – G62, changed to ERG values
Excluding utility decrements for upper limb impairment	Includes utility decrements for upper limb impairment	"Main screen" sheet: cell F44, changed to 'No'
Excluding utility decrements for fatigue	Includes utility decrements for fatigue	"Main screen" sheet: cell F47, changed to 'No'
Relative risk for 20% increase in 9-HPT sustained for 12 weeks	-	"Inputs-utilities" sheet: cells R75, S75 and T75
Including treatment effect, costs and disutilities associated with relapses	Excluded treatment effect, costs and disutilities associated with relapses	"Main screen" sheet: cells F36 and F37, change to 'Yes'
Exploratory scenario analysis on the ERG preferred base-case		
Efficacy set to CDP-24	Treatment effect based on CDP-24	"Main screen" sheet: cell F33
50% decrease in effectiveness from 5 years	No treatment waning	"Inputs-treatment effect": cells F57 – F62, changed to 50%
50% decrease in effectiveness from 5 years + increase of discontinuation rate	No treatment waning; Discontinuation rate based on the Gompertz model	Waning: "Inputs-treatment effect" sheet: cells F57 – F62, changed to 50% Discontinuation: "Main screen" sheet: cell F72 changed to 'User inputs'

		"Inputs-treatment effect" sheet: cells G57 – G62, changed to ERG values
Excluding utility decrements for upper limb impairment	Includes utility decrements for upper limb impairment	"Main screen" sheet: cell F44, changed to 'No'
Excluding utility decrements for fatigue	Includes utility decrements for fatigue	"Main screen" sheet: cell F47, changed to 'No'
Relative risk for 9-HPT	-	"Inputs-utilities" sheet: cells R75, S75 and T75
Including treatment effect, costs and disutility for relapses	Excluded treatment effect, costs and disutilities associated with relapses	"Main screen" sheet: cells F36 and F37, change to 'Yes'
9-HPT, nine-hole peg test; CDP-12, confirmed disability progression at 12-weeks; CDP-24, confirmed disability progression at 24-weeks; ERG, evidence review group;		

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 15 May 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 17 and Page 58: "[...] difference in adjusted means not statistically significant: -3.456 [95% CI: -6.048 to 0.863])."	"[...] difference in adjusted means is statistically significant: -3.456 [95% CI: -6.048 to 0.863], p=0.0091)."	The ERG statement is inaccurate as the MFIS results in the ITT analysis were statistically significant, as described on page 50 in the CS.	On checking the CSR, the ERG has discovered that there is an error on p.50 of the CS that is repeated here in the description of the company's proposed amendment. The upper limit of the CI should be a negative value (-0.863) and the difference is therefore statistically significant. Sentences amended to reflect this.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 29/30: "The company have stated (CS page 62) that the ITT population of the ORATORIO trial was early in their disease course and level of disability (given the inclusion/exclusion criteria of EDSS ≤6.5 and disease duration from MS symptoms	"The company have stated (CS page 62) that the ITT population of the ORATORIO trial was early in their disease course and level of disability (given the inclusion/exclusion criteria of EDSS ≤6.5 and disease duration from MS symptoms onset of <15 years [EDSS at screening >5.0] or 10 years [EDSS at screening ≤5.0]). **This had been extensively discussed and subsequently agreed during the discussions about marketing**	The SPC and EPAR define early PPMS as related to disease duration and level of disability, in line with the inclusion criteria in the ORATORIO study. EPAR page 176: [...] After a number of discussions with the applicant and among experts, it was agreed that based on the available data presented in the analyses, it was reasonable to believe that **patients for whom disease duration and level of disability**, as well as available	This is not a factual error or inaccuracy

onset of <15 years [EDSS at screening >5.0] or 10 years [EDSS at screening ≤5.0]). The ERG's clinical experts have disagreed with this statement and consider that these inclusion criteria do not indicate early disease. They have indicated that early PPMS pertains more to a time variable rather than a level of disability and that early PPMS would be better defined as PPMS within five years from symptoms onset."	**authorisation with the EMA and clinical experts.** The ERG's clinical experts have disagreed with this statement and consider that these inclusion criteria do not indicate early disease. They have indicated that early PPMS pertains more to a time variable rather than a level of disability and that early PPMS would be better defined as PPMS within five years from symptoms onset."	imaging features characteristic of inflammatory activity (i.e. T1 Gd-enhancing lesions and/or active [new or enlarging T2 lesions]) suggested that they are in the **early phase of PPMS**, were most likely to experience the most benefit from ocrelizumab treatment. The SPC section 5.1 (page 17): 'Efficacy and safety of Ocrevus were also evaluated in a randomised, double-blind, placebo-controlled clinical trial in patients with primary progressive MS (Study WA25046) **who were early in their disease course according to the main inclusion criteria, i.e. ages 18-55 years, inclusive; EDSS at** **screening from 3.0 to 6.5 points; disease duration from the onset of MS symptoms less than 10 years in patients with an EDSS at screening ≤5.0 or less than 15 years in patients with an EDSS at screening >5.0.**'	

		The ERG statement should clarify that the company's definition of early PPMS is in line with the EMA's definition.	

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 93: "[...] The same conclusion was reached by the Appraisal Committee on the ongoing appraisal on ocrelizumab used in RRMS."	'The Appraisal Committee on the ongoing appraisal on ocrelizumab used in RRMS concluded that all-cause discontinuation could be considered a proxy for treatment waning.'	The ERG statement is inaccurate and does not fully reflect the conclusion of the Appraisal Committee as described in the ACD of the ongoing appraisal on ocrelizumab used in RRMS. The Appraisal Committee concluded (page 16 of ACD) that 'the rate of stopping treatments could have acted as a proxy to account for treatment waning in the absence of evidence for a waning effect for ocrelizumab after 4 years.' This appraisal on ocrelizumab used in RRMS has not completed yet.	Our statement refers to link between neutralising antibodies and excluding treatment waning effect, so we do not consider it to be a factual error or inaccuracy.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 18: "The CS selectively reports outcomes, placing greater	Delete the sentences.	The company objects to this ERG statement which is speculative. All outcomes deemed relevant to	This is not a factual error or inaccuracy.

emphasis on statistically significant exploratory outcomes in the main submission. Several pre-defined exploratory outcomes measured in the ORATORIO trial were not presented in the main CS or its appendices"		the UK clinical practice and economic modelling were reported, in addition the CSR was also provided for transparency. If the ERG believed outcomes were not reported, they should have made us aware of this at clarification question stage and we would have provided what was identified as missing.	

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 20: "The company incorporated disutilities to reflect fatigue and cognitive impairment …[]. Our understanding is that MFIS denotes how fatigue impacts patients' lives, but does not measure cognitive impairment."	'The company incorporated disutilities to reflect the impact of fatigue on physical, cognitive, and psychosocial functioning …[].'	As explained on CS page 51, the MFIS scale measures the impact of fatigue on physical, cognitive, and psychosocial functioning. It does not measure cognitive impairment.	This is not a factual error or inaccuracy (the company states 'cognitive impairment' rather than 'functioning' in CS Table 52 p. 111)

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 17, Page 100 "[...] Figures provided by the company suggest that ocrelizumab had no impact on	"[...] Figures provided by the company suggest that results in the MRI active subgroup were broadly similar to the ITT population, albeit less pronounced."	This does not accurately reflect the data provided. These post hoc subgroup analyses were not adequately powered and	This is not a factual error or inaccuracy. Our statement does reflect what is observed on CS figure 24A.

fatigue compared to placebo based on the mean change in the MFIS."		therefore it cannot be concluded that there is no impact.	

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 26: "[...], since preserving upper limb function is deemed by the company more important than lower limb function in PPMS."	'[...], since preserving upper limb function is deemed by the company more important than lower limb function in PPMS as a typical PPMS patient has already irreversibly lost substantial lower limb function at the time of diagnosis.'	The ERG statement would benefit from more contextualisation to explain why upper limb function is considered by the company more important in PPMS.	This is not a factual inaccuracy

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 96: "Upper limb function and fatigue were considered to be factors that impacts on the HRQoL in addition to EDSS."	'Upper limb function and fatigue were considered to be factors that impact on the HRQoL in addition to EDSS, as indicated by regression analysis of EQ-5D data from the ORATORIO trial.'	The ERG statement is incomplete and would benefit from more contextualisation to explain why the company included HRQoL decrements due to upper limb function and fatigue in the economic model.	This is not a factual inaccuracy

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 101: "The inclusion of a number of additional disutilities appear selective and opportunistic rather than scientific and robust."	"The inclusion of a number of additional disutilities appears without precedent."	We encourage the ERG to amend the statement as it implies arbitrary inclusion of additional disutilities in the economic model. Instead, the inclusion of additional disutilities in PPMS was informed by clinical expert opinion throughout the development of the economic model. As stated in the CS page 89, 'Consultation with clinical experts revealed that they believe EDSS underestimates the broader disability in PPMS patients. Some patients may appear stable on EDSS but experience deterioration in other functions that affect their independence.'	This is not a factual inaccuracy. We note that the Company disagree with our opinion.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 27 "[...] rituximab, which has exactly the same mechanism of action as ocrelizumab [...]"	"[...] rituximab, which also targets CD20-expressing B cells [...]"	This is inaccurate as there are small, yet potentially clinically relevant, differences in rituximab's and ocrelizumab's mechanism of action. Whilst it is true that rituximab and ocrelizumab both target CD20-	We have revised this as following: "[...] rituximab, which has a similar mechanism of action as ocrelizumab [...]" .

		expressing B cells, the differences in the antibody structure result in differences in their mechanism of B cell depletion; as a consequence, there are anticipated differences in their safety and efficacy profiles.	

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 33 "another monoclonal antibody rituximab is also available and currently licensed for the treatment of some hematologic malignancies and specific autoimmune disorders."	"another monoclonal antibody rituximab, although not available nor licensed for the treatment of MS in the UK, is available and currently licensed for the treatment of some hematologic malignancies and specific autoimmune disorders."	This statement is incomplete and should clarify that rituximab is not licensed for the treatment of MS in the UK, nor is it used off-label for MS as confirmed by the ERG clinical experts (page 34 of the ERG report).	This is not a factual error.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 92: "[...] (Kaplan-Meier plots along with parametric models were not presented in the main report)."	'[...] (Kaplan-Meier plots along with parametric models were not presented in the main report, however the K-M plot for ITT population was provided in response to clarification questions and parametric models are included in the economic model).'	The statement does not make it clear that the company provided additional information as requested by the ERG.	This is not a factual error.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 144 "Across all ERG scenario analyses, the impact of the changes leads to an increase to the ICER based on cost per QALY."	"Across most of the ERG scenario analyses, the impact of the changes leads to an increase to the ICER based on cost per QALY. Several of the company scenario analyses decrease the ICER, primarily those relating to changes to natural history."	This statement does not accurately reflect the totality of scenario analyses conducted by the ERG and company. The ERG scenario of increasing the discontinuation rate such that the average time spent in treatment beyond 5 years is reduced to 50% decreases the ICER, and several company scenarios related to natural history all decrease the ICER.	Our summary refers to tables 60 and 61 that indeed show the ICER becomes less favourable across all scenario analyses bar one (inclusion of a treatment effect, costs and disutilities for people who experienced a relapse). In table 61, there was an error for the impact on the ICER by including costs and disutility for relapses. We have corrected in an erratum.

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 22: "The proportion of people who are likely to experience upper limb [...] impairment at each EDSS level was based solely on the company's clinical expert opinion."	'The proportion of people who are likely to experience upper limb [...] impairment at each EDSS level was based on the company's clinical expert opinion and supportive evidence from the ORATORIO study.'	The ERG statement is inaccurate and incomplete. Tables 38 and 39 in the Appendix depict proportion of patients in the ORATORIO study placebo arm experiencing upper limb impairment and fatigue, respectively. Given the low patient numbers for some EDSS scores, clinical opinion was preferred as the basis for the estimated proportions in the economic model. The impact of	This is not a factual error.

		different proportions was explored in scenario analysis.	

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 22: "There is a lack of transparency about the number of people randomised to ocrelizumab who experienced 12-week sustained 20% increase in 9-HPT."	Delete the sentence	The ERG statement is inaccurate. The number of people randomised to ocrelizumab who experienced 12-week sustained 20% increase in 9-HPT are reported on Page 50 of the CS (document B).	In our report we state that 'There is a lack of transparency about the number of people randomised to ocrelizumab who experienced a 12-week sustained 20% increase in 9-HPT. Results are presented for each EDSS level for the placebo group' Though we agree that the proportion of people randomised who experienced a 12-week sustained 20% increase in the 9-HPT is presented, there is a lack of transparency on the proportion who experienced a 12-week sustained 20% increase in 9-HPT for each EDSS level for ocrelizumab. We have amended to 'There is a lack of transparency about the number of people randomised to ocrelizumab who experienced a 12-week sustained 20% increase in 9-HPT by EDSS level. Results

			are presented for each EDSS level for the placebo group'

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 26: "The disease can develop and progress in four major forms: i) relapsing remitting (RRMS); (ii) primary progressive (PPMS); (iii) secondary progressive (SPMS); (iv) progressive relapsing (PRMS)."	'The disease can develop and progress in three major forms: i) relapsing remitting (RRMS); (ii) primary progressive (PPMS); and (iii) secondary progressive (SPMS).	The description of MS clinical subtypes by the ERG is outdated and PRMS is no longer considered a separate subtype. Instead, the International Advisory Committee on Clinical Trials in MS further divides progressive disease (i.e. PPMS and SPMS) into four phenotypes defined by status of disease activity (including relapses) and progression. See reference 21 in the CS: Lublin, F.D., et al., Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology, 2014. 83(3): p. 278–86.	We have revised this

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 57: "[...] The positive finding from this exploratory analysis with the 9-HPT in the ORATORIO trial might explain why the company has chosen the 9-HPT as the primary endpoint of the planned phase IIIb in PPMS patients aged up to 65 years (CS p.86)."	Delete the sentence	This interpretation is speculative from the ERG and irrelevant to the decision problem at hand. As per EPAR, page 134: "The CHMP agreed with the Applicant's proposal to continue investigating the long term safety and efficacy in the whole PPMS population in a randomized, double blind, placebo controlled study including also older (>55 years) patients and patients more advanced in their disease course" The 9-HPT as primary endpoint has never been chosen before and the proposal to do so reflects the evolving understanding of the impact of different disease facets in PPMS and the increasing importance put on upper limb function by the clinical community due to its impact on patients' independence. The final study protocol is still pending.	Not a factual error (we say 'might') and there was no alternative rational provided by the company.

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 48, Table 5: "The CS is unclear in places as to what is being reported, for example using the terms "at 12 weeks" or "at 24 weeks"""	Delete entire sentence or re-phrase for greater clarity on the exact issue. .	Throughout the entire CS it has been made clear in every circumstance whether the 12 or 24 week outcome is reported for 9-HPT. Should this sentence refer to a change in terminology ("at 12 weeks" versus "for 12 weeks") this needs to be clarified.	Not a factual error. 'At 12' or 'at 24' (rather than 'sustained for') is used in text on p48 and Table on CS p49.

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 117 (table 35), page 138 (table 59), and page 143 (table 61) ICERs (and impact on ICERs) based on approved PAS do not need to be marked commercial in confidence.	Remove confidentiality markings for ICERs (and impact on ICERs) based on approved PAS.	As agreed with NICE, ICERs based on list price and CAA price are marked confidential but not the ICERs based on approved PAS.	We have revised

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 47, Table 5: "The T25FW is a widely used measure of disability,[20] although the ERG's clinical experts consider **its** lacks clinical relevance as it does not measure function (activity limitation)".	"The T25FW is a widely used measure of disability,[20] although the ERG's clinical experts consider **it** lacks clinical relevance as it does not measure function (activity limitation)"	Typo	Typographical error and not a factual error. Noted but unimportant. No change made

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 76: "[...] This search was also used to identify resource use information and studies reporting HRQoL for people PPMS [...]"	"[...] This search was also used to identify resource use information and studies reporting HRQoL for people **with** PPMS [...]"	Word missing	Typographical error and not a factual error. Noted but unimportant. No change made

Other changes:

The ERG has become aware of two errors in the analyses related to the subgroup of patients with MRI activity <50 years. Changes have been made on tables 58 and 59 of the report.

Ocrelizumab for treating primary progressive multiple sclerosis [ID 938]- Erratum to ERG final report

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows

Ocrelizumab for treating primary progressive multiple sclerosis, Warwick Evidence, 2018

Contributions of authors:

Peter Auguste (Research Fellow) reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses; Jill Colquitt (Senior Researcher) co-ordinated and conducted the critique of the clinical effectiveness evidence; Martin Connock (Senior Research Fellow) reviewed and critiqued the survival analysis and cost-effectiveness evidence and undertook additional analyses; Emma Loveman (Senior Researcher) conducted the critique of clinical effectiveness evidence; Rachel Court (Information Specialist) critiqued the company searches and undertook additional searches; Olga Ciccarelli (Clinical Professor) provided expert clinical advice; Carl Counsell (Reader) provided expert clinical advice; Xavier Armoiry (Senior Research Fellow) co-ordinated the project and the report, and reviewed and critiqued the clinical effectiveness evidence.

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

- There was no statistically significant difference in the change from baseline to week 120 in the PASAT score (measure of cognitive impairment).

- Based on the Modified Fatigue Impact Scale (MFIS, scored 0-84), the total score of fatigue decreased at week 120 by 0.462 (95% CI: -2.145 to 1.222) with ocrelizumab while it increased by 2.994 (95% CI: 0.658 to 5.330) with placebo (difference in adjusted means statistically significant: -3.456 [95% CI: -6.048 to -0.863]).

Post-hoc MRI active subgroup (matching the label indication):

- The risk of disability progression, with progression confirmed for 12 or 24 weeks, was delayed in the ocrelizumab group compared to the placebo group: with the less relevant endpoint, namely 12-week CDP, the benefit reached statistical significance (HR for 12-week CDP, 0.68; 95% CI: 0.46 to 0.99; p = 0.0448) while with the most relevant endpoint, namely 24-week CDP, it did not (HR for 24-week CDP, 0.71; 95% CI: 0.47 to 1.06; p = 0.0917).
- The change in T25FW from baseline to week 120 was not reported in the CS so the relative effect in reducing progression in T25FW is not known.
- No results for HRQoL were presented
- The benefit of ocrelizumab on functional outcomes (all exploratory) was unclear:
    - There was a positive impact of ocrelizumab over placebo: the HR for the risk of 20% increase in 9-HPT (sustained for 12 weeks) was 0.52 (95% CI 0.32-0.85).
    - No results on the MSFC were reported
    - No results measuring the PASAT score were reported
- Figures provided by the company suggest that ocrelizumab had no impact on fatigue compared to placebo based on the mean changes on the MFIS.

1.1 Summary of the ERG's critique of clinical effectiveness evidence submitted

As noted above, the key concern regarding the ORATORIO trial is the difference between the ITT population and the marketing authorisation indication, and the selection of a post-hoc

emphasis in PPMS compared to RRMS. Moreover, the ERG has noted that this outcome was not incorporated in the submission by the company for ocrelizumab in RRMS.

6. Regarding the hazard ratio and disutilities derived from 20% increase in the 9-HPT:

• A hazard ratio of 0.52 is presented based on the 12-week 9-HPT: as noted, the hazard ratio should be better based on 24-week sustained 20% increase in 9-HPT (this was not provided by the company);

• It appears the hazard ratio was derived from people with EDSS 2 to 6 but was applied to people with EDSS ≥7: it is unclear whether this hazard ratio generalises to people in lower (0-1) and higher (≥7) EDSS states;

• There is a lack of transparency about the number of people randomised to ocrelizumab who experienced a 12-week sustained 20% increase in 9-HPT by EDSS level. Results are presented for each EDSS level for the placebo group;

• For time to 20% increase in 9-HPT, it appears that the hazard ratio was used in the model as a relative risk;

• Should utility decrements based on 20% increase in 9-HPT be incorporated in the model, the ERG believes that the model should include a feature to allow a waning of the benefit consistent with that using CDP, which is not currently the case.

7. Regarding the relative risk and disutilities derived for fatigue

• MFIS was used to measure fatigue, with a score ≥38 representing clinically meaningful fatigue. The company noted that 'cut-offs are not commonly used with fatigue scales and have not been extensively researched in PPMS.' The ERG note that the baseline mean score for fatigue was 41.6 (17.2), suggesting that the majority people were already fatigued upon entering the trial. Figures provided by the company suggest that ocrelizumab had no significant impact on fatigue compared to placebo based on MFIS mean changes;

• The proportion of people who are likely to experience upper limb, and fatigue and cognitive impairment at each EDSS level was based solely on the company's clinical expert opinion.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem.

On pages 14 to 18, the company presents an overview on the disease including its clinical presentation and characteristics.

Multiple sclerosis (MS) is a progressive, degenerative disease affecting the central nervous system which is characterised by inflammation and demyelination of the neurons, mediated by an autoimmune response by T-cells to white matter.[2]

The disease can develop and progress in three major forms: (i) relapsing remitting (RRMS); (ii) Primary progressive (PPMS); and (iii) Secondary progressive (SPMS).[3]

In 80% of cases, RRMS is the form of MS at time of diagnosis. In RRMS patients experience an exacerbation of symptoms followed by periods of remission.

PPMS has an older age of onset, with greater susceptibility in men,[4] and is typically characterised by occasional plateaus in disease progression, with temporary minor improvements from onset.[5]

The company has stated that PPMS represents around 14% of cases of MS in the UK which the ERG confirms is accurate.

The company has indicated on page 16 of the CS that the focus of new treatment for PPMS should be the preservation of patient independence (upper limb function) rather than just patient mobility referring to a review by Lamers et al. [6]. While this review highlights the need to fully assess upper limb function, this is not be specific to PPMS being equally applicable to RRMS.

On pages 18 to 21, the company provides a very detailed critique of the EDSS which is a well-known and accepted tool used in clinical research that has mainly been used for drugs developed in RRMS. The rationale for the critique is that, according to the company, the EDSS is a tool more relevant to capture walking disability, making it less relevant to PPMS, since preserving upper limb function is deemed by the company more important than lower limb function in PPMS.

The limitations that the EDSS does not adequately assess upper limb function and cognitive impairment have been emphasised within the EMA guidelines on clinical investigation of drugs for MS, although guidelines have not been especially focused on this concern in PPMS [7]. On that basis, the EMA advocates the use of additional rating scales and quantitative neurological

performance tests (such as the multiple sclerosis functional composite measure [MSFC]) as secondary measurements of disability[7].

The emphasis by the company on upper limb function outcomes as opposed to lower limb function outcomes contradicts the choice made by the company to use confirmed disability progression through EDSS levels (denoting lower limb function worsening) as the primary endpoint of the ORATORIO trial [8] while the 9-HPT, which is specific to upper limb function, was only an exploratory endpoint of this trial.

On page 22 of the CS, the company has highlighted fatigue as one of the most debilitating patient reported symptom that occur in MS. While the ERG agrees that fatigue is a very commonly reported symptom in MS patients, the ERG would underline that fatigue, measured through MFIS, was an exploratory outcome assessed as part of exploratory objectives.

On page 23, the company has presented composite endpoints which have been proposed in PPMS as a way to develop meaningful measures of disability progression, this includes No Evidence of Progression (NEP) and No Evidence of Progression and Active Disease (NEPAD). These outcomes will be reviewed in section **Error! Reference source not found.**.

On pages 24 and 25, the company has presented a section describing the hypothesis of functional reserve but the clinical relevance of this is a matter of debate.

2.2 Critique of company's overview of current service provision

The company has described the current treatment for PPMS in the UK indicating that no treatment has been approved in this indication. High-dose biotin was examined by the EMA within the scope of an application for marketing authorisation in people with progressive MS but the company withdrew its application in November 2017 [9].

On CS Table 5 page 31, the company has reported results from different RCTs that have tested DMTs for PPMS and failed to demonstrate significant impact on clinical progression and/or did meet their primary endpoints. Of these, the OLYMPUS trial has tested the effectiveness of rituximab, which has a similar mechanism of action as ocrelizumab: in the ITT population the authors have concluded there was no evidence of significant difference (p=0.1442) in time to 12-week CDP between rituximab and placebo after 96 weeks of follow-up [10]. Interestingly, the proportion of patients with CDP at week 96 with rituximab was very similar to that with ocrelizumab in the ORATORIO trial [8] at week 120 (respectively 30.2% vs 32.9%).

- **Other exploratory endpoints**

Modified Fatigue Impact Scale:

In the ITT population, compared to a baseline mean total score of 41.6 based on the modified fatigue impact scale (MFIS), the total score of fatigue decreased to week 120 by 0.462 (95% CI: -2.145 to 1.222) with ocrelizumab while it increased by 2.994 (95% CI: 0.658 to 5.330) with placebo (difference in adjusted means: -3.456 [95% CI: -6.048 to -0.863], CS page 50-51), i.e. statistical difference was observed between the two arms.

On CS p.112, the company has stated that the MFIS is a reliable measure to assess the burden of fatigue in people with MS and that clinically meaningful fatigue was defined as a total score ≥ 38 (section **Error! Reference source not found.** for ERG's review of this). In the cost-effectiveness model, the company has used the proportion of patients experiencing clinically meaningful fatigue accordingly.

The ERG has made two comments with regards to this statement:

- The relative changes compared to baseline appear very small given that the MFIS is a scale that goes from 0 to 84; similarly, on average the MFIS total score remained above 38 in both arms and the change was small and potentially clinically unimportant.
- The proportion of patients with MFIS score >38 was not an outcome measure defined in the study protocol and was not reported in the CSR; indeed, the protocol only planned to measure change in MFIS between baseline and week 120. Therefore, the ERG believes there is a lack of transparency concerning the use of fatigue-related outcomes in the cost-effectiveness model (see section **Error! Reference source not found.**).

No Evidence of Progression

Based on the composite endpoint defined as NEP, which combines disability (as measured by EDSS), upper limb function (9-HPT), and ambulation (T25FW) components, ocrelizumab reached better outcomes compared with placebo (42.7% having NEP with ocrelizumab at week 120 vs 29.1% with placebo; Relative Risk [RR] 1.47, 95% CI 1.17, 1.84). Given the composite nature of NEP as an outcome, the ERG believes the suggested benefit of ocrelizumab on NEP is hard to interpret.

The company has also presented another composite endpoint called NEPAD (CS p.53-55) which was deemed to lack clinical relevance (see section **Error! Reference source not found.** outcomes) and therefore was not reported here.

Table 1: Probabilistic sensitivity analysis, MRI active ≤ 50 years under the approved PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	61,241
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Figure 1 and **Error! Reference source not found.** show the scatterplot and the cost-effectiveness acceptability curve for ocrelizumab compared to BSC for the MRI active ≤50 years subgroup, with the PAS. In Figure 1, it can be seen that majority of the simulations are in the north-east quadrant suggesting that ocrelizumab is more costly and effective than BSC. In **Error! Reference source not found.**, at a WTP threshold of £30,000 per QALY there is zero probability of ocrelizumab being cost-effective when compared to BSC.

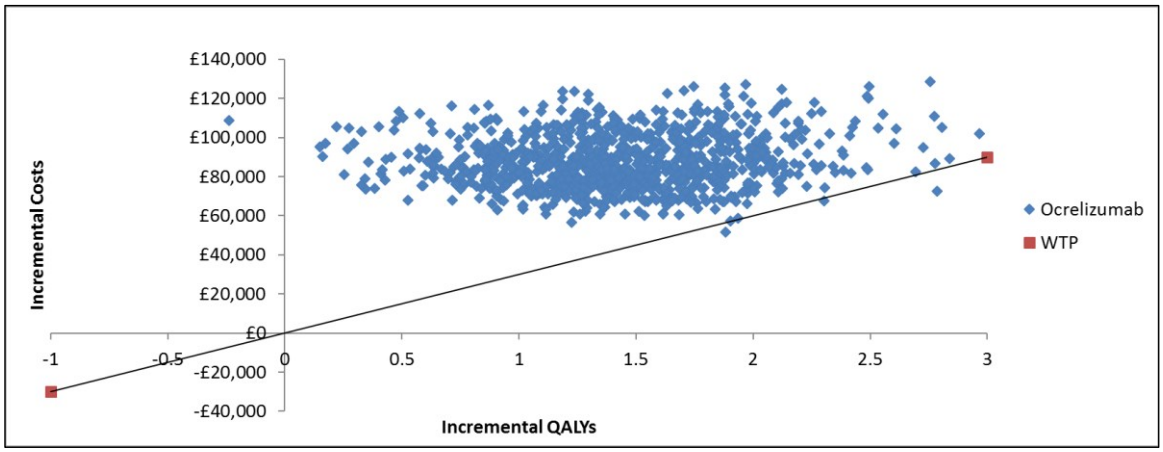

Figure 1: Cost-effectiveness plane, MRI active ≤ 50 years under the approved PAS

Table 2: Scenario analysis results based on individual changes made to ERG base-case, using the list price

Model inputs	Incremental costs	Incremental QALYs	Incremental LYGs	ICER (cost per QALY)	Impact on the ICER
ERG base-case results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analyses undertaken by the ERG					
Efficacy set to CDP-12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No waning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50% decrease in effectiveness from 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increase in annual discontinuation rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRI active ≤50 years subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility values from Orme et al. (2007)[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including utility decrements for upper limb impairment*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including utility decrements for fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Including utility decrements for limb impairment and fatigue*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluding costs and disutility for relapses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CDP, confirmed disability progression; CS, company submission; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life years gained
* this scenario analysis also includes the use of an imputed relative risk for 20% increase in 9-HPT

Table 3: Scenario analysis results based on individual changes made to ERG base-case, under the approved PAS

Model inputs	Incremental costs	Incremental QALYs	Incremental LYGs	ICER (cost per QALY)	Impact on the ICER
ERG base-case results	[redacted]	[redacted]	[redacted]	145,717	-
Exploratory analyses undertaken by the ERG					
Efficacy set to CDP-12	[redacted]	[redacted]	[redacted]	130,360	-15,357
Extended	[redacted]	[redacted]	[redacted]	130,360	-15,357
No waning	[redacted]	[redacted]	[redacted]	114,296	-31,421
50% decrease in effectiveness from 5 years	[redacted]	[redacted]	[redacted]	164,982	19,265
Increase in annual discontinuation rate	[redacted]	[redacted]	[redacted]	114,296	-31,421
MRI active ≤50 years subgroup	[redacted]	[redacted]	[redacted]	76,910	-68,807
Utility values from Orme et al. (2007)[1]	[redacted]	[redacted]	[redacted]	165,288	19,571
Including utility decrements for upper limb impairment*	[redacted]	[redacted]	[redacted]	130,265	-15,452
Including utility decrements for fatigue	[redacted]	[redacted]	[redacted]	130,204	-15,513
Including utility decrements for limb impairment and fatigue*	[redacted]	[redacted]	[redacted]	117,726	-27,991
Excluding costs and disutility for relapses	[redacted]	[redacted]	[redacted]	146,037	-320

Relative risk for 9-HPT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs and disutility for relapses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CDP, confirmed disability progression; CS, company submission; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life years gained					

Table 4: Deterministic results based on individual changes made to inputs, under the approved PAS

Model inputs	Incremental costs	Incremental QALYs	Incremental LYGs	ICER (cost per QALY)	Impact on ICER
CS base-case results	[redacted]	[redacted]	[redacted]	88,214	-
Exploratory analyses undertaken by the ERG					
Efficacy set to CDP-24	[redacted]	[redacted]	[redacted]	97,625	9,411
50% decrease in effectiveness from 5 years	[redacted]	[redacted]	[redacted]	116,550	28,336
50% decrease in effectiveness from 5 years + increase of discontinuation rate	[redacted]	[redacted]	[redacted]	104,697	16,483
Excluding utility decrements for upper limb impairment	[redacted]	[redacted]	[redacted]	98,038	9,824
Excluding utility decrements for fatigue	[redacted]	[redacted]	[redacted]	95,696	7,482
Relative risk for 9-HPT	[redacted]	[redacted]	[redacted]	89,827	1,613
Costs and disutility for relapses	[redacted]	[redacted]	[redacted]	88,047	-167
CDP, confirmed disability progression; CS, company submission; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life years gained					

ERG summary

Across most of the ERG scenario analyses, the impact of the changes leads to an increase to the ICER based on cost per QALY. The assumption of a 50% reduction in the treatment effect from five years onwards had the greatest impact. Inclusion of costs and disutilities related to relapses were considered to be negligible.

3 END OF LIFE

No end of life considerations have been discussed in the CS.

4 OVERALL CONCLUSION

Regarding the clinical effectiveness analyses, the main differences of opinion between the company and the ERG are:

- Is the MRI active population, which was defined from the ORATORIO trial, representative to the UK?
- Are eligibility criteria to ocrelizumab treatment defined by the company, which are based on MRI scans, currently applicable and relevant to the clinical practice in the UK?
- Is there reasonable evidence suggesting that treatment effect varies by age?
- Should clinical effectiveness analyses be based upon confirmed disability progression for 12 weeks or upon confirmed disability progression for 24 weeks?
- What is the impact of ocrelizumab in improving HRQoL?
- What is the impact of ocrelizumab in reducing functional impairment using outcomes other than those related to progression through EDSS?
- What is the impact of ocrelizumab in reducing fatigue?
- What is the impact of ocrelizumab in delaying time to EDSS 7?

Regarding the cost-effectiveness analyses, the main differences of opinion between the company and the ERG are:

Ocrelizumab for treating primary progressive multiple sclerosis [ID 938]- Addendum to the report

Produced by: Warwick Evidence

Authors: Peter Auguste, Research Fellow, Warwick Evidence
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Prof. Carl Counsell received funding through Biogen-Idec, who provided some funding for a departmental MS nurse.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows

Ocrelizumab for treating primary progressive multiple sclerosis, Warwick Evidence, 2018

Contributions of authors:

Peter Auguste (Research Fellow) reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses; Jill Colquitt (Senior Researcher) co-ordinated and conducted the critique of the clinical effectiveness evidence; Martin Connock (Senior Research Fellow) reviewed and critiqued the survival analysis and cost-effectiveness evidence and undertook additional analyses; Emma Loveman (Senior Researcher) conducted the critique of clinical effectiveness evidence; Rachel Court (Information Specialist) critiqued the company searches and undertook additional searches; Olga Cicarelli (Clinical Professor) provided expert clinical advice; Carl Counsell (Reader) provided expert clinical advice; Xavier Armoiry (Senior Research Fellow) co-ordinated the project and the report, and reviewed and critiqued the clinical effectiveness evidence.

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

Table 62 of the ERG report (see page 151) presents the details of changes made to the company's base-case model. This includes the change on the discontinuation rates where we refer to "ERG values". In table 1, we report the ERG values for annual discontinuation rate to be used in the company's model. These values were derived from figure 18 presented in the ERG report (page 123).

Table 1: Annual discontinuation rate used in Evidence review group's base-case

Year	Annual discontinuation	
	Company submission	ERG values
1	[redacted]	6.50%
2	[redacted]	7.07%
3	[redacted]	7.69%
4	[redacted]	8.35%
5	[redacted]	9.10%
6	[redacted]	25.19%
7	[redacted]	27.13%
8	[redacted]	29.19%
9	[redacted]	31.37%
10+	[redacted]	33.68%

Ocrelizumab for treating primary progressive multiple sclerosis [ID 938]- Addendum 2 to the report

Produced by: Warwick Evidence

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Ocrelizumab for treating primary progressive multiple sclerosis, Warwick Evidence, 2018

Contributions of authors:

Peter Auguste (Research Fellow) reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses; Jill Colquitt (Senior Researcher) co-ordinated and conducted the critique of the clinical effectiveness evidence; Martin Connock (Senior Research Fellow) reviewed and critiqued the survival analysis and cost-effectiveness evidence and undertook additional analyses; Emma Loveman (Senior Researcher) conducted the critique of clinical effectiveness evidence; Rachel Court (Information Specialist) critiqued the company searches and undertook additional searches; Olga Cicarelli (Clinical Professor) provided expert clinical advice; Carl Counsell (Reader) provided expert clinical advice; Xavier Armoiry (Senior Research Fellow) co-ordinated the project and the report, and reviewed and critiqued the clinical effectiveness evidence.

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1. Introduction

In this document we validate the company's analyses which are based on a revised PAS submitted to NICE and received by the ERG on 21 May 2018. Then, we report the results of the ERG's parameter changes to the company's base-case. Additionally, we report the results for our preferred analysis and scenario analyses under the revised PAS.

2. Replication of the company's ICERs using the revised PAS

2.1. Company's base case and probabilistic results: MRI active patients using the revised PAS

Under the revised discount, applied to the price of ocrelizumab results in an ICER of approximately £78,300 per QALY (Table 1).

Table 1: Deterministic results, company's base-case under the revised PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	78,316
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Our results are in line with those provided by the company for their base-case as well for the scenario analyses (see table 69 of document with updated ICERs).

As expected, there were slight differences between the probabilistic sensitivity analysis results submitted by the company and those reported by the ERG (Table 2 and Table 3).

Table 2: Probabilistic sensitivity analysis results, under the revised PAS (Company's results)

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	84,249
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Table 3 : Probabilistic sensitivity analysis results, under the revised PAS (ERG's replication)

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	85,822
ICER, incremental life years gained; QALY, quality adjusted life years gained					

2.2. MRI active ≤ 50 years subgroup using the revised PAS

Our deterministic results are in line with those provided by the company for the MRI active ≤ 50 years subgroup (the deterministic results are not reported here). As expected, there were slight differences between the probabilistic sensitivity analysis results submitted by the company and those reported by the ERG (Table 4 and Table 5).

Table 4: Probabilistic sensitivity analysis results, under the revised PAS (Company's results)

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	54,341
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Table 5: Probabilistic sensitivity analysis results, under the revised PAS (ERG's replication)

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	53,235
ICER, incremental life years gained; QALY, quality adjusted life years gained					

3. Exploratory and sensitivity analyses undertaken by the ERG using the revised PAS

3.1. ERG's individual parameter changes to the Company's base-case

Here we have used a modified version of the company's base-case model to undertake exploratory analyses, by incorporating the following changes/assumptions:

- *SA1: Efficacy set to CDP-24 for the un-extended treatment controlled period (minimum of 120 weeks of double-blinded controlled period)*
- *SA2: 50% decrease in the effectiveness from 5 years onwards*
- *SA3: Increase in annual discontinuation rate from 5 years onwards such that the average time spent in treatment beyond 5 years was reduced to 50%*
- *SA4 (SA2+SA3): 50% decrease in the effectiveness from 5 years onwards and an increase in annual discontinuation rate from 5 years onwards such that the average time spent in treatment beyond 5 years was reduced to 50%*
- *SA5: Excluding utility decrements for upper limb impairment*
- *SA6: Excluding utility decrements for fatigue and cognitive impairment*
- *SA7: Relative risk for 20% increase in 9-HPT sustained for 12 weeks*
- *SA8: Including costs, disutilities and treatment effect associated with relapses*

In our exploratory analyses we present the results based on each change made. Deterministic analysis results are presented for the MRI active group, under the revised PAS.

- **SA1: Efficacy set to CDP-24 for un-extended treatment controlled period (minimum of 120 weeks of double-blinded controlled period)**

Table 6: Deterministic results, SA1 under the revised PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	86,824
ICER, incremental life years gained; QALY, quality adjusted life years gained					

- **SA2: 50% decrease in the effectiveness (by changing the HR from 0.71 to 0.86) from 5 years onwards**

Table 7: Deterministic results, SA2 under the revised PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	103,923
ICER, incremental life years gained; QALY, quality adjusted life years gained					

- **SA3: Increase in annual discontinuation rate**

Table 8: Deterministic results, SA3 under the revised PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	74,707
ICER, incremental life years gained; QALY, quality adjusted life years gained					

- **SA4 (SA2+SA3): 50% decrease in the effectiveness from 5 years onwards and an increase in annual discontinuation rate**

Table 9: Deterministic results, SA4 under the revised PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	93,197
ICER, incremental life years gained; QALY, quality adjusted life years gained					

- **SA5: Excluding utility decrements for upper limb impairment**

Table 10: Deterministic results, SA5 under the revised PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	87,038
ICER, incremental life years gained; QALY, quality adjusted life years gained					

- **SA6: Excluding utility decrements for fatigue**

Table 11: Deterministic results, SA6 under the revised PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	84,959
ICER, incremental life years gained; QALY, quality adjusted life years gained					

- **SA7: Relative risk for 20% increase in 9-HPT sustained for 12 weeks**

Table 12: Deterministic results, SA7 under the revised PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	79,749
ICER, incremental life years gained; QALY, quality adjusted life years gained					

- **SA8: Including costs and disutilities associated with relapses**

Table 13: Deterministic results, SA8 under the revised PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	78,155
ICER, incremental life years gained; QALY, quality adjusted life years gained					

ERG summary

In these analyses, we explored the impact of each change to company's deterministic base-case ICER while all other inputs/assumptions remained constant. Including waning of a 50% decrease in the treatment effectiveness from 5 years onwards had the greatest impact on the base-case results.

3.2. ERG's preferred base-case and sensitivity analyses under the revised PAS

The ERG preferred base-case includes the following changes:

- *Efficacy set to CDP-24 for un-extended treatment controlled period (minimum of 120 weeks of double-blinded controlled period)*
- *50% decrease in treatment efficacy from 5 years onwards and an increase in annual discontinuation rate from active treatment such that the average time spent in treatment beyond 5 years was reduced to 50%*
- *Excluding utility decrements for upper limb impairment*
- *Excluding utility decrements for fatigue*
- *Including costs, disutilities, and treatment effect associated with relapses*

The summary of the ERG's base case and scenario analyses with justifications to changes made to the company's base-case is provided in ***Error! Reference source not found.*** *of the original report*.

- **ERG's preferred base-case**

Under the revised PAS, results in Table 14 show that ocrelizumab is expected to cost approximately [redacted] more than BSC and expected to yield [redacted] QALYs, with an ICER of approximately [redacted] per QALY gained.

Table 14: Deterministic results, ERG's base-case under the new PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	129,877
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Table 15: Probabilistic sensitivity analysis results, ERG's base-case under the revised PAS

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	145,161
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Figure 1: Cost-effectiveness plane, ERG base-case under the revised PAS

Figure 2: Cost-effectiveness acceptability curve, ERG base case under the revised PAS

Figure 3: One-way deterministic results on the ERG base-case, under the revised PAS

- **Scenario analysis results, using the revised PAS**

In Table 16, we present the scenario analysis results undertaken on our preferred base-case using the revised PAS. These results show the impact of each change to our preferred base-case ICER while all other inputs/assumptions remain constant. Under the revised PAS, and changing the subgroup to MRI active ≤ 50 years had the greatest impact to our ICER, with a reduction from approximately £129,900 to £67,800 per QALY gained.

Table 16: Scenario analysis results based on individual changes made to ERG base-case, under the revised PAS

Model inputs	Incremental costs	Incremental QALYs	Incremental LYGs	ICER (cost per QALY)	Impact on the ICER
ERG base-case results	[redacted]	[redacted]	[redacted]	129,877	-
Exploratory analyses undertaken by the ERG					
Efficacy set to CDP-12	[redacted]	[redacted]	[redacted]	116,022	-13,855
Extended	[redacted]	[redacted]	[redacted]	116,022	-13,855
No waning	[redacted]	[redacted]	[redacted]	101,540	-28,337
50% decrease in effectiveness from 5 years	[redacted]	[redacted]	[redacted]	147,266	+17,389
Increase in annual discontinuation rate	[redacted]	[redacted]	[redacted]	101,540	-28,337
MRI active ≤50 years subgroup	[redacted]	[redacted]	[redacted]	67,813	-62,064
Utility values from Orme et al. (2007)[1]	[redacted]	[redacted]	[redacted]	147,321	+17,444
Including utility decrements for upper limb impairment*	[redacted]	[redacted]	[redacted]	116,105	-13,772
Including utility decrements for fatigue	[redacted]	[redacted]	[redacted]	116,051	-13,826
Including utility decrements for limb impairment and fatigue*	[redacted]	[redacted]	[redacted]	104,929	-24,948
Excluding costs and disutility for relapses	[redacted]	[redacted]	[redacted]	130,184	+307

CDP, confirmed disability progression; CS, company submission; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life years gained
* this scenario analysis also includes the use of an imputed relative risk for 20% increase in 9-HPT