Public observer slides [redacted]

Lead team presentation
Ocrelizumab for treating relapsing multiple sclerosis

1st Appraisal Committee meeting
Committee B, 6th March 2018

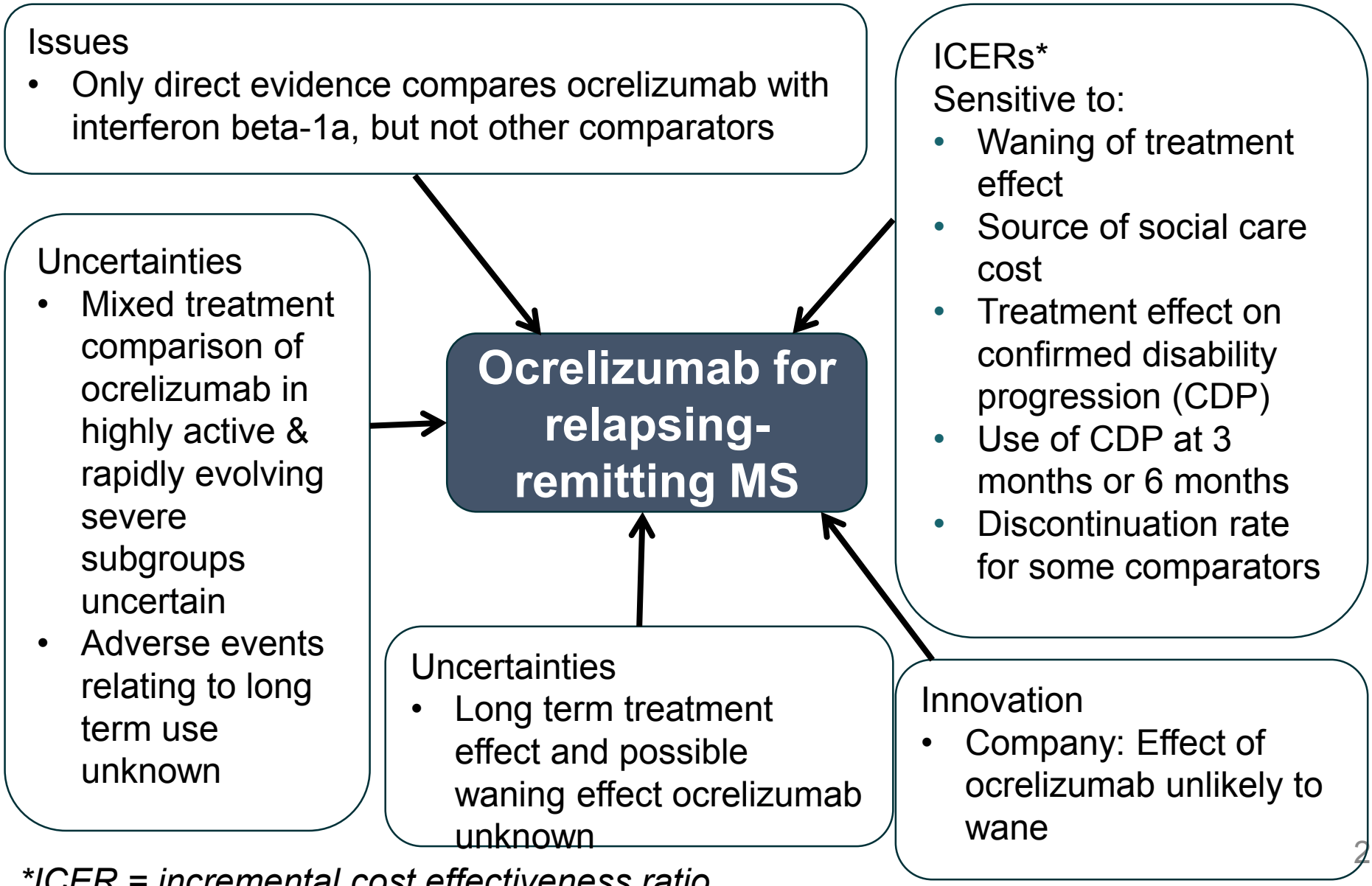
Lead team: Mark Chapman, Richard Hoddes and Nigel Westwood

Chair: Amanda Adler

Assessment group: Southampton Health Technology Assessments Centre

NICE technical team: Jessica Maloney, Frances Nixon

Summary of evidence and key issues



**ICER = incremental cost effectiveness ratio*

Multiple sclerosis

- Multiple sclerosis (MS) is a chronic, neurodegenerative disorder which affects the brain, optic nerves, and spinal cord
- It often results in progressive neurological impairment and severe disability
- Associated with symptoms such as pain, disturbance to muscle tone, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment
- Approximately 100,000 people in the UK have MS, and about 2,500 people are newly diagnosed each year
- Onset typically between 20 and 50 years of age

Multiple sclerosis

Primary progressive MS
- Limited treatment options

Relapsing-remitting MS
- 85-90% of people at diagnosis
- Treatment strategy depends on patient choice, number of relapses, MRI, and response to previous treatment

~50% within 10 years

Secondary progressive MS
- Disease-modifying therapy not used for primary or secondary progressive MS, but some drugs licensed for secondary progressive disease *with relapses*

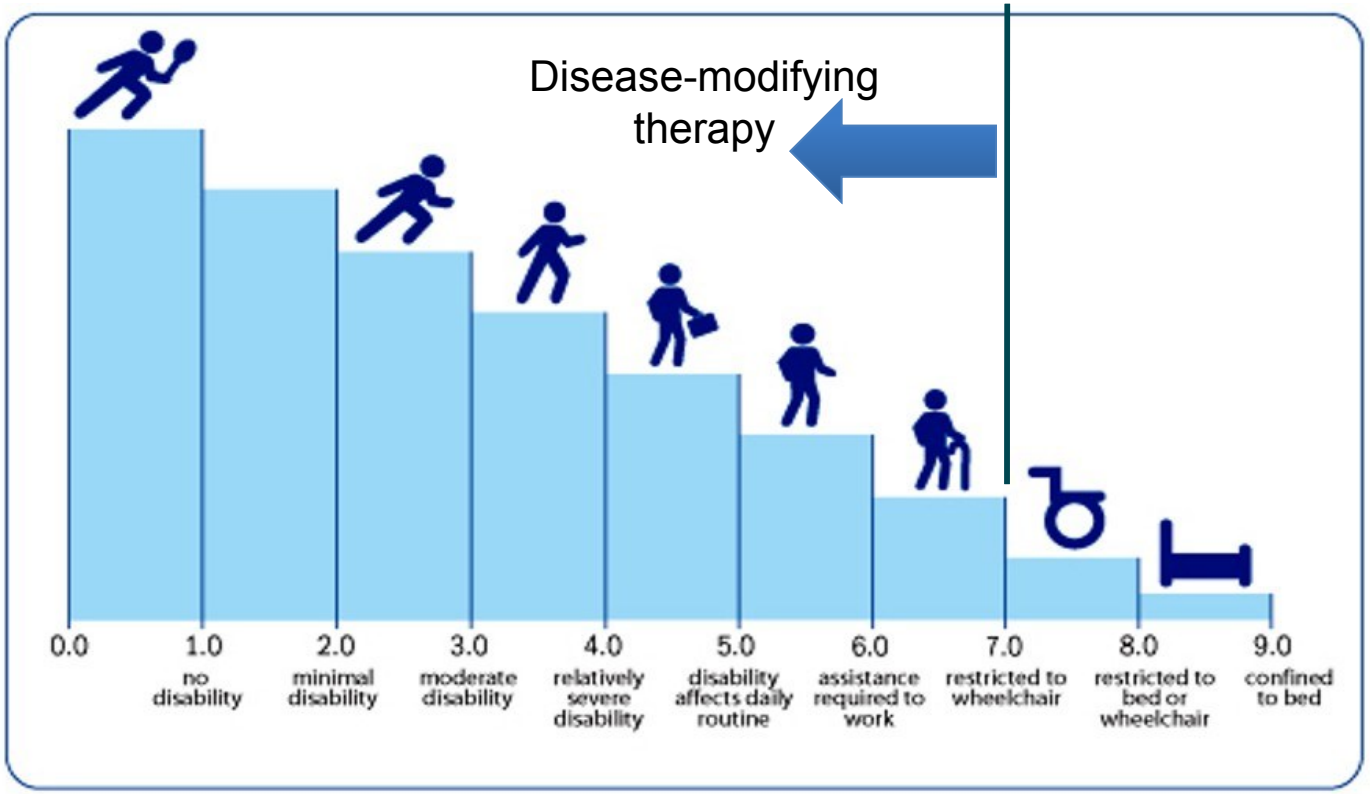
SUBGROUPS of RRMS

1. No prior disease modifying therapy
2. Previously treated (yet not highly active)
3. Highly active (HA) (despite disease modifying therapy)
4. Rapidly evolving severe (RES)

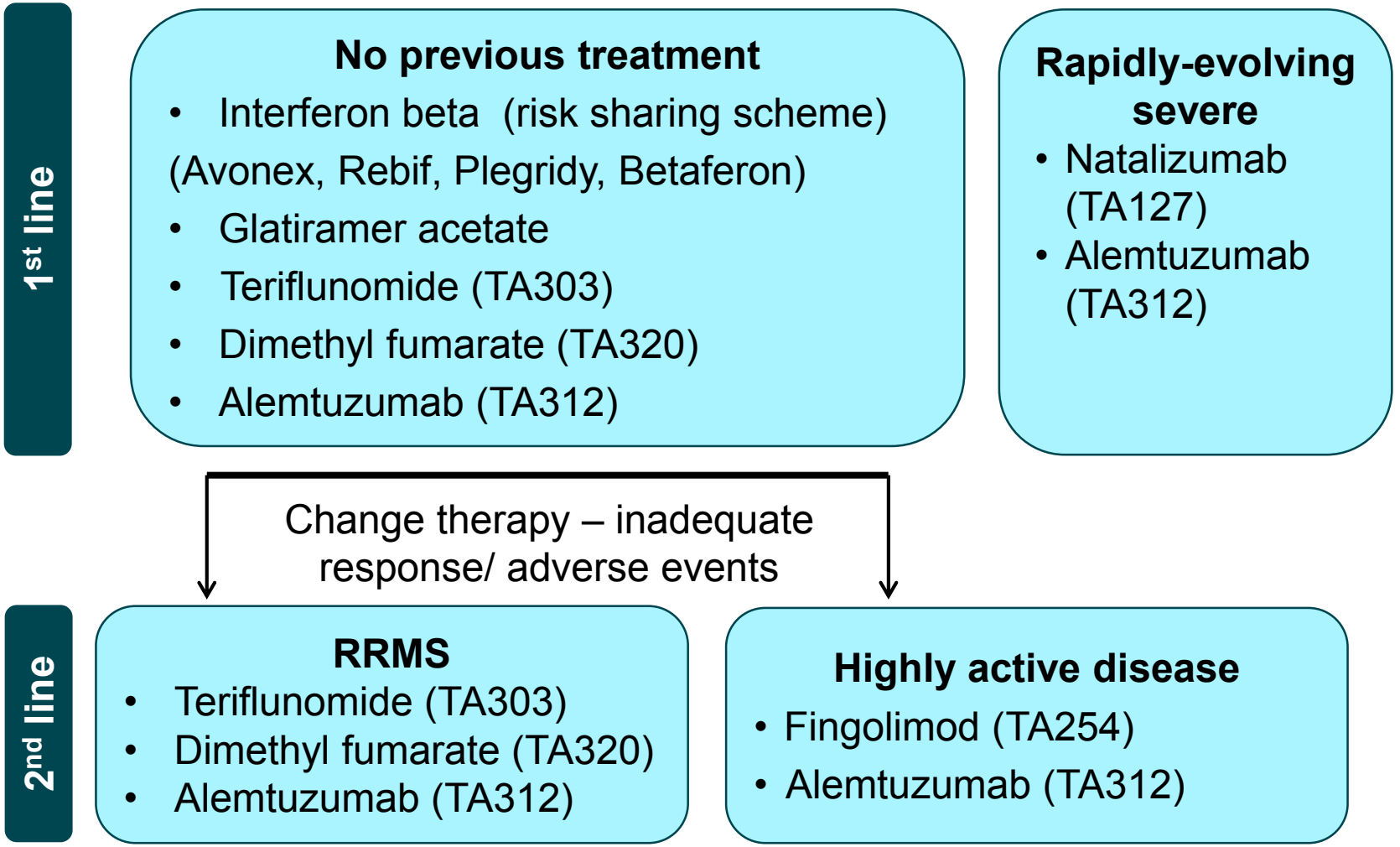
Relapsing-remitting multiple sclerosis

Treatment aims to reduce frequency of **relapse** and slow **disability**

1. ***Relapses –*** symptoms lasting ≥24 hours without fever or infection
2. ***Disability*** *Expanded Disability Status Scale = EDSS*



Current management of relapsing-remitting multiple sclerosis



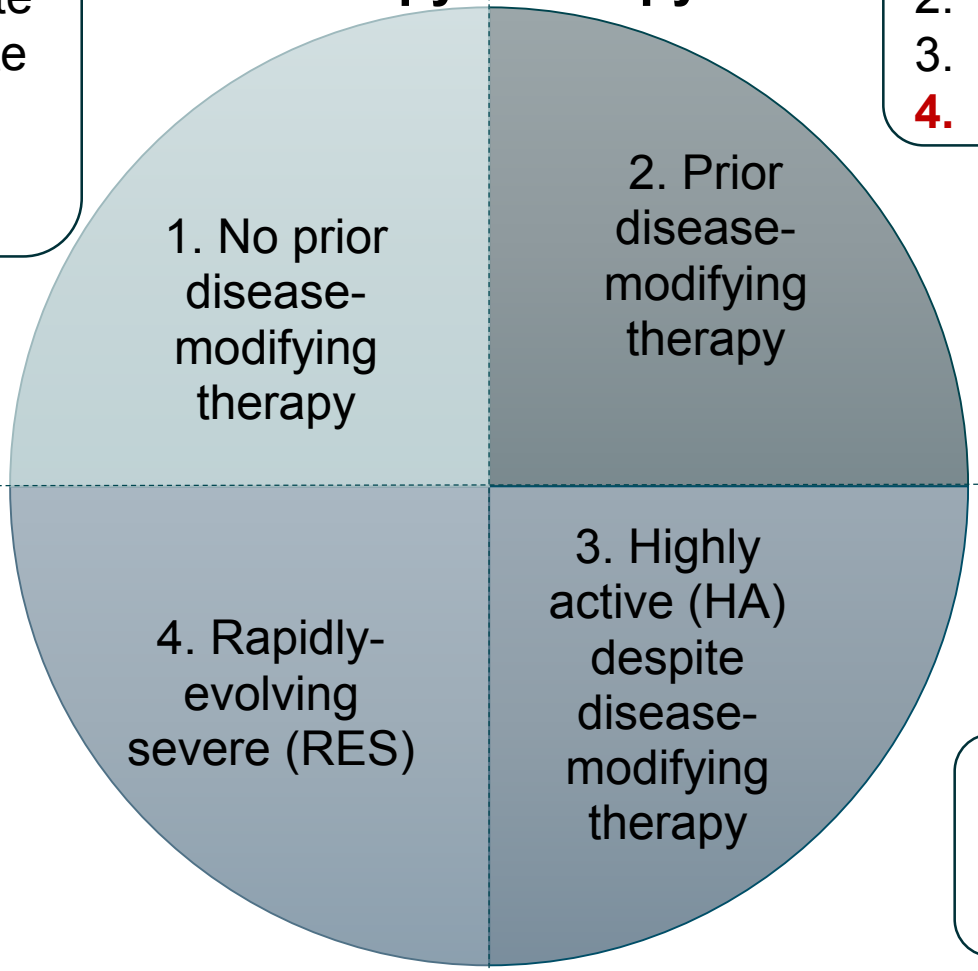
European Medicines Agency has restricted use of daclizumab to patients whose disease has responded inadequately to >2 disease modifying therapies (DMTs) and cannot be treated with any other DMTs

Ocrelizumab (Ocrevis)

Marketing authorisation	For ‘adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features’
Mechanism	Humanised monoclonal antibody that selectively depletes CD20+ B cells
Administration and dose	Intravenous (IV) infusion. First 600 mg dose administered as two 300 mg infusions 2 weeks apart. Subsequent doses administered as a single 600 mg infusion every **6 months**.
Cost	List price £4,790 per 300 mg vial. Simple discount PAS* for ocrelizumab approved
Cost of a course of treatment	Per patient per year £19,160 based on twice yearly 600 mg infusions (list price)

*PAS – patient access scheme

Potential place for ocrelizumab in treatment and relevant comparators



1. Interferon beta
2. Glatiramer acetate
3. Dimethyl fumarate
4. Teriflunomide
5. Alemtuzumab
6. **Ocrelizumab?**

1. Dimethyl fumarate
2. Teriflunomide
3. Alemtuzumab
4. **Ocrelizumab?**

1. Natalizumab
2. Alemtuzumab
3. Daclizumab*
4. **Ocrelizumab?**

1. Fingolimod
2. Alemtuzumab
3. Daclizumab*
4. **Ocrelizumab?**

** 3rd line only, if alemtuzumab not appropriate*

Patient and professional feedback

- Relapses unpredictable in onset, severity, symptoms and duration. Recovery often incomplete, disability accumulates with each relapse.
- People want to minimise impact of disease. People take 'disease-modifying therapies' to reduce risk of disease progression and disability.
- Potential benefits of infusion every 6 months:
  - administered less frequently than most therapies
  - disrupts daily routines less
  - patients adhere better
  - fewer side-effects
- Longer term studies needed to understand safety profile of ocrelizumab
  - Weakening immune system increases risk of infection and of cancer
  - One person contracted progressive multifocal leukoencephalopathy (PML) after switching from natalizumab to ocrelizumab*. Unclear whether PML was linked to use of ocrelizumab, Roche are investigating further
- People with relapsing MS would welcome an effective treatment taken infrequently which carries minimal side effects

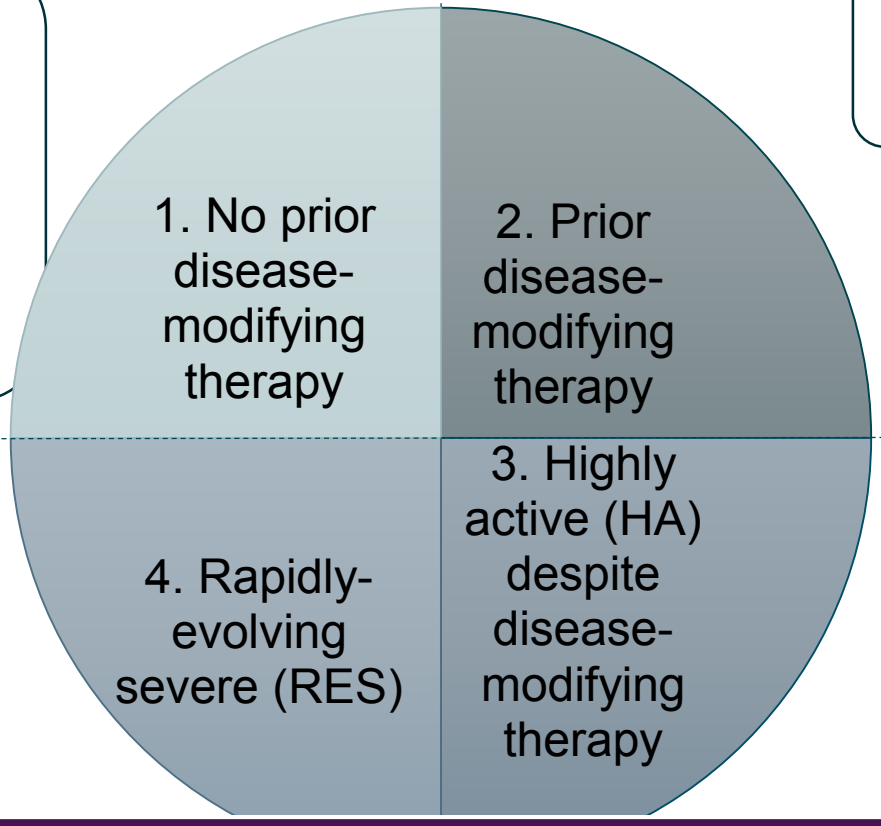
**on the compassionate use program in Germany*

Company's decision problem and deviations from final scope

	Final NICE scope	Company submission	Company rationale	ERG comments
Population	People with relapsing forms of multiple sclerosis	Adults with relapsing remitting multiple sclerosis (excluded secondary progressive MS)	OPERA I and II trial mostly included patients with RRMS, no data for SPMS	• Narrower than scope Only patients ≤55 years included in trials • Clinical experts: infrequent use in people over 55 years
Outcomes	• Relapse rate • Severity of relapse • Disability • Symptoms • No disease activity • Mortality • Adverse effects • Health-related quality of life	Not assessed: • Severity of relapse • Symptoms	No comparative data to use in mixed treatment comparison	• Limited information on statistical analyses in company submission • Obtained and critiqued missing outcomes through clarification process

RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Comparators used by the company – whole RRMS population



1. Interferon beta + glatiramer acetate as a blended comparator
2. Dimethyl fumarate
3. Teriflunomide
4. Alemtuzumab

1. Dimethyl fumarate
2. Teriflunomide
3. Alemtuzumab

Low activity
High activity

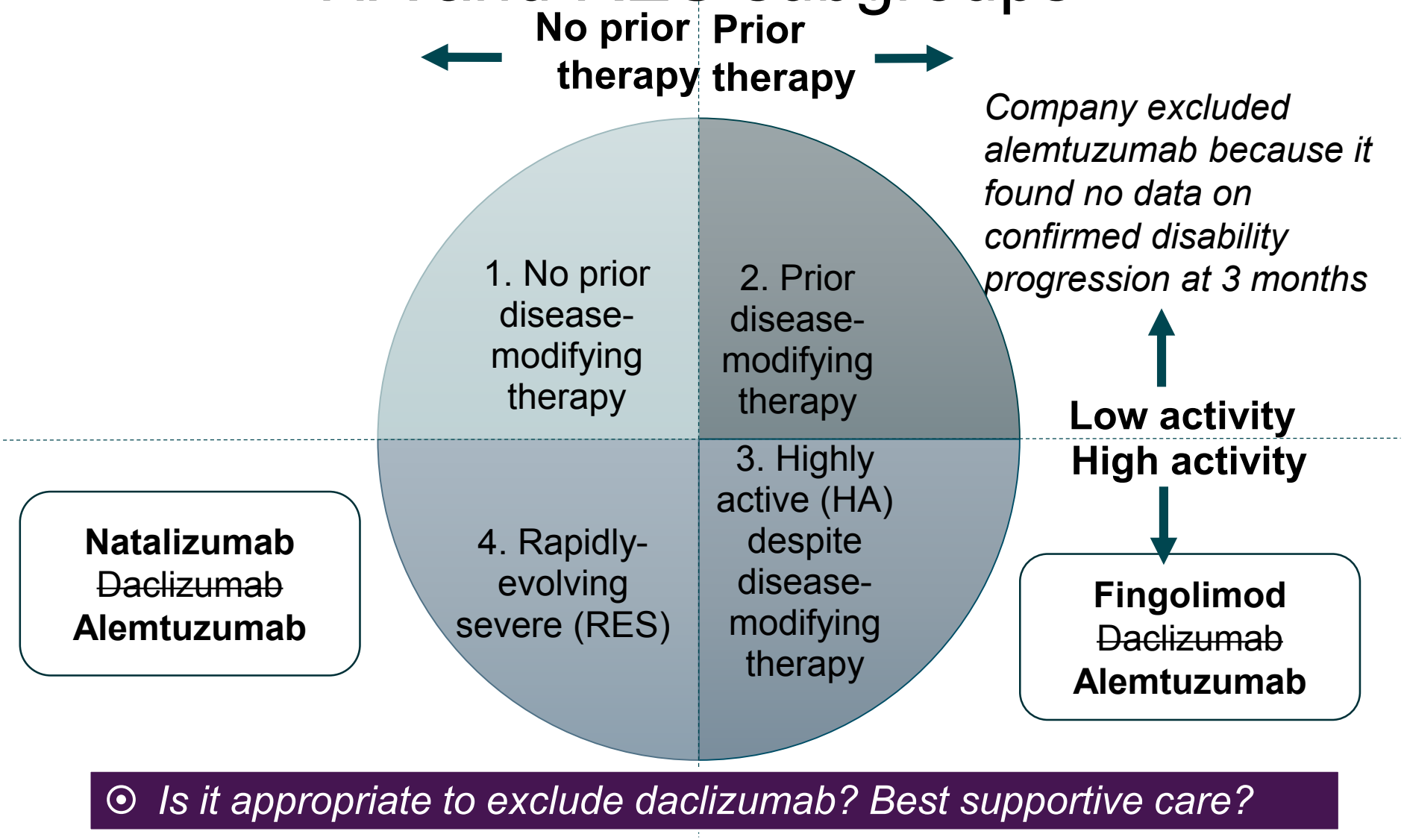
1. Natalizumab
2. ~~Daclizumab~~
3. Alemtuzumab

1. Fingolimod
2. ~~Daclizumab~~
3. Alemtuzumab

⊙ *Are the comparators appropriate? Is it appropriate to include a blended comparator? Exclude best supportive care?*

Natalizumab and fingolimod licenced for subgroups only; daclizumab licensed for 3rd line treatment only

Comparators used by company – HA and RES subgroups



Company excluded alemtuzumab because it found no data on confirmed disability progression at 3 months

⊙ *Is it appropriate to exclude daclizumab? Best supportive care?*

Clinical evidence: OPERA trials

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

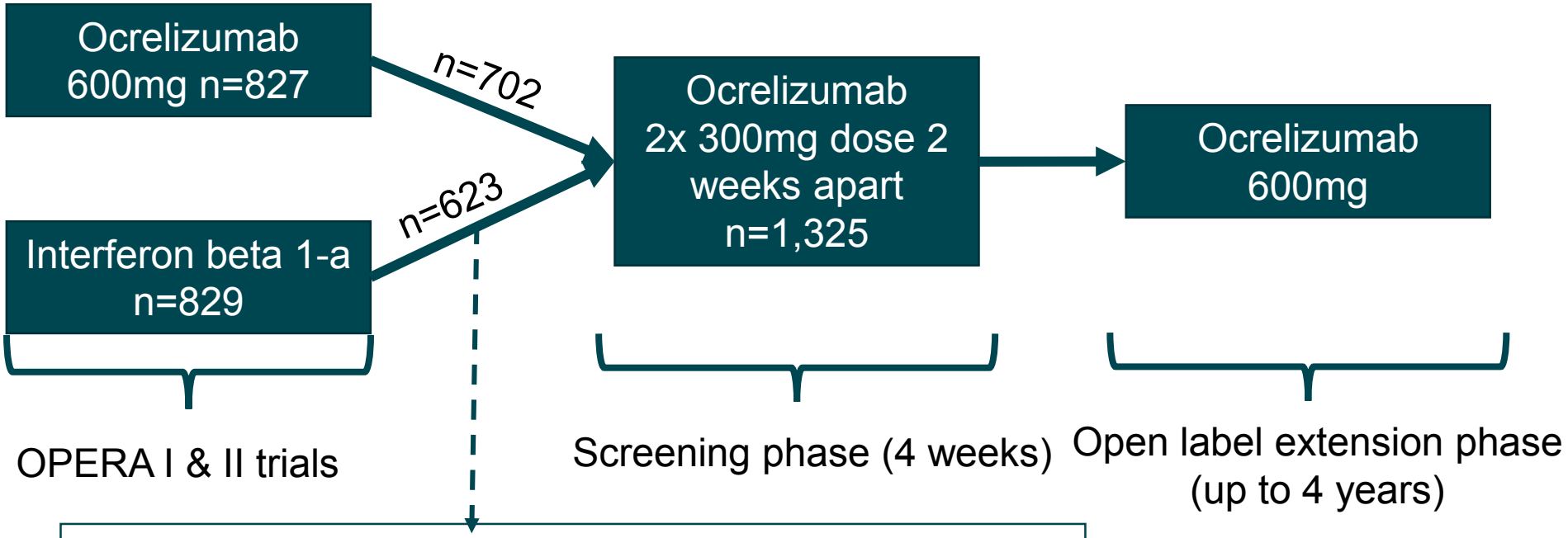
***used in company economic model**

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

Open label extension OPERA I & II

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

- To evaluate long term safety, tolerability and efficacy



Eligible for open label extension if:

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

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

Baseline characteristics (1)

characteristics similar in OPERA I & II and across study arms

Characteristic	OPERA I		OPERA II	
	Ocrelizumab n=410	IFNB-1a (Rebif) n=411	Ocrelizumab n=418	IFNB-1a (Rebif) n=418
Mean age, years (SD)	37.1 (9.3)	36.9 (9.3)	37.2 (9.1)	37.4 (9.0)
Female, n (%)	270 (65.9)	272 (66.2)	271 (65.0)	280 (67.0)
Region, n (%)				
United States	105 (25.6)	105 (25.5)	112 (26.9)	114 (27.3)
Rest of the world	305 (74.4)	306 (74.5)	305 (73.1)	304 (72.7)
Mean time since symptom onset, years (SD)	6.74 (6.37)	6.25 (5.98)	6.72 (6.10)	6.68 (6.13)
Mean time since diagnosis, years (SD)	3.82 (4.80)	3.71 (4.63)	4.15 (4.95)	4.13 (5.07)
Mean no. of relapses in previous 12 months (SD)	1.31 (0.65)	1.33 (0.64)	1.32 (0.69)	1.34 (0.73)
Mean expanded disability status scale (EDSS) score	2.86±1.24	2.75±1.29	2.78±1.30	2.84±1.38

Baseline characteristics (2)

Characteristic	OPERA I		OPERA II	
	Ocrelizumab n=410	IFNB-1a (Rebif) n=411	Ocrelizumab n=418	IFNB-1a (Rebif) n=418
No DMT	301 (73.8)	292 (71.4)	304 (72.9)	314 (75.3)
Previous DMT, n (%)*	107 (26.2)	117 (28.6)	113 (27.1)	103 (24.7)
No. of Gd-enhancing lesions on T1-weighted MRI, n (%)				
0	233 (57.5)	252 (61.9)	252 (61.0)	243 (58.6)
1	64 (15.8)	52 (12.8)	58 (14.0)	62 (14.9)
2	30 (7.4)	30 (7.4)	33 (8.0)	38 (9.2)
3	20 (4.9)	16 (3.9)	15 (3.6)	14 (3.4)
≥4	58 (14.3)	57 (14.0)	55 (13.3)	58 (14.0)

ERG: Previous DMT use slightly higher for ocrelizumab than IFNB-1a in OPERA II

⊙ *Are the baseline characteristics representative of patients seen in the NHS?*

*Previous disease modifying therapies (DMTs) included: interferon (most common ~20%), glatiramer acetate (~10%), natalizumab, fingolimod, dimethyl fumarate, other

Clinical effectiveness results: OPERA I & II

Annualised relapse rate (primary endpoint)

	OPERA I n=821		OPERA II n=835	
	Ocrelizumab 600 mg	IFNB-1a 44 µg	Ocrelizumab 600 mg	IFNB-1a 44 µg
Week 96 (95% CI)	0.16 (0.12, 0.20)	0.29 (0.24, 0.36)	0.16 (0.12, 0.20)	0.29 (0.23, 0.36)
Rate ratio (95% CI)	0.54 (0.40, 0.72)		0.53 (0.40, 0.71)	

Note: numbers in table rounded to 2 decimal places

Disability progression (secondary endpoint, pre-specified pooled analysis)

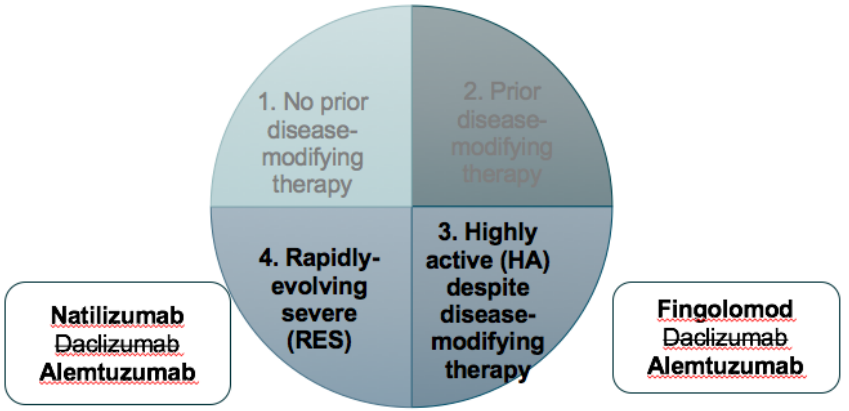
	Ocrelizumab 600 mg	IFNB-1a 44 µg
% Confirmed disability progression at 3 months (95% CI)*	9.8 (7.6, 11.9)	15.2 (12.6, 17.8)
Hazard ratio (95% CI)	0.6 (0.5, 0.8)	
% Confirmed disability progression at 6 months (95% CI)*	7.6 (5.7, 9.5)	12.0 (9.6, 14.4)
Hazard ratio (95% CI)	0.6 (0.4, 0.8)	
% Confirmed disability improvement at 3 months (95% CI)*	20.7 (17.6, 24.1)	15.6 (12.9, 18.8)
Relative risk (95% CI)	1.3 (1.1, 1.7)	

*Kaplan-Meier estimate for proportion of patients with outcome specified in table, 96 weeks from start of trial

used in economic model

Subgroups results from OPERA I & II

- Subgroups (included in company's economic analysis)
  - Previously treated highly active (pre-specified)
  - Rapidly evolving severe (post-hoc)
- In both subgroups ocrelizumab compared with INFB-1a reduced:
  - annual relapse rate
  - confirmed disability progression at 3 months
  - confirmed disability progression at 6 months



Company's mixed treatment comparisons

Required to compare ocrelizumab to comparators

- Direct evidence comparing ocrelizumab with INFB-1a only
- Outcomes and method for mixed treatment comparisons (MTCs)
  - Annualised relapse rate: random effects model with vague prior distribution for between-study variance
  - Disability progression and discontinuation: random effects model with informative prior distribution for the between-study variance
- Whole population: 33 studies included in mixed treatment comparison identified through systematic review, includes comparators not in scope (cladribine, teriflunomide)
  - Company & ERG: including comparators outside scope has negligible impact on results
- Subgroups: 16 studies HA/RES subgroup MTC, networks disconnected
  - Connected using whole RRMS population data from ABCR treatments, assumes treatment effect is same as subgroups

ERG: MTCs are appropriate and unlikely to have omitted any evidence

Abbreviations: ABCR, avonex, betaferon, copaxone, rebif; MTC mixed treatment comparison RE, random effects model; FE, fixed effects model

Evidence informing mixed treatment comparison (1)

Company: prefer confirmed disability progression **3 months** over **6 months**:

- More data for 3 months than 6 months
- 3 months – pre-specified in 71% trials in mixed treatment comparison
- 6 months – pre-specified in 48% of the trials

ERG: confirmed disability progression 6 months more robust measure of lasting disability progression, less likely to be confused with longer relapses

Analysis network		Outcome			
		Annualised relapse rate	Confirmed disability progression 3 months	Confirmed disability progression 6 months	All-cause discontinuation
Whole RRMS population and meta-regression on trial duration	Trials, n	30	22	21	26
	DMTs, n	17	17	15	17
Highly active subgroup	Trials, n	8 (21)*	9 (16)*	9 (15)*	Not applicable
	DMTs, n	7 (10)*	7 (10)*	8 (9)*	Not applicable
Rapidly evolving severe subgroup	Trials, n	9 (22)*	9 (16)*	4 (10)*	Not applicable
	DMTs, n	8 (11)*	10 (13)*	5 (7)*	Not applicable

⊙ *Is it appropriate to use disability progression 3 months over disability progression at 6 months?*

*outside brackets - number of studies reporting subgroup data. Inside brackets - total number of studies in the network, including studies that only report data for the whole RRMS population

Evidence informing mixed treatment comparison (2)

Analysis network		Outcome			
		Annualised relapse rate	Confirmed disability progression 3 months	Confirmed disability progression 6 months	All-cause discontinuation
Whole RRMS population and meta-regression on trial duration	Trials, n	30	22	21	26
	DMTs, n	17	17	15	17
Highly active subgroup	Trials, n	8 (21)*	9 (16)*	9 (15)*	Not applicable
	DMTs, n	7 (10)*	7 (10)*	8 (9)*	Not applicable
Rapidly evolving severe subgroup	Trials, n	9 (22)*	9 (16)*	4 (10)*	Not applicable
	DMTs, n	8 (11)*	10 (13)*	5 (7)*	Not applicable

- subgroup networks connected using total RRMS population data for interferons and glatiramer acetate
- assumes treatment effect in total RRMS population is the same as subgroups (**ERG:** do not support assumption)

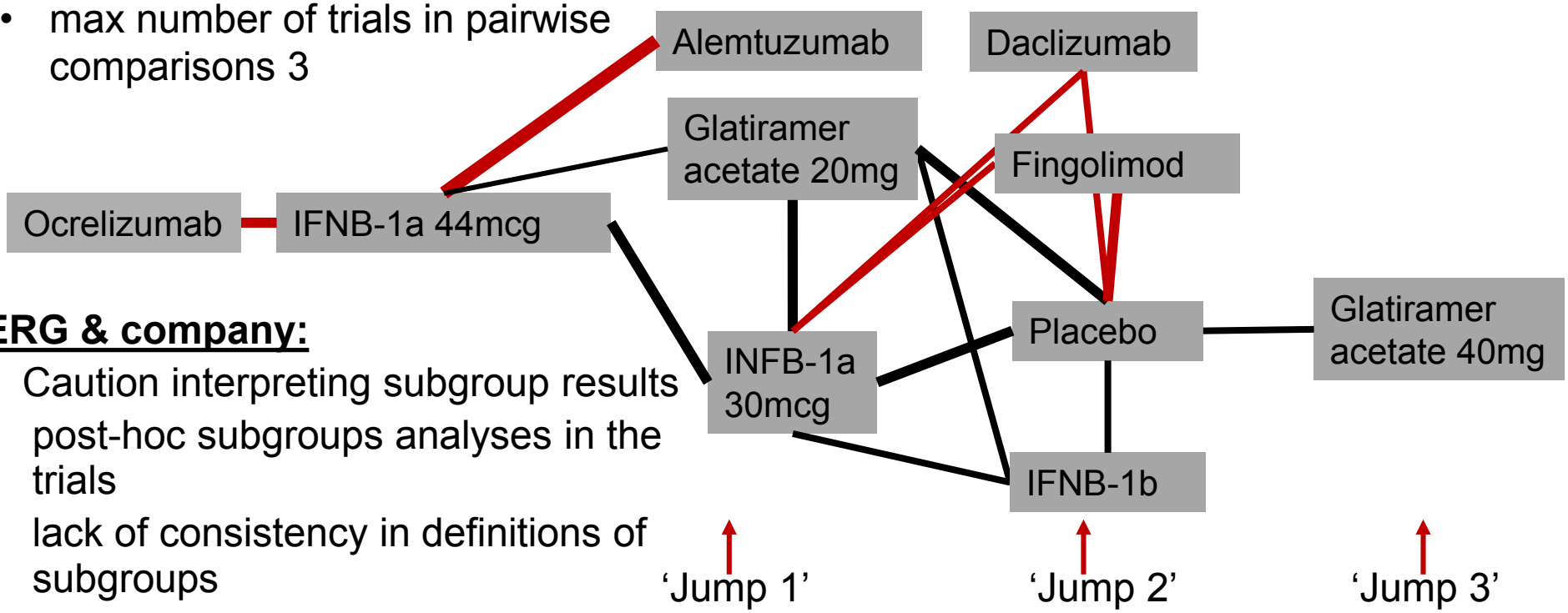
⊙ *Is it reasonable to assume same treatment effect in the total population as the highly active and rapidly evolving severe subgroups for interferons and glatiramer acetate?*

*outside brackets - number of studies reporting subgroup data. Inside brackets - total number of studies in the network, including studies that only report data for the whole RRMS population

Annual relapse rate, highly active, network of studies (example)

ERG:

- assumes treatment effect in total RRMS population is the same as subgroups
- majority of comparisons (63/97; 65%) informed by a single trial
- max number of trials in pairwise comparisons 3



ERG & company:

- Caution interpreting subgroup results
- post-hoc subgroups analyses in the trials
- lack of consistency in definitions of subgroups
- subgroup data observational

Note: Black lines represent 'linking' studies using whole RRMS population data
Number of 'Jumps' relates to the number of intermediate comparisons

Mixed treatment comparison: annual relapse rate

no significant difference for ocrelizumab compared with natalizumab and alemtuzumab

Whole RRMS population
Second line highly active
Rapidly evolving severe

Mixed treatment comparison: confirmed disability progression 3 months

company preferred measure of disability progression

Whole RRMS population
Second line highly active
Rapidly evolving severe

No significant difference when ocrelizumab compared with peg-INFB-1a, natalizumab, daclizumab and alemtuzumab

Mixed treatment comparison: confirmed disability progression 6 months

ERG preferred measure of disability progression

Whole RRMS population
Second line highly active
Rapidly evolving severe

Only significant difference when ocrelizumab compared with placebo and interferon beta-1a

Mixed treatment comparison: all-cause discontinuation

ocrelizumab significantly better than interferon beta-1a and peginterferon-1a

Note: not reported for subgroups, assume all-cause discontinuation is the same in total population

Adverse reactions

Similar in ocrelizumab and interferon beta-1a arms

Variable, n (%)	OPERA I Trial		OPERA II Trial	
	Ocrelizumab n=408	IFNB-1a n=409	Ocrelizumab n=417	IFNB-1a n=417
Any adverse event	327 (80.1)	331 (80.9)	360 (86.3)	357 (85.6)
Adverse event leading to treatment discontinuation	13 (3.2)	26 (6.4)	16 (3.8)	25 (6.0)
At least 1 infusion-related reaction	126 (30.9)	30 (7.3)	157 (37.6)	50 (12.0)
Infection*	232 (56.9)	222 (54.3)	251 (60.2)	219 (52.5)
System organ class infection or infestation	231 (56.6)	216 (52.8)	251 (60.2)	217 (52.0)
Herpes zoster	9 (2.2)	4 (1.0)	8 (1.9)	4 (1.0)
Oral herpes	9 (2.2)	8 (2.0)	15 (3.6)	9 (2.2)
Neoplasm	3 (0.7)	1 (0.2)	1 (0.2)	1 (0.2)
Death	0	1 (0.2)	1 (0.2)	1 (0.2)
Any serious adverse event	28 (6.9)	32 (7.8)	29 (7.0)	40 (9.6)

Infusion-related reactions, upper respiratory tract infections, and nasopharyngitis were more common in the ocrelizumab group

*infection as defined in the Medical Dictionary for Regulatory Activities or with evidence of pathogen

Anti-drug antibodies

Company: since ocrelizumab unlikely to generate neutralising antibodies, no long term treatment waning effect

- Low anti-drug anti-bodies <1%

	Ocrelizumab n=825	IFNB-1a (Rebif®) n=826
Anti-ocrelizumab neutralising antibodies		
Baseline prevalence of anti-drug anti-bodies , n Positive sample at baseline, n (%)	5 (0.6)	4 (0.5)
Post-baseline incidence of anti-drug anti-bodies , n Positive for ADA, n (%)	3 (0.4)	7 (0.9)
Anti-IFNB-1a neutralising antibodies		
Baseline prevalence of anti-drug anti-bodies , n Positive sample at baseline, n (%)	42 (5.3)	35 (4.4)
Post-baseline incidence of anti-drug anti-bodies , n Positive for anti-drug antibodies, n (%)	67 (8.4)	170 (21.3)

Higher proportion anti-drug antibodies for IFNB-1a than ocrelizumab

Open label extension trial OPERA I & II

Company assumes no treatment waning effect for ocrelizumab, economic model sensitive to changes in assumption

Annualised relapse rate in open label extension

[redacted]

ERG: prefer conservative approach to assumptions in line with previous appraisal, sustained effect in long term not yet proven.

- Base case: decline 25% after 2 years and 50% after 5 years for all treatments

Confirmed disability progression at 6 months in open label extension

Company assume no treatment waning effect for all therapies, economic model sensitive to changes in this assumption

interferon beta-1a ocrelizumab

⊙ *Has the committee seen evidence to deviate from previous assumptions of waning in appraisal of disease modifying drugs for MS?*

Key issues: cost effectiveness

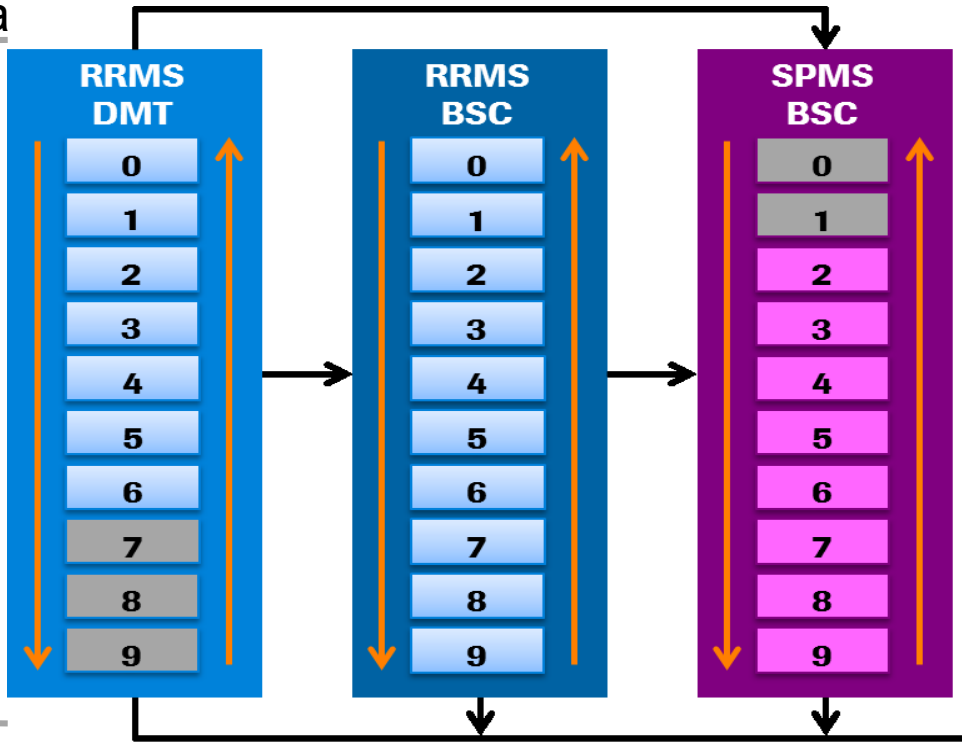
- Is it appropriate to
  - not include a treatment waning effect for ocrelizumab?
  - use confirmed disability progression at 3 months rather than at 6 months?
  - use EDSS health state costs from Tyas et al 2007?
  - assume that adverse event rate and health state utilities are the same for whole RRMS population and rapidly evolving severe / highly active subgroups?
  - exclude PML for ocrelizumab in adverse events (included for natalizumab)?
  - include beta-interferons and glatiramer acetate as blended comparator?

Company's model

- Cohort multi-state Markov model with 1 year cycle length, time horizon 50 years
- Based on disability states
- Discount rate costs and outcomes 3.5%
- Population - people with RRMS, age 37
- Subgroups: Analyses done for RRMS, rapidly evolving severe RRMS and highly active RRMS
- Treatment effect – for its base case, company takes hazard ratios from mixed treatment comparison using confirmed disability progression at 3 months applied to natural history data

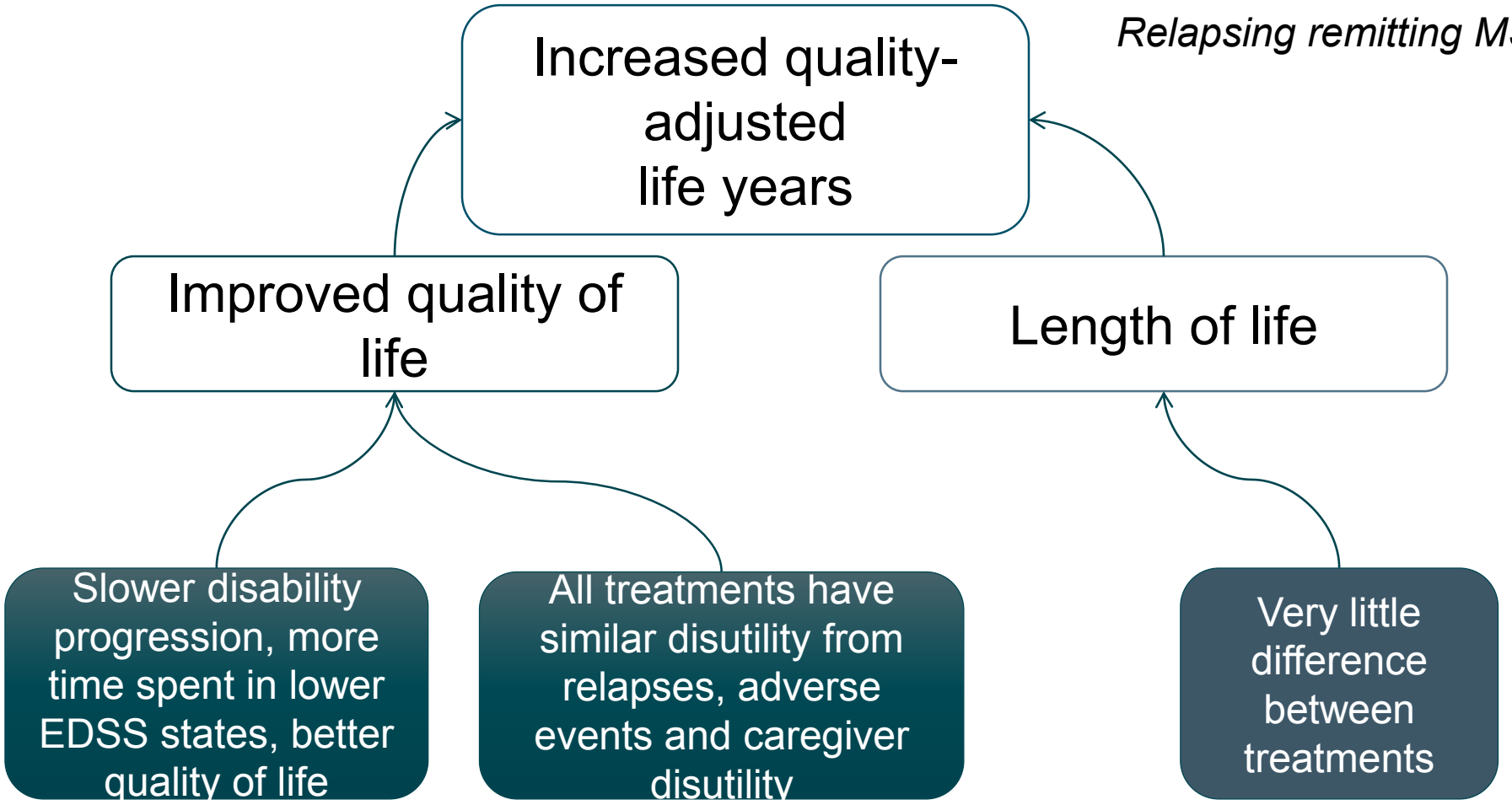
Probability of changing EDSS state - natural history data

assumed treatment slows progression & reduce relapses



EDSS = Expanded Disability Status Scale
RRMS= relapsing remitting MS
DMT = disease modifing therapy;
BSC = best supportive care
SPMS = secondary progressive MS

How QALYs accrue



Company model assumptions (1)

Factor	Company base case	Company justification	ERG preferred
Measure of disability progression	confirmed disability progression 3 months	quality and amount of data in MTC for confirmed disability progression 6 months low	confirmed disability progression 6 months • more robust measure • long episodes of relapse less likely
Source of EDSS cost	Tyas et al. (2007) direct medical costs and 25% of non-medical costs	In line with previous appraisals TA303 (teriflunomide), TA312 (alemtuzumab)	UK MS Survey 2007 updated to 2015/16 costs from ERG report TA320. • Daclizumab committee considerations.
Effect on converting to secondary progressive MS	50% of confirmed disability progression treatment effect	Consistent with natalizumab appraisal	No additional effect on converting to secondary progressive: • not evidence based • accounted for via EDSS progression
Highly active and rapidly evolving severe subgroups	Subgroup mixed treatment comparison	-	Mixed treatment comparison of whole population - Sparse data and post-hoc nature of mixed treatment comparison for subgroup

ERG: One small correction to model, added 3 decimal places to annualised relapse rate natural history data to increase precision

Company model assumptions (2)

Factor	Chosen values	Company justification	ERG preferred
Treatment waning effect	None	Low probability of treatment waning sustained treatment effect demonstrated	Decline 25% after 2 years and 50% after 5 years for all treatments Conservative in line with previous appraisals
Increase in EDSS on conversion to SPMS	EDSS state always increases by 1	Similar to previous appraisals	No increase • EDSS transitions captured in the transition matrix
Source of caregiver disutility	Maximum disutility 0.14 at EDSS 9	TA127 (natalizumab)	Assume maximum disutility of 0.05 • Daclizumab appraisal and expert opinion
Alemtuzumab retreatment rates	13% continuing retreatment from year 6 onwards	Estimated from Touhy et al	Max 4 courses of treatment • Company assumption not supported by evidence • Daclizumab appraisal
Half-cycle correction	Applied with 5% adjustment for alemtuzumab	-	Addition of 5% uplift in half the cost of ocrelizumab • To offset for cost of drugs at beginning of model cycle

Natural history data disability progression RRMS & Secondary Progressive MS

- Company used British Columbia dataset for long-term natural history
  - does not differentiate between patients with RRMS and Secondary Progressive MS
  - Company did a scenario analysis with London Ontario dataset - different transitions for RRMS and Secondary Progressive MS
  - Some NICE appraisals combined British Columbia or London, Ontario with trial placebo arm data; no placebo arm in OPERA I & II

British Columbia	London Ontario
Used in UK Risk Sharing Scheme and recent NICE appraisals (TA441 and ongoing ID809)	Used in older NICE appraisals (TA32, TA127, TA254, TA303, TA312, TA320)
Includes data on 898 patients	Includes data on 345 patients
Follow up period 1980 - 1995	Follow up period 1972 – 1989
Improvements in EDSS (going to a lower-numbered state) allowed	No improvements in EDSS allowed
Transitions available for all health states	No transitions available for EDSS 0 and 9 (RRMS) or EDSS 0, 1, and 9 (SPMS)
Single matrix for mixed population of RRMS and SPMS patients	Separate matrices for RRMS and SPMS patients

Company's modelling of health related quality of life

- Compared with literature, OPERA trial utility values are higher (younger age at baseline; 37 years)
- Disutility applied for relapse, secondary progressive MS, caregiver's and adverse events

EQ-5D-3L from OPERA I and II pooled for both treatment arms & trials

Company took utility decrements for EDSS state 7-9 from MS Trust Survey (TA127, 254, 303, 312 & 320)

	OPERA studies (pooled analysis), adjusted using Orme et al 2007		Caregiver disutility
EDSS	**RRMS**	**SPMS**	
0	0.881	0.836	0.000
1	0.843	0.798	-0.001
2	0.770	0.725	-0.003
3	0.705	0.660	-0.009
4	0.644	0.599	-0.009
5	0.601	0.556	-0.020
6	0.493	0.448	-0.027
7	0.308	0.263	-0.053
8	-0.038	-0.083	-0.107
9	-0.184	-0.229	-0.140

⊙ *Is it appropriate to assume that health state utilities are the same for whole RRMS population and rapidly evolving severe / highly active subgroups?*

Adverse events in economic model

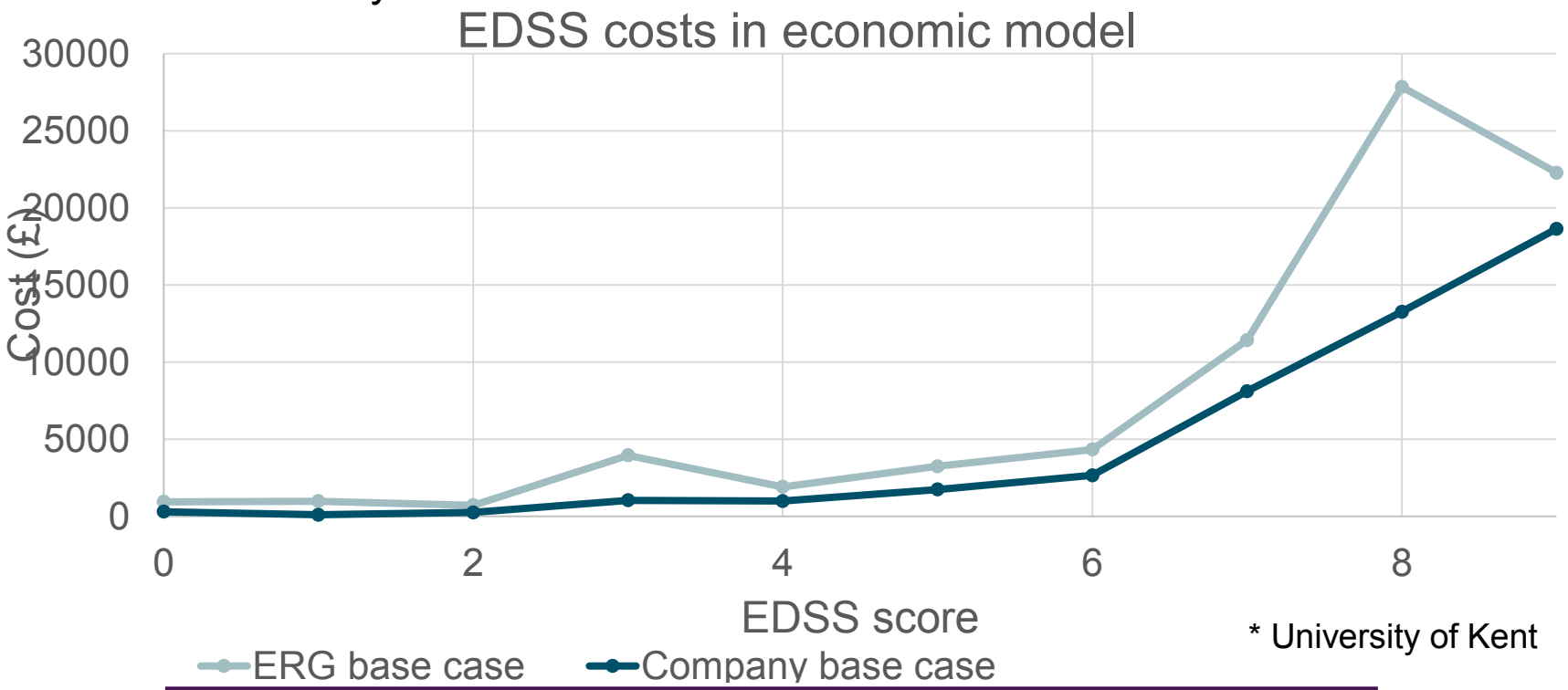
- Company included in model if they occurred ≥5% in either arm in pooled analysis of OPERA I and II; assumed constant over time
- Company assumed same adverse events in whole RRMS population and rapidly evolving severe highly active subgroups because of lack of data
- Company did not include progressive multifocal leukoencephalopathy (PML) for ocrelizumab (one unconfirmed case on compassionate care programme Germany), included for natalizumab (2.1%)

Adverse events (%)	Ocrelizumab	Natalizumab
Arthralgia	2.3	10.0
Back pain	5.2	-
Bronchitis	5.1	-
Depression	13.1	10.0
Fatigue	12.0	14.5
Headache	7.7	21.2
Influenza-like illness	2.6	-
Infusion related reaction	34.3	-
Injection site pain	0.4	-
Insomnia	5.6	-
Nasopharyngitis	10.8	-
PML	-	2.1
Sinusitis	5.6	-
Upper respiratory tract infection	6.4	-
Urinary tract infection	3.1	10.5

⊙ *Reasonable not to include PML as an adverse event for ocrelizumab?*

Health-state costs

- Company uses health-state costs from Tyas et al. 2007 based on the MS Trust survey
  - Company: robust and used in previous appraisals
  - Adjusted to include direct medical costs and 25% direct non-medical costs
  - Inflated to 2016 prices using Personal Social Services Research Unit* (PSSRU) 2016 inflation index
- ERG uses costs preferred by committee for interferon beta and glatiramer acetate MTA ID809 UK MS survey costs inflated to 2015/16



* University of Kent

⊙ *Is it appropriate to use costs from Tyas et al. 2007?*

Cost-effectiveness results

- Company presented interferons as blended comparator in base case

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

Sensitivity and scenario analyses

- Model results sensitive to changes in:
  - Treatment waning assumptions
    - Lower ICERs for ocrelizumab when no treatment waning effect assumed for ocrelizumab
  - Treatment effect on confirmed disability progression
    - Higher ICERs for some lower for others
  - Source of EDSS costs
- Probabilistic results similar to deterministic

Innovation

Company:

- Only disease modifying therapy to consistently demonstrate efficacy across all disease outcomes in RRMS
- Glycoengineered humanised monoclonal antibody
  - selectively targets circulating B cells expressing CD20
  - immune responses to antigen challenge remain despite depleting B cells
- Single infusion every 6 months, less than most disease modifying therapies
- Safety profile – monitoring less frequent
- Treatment waning chance low
- Half life 26 days, reversibility allows patient to receive other therapies in future

Equality and diversity

- No potential issues relating to equality and diversity identified

Authors

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