Natalizumab and Tyruko (natalizumab biosimilar) for treating highly active relapsing-remitting multiple sclerosis after at least 1 disease modifying therapy

For committee – contains CON information

Technology appraisal committee B – 5 February 2025

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Natalizumab and Tyruko (natalizumab biosimilar) for treating highly active relapsing-remitting multiple sclerosis after at least 1 disease modifying therapy

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

NICE National Institute for Health and Care Excellence

Relapsing remitting multiple sclerosis (RRMS)

Condition: Chronic, lifelong, neurological disease with no cure, resulting in progressive, irreversible disability

Cause: immune system mistakenly attacks myelin sheath (layer that surrounds and protects nerves), disrupting signals travelling along the nerves

Symptoms: Pain, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment

- Onset typically between 25 and 35 years of age
- 85% of MS is relapsing-remitting (RRMS): episodes of relapses (neurological worsening) separated by remission (periods of stability)

Epidemiology: Approximately 130,000 people in the UK have MS, and about 7,000 people are newly diagnosed each year

Treatment: disease-modifying therapies (DMTs) to decrease frequency and severity of relapses, reduce accumulation of lesions, slow accumulation of physical and mental disability, maintain or improve patient quality of life

MS, multiple sclerosis

Types of multiple sclerosis

Link to supplementary appendix: classification of RRMS

Natalizumab already recommended for RES RRMS but not HA RRMS

50%-60% in 15-20 yrs

Primary progressive MS
- 10-15% people at diagnosis
- Gradual disability progression from onset with no obvious relapses or remission

Relapsing-remitting MS (RRMS)
- 85% of people at diagnosis
- Treatment strategy: patient choice, number of relapses, MRI activity and response to previous treatment

Secondary progressive MS (SPMS)
- Steady progression of neurological damage with or without relapses
- After RRMS for many people

Active
- At least 2 clinically significant relapses occur within the last 2 years

Highly active (HA)
- 1 relapse in previous year and MRI evidence of disease activity despite treatment with DMT
- **Population of interest for this appraisal**
- **Natalizumab originator not recommended in this population in TA127**

Rapidly evolving severe (RES)
- 2 or more relapses in the previous year
- Baseline MRI evidence of disease activity
- **Natalizumab originator and biosimilar recommended in this population (TA127)**

Does this diagram accurately reflect the relationship between the different forms of RRMS?

DMT, disease-modifying therapy; MRI, magnetic resonance imaging; MS, multiple sclerosis; TA, technology appraisal

Originator (Tysabri, Biogen) & biosimilar natalizumab (Tyruko, Sandoz)[5]

- NICE's biosimilar position statement: "*normally all relevant published guidance that includes the originator molecule will apply to the biosimilar medicinal product*"
- Originator natalizumab not recommended in HA RRMS (TA127), so MTA required to assessed originator and biosimilar natalizumab ("*…biosimilars will only be appraised together with the reference products as part of a MTA.*")

	Originator natalizumab (Tysabri)	Biosimilar natalizumab (Tyruko)

Marketing authorisation	Adults with highly active RRMS with:
	• Highly active disease despite adequate treatment with at least 1 DMT ***or***
	• Rapidly evolving severe RRMS = 2 or more disabling relapses in 1 year, and
	  • 1 or more Gd-enhancing lesions on brain MRI ***or***
	  • significant increase in T2 lesion load compared to previous recent MRI	

Mechanism of action	• Humanised monoclonal antibody • Binds alpha 4-integrin on leukocytes and blocking transport across blood-brain barrier → inhibits inflammatory activity of activated immune cells	
Administration	• 300 mg IV once every 4 weeks • 2 x 150 mg SC once every 4 weeks	• 300 mg IV once every 4 weeks • Not available SC
Price	• 300 mg vial: £1,130 • 2 x 150 mg syringes: £1,130	• 300 mg vial: £1,017
	• Extended interval dosing regimen (EID) also possible every 6 weeks with IV and SC dosing • No patient access scheme in place but confidential framework tender prices available	

DMT, disease modifying therapy; Gd, Gadolinium; HA, highly active; MRI, magnetic resonance imaging; IV, intravenous; MS, multiple sclerosis; MTA, multiple technology appraisal; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous. Link to supplementary appendix: MTA process

Patient perspectives

Submissions from MS Society

Relapses can cause painful, debilitating symptoms and emotional distress

- Symptoms make everyday activities harder and often result in increased long-term disability
- Significant emotional impact from loss of independence (people often feel burden on family) and unpredictable and distressing nature of relapse
- Associated with costs (accessible transport, household aid, medications)

Progressive, fluctuating and unpredictability of MS challenging for families and carers

- Hard to balance work, education and wellbeing of carers with support for someone with MS → complexity of care progresses with age and increasing disability
- Psychological impact (stress, worry, anxiety) for carers and families

Need for multiple effective DMTs

- Choice of DMT highly personal based on eligibility, efficacy, risks, possible side effects, method /location/ frequency of administration, and lifestyle factors.
- Many switch or stop DMTs due to side effects
- Not every DMT accessible across UK (commissioning barriers / lack of resources)
- Natalizumab: Option for people considering pregnancy. SC option helpful for some people

"MS can be relentless, painful and exhausting"

"…People with MS live with great uncertainty, not knowing from one day to the next whether they will be able to move, to see or to live even a remotely 'normal' life"

"Side effects can have a considerable effect on quality of life"

DMT, disease modifying therapy; HA, highly active; MS, multiple sclerosis; SC, subcutaneous

Clinical perspectives

Submissions from the Association of British Neurologists and clinical experts

Unmet need for highly effective treatments when relapses on 1st line treatment:

- Unmet need for non-immunosuppressive treatments and those safe in people planning pregnancy (who cannot have high efficacy treatments)
- Pathway well defined in NHS England clinical commissioning policy
  - Natalizumab only 2nd line DMT available for RES and not HA RRMS: requires extra relapse per year
- Clinically significant response: reduction and/or suppression of clinical relapses and inflammatory MRI activity

Natalizumab is highly effective non-immunosuppressive treatment for MS:

- Use in HA RRMS aligns with natalizumab trial data and eligibility for other 2nd line DMTs
  - ❖ Early treatment likely to reduce long-term disability
- No additional capacity requirements as already available for RES RRMS in NHS
- Used in HA RRMS in COVID → no destabilisation of services, used appropriately and clinically welcomed.
- Associated with risk of AEs (including progressive multifocal leukoencephalopathy (PML))
  - ❖ Clinicians experienced at mitigating PML risk and targeting intensive monitoring

"[Currently]…patients have to wait for a second, potentially disabling relapse in order to meet RES criteria for escalation to this therapy"

AE, adverse event; DMT, disease modifying therapy; HA, highly active; MRI, magnetic resonance imaging; MS, multiple sclerosis; PML, Progressive Multifocal Leukoencephalopathy; RES, rapidly evolving severe; RRMS, relapsing-remitting multiple sclerosis. Link to supplementary appendix: PML

Equality considerations

Unmet need in pregnancy and disproportionate impact on women

Professional organisation:

- Natalizumab has proven safety data in pregnancy → addresses unmet need in population:
    - High efficacy DMTs (ocrelizumab, ofatumumab) not recommended in people who are pregnant (teratogenic) or planning pregnancy (require full course of induction therapy, potentially mandating delaying of pregnancy for 18 months)
- A negative recommendation in HA RRMS means people would need a 2nd, potentially disabling relapse to meet RES criteria for escalation to natalizumab.

Patient organisation:

- MS affects 3 times more women than men → disproportionate impact of negative recommendation in this population

DMT, disease modifying therapy; HA, highly active; MS, multiple sclerosis; RES, rapidly evolving severe; RRMS, relapsing-remitting multiple sclerosis

Key issues

Issue
Comparators: What are the relevant comparators for natalizumab originator and biosimilar? • High efficacy DMTs only (ocrelizumab, ofatumumab and alemtuzumab)? • Interferons and glatiramer acetate? • SC ocrelizumab? Ublituximab?
Network meta-analysis (NMA): Is the EAG's NMA appropriate for decision making?
Use of MS Registry data: Is the use of MS Registry data appropriate?
Efficacy assumptions: Is it appropriate to assume equal efficacy of: • originator and biosimilar natalizumab for all outcomes? • natalizumab, ocrelizumab and ofatumumab for all outcomes? • treatments in the same class where NMA outcomes are missing
Treatment waning and sequencing: Is it appropriate to assume an equal distribution of subsequent treatments from 3rd line onwards?
Mortality: Should standard mortality rates be modelled as EDSS specific?
Extended dosing: Should model include extended interval (6 weekly) dosing? If yes, in what proportion of people?
SC/IV administration: Are subcutaneous and intravenous natalizumab appropriately modelled? Should home administration costs for subcutaneous natalizumab be included in the model?
JCV testing: Should the cost of JCV testing be included in the model?

DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; HA, highly active; IV, intravenous; JCV, John Cunningham Virus; SC, subcutaneous

Treatment pathway

NHS England algorithm defines treatments used for HA RRMS

Link to supplementary appendix: MS treatments

KEY
- In NHS algorithm
- Not in NHS algorithm
- Proposed natalizumab positioning

Diagnosis of active RRMS: *2 relapses in last 2 years or 1 relapse in last 2 years + MRI activity*

1st line
- Interferon β 1b
- Diroximel fumarate
- Ofatumumab
- Ponesimod
- Ublituximab
- Interferon β 1a
- Dimethyl fumarate
- Ocrelizumab
- Glatiramer acetate
- Teriflunomide

1 relapse on 1st line therapy – ***highly active RRMS***

2nd line
- Alemtuzumab
- Ocrelizumab
- Fingolimod
- ASCT
- Cladribine
- Ofatumumab
- Ponesimod
- Ublituximab

Natalizumab originator & biosimilar

1 relapse on 2nd line therapy

3rd line +
- Alemtuzumab
- Cladribine
- Ocrelizumab
- Ofatumumab
- ASCT
- 2nd line therapy
- Ublituximab

Natalizumab originator & biosimilar

- Does the proposed pathway reflect clinical practice for MS?
- Are there distinct lines of treatment 2nd line onwards?
- Is the proposed positioning for natalizumab appropriate?

ASCT, autologous stem cell transplant; HA, highly active; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

Key issues: Comparators (1)

EAG include all comparators in NICE scope, companies state only high efficacy DMTs are relevant comparators for natalizumab

	Comparator	Scope	EAG	Biogen	Sandoz	Comments
Low/moderate efficacy	Glatiramer acetate	✓	✓	x	x	**Biogen:** Not included in NHS England MS treatment algorithm
	Interferon beta 1a	✓	✓	x	x	
	Interferon beta 1b	✓	✓	x	x	
	Cladribine	✓	✓	✓	x	
	Fingolimod	✓	✓	x	x	**Biogen:** Use declining in UK
	Ponesimod	✓	✓	✓	x	
High efficacy	Alemtuzumab	✓	✓	x	x	**Biogen:** Used at last-line after DMTs exhausted **Sandoz:** Limited use in HA RRMS because safety concerns
	Ocrelizumab	✓	✓	✓	✓	**Biogen:** Only high-efficacy DMTs relevant comparators **Sandoz**: Natalizumab used in people having other high-efficacy DMTs despite more complex safety profile
	Ofatumumab	✓	✓	✓	✓	
	AHSCT	✓	✓	x	x	**Biogen:** Used at last-line after DMTs exhausted

AHSCT, autologous haematopoietic stem cell transplant; DMT, disease modifying therapy; HA, highly active; RRMS, relapsing-remitting multiple sclerosis

Key issues: Comparators (2)

Recent additions to disease landscape could affect relevant comparators for natalizumab

EAG: NICE scope restricts ocrelizumab use to people who cannot have alemtuzumab → clinical expert advice suggests used in full population in clinical practice

Technical team comments:

- Ublituximab recommended for treating relapsing MS (18 December 2024) – cost comparison with ocrelizumab
- Ocrelizumab now available in SC (as well as IV form)

Clinical and patient experts: NHS England algorithm overly complex due to differences in defining MS categories in trials and TAs. Some differences in clinical practice remain.

- HSCT used from 2nd line onwards but not if planning pregnancy as affects fertility
- Factors influencing choice of DMT: initial therapy, MS disease activity at diagnosis and time of escalation, patient preference, pregnancy and family plans
  - ❖ Safety profile also important → many people may need to stop or switch DMTs

What are the relevant comparators for natalizumab originator and biosimilar?

- High efficacy DMTs only (ocrelizumab, ofatumumab, cladribine and alemtuzumab)?
- Should interferons and glatiramer acetate be included as comparators?
- Should SC ocrelizumab be included as a comparator?
- Is ublituximab a relevant comparator?
- Is ocrelizumab used in all people with HA RRMS or only those for whom alemtuzumab is contraindicated or unsuitable?

DMT, disease modifying therapy; HA, highly active; HSCT, haematopoietic stem cell transplant; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous; TA, technology appraisal

Natalizumab and Tyruko (natalizumab biosimilar) for treating highly active relapsing-remitting multiple sclerosis after at least 1 disease modifying therapy

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NICE National Institute for Health and Care Excellence

Overview of key evidence for natalizumab

No RCTs in HA RRMS, results in all RRMS favour originator natalizumab vs placebo and fingolimod

RCT data (see appendix):

- Data for natalizumab available from AFFIRM and Saida 2017 (originator natalizumab vs placebo), ANTELOPE (originator natalizumab vs biosimilar natalizumab) and REVEAL (originator natalizumab vs fingolimod) – all in people with RRMS. No RCT data in people with HA RRMS
- Originator natalizumab improves disease control vs placebo and fingolimod

Non-RCT data (see appendix):

- **TOPs:** large real-world study of natalizumab in RRMS (N=6,321, 134 in UK), 15-year follow-up.
  - Over 90% reduction in ARR vs. year before starting natalizumab in global and UK population
  - Similar results in post hoc HA RRMS subgroup

DELIVER and REFINE (natalizumab IV vs SC every 4 weeks): ARR, CDP3, PK, PD, safety outcomes comparable

EAG: No RCTs for SC natalizumab or HA RRMS

- Short follow up in Saida 2017, ANTELOPE and REVEAL studies
- Saida 2017 most generalisable to HA RRMS (1 or more relapse and 88% had prior DMT at baseline).
- **Non-RCT data:** improved outcomes in RRMS and HA RRMS with natalizumab but non-comparative with other MS treatments

ARR, annualised relapse rate; CDP3, confirmed disease progression at 3 months; EDSS, Expanded Disability Status Scale; HA, highly active; PD, pharmacodynamic; PK, pharmacokinetic; QALY, quality-adjusted life year; RRMS, relapsing-remitting MS; RCT, randomised controlled trial; SC, subcutaneous; SPMS, secondary progressive MS

Link to supplementary appendix: key RCT results, non-RCT results, outcomes in trials

Summary of EAG's NMA

Link to supplementary appendix: network diagrams 1, 2, trials in NMA 1, 2, trials excluded from NMA, key NMA results 1, 2, 3, 4, 5

Results suggest 'high efficacy DMTs' most effective for key NMA outcomes

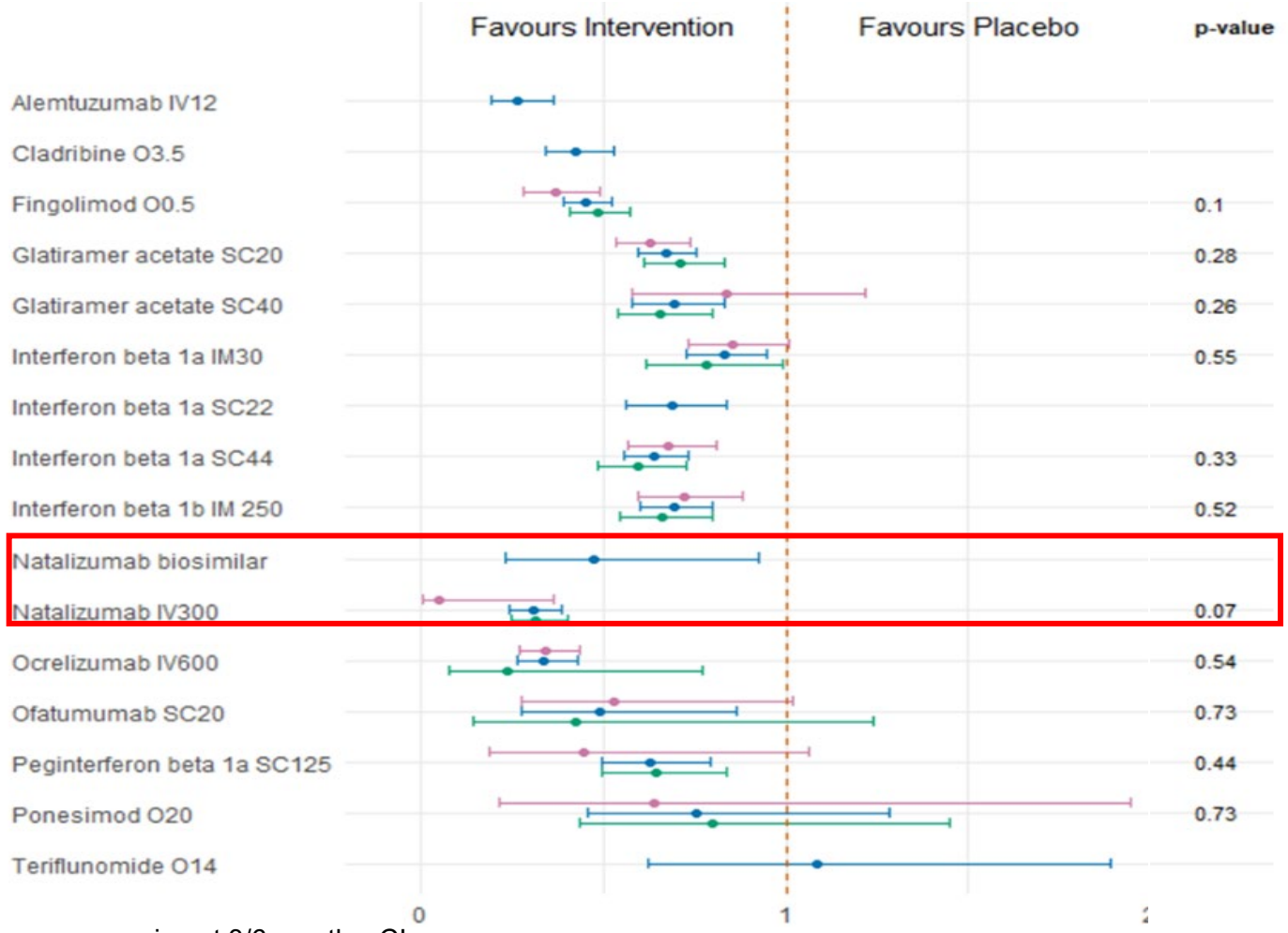
Background: Population: Any RRMS; RCTs including >90% RRMS – subgroup analyses in HA RRMS

Outcomes included: ARR; MRI measurements (Gd+ enhancing and T2 weighted lesions); disease progression (CDP3, CDP6, combined CDP3/6); AEs of treatment; health-related QoL

Results:

- Natalizumab, alemtuzumab and ocrelizumab show greatest improvements for most efficacy outcomes
- SAEs: No difference between all treatments included in network
- Limited results in HA RRMS subgroup, but show similar trends to those in general RRMS

EAG's forest plot of hazard ratios (HR) and 95% CIs for ARR (fixed effects NMA, full RRMS population)



AE, adverse event; ARR, annualised relapse rate; CDP, confirmed disease progression at 3/6 months; CI, confidence interval; HA, highly active QoL, quality of life NMA, network meta-analysis; RRMS, relapsing-remitting MS; SAE, serious adverse event

Key issue: EAG's NMA (1)

Companies raise concerns about included trials and outcomes in EAG's NMA

Company comments:

Biogen:

- NMA population (all RRMS) broader than decision problem (HA RRMS)
- Heterogeneity in studies (types and diagnostic criteria of MS, ages, other factors prognostic of disease progression) → comparative clinical efficacy of MS therapies uncertain
- Data for natalizumab in HA RRMS available from TOP study
- NMA should include teriflunomide studies vs. placebo → would allow fully connected network
- NMA should exclude INCOMIN trial (interferon β1a vs β1b – as per TA533 and TA699):
  - Widely considered outlier by clinical experts → inconsistent CDP3 and 6 outcomes.
- Inappropriate to include studies with 6 months follow up as unlikely CDP6 data available
- Disease improvement/regression with natalizumab should be considered:
  - Higher rates of confirmed disability improvement (CDI) with natalizumab vs. platform DMT at 24 months (Chappell et al) or fingolimod at 6 months (Spelman et al).

Abbreviations: CDP3/6, confirmed disease progression at 3/6 months; DMT, disease-modifying therapy; HA, highly active; NMA, network meta-analysis; RRMS, relapsing-remitting MS; RCT, randomised controlled trial; SC, subcutaneous;

Key issue: EAG's NMA (2)

Companies raise concerns about included trials and outcomes in EAG's NMA

Company comments continued: Sandoz:

- Key high efficacy DMT, ofatumumab, is disconnected or minimally connected for some outcomes
- All DMT trials, including teriflunomide and DMF, should be included to better connect NMA
- Published NMA by Samjoo et al (2023) should be used for better connectivity
  - ❖ Appropriate to assume equivalent efficacy for natalizumab, ocrelizumab and ofatumumab based on comparable annualised relapse rate and 6-month confirmed disability progression in NMA

EAG comments

- Note heterogeneity in NMA studies but clinicians confirmed studies reasonably comparable
- INCOMIN used in other recent SLRs but acknowledge uncertainty re CDP3 /6
- Teriflunomide not in scope: reasonable to include only studies needed to connect network → EAG do not expect fully connected network to substantially alter results
- Only 1 study in NMA with 6 month follow up → EAG scenario for CDP3 and 6 includes only studies with ≥ 24 months follow up
- Disease improvement not considered as outcome due to time constraints

Is the EAG's NMA acceptable for decision making?

- Any changes to studies included in NMA?
- Are studies sufficiently homogenous for reliable results?
- Is it appropriate to assume equal efficacy for natalizumab, ocrelizumab and ofatumumab?

CDP3/6, confirmed disease progression at 3/6 months; DMT, disease-modifying therapy; DMF, dimethyl fumarate; NMA, network meta-analysis; SLR, systematic literature review

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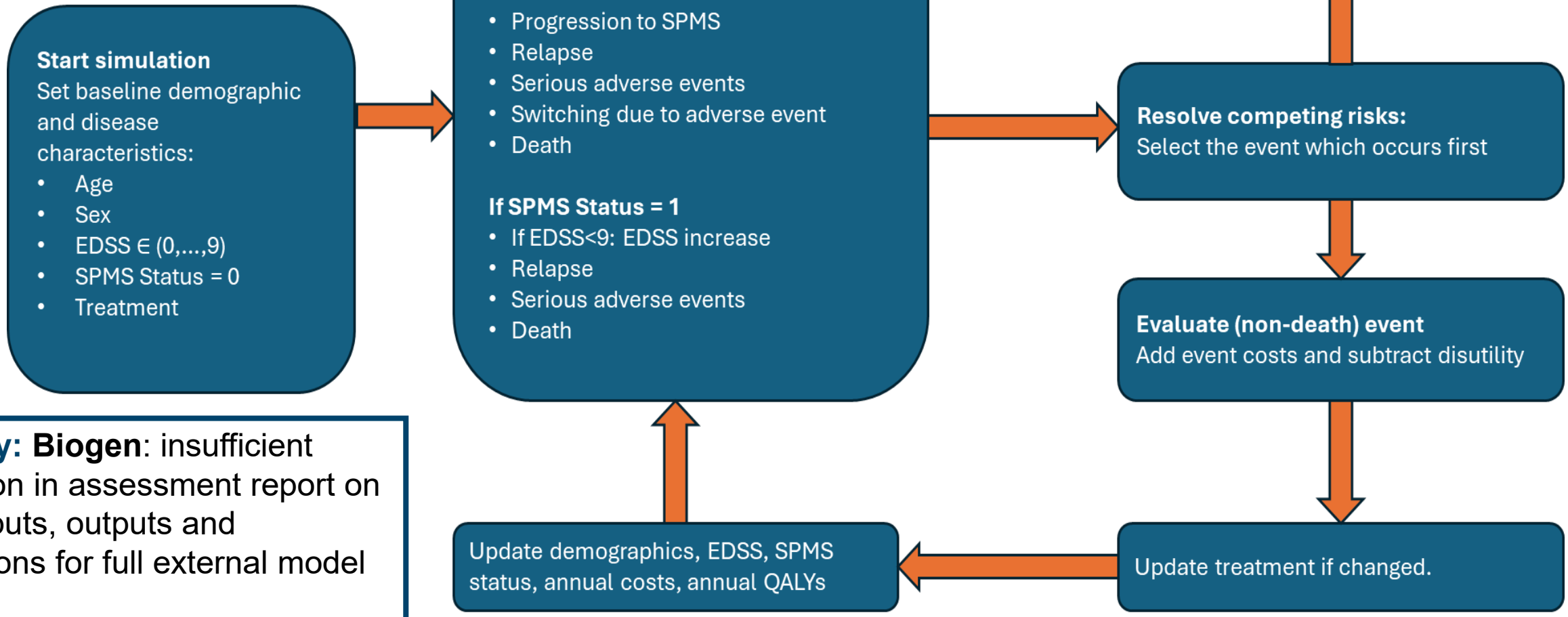
Link to supplementary appendix: utilities in the EAG's model and costs and utilities for SAEs

EAG's clinical effectiveness model

Link to supplementary appendix: DES models

EAG built an individual-level discrete-event simulation (DES) model in R

Event rates based on some or all baseline demographic & disease characteristics



Company: Biogen: insufficient information in assessment report on model inputs, outputs and assumptions for full external model validation

Abbreviations: CDP6, confirmed disease progression at 6 months; EDSS, Expanded Disability Status Scale; QALY, quality-adjusted life year; SPMS, secondary progressive MS

How the EAG incorporated evidence into model

Input	Assumption and evidence source
Baseline characteristics	Baseline characteristics: AFFIRM; Initial EDSS distribution for HA RRMS: MS Registry; Baseline SAEs and discontinuation from AFFIRM and ANTELOPE
Efficacy estimates	• Baseline disease history from MS Registry. Treatment effects from all RRMS population in NMA for natalizumab and comparators • Class effect assumed for treatments with missing NMA outcomes • No treatment effects assumed for SPMS population
Utilities	• Health State Utilities by EDSS: UK MS Survey 2005 by Orme et al. 2007 • Relapse disutility: Orme et al. 2007, caregiver disutilities: Acaster et al. 2013
Costs and resource use	• Health state costs: Tyas et al. 2007; Relapse costs: Hawton et al 2016 • Treatment administration and monitoring costs: Past RRMS TAs, PSRRU, company submissions, 2021/22 National Cost Collection Data Publication • Cost for JCV testing included for natalizumab and natalizumab biosimilar
SAEs	• One off cost and disutility per event + annual disutility for SAEs • Prevalence from previous RRMS TAs weighted by occurrence in AFFIRM with % PML from TOP
Discontinuation	• If stop treatment, can switch to different treatment. People stop treatment once reach EDSS7. • If progress to SPMS have siponimod or beta-interferon for rest of time in model
Mortality	• Standardised mortality ratio (SMR) for MS patients from Jick 2014 • General population mortality from ONS data

EDSS, Expanded Disability Status Scale; HA, highly active; JCV, John Cunningham virus; MS, multiple sclerosis; NMA, network meta-analysis; ONS, Office for National Statistics; PML, Progressive Multifocal Leukoencephalopathy; PSRRU: personal social services research unit; RRMS, relapsing-remitting MS; SAE, serious adverse event; SPMS, secondary progressive MS; TA, technology appraisal

Treatment effectiveness in model

Treatment effectiveness based on MS registry data with NMA treatment effects applied

Background:

Sources of clinical effectiveness evidence in company model

Event rates

Natural history data from MS registry

Exponential survival & continuous-time multistate models fit to interval censored data:

	MS Registry	Time to event data for:
HA RRMS	HA RRMS	time to EDSS increase, progression to SPMS, relapse in HA RRMS
HA RRMS	All RRMS	time to EDSS decrease in HA RRMS
SPMS	All SPMS	time to EDSS increase and relapse SPMS

Apply treatment effects

NMA relative treatment effects applied to:

- **MS Registry data for:** EDSS increase (CDP6) and relapse (ARR)
- **AFFIRM baseline rates for:** SAEs and discontinuation due to AEs

Events in SPMS not treatment specific

- No treatment effect was assumed for EDSS decrease, or mortality
- Natalizumab and biosimilar considered separate clinical products, associated with different costs and QALYs
- CDP6 used for EDSS increase as preferred by past committees

AE, adverse event; ARR, annualised relapse rate; CDP6, confirmed disease progression at 6 months; EDSS, Expanded Disability Status Scale; HA, highly active; NMA, network meta-analysis; MS, multiple sclerosis; RRMS, relapsing-remitting MS; QALY, quality-adjusted life year; SAE, serious adverse event; SPMS, secondary progressive MS

Key issue: Use of MS Registry data

Link to supplementary appendix: MS registry data and MS Registry results

Previous TAs used natural history data that resulted in high occupancy of worst EDSS states

Background: Previous TAs:

- Markov models with EDSS based health states. Transition rates through EDSS states from British Columbia Multiple Sclerosis (BCMS; from 1980 to 1995) or London Ontario MS databases (data from 1970s and 1980s)
- Treatment effects by individual trials and NMA

Past committee conclusions: Natural history data from BCMS and London Ontario does not represent NHS population → collected before use of DMTs

- Current treatment and care for MS improved prognosis → progression to higher EDSS states less common.

EAG comments: DES more appropriate way to model MS:

- Reflects treatment aims to reduce relapse events & disability progression, not EDSS severity or SPMS status
- Allows accurate modelling of current treatments and treatment sequencing

Natural history data from MS Registry (collected in UK between 2017-2024) captures outcomes with current available treatments

Registry analysis not a randomised, controlled and blinded → not appropriate for estimation of relative effects.

Company: Biogen: limited information on MS Registry data and interpretation (e.g. follow-up duration for each treatment, whether length of follow-up impacted by treatment)

- No justification for using baseline rates for natalizumab vs. other treatments
- Relative outcomes from MS Registry do not align with mean rankings from NMA
- Show number of people and events in MS Registry data and comment on potential impact of low numbers

NICE  Is the use of MS Registry data appropriate?

Abbreviations: DES, discrete event simulation; DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; NMA, network meta-analysis; SPMS, secondary progressive MS

Key issue: Efficacy assumptions

Sandoz: should assume equal clinical effectiveness between originator and biosimilar natalizumab

Company

Sandoz: Concerned that natalizumab and biosimilar considered separate clinical products

- Clinical data from small studies focussed on meeting regulatory requirements → biosimilar at disadvantage if treated as separate product
- NICE position statement on biosimilars: approval for originator automatically applies to future biosimilar → should consider natalizumab and biosimilar equal effective and differing only in costs

- Proposes cost comparison approach should be considered, assuming equal effectiveness for natalizumab, ocrelizumab and ofatumumab

Biogen: Unclear from report what assumptions made where no relative efficacy data available from NMAs.

EAG response to consultation:

- Treatments with outcomes missing from NMA assumed equivalent to those in same class for that outcome
- **Scenario:** assuming equal effectiveness for natalizumab and biosimilar

Is it appropriate to assume equal efficacy of:

a) originator and biosimilar natalizumab for all outcomes?
b) natalizumab, ocrelizumab and ofatumumab for all outcomes?
c) treatments in the same class where NMA outcomes are missing?

Abbreviations: CDP, confirmed disease progression at 6 months; NMA, network meta-analysis

Subsequent treatments in EAG's model

Start simulation
Set baseline demographics and disease characteristics:
- Age
- Sex
- EDSS (0…9)
- SPMS status = 0
- Treatment

Interventions: Natalizumab originator and biosimilar
Comparators:
- Glatiramer acetate
- Interferon beta 1a and 1b
- Alemtuzumab with some proportion on ocrelizumab
- Cladribine tablets
- Fingolimod
- Ofatumumab
- Ponesimod
- AHSCT

Rescue therapy
- No change
- Natalizumab originator and biosimilar
- Alemtuzumab with some proportion on ocrelizumab
- Cladribine tablets
- AHSCT

Final therapy
- No change
- Natalizumab originator and biosimilar
- Alemtuzumab with some proportion on ocrelizumab
- Cladribine tablets
- AHSCT

SPMS: average 'basket' of approved therapies used → interferon beta or Siponimod if patient:
- Can walk 10m or more (EDSS <7)
- >18 years old
- No contraindications
- Informed of and agreed to stopping criteria
- Activity (new lesions/ enhancements) on MRI

AHSCT, autologous haemopoietic stem cell transplant; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; SPMS, secondary progressive MS

Key issue: Treatment waning and sequencing

EAG assumes equal distribution of subsequent treatments after progression on 2nd line DMTs

Background: Past TAs noted issues with lack of treatment switching in model and assuming treatment discontinuation as proxy for loss of effect, despite lack of evidence from trials

EAG model includes:

1. Discontinuation due to AEs as proxy to waning → stopping rates from AFFIRM (originator natalizumab), ANTELOPE (biosimilar natalizumab), NMA treatment effects applied to baseline AFFIRM rates (comparators)
2. Treatment switching: Subsequent treatments in model as per NHS algorithm at 3rd line onwards except for ofatumumab
   - ❖ Equal likelihood of having any available subsequent treatment when switch.

Company: Biogen: Cladribine, ID6263: committee agreed broader definition of discontinuation (beyond only AEs):

- Treatment switching should be reflected in discontinuation rates.
- Committee preferred time to next treatment from CLASSIC-MS for discontinuation data for MS treatments

EAG: maintains preference for using discontinuation due to AEs to inform stopping rates

- CLASSIC-MS is all-cause discontinuation data in different population (active not HA RRMS)
- No data on treatment sequencing available from past TAs or MS registry

Scenarios: a) excluding treatment switching – no treatment after 2nd line, b) including ofatumumab at 3rd line onwards

Should all cause discontinuation or discontinuation due to AEs be used to represent waning? How are subsequent treatments chosen in the NHS? Is an equal distribution of treatments at 3rd line onwards clinically plausible?

AE, adverse event; HA, highly active; NMA, network meta-analysis; MS, multiple sclerosis; RRMS, relapsing-remitting MS; TA, technology appraisal

Validity of model outputs

Link to supplementary appendix: Full time to event outputs 1, 2, 3

Treatment effectiveness based on MS registry data with NMA treatment effects applied

- Average starting age: **36** years
- Average age at death: **77** years
- Average time to disease progression (i.e., EDSS disability) : **10.4** years
- Average time to SPMS: **9.7** years
- % progressed to SPMS: **86%**
- % who received a subsequent treatment line (note this is similar across treatments):
  - 35% of patients receive 2nd and 3rd line treatments
  - 34% of patients receive 2nd, 3rd and 4th line treatments

Question for clinical and patient experts: Does this align with your experience of MS in clinical practice?

Key outputs from the EAG's model

	Natalizumab originator		Natalizumab biosimilar IV	Mean across all MS treatments
	IV	SC		
Average time to event (years)				
Progression	10.32	10.37	10.42	**10.36**
Relapse	10.91	11.01	10.96	**10.92**
Average time spent on treatment (years)				
2nd line	9.62	9.81	9.75	**9.67**
3rd line	2.59	2.55	2.7	**2.66**
4th line	1.1	1.1	1.22	**1.11**
Average time spent in severity states (years)				
EDSS 0	1.46	1.47	1.44	**1.48**
EDSS 1	2.64	2.65	2.71	**2.63**
EDSS 2	5.04	5.27	5.16	**5.10**
EDSS 3	6.81	6.55	6.43	**6.54**
EDSS 4	7.71	7.55	7.59	**7.56**
EDSS 5	6.97	6.89	6.98	**6.95**
EDSS 6	5.03	5.15	5.07	**5.20**
EDSS 7	0.19	0.2	0.2	**0.20**
EDSS 8	0.00	0.01	0.00	**0.00**
EDSS 9	0.00	0.00	0.00	**0.00**

EDSS, Expanded Disability Status Scale; IV, intravenous; MS, multiple sclerosis; SPMS, secondary progressive MS; SC, subcutaneous

Key issue: Mortality

EAG assumes excess mortality from MS not EDSS specific

Background: Past committees agreed mortality risk increases with disability → criticised MS models for not using EDSS specific mortality rates as suggests no mortality benefit from slowing disease progression

EAG base case: single all cause excess SMR for MS vs. general public from Jick et al 2014 → not EDSS specific

Company: Biogen: EAG in cladribine appraisal (ID6263) preferred EDSS specific mortality rates from Pokorski et al (1997)
Sandoz: widely recognised that mortality risk increases with severity → EAG's base case assumption implausible

- Supported by more recent UK data by Harding et al. (2018)

Technical team: ID6263 (cladribine): current treatments improved mortality. Deaths from MS now rare → not reflected in old data set by Pokorski et al.

EAG: maintain preference for Jick et al after consultation (rates informed by 1,822 MS patients)
Scenarios: applying EDSS specific SMRs from a) Pokorski (1997) b) Harding et al (2018)

MS specific SMRs in the EAGs model

EAG base case: all cause excess SMR for MS, Jick et al (2014)	**Mean HR** 1.68
Excess SMR for MS patients by severity	
Pokorski (1997), EAG scenario	
EDSS 0-3 (mild)	1.6
EDSS 4-6 (moderate)	1.84
EDSS 7-9 (severe)	4.44
Harding et al. (2018), EAG scenario	
EDSS 4-5.5	2.02
EDSS 6-6.5	3.86
EDSS 7-7.5	4.76
EDSS 8-8.5	22.17
EDSS 9-9.5	60.74

Do mortality rates increase with increasing disability in people with HA RRMS? If yes, which source of SMRs should be used in the model?

Abbreviations: EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; SMR, standardised mortality ratio

Key issue: Natalizumab extended dosing regimen

Biogen and Sandoz say extended interval dosing should be included in model

Background: EAG model and licence: natalizumab 300mg given every 4 weeks

- SmPC: Natalizumab given 4 weekly, but 6 weekly extended interval dosing (EID) may be used in anti-JCV antibody positive patients to lower risk of progressive multifocal leukoencephalopathy (PML)

Company

Biogen: EID used in some people to reduce the risk of PML or during pregnancy

- EID cost saving to a) NHS (reduced drug costs and HCP time for drug administration), b) patients and carers (reduced travel and in-clinic time).
- Phase 3b RCT (NOVA) suggest most patients who have stable dose of natalizumab 4 weekly can switch to natalizumab 6 weekly without meaningful loss of efficacy and safety

Sandoz: EID should be included in economic analysis.

- Clinical expert advice: ~25% of patients had EID natalizumab dosing in 1 UK centre

Stakeholder comments: 6-weekly natalizumab EID now widespread across the NHS, mitigates some of PML risk and reduces cost over the course of a calendar year

EAG comments to consultation

Scenario: uses 6 weekly dosing for everyone having natalizumab originator and biosimilar as extreme scenario

Would extended interval dosing be used for natalizumab in people with HA RRMS?
If yes, what in what proportion of the population?

Abbreviations: EID, extended interval dosing; HA, highly active; HCP, healthcare professional; JCV, John Cunningham virus; RCT, randomised controlled trial; RRMS, relapsing-remitting MS; PML, progressive multifocal leukoencephalopathy; QALY, quality-adjusted life year; RCT, randomised controlled trial

Key issue: Modelling SC and IV natalizumab

EAG assumes equal resource use and benefits for IV and SC natalizumab

Background: Natalizumab licenced as SC injection or IV infusion, natalizumab biosimilar has a licence for IV only

EAG: clinical advisers suggest no differences in resource use between SC and IV in clinical practice.
Base case: Equal administration costs for SC and IV natalizumab (13 x the cost of a day case per year)

Company: Biogen: clear differences in costs and benefits for IV and SC natalizumab. SC natalizumab has:

- Reduced burden: enables care closer to home, reduces heath inequalities by reducing travel and treatment time
- Cost savings: reduced administration costs and associated patient costs (transport, childcare, lost patient and caregiver productivity). Silingardi et al. (2023): total staff time saving of 1 hr 32 mins for SC vs IV natalizumab

Model misses savings from SC natalizumab home-delivery service (Biogen funded delivery & nurse administration)
Sandoz: cost code used for IV administration lower in budget impact test than used in EAG's model

Professional and patient organisations:

- Unclear if homecare supported in NHS
- Use of SC vs IV natalizumab differs, based on:
  - Local practice → largest driver is pressures around infusion capacity
  - Patient preference and ease of venepuncture
- Would not expect different clinical outcomes with different formulations
- Would not normally switch between formulations once established on dose

NICE Is it appropriate to assume equal costs and resource for IV and SC natalizumab? Should home-delivery of SC natalizumab be modelled?

Abbreviations: IV, intravenous; SC, subcutaneous

Key issue: Costs for anti-JCV testing

EAG includes costs for anti-JCV testing for originator or biosimilar natalizumab

Background: anti-JCV testing required before started originator or biosimilar natalizumab. Anti-JCV tests provided by both Biogen and Sandoz

EAG: clinical advice suggests Biogen-funded JCV test not widely available → unclear what % have funded test
Base case: include JCV test costs for both natalizumab and biosimilar.
Scenario: JCV test costs only included for biosimilar.

Company
Biogen: JCV testing nationally available and funded for all UK patients being considered for natalizumab. Exclude cost of JCV test from model.
Sandoz: provides JCV testing to NHS → not aware of issues in accessing tests funded by either Biogen or Sandoz. Exclude cost of JCV test from model for both natalizumab originator and biosimilar

Should the cost of JCV testing be included in the model?
If so, how?

Link to supplementary appendix: PML and anti-JCV testing requirements

Abbreviations: JCV, John Cunningham virus; PML, progressive multifocal leukoencephalopathy.

Natalizumab and Tyruko (natalizumab biosimilar) for treating highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ Summary

NICE National Institute for Health and Care Excellence

Cost effectiveness results

Cost-effectiveness results are reported in Part 2 because they include confidential discounts

- Cost effectiveness results include updated tender prices for MS treatments.
- Some treatments have differing MPSC prices by region. As per NICE methods guide:
  - Scenarios provided using lowest and highest regionally available prices
  - Midpoint used in scenarios varying other assumptions

EAG, external assessment group; ICER, incremental cost-effectiveness ratio; IV, intravenous; MPSC, Medicines Procurement and Supply Chain; QALY, quality-adjusted life year; SC, subcutaneous;

EAG scenarios

#	Analysis	Description
1	Natural history data = all RRMS	Baseline rates & EDSS starting distribution: all RRMS from MS Registry
2	NMA = random effects	Uses all RRMS random effects results from the NMA for treatment effects
3	Including JCV testing	Excludes one-off cost (£247) for JCV testing for originator natalizumab IV and SC but includes for natalizumab biosimilar IV.
4	Using lowest price generic	Switches to using lowest price generic for comparators.
5	SC administration costs	Reduces administration cost by 0.5x for Natalizumab-SC
6	Using HA RRMS NMA	HA RRMS for ARR, all RRMS NMA for other outcomes. Restricted to treatments included in the HA RRMS NMA network
7	EDSS specific mortality	EDSS specific SMRs from Pokorski et al
EAG scenarios provided after consultation		
8	Clinical equivalence	Equal treatment effects (efficacy & safety) for IV natalizumab originator & biosimilar
9	Including EID	Uses EID for natalizumab originator (IV & SC) and natalizumab biosimilar IV
10	OPERA RRMS utilities	Uses utilities from OPERA for RRMS
11	CLARITY RRMS utilities	Uses utilities from CLARITY for RRMS
12	TA127 carer disutilities	Uses TA127 carer disutilities from Loveman et al (Alzheimer's)
13	EDSS specific mortality	Uses EDSS specific mortality data from Harding et al.
14	CDP3 for missing CDP6	Uses NMA estimates where CDP3 used for studies with missing CDP6
15	Lowest regional prices	Uses lowest regional price for alemtuzumab, glatiramer acetate and cladribine
16	Highest regional prices	Uses highest regional price for alemtuzumab glatiramer acetate and cladribine
17	Ofatumumab at 3rd line +	Subsequent treatments include people have ofatumumab at 3rd line onwards
18	No treatment after 2nd line	People switch to placebo after stopping treatment

AE, adverse event; ARR, annualised relapse rate; CDP3/6, confirmed disease progression at 3/6 months; EDSS, Expanded Disability Status Scale; EID, extended interval dosing; HA, highly active; IV, intravenous; JCV, John Cunningham virus; NMA, network meta-analysis; MS, multiple sclerosis; RRMS, relapsing-remitting MS; QALY, quality-adjusted life year; SAE, serious adverse event; SC, subcutaneous; SPMS, secondary progressive MS, SMR, standardised mortality rate; TA, technology appraisal

Natalizumab and Tyruko (natalizumab biosimilar) for treating highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy

Supplementary appendix

NICE National Institute for Health and Care Excellence

Decision problem

Population, intervention, comparators and outcomes from the scope

	Final scope	EAG
Population	Adults with highly active relapsing remitting multiple sclerosis despite a full and adequate course of treatment with at least one disease modifying therapy	People with highly active relapsing-remitting multiple sclerosis after at least one disease modifying therapy
Intervention	• natalizumab originator (Tysabri) • natalizumab biosimilar (Tyruko)	As scope
Comparators	Glatiramer acetate, interferon beta 1a, interferon beta 1b, alemtuzumab, cladribine tablets, fingolimod, ocrelizumab (if alemtuzumab contraindicated or otherwise unsuitable), ofatumumab, ponesimod, autologous haematopoietic stem cell transplantation	Clinical advice suggests restriction on ocrelizumab not used in clinical practice → ocrelizumab used for full population
Outcomes	Relapse rate, severity of relapse, disability (for example, expanded disability status scale [EDSS]), disease progression, symptoms of multiple sclerosis (such as fatigue, cognition, and visual disturbance), freedom of disease activity (for example lesions on MRI scans), mortality, adverse effects of treatment, health-related quality of life.	Did not consider severity of relapses or symptoms of multiple sclerosis due to time constraints

EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging

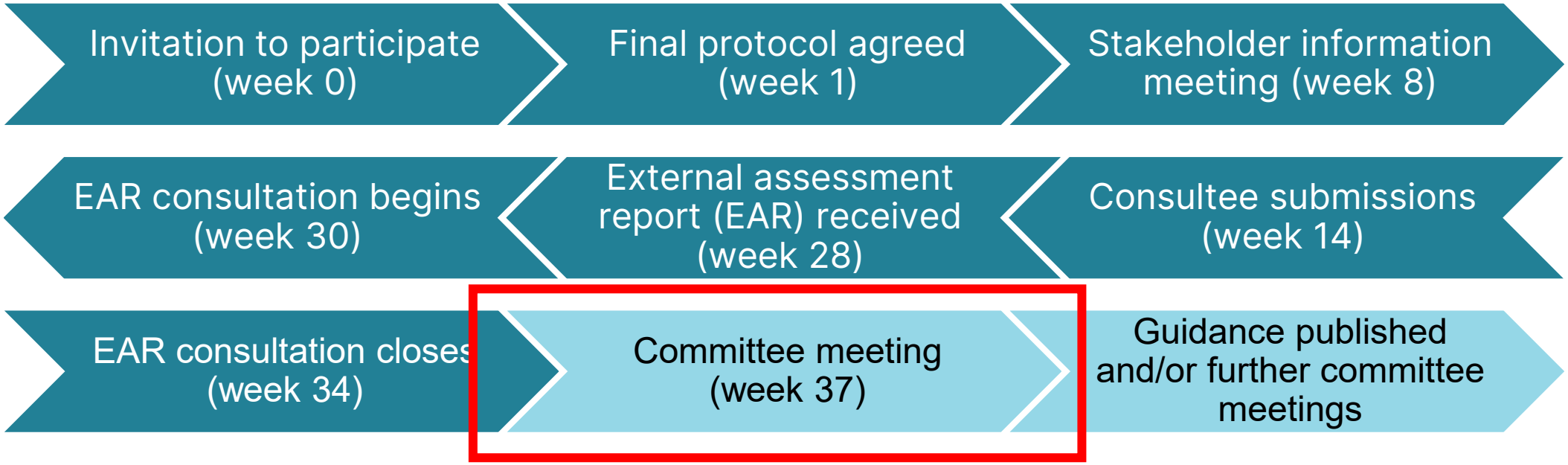
Background: previous natalizumab appraisals

Population	Tysabri (originator)	Tyruko (biosimilar)
Rapidly evolving severe RRMS *≥2 disabling relapses in 1 year, and with ≥1 Gadolinium enhancing lesions on brain MRI or significant increase in T2 lesion load vs. previous recent MRI.*	**Recommended** in TA127	**Recommended**: TA127 recently updated to include use of biosimilars for RES RRMS
Licence extension for appraisal: **Highly active disease despite a full and adequate course of treatment with ≥1 disease modifying therapy (DMT).**	Appraised in TA127 for patients with high disease activity despite treatment with beta interferon. • SENTINAL study considered use of natalizumab in combination with beta interferon (not licensed because of safety concerns) • **Not recommended:** no direct evidence for natalizumab monotherapy in this population	**Not appraised**.

Link to main slides: types of multiple sclerosis

RES, rapidly evolving severe; MRI, magnetic resonance imaging; RRMS, relapsing-remitting multiple sclerosis, TA, technology appraisal

Multiple Technology Appraisal (MTA) process



Abbreviations: EAR, External Assessment Report; MTA, Multiple Technology Appraisal.

Background: previous natalizumab appraisals

Natalizumab already recommended for RES RRMS but not HA RRMS

2007 NICE STA (TA127)
- Originator natalizumab recommended in RES RRMS
- Not recommended in HA RRMS

2022 Originator natalizumab scoped for HA RRMS as monotherapy → terminated as NICE concluded no separate appraisal warranted

2024 TA127 updated to allow use of biosimilars in RES RRMS

TA127: Originator natalizumab + beta interferon appraised for people with high disease activity despite treatment with beta interferon.
- Combination therapy not licensed because of safety concerns
- **Not recommended as monotherapy:** no direct evidence in population

2023 Natalizumab biosimilar (Tyruko) licenced in UK

2025 NICE MTA of natalizumab and biosimilar in HA RRMS
- NICE's biosimilar position statement: *Biosimilars will only be appraised together with the reference products as part of a Multiple Technology Appraisal.*
- Originator natalizumab not appraised in HA RRMS population as monotherapy: MTA necessary to establish cost effectiveness

HA, highly active; MTA, multiple technology appraisal; RES, rapidly evolving severe; RRMS, relapsing-remitting MS; STA, single technology appraisal

Link to main slides: technology

Definition of outcomes in trials

Link to main slides: key clinical evidence

Treatments offered to ambulatory patients only EDSS ≤5 at screening

- Relapse: new or recurrent neurological symptoms lasting ≥24 hours without fever or infection; separate events are at least 30 days apart
- Disability assessed using **Expanded Disability Status Scale (EDSS)**
- Disability that lasts for 3 or 6 months is 'confirmed disability progression' CDP3/6M
- Defined as for baseline score of:
  - 3.0 to 5.0 - 1-point increase in EDSS
  - 5.5 to 6.5 - 0.5 point increase in EDSS
- MRI measures include the development of new T2 lesions, enlarging T2 lesions and gadolinium-enhancing lesions.

Source: *http://www.msunites.com/understanding-the-expanded-disability-status-scale-edss-scale/*

Progressive multifocal leukoencephalopathy (PML)

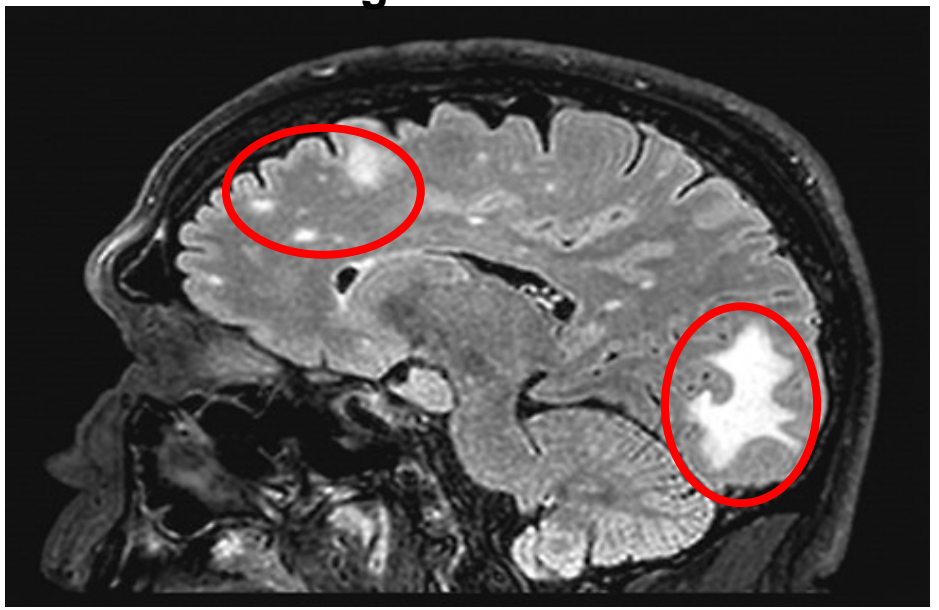
Potentially fatal side effect of natalizumab causing white matter inflammation in brain

- Suppression of immune system can activate John Cunningham human polyomavirus (JCV) leading to rare but potentially fatal demyelinating brain disorder, PML
- Increase risk of PML in several DMTs → fingolimod, ocrelizumab, ofatumumab, cladribine, ponesimod, alemtuzumab, natalizumab
- Natalizumab voluntarily withdrawn from market in 2005 → 3 PML cases in clinical trials (~1:1000 (95% CI, 0.2 to 2.8)
- Reintroduced 2006 with intensive global risk-management program

Extended interval dosing: may reduce blood levels of natalizumab so some immune cells can pass into brain and prevent PML.

- Anti-JCV testing available on NHS: See key issue slide

MRI showing PML lesions in brain



PML in originator natalizumab studies: No PML reported in AFFIRM or ANTELOPE (pivotal RCTs for natalizumab and biosimilar). Observational data submitted by company shows low rates:

Study	Natalizumab	N	Follow up	PML cases, N (%)
TOP	300 mg IV	6,321	15 years	53 (0.9%)
REFINE	300 mg SC after 300mg IV for at least 12 months	289	60 weeks	1 (1.9%)
NOVA Part 2	300 mg IV Q6W for 36 weeks	153	48 weeks	0 (0%)

CI, confidence interval; DMT, disease-modifying therapy; IV, intravenous; JCV, John Cunningham virus; mg, milligram; MRI, magnetic resonance imaging; N, number; PML, progressive multifocal leukoencephalopathy; SC subcutaneous. Link to main slides: clinical expert perspectives, JCV testing

Treatment pathway

Drug name	Administration route and frequency	NICE TA	NICE recommended for
Recommended for RRMS			
Glatiramer Acetate	SC injection, OD or 3 times weekly	TA527	RRMS
Interferon beta-1a	IM injection, QW or SC injection, 3 times weekly	TA527	RRMS
Peginterferon beta-1a	SC injection, Q2W	TA624	RRMS
Interferon beta-1b	SC injection, every other day	TA527	RRMS with 2 or more relapses with past 2 years. Currently not available in the UK
Ofatumumab	SC injection, Q4W	TA699	active RRMS defined by clinical or imaging features
Ponesimod	Oral, OD	TA767	active RRMS defined by clinical or imaging features
Recommended for RRMS in specific situations or specific subtypes			
Ocrelizumab	IV infusion, 6 monthly	TA533	Active RRMS only if alemtuzumab is contraindicated or otherwise unsuitable
Recommended for previously treated RRMS			
Alemtuzumab	IV infusion, OD	TA312	HA RRMS despite a full and adequate course of treatment with at least 1 DMT OR rapidly evolving severe RRMS
Fingolimod	Oral, OD	TA254	HA RRMS with unchanged or increased relapse rate or ongoing severe relapses vs. previous year despite treatment with beta interferon
Cladribine	Oral, 4-5 days over 2-week courses	TA616	HA MS only if RES RRMS or disease responded inadequately to treatment with DMT

DMT, disease-modifying therapy; HA, highly active; IM, intramuscular; IV, intravenous; OD, once daily; QW, weekly; Q2W, 2 weekly; Q4W, 4 weekly; RES, rapidly evolving severe; RRMS, relapsing-remitting MS; SC subcutaneous; TA, technology appraisal

Key issue: Classification of RRMS

Link to main slides: types of MS

Variation in definition of highly active RRMS across NICE TAs

Background: Previous MS TAs and studies used different definitions of highly active RRMS

EAG: lack of clinical consensus regarding subgroup definitions in RRMS

- Used broad definition to encompass most HA RRMS definitions used in existing appraisals and studies

Company: Biogen: welcome NICE aligning subgroup definitions across appraisals

- Inconsistency means challenging to select appropriate evidence for decision making
- EAG's target population (HA RRMS) should specify at least 12 months of prior DMT → rules out intolerance
- RES is subgroup of HA RRMS (2 relapses in 12 months considered to meet HA and RES criteria)

Clinical experts: Variable eligibility requirements for DMTs major challenge for prescribing clinicians.

- In clinical practice, anticipate HA RRMS criteria same as other DMTs: "unchanged relapse rate or breakthrough disease despite full course of DMT defined using standard clinical and MRI criteria"

Definitions of highly active RRMS in past NICE TAs

Definition of highly active RRMS in FDG	Used in TA #:
1 relapse in previous year on DMT and MRI activity (where specified, at least 9 T2 lesions in cranial MRI or 1 Gd+ lesion)	127 (originator natalizumab), 320 (dimethyl fumarate), 616 (cladribine), 767 (ponesimod)
Unchanged or increased relapse rate or ongoing severe relapses vs. previous year despite treatment with β interferon	303 (teriflunomide), 320 (dimethyl fumarate)
Highly active disease despite full & adequate course of treatment with ≥1 DMT	312 (alemtuzumab)
Active disease defined by clinical or imaging features	533 (ocrelizumab), 1025 (ublituximab)
Previous DMT stopped due to lack of efficacy	699 (ofatumumab)
Unchanged or increased clinical or radiological evidence of disease activity despite treatment with ≥1 DMT	**EAG's preferred definition (ID6369)**

How is highly active RRMS defined in clinical practice? Is the EAG's definition appropriate?

DMT, disease-modifying therapy; HA, highly active; MRI, magnetic resonance imaging; RES, rapidly evolving severe; RRMS, relapsing-remitting MS; TA, technology appraisal

Overview of key evidence for natalizumab

No RCTs in HA RRMS, results in all RRMS favour originator natalizumab vs placebo and fingolimod

RCT name	AFFIRM (N=943)	ANTELOPE (N=265)	REVEAL (N=111)	Saida 2017 (N=94)
Intervention	Originator natalizumab	Biosimilar natalizumab	Originator natalizumab	Originator natalizumab
Comparator	Placebo	Originator natalizumab	Fingolimod O0.5	Placebo
Median follow-up	2 years	11 months	52 weeks	24 weeks
Results: intervention vs comparator *(HR/RRs less than 1 favour intervention, over 1 favour comparator)*				
Timepoint	24 months	24 weeks	6 months (unless stated)	6 months
ARR	RR 0.32 (0.24, 0.41)	biosimilar 0.21; originator 0.15	RR 0.09 (0.01, 0.72) at 9 months	RR 0.31 (0.15, 0.62)
CDP6, HR	0.46 (0.33, 0.64)	NR	NR	NR
Change in Gd+ lesions	3% vs. 28%	13% vs. 17%	34% vs. 53%	NR
Change in T2 lesions	43% vs. 85%	40% vs. 43%	40% vs. 63%	NR
SAEs	19% vs. 24%	NR	0% vs. 4%	9% vs. 24%

ARR, annualised relapse rate; CDP, confirmed disease progression at 3/6 months; DMT, disease-modifying therapy; HA, highly active; HR, hazard ratio; N, number; NR, not reported; RCT, randomised controlled trial; RR, rate ratio; RRMS, relapsing-remitting MS; SAEs, severe adverse events

Link to main slides: clinical evidence summary

Originator natalizumab studies in company submissions

Results support long-term treatment effect & comparable efficacy of IV/SC and 4/6 weekly dosing

TOP study (15-year final analysis, July 2007 to November 2022, full population)

Outcome	UK population (n=134)		Global population (n=6,321)	
	Time (years)	Result	Time (years)	Result
ARR reduction vs pre-treatment year	15	93% [p<0.0001]	15	91% [p<0.0001] HA RRMS subgroup (over 1 prior DMT): [redacted]%
Cumulative CDW (CDP)	10.5	60%	15	43%
Cumulative CDI	15	46%	15	40%

- No new safety signals. Low incidence of opportunistic infections, PML, malignancies
- Comparable efficacy and safety for people who switched to SC natalizumab → global and HA RRMS populations

Other supportive studies

Study	Design	Result
DELIVER	Phase 1b, 32-week randomised, open-label parallel group, 300 mg natalizumab SC vs IV vs IM	Similar PK parameters with SC and IV from 2nd dose onwards
REFINE	Phase 2, 72-week, randomised, blinded, dose-ranging, 300 mg or 150 mg natalizumab SC vs IV	Comparable PK and efficacy outcomes (number of MRI lesions and ARR) for 300 mg IV and SC
NOVA	Phase 3b, 72-week,randomised open-label study, 300 mg natalizumab IV or SC Q6W (EID) vs Q4W	No meaningful loss of efficacy and safety for natalizumab EID (both SC and IV formulations)

ARR, annualised relapse rate; CDI, confirmed disability improvement; CDP, confirmed disease progression; CDW, confirmed disability worsening DMT, disease-modifying therapy; EID, extended interval dosing; HA, highly active; IV, intravenous; mg, milligram; MRI, magnetic resonance imaging; N, number; PML, progressive multifocal leukoencephalopathy, PK, pharmacokinetic; Q4/6W, 4/6 weekly; SC subcutaneous

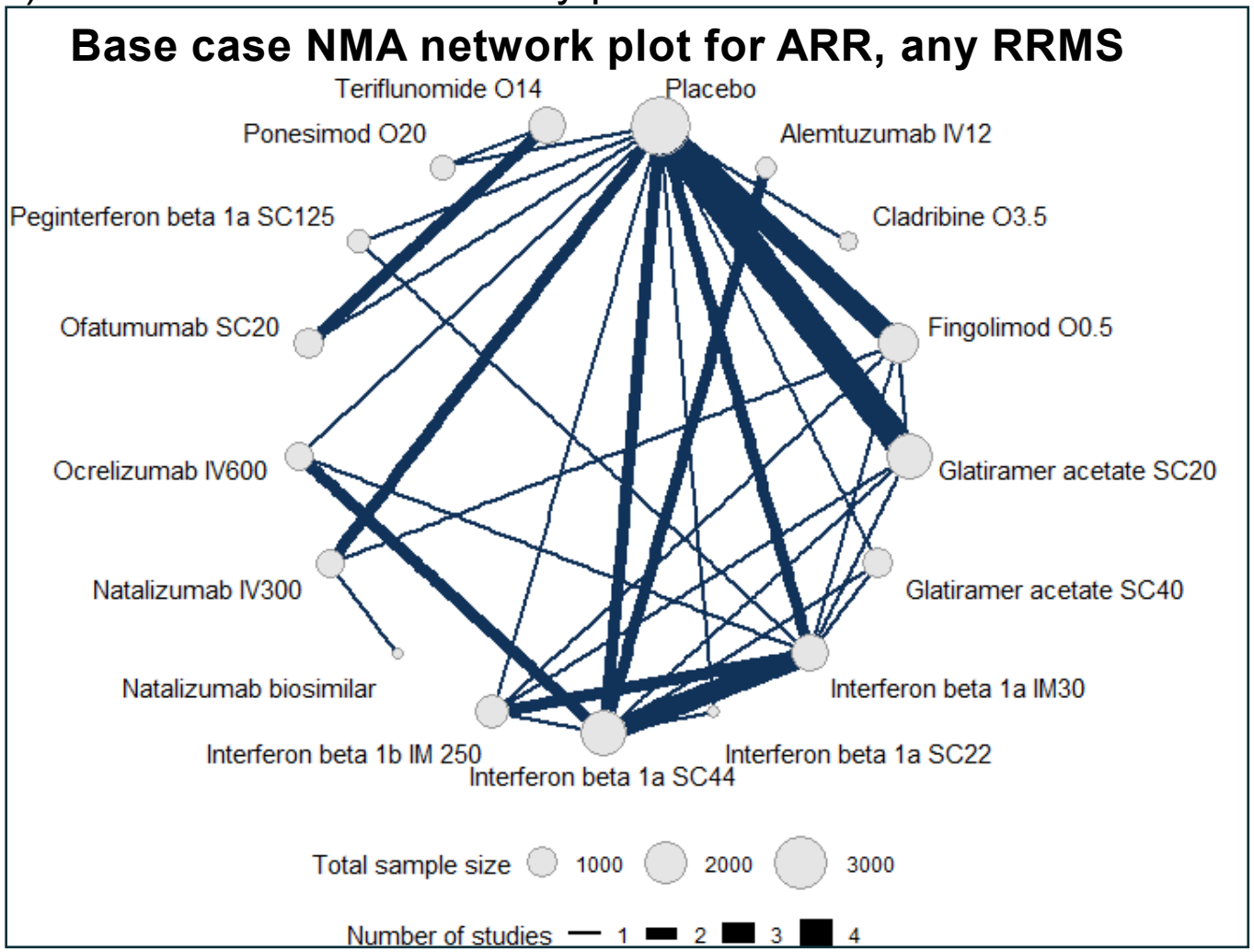
Overview of EAG's NMA

EAG's NMA focuses on studies in all RRM due to limited RCTs in HA RRMS

Results: 42 RCTs (N=22,409 participants) reported relevant data:

- 40 RCTs (N=21,671) for general RRMS
- 8 RCTs (N=2,097) included HA RRMS → only possible to form network for ARR: see supplementary appendix for full results

Base case NMA network plot for ARR, any RRMS



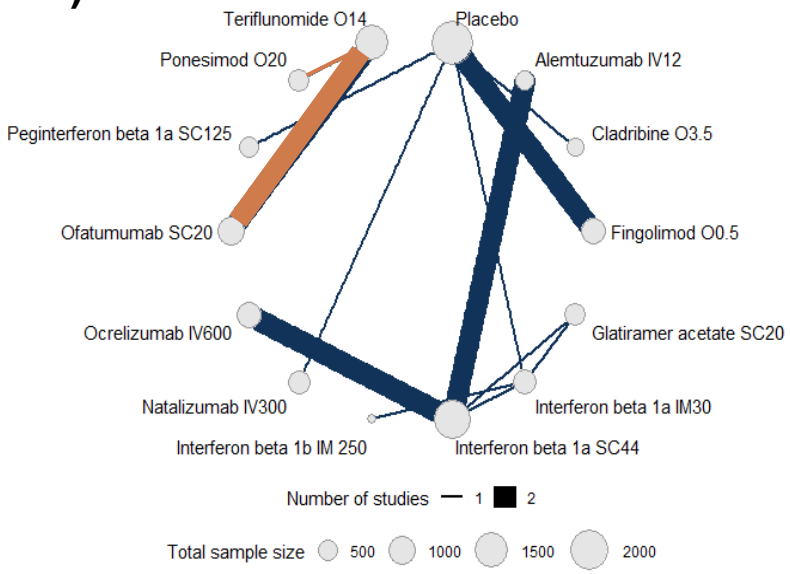
ARR, annualised relapse rate; HA, highly active, IV, intravenous RCT, randomised controlled trial; RRMS, relapsing-remitting MS; N, number; NMA, network meta-analysis; SC subcutaneous

EAG's NMA, other key outcomes, all RRMS

Data paucity means not all treatments included in NMA for key NMA outcomes, especially CDP6

NMA network plots for a) CDP6, b) SAEs (updated after consultation) and c) discontinuations due to AEs. Disconnected treatments shown with orange lines

a)



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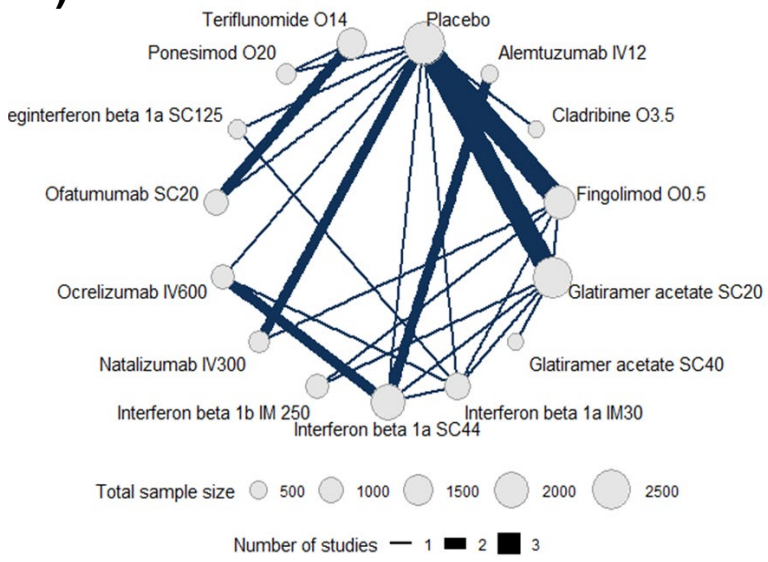

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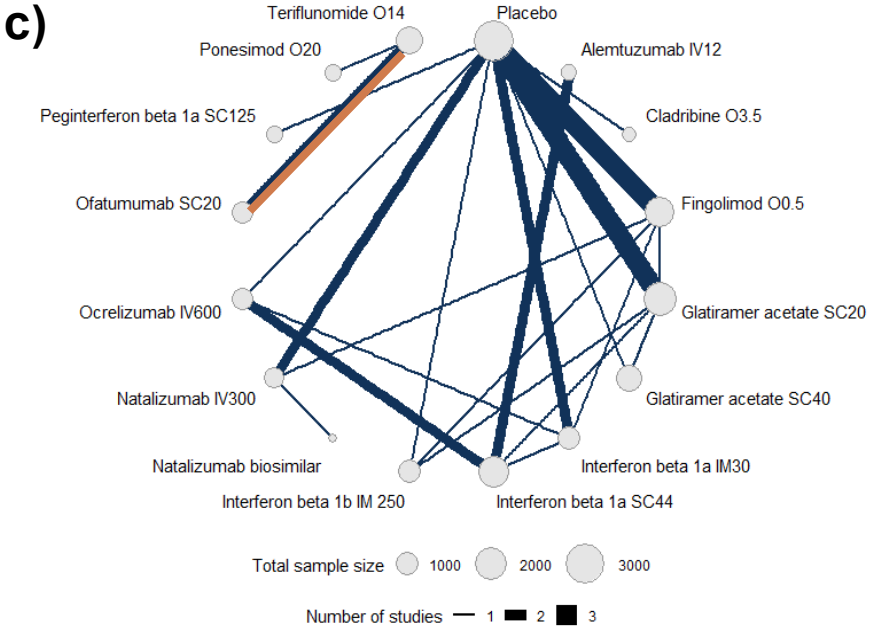


- Fixed effects models used for all NMA outcomes -> generally have best fit to data and increases number of trials in network
- Sensitivity analyses conducted for: ARR (studies with low risk of bias), CDP3 and 6 (studies with follow up time 24 months and over, CDP3 and 6 combined),

AE, adverse effects; ARR, annualised relapse rate; CDP, confirmed disease progression at 3/6 months; NMA, network meta-analysis; RRMS, relapsing-remitting MS; SAEs, severe adverse events

Link to main slides: summary of EAG's NMA

Link to main slides: summary of EAG's NMA

Full list of trials in the EAG's NMA (1)

Study Name	Intervention	Follow-up (months)	N
ADVANCE	Peginterferon beta 1a SC125, Placebo	12	1012
AFFIRM	Natalizumab IV300, Placebo	12, 24	942
ANTELOPE	Natalizumab biosimilar, Natalizumab IV300	11	264
APOLITOS	Ofatumumab SC20, Placebo	6	64
ASCLEPIOS I	Ofatumumab SC20, Teriflunomide O14	30	906
ASCLEPIOS II	Ofatumumab SC20, Teriflunomide O14	30	938
ASSESS	Fingolimod O0.5, Glatiramer acetate SC20	12	669
BEYOND	Glatiramer acetate SC20, Interferon beta 1b IM 250	24	1345
Calabrese 2012	Glatiramer acetate SC40, Interferon beta 1a IM30 and SC44	24	141
CAMMS223	Alemtuzumab IV12, Interferon beta 1a SC44	36	223
CARE-MS I	Alemtuzumab IV12, Interferon beta 1a SC44	24	563
CLARITY	Cladribine O3.5, Placebo	24	870
CombiRx	Glatiramer acetate SC20,Interferon beta 1a IM30	36	509
CONFIRM	Glatiramer acetate SC20, Placebo	24	713
Copolymer 1 Multiple Sclerosis Study Group	Glatiramer acetate SC20, Placebo	24	251
Etemedifar 2006	Interferon beta 1a IM30, SC44, Interferon beta 1b IM 250	24	90
European/Canadian glatiramer acetate study group	Glatiramer acetate SC20, Placebo	9	239
EVIDENCE	Interferon beta 1a IM30, SC44	16	677
FREEDOMS	Fingolimod O0.5, Placebo	24	843
FREEDOMS II	Fingolimod O0.5, Placebo	24	713
GALA	Glatiramer acetate SC40, Placebo	12	1404

IV, intravenous; IM, intramuscular; NMA, network meta-analysis; SC subcutaneous

Link to main slides: summary of EAG's NMA

Full list of trials in the EAG's NMA (2)

Study Name	Intervention	Follow-up (months)	N
GATE	Glatiramer acetate SC20, Placebo	9	441
GOLDEN	Fingolimod O0.5, Interferon beta 1b IM 250	18	151
IFNB Multiple Sclerosis Study Group	Interferon beta 1b IM 250, Placebo	21-22, 36	247
IMPROVE	Interferon beta 1a SC44, Placebo	4	180
INCOMIN	Interferon beta 1b IM 250, Interferon beta 1a IM30	24	188
Kappos 2011	Interferon beta 1a IM30, Ocrelizumab IV600, Placebo	6	163
Multiple Sclerosis Collaborative Research Group	Interferon beta 1a IM30, Placebo	24	301
OPERA I	Ocrelizumab IV600, Interferon beta 1a SC44	24	821
OPERA II	Ocrelizumab IV600, Interferon beta 1a SC44	24	835
OPTIMUM	Ponesimod O20, Teriflunomide O14	27	1133
PEGINTEGRITY	Interferon beta 1a IM30, Peginterferon beta 1a SC125	24	167
Ponesimod Phase II study Group	Ponesimod O20, Placebo	6	235
REGARD	Glatiramer acetate SC20, Interferon beta 1a SC44	24	764
REVEAL	Natalizumab IV300, Fingolimod O0.5	9	108
Saida 2012	Fingolimod O0.5, Placebo	6	114
Saida 2017	Natalizumab IV300, Placebo	6	94
TRANSFORMS	Fingolimod O0.5, Interferon beta 1a IM30	12	860

 IV, intravenous; IM, intramuscular; NMA, network meta-analysis; SC subcutaneous

Clinical evidence for natalizumab not included in NMA

Several studies in the company's submissions did not meet eligibility criteria for NMA

Study name	Reason for exclusion from NMA
DELIVER	Not informative to network – compares different protocols
NEXT-MS	Not an RCT
NOVA	Comparison of different dosing schedules
REFINE	Comparison of different doses
TOP	Observational Study
Samjoo IA, et al.	Review (references screened)
Filippi M, et al.	Commentary
Pfeuffer S, et al.	Observational Study
Killestein J, et al.	Editorial
Safety Study of Natalizumab to Treat Multiple Sclerosis (MS).	Not informative to network – compares different protocols
A Study to Evaluate Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of Natalizumab (BG00002) Administered Subcutaneously to Japanese Participants With Relapsing-Remitting Multiple Sclerosis.	Not an RCT
A Study to Investigate the Radiological Onset of Action After Treatment Initiation With Subcutaneous (SC) Natalizumab in Participants With Relapsing-Remitting Multiple Sclerosis (RRMS)	Not an RCT (& terminated)
Gelissen LMY, et al.	Not an RCT
Pelle J, et al.	Observational study
Perncezky J, et al.	Review
Achtnichts L, et al.	Observational study

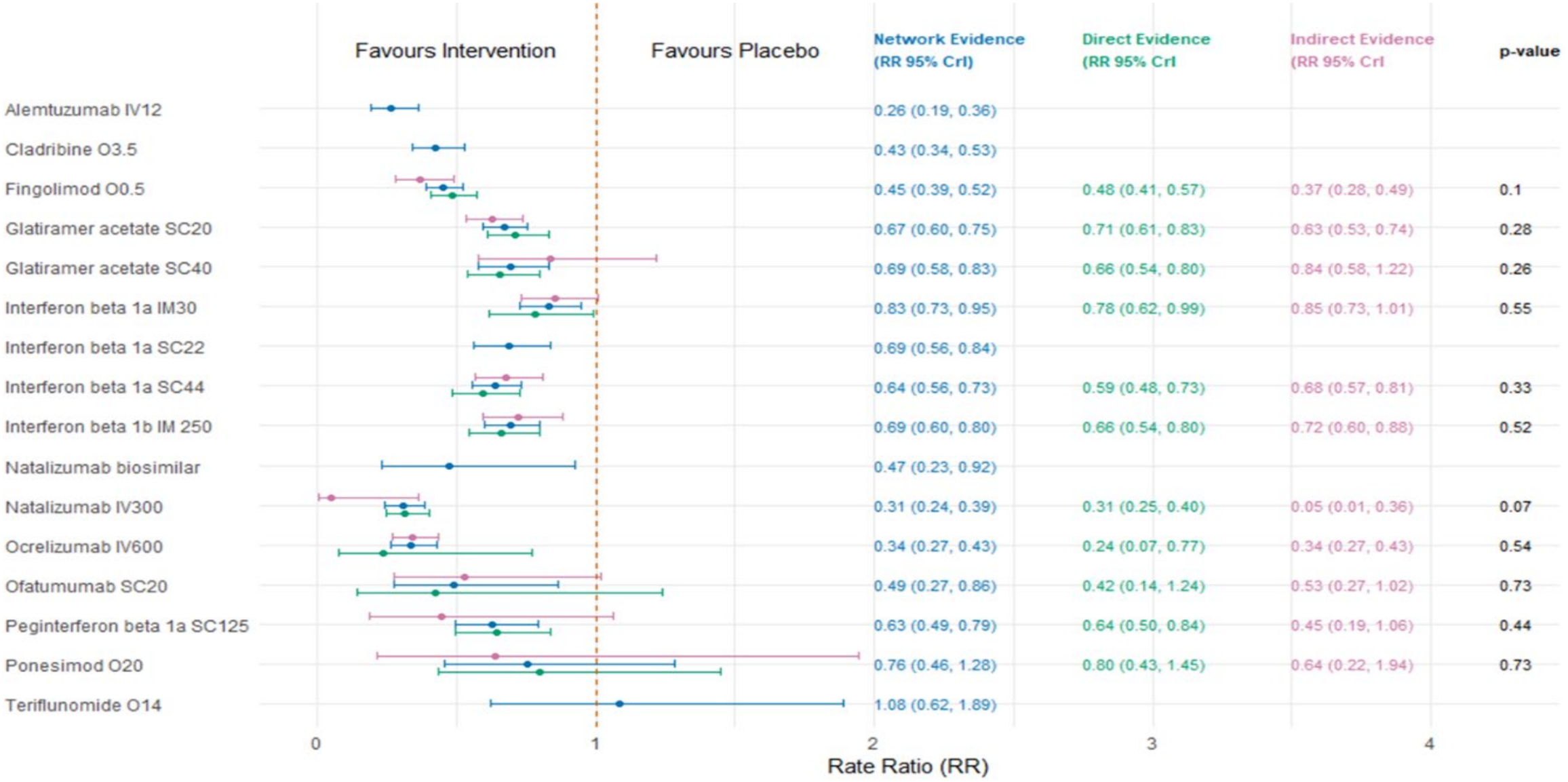
NMA, network meta-analysis; RCT, randomised controlled trial

Link to main slides: summary of EAG's NMA 49

NMA results in full RRMS population: ARR

Link to main slides: summary of EAG's NMA

EAG's forest plot of hazard ratios (HR) and 95% CrIs for ARR (fixed effects NMA, full RRMS population)

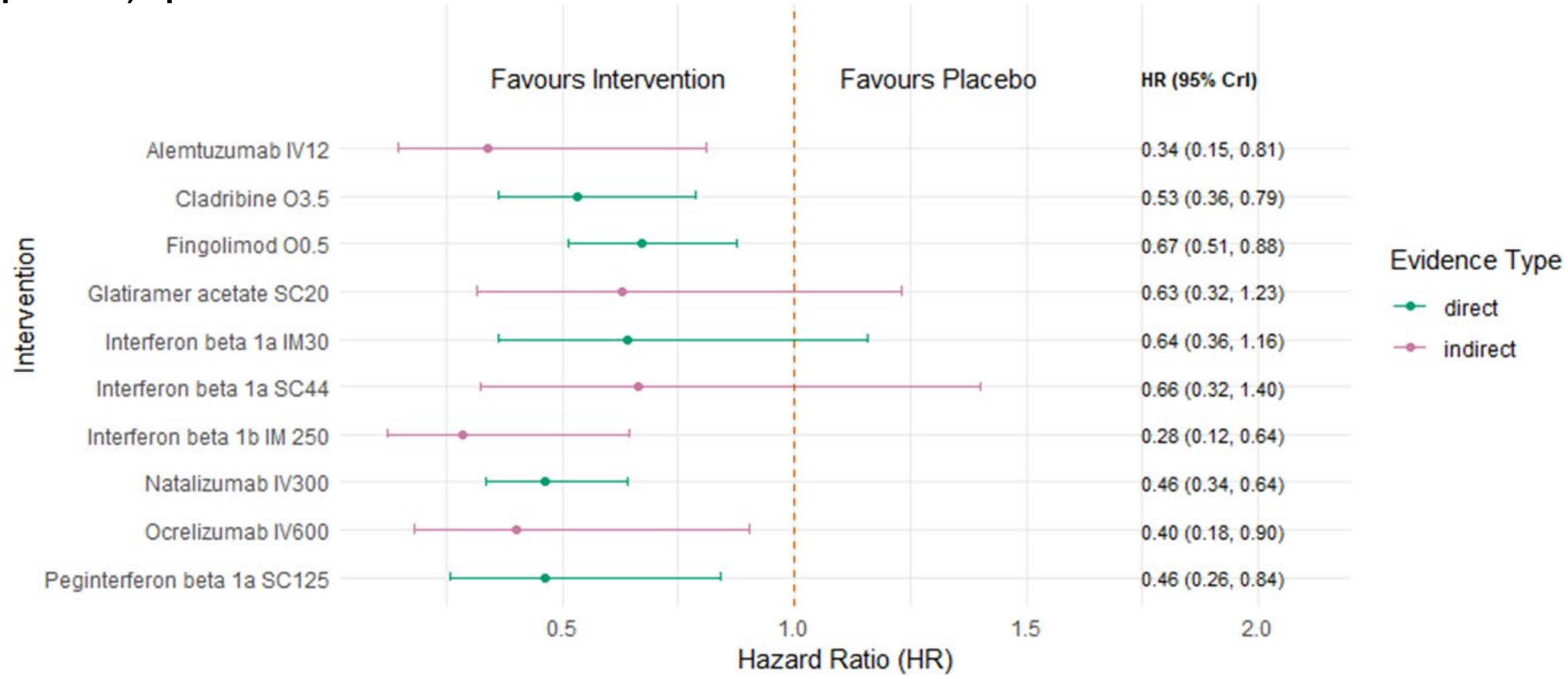


ARR, annualised relapse rate; CrI, confidence interval; IM, intramuscular; IV, intravenous; NMA, network meta-analysis; RRMS, relapsing-remitting MS; SC, subcutaneous

NMA results in full RRMS population: CDP6

Link to main slides: summary of EAG's NMA

EAG's forest plot of hazard ratios (HR) and 95% CrIs for CDP6 (fixed effects NMA, full RRMS population) updated after consultation

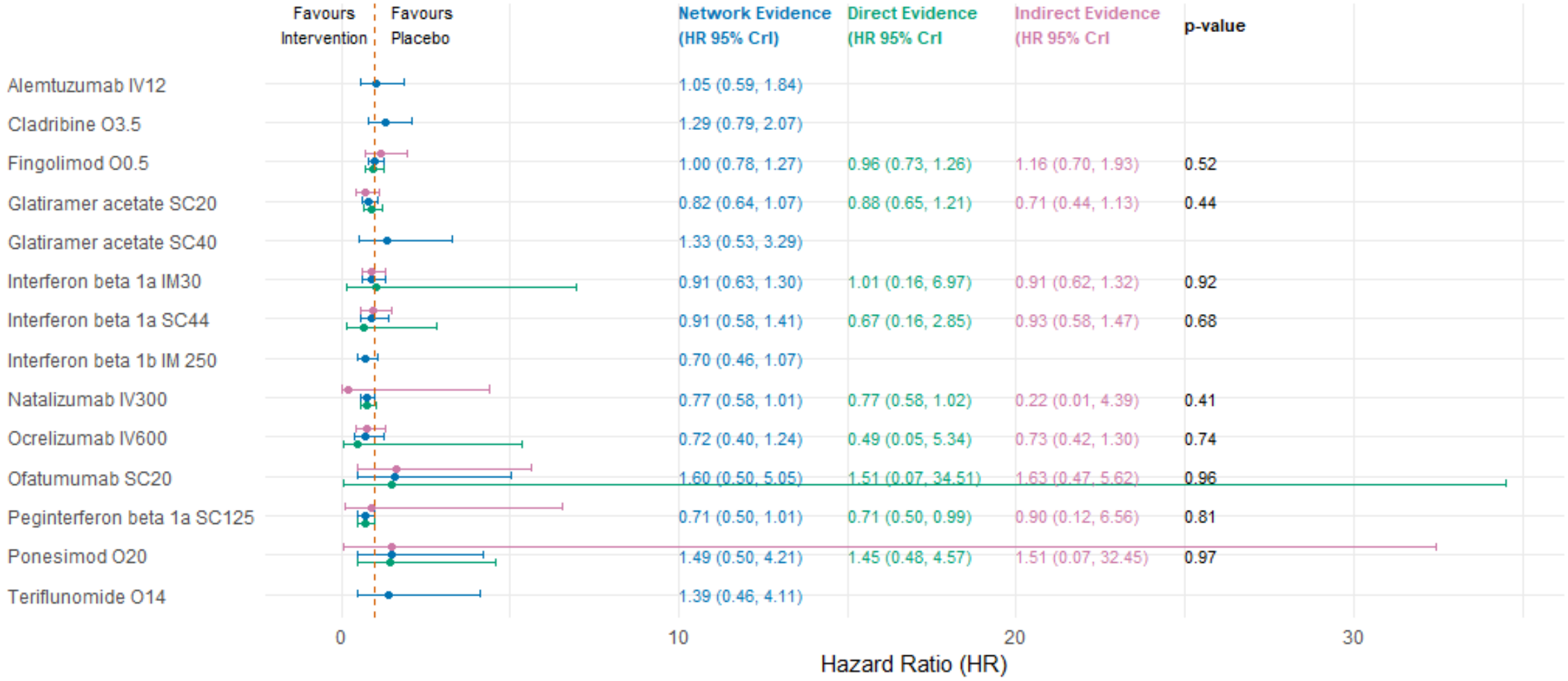


CDP, confirmed disease progression at 6 months; CrI, confidence interval; IM, intramuscular; IV, intravenous; NMA, network meta-analysis; RRMS, relapsing-remitting MS; SC, subcutaneous

NMA results in full RRMS population: SAEs

Link to main slides: summary of EAG's NMA

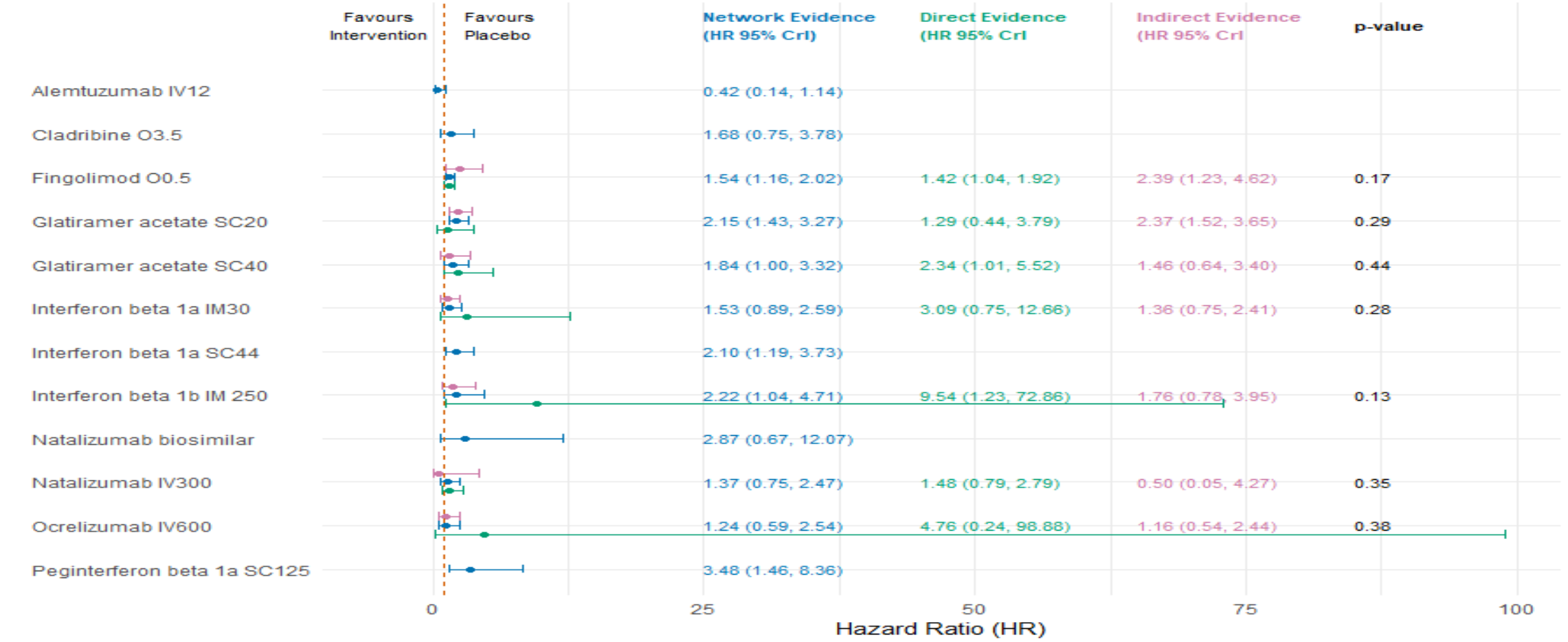
EAG's forest plot of hazard ratios (HR) and 95% CrIs for time to developing at least one SAE (fixed effects NMA, full RRMS population) updated after consultation



CrI, confidence interval; IM, intramuscular; IV, intravenous; NMA, network meta-analysis; RRMS, relapsing-remitting MS; SAE, serious adverse event; SC, subcutaneous

NMA results in full RRMS population: time to treatment discontinuation from AEs

EAG's forest plot of hazard ratios (HR) and 95% CrIs for time to treatment discontinuation from AEs (fixed effects NMA, full RRMS population)



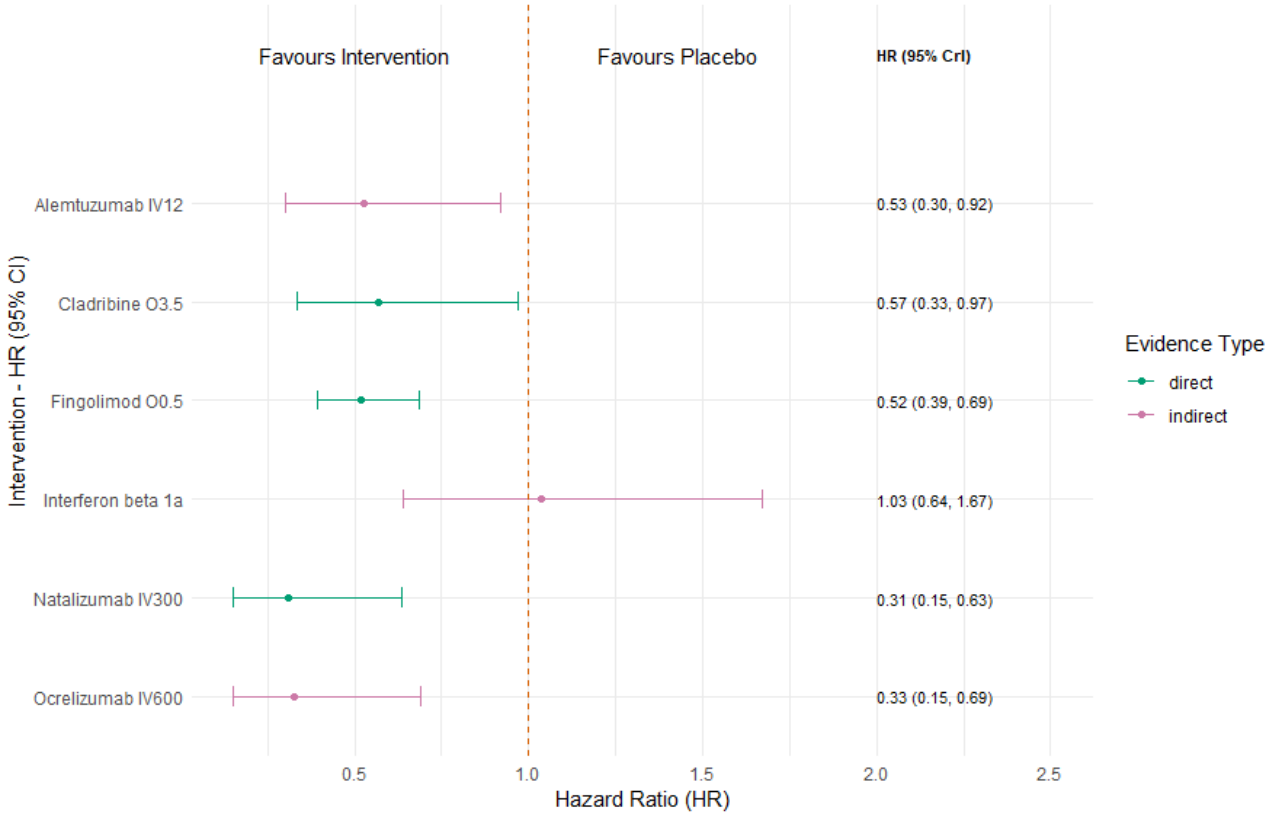
AE, adverse event; CrI, confidence interval; IM, intramuscular; IV, intravenous; NMA, network meta-analysis; RRMS, relapsing-remitting MS; SC, subcutaneous

Link to main slides: summary of EAG's NMA

NMA results in HA RRMS population: ARR

Link to main slides: summary of EAG's NMA

EAG's forest plot of hazard ratios (HR) and 95% CrIs for annualised relapse rate (fixed effects NMA, HA RRMS population)

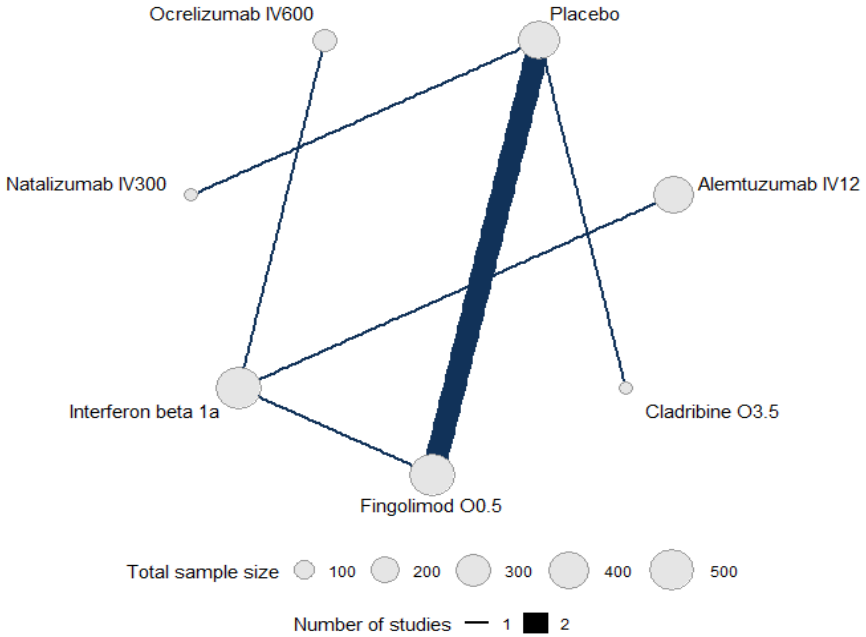


ARR, annualised relapse rate; CrI, confidence interval; IV, intravenous; NMA, network meta-analysis; HA RRMS, highly active relapsing-remitting MS;

EAG's NMA subgroup analyses in HA RRMS

Limited results in HA RRMS subgroup show similar trends to those in general RRMS

ARR: NMA network plot for HA RRMS (EAG scenario)



- All interventions except interferon beta 1a had greater reduction in ARR vs. placebo.
- Ocrelizumab & natalizumab had highest mean rankings (1.8 (95% CI 1, 5)) → natalizumab higher chance of ranking 1st (53%)
- All others had ≤2% chance of ranking 1st

Lack of data in HA RRMS for other outcomes → could not form network

Outcome	Reported in	Result
CDP	CARE-MS II, CLARITY, FREEDOMS I/II, OPERA I/II, MIST	All interventions (alemtuzumab, cladribine, fingolimod, ocrelizumab, AHSCT) reduced risk of CDP3 and 6 vs. comparator interventions (interferon beta 1a, placebo or DMT).
MRI outcomes	CARE-II	Alemtuzumab vs beta interferon 1a: • RR Gd+ lesions: 0.40 (95% CI 0.27, 0.60) • RR new or enlarging T2 lesions 0.68 (95% CI 0.59, 0.79)
AEs	CARE-II, Saida 2017 (not HA RRMS specific)	Alemtuzumab vs beta interferon 1a: • RR any AE 1.04 (95% CI 1.00, 1.08) • RR treatment discontinuation 0.43 (95% CI 0.21, 0.88) • RR SAEs 0.83 (95% CI 0.67, 1.04).
QoL	CARE-MS II and MIST	Increased QoL with AHCT vs. DMT (p<0.001). Significantly greater improvement with alemtuzumab PCS score vs. interferon beta 1a, no difference in SF-36 MCS score.

AE, adverse event; ARR, annualised relapse rate; CDP3/6, confirmed disease progression at 3/6 months; CI, confidence interval; DMT, disease-modifying therapy; HA, highly active; IV, intravenous; MRI, magnetic resonance imaging; NMA, network meta-analysis; QoL, quality of life; RRMS, relapsing-remitting MS; RR, rate ratio; SAEs, severe adverse events; Link to main slides: summary of EAG's NMA

Link to main slides: EAG's model

Discrete event simulation (DES) models

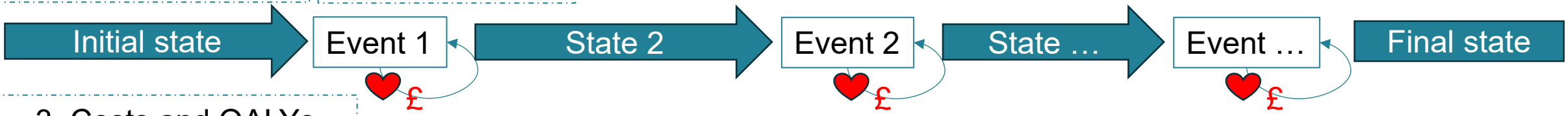
Differs from Markov model as uses individual patient time to event not cohort data

1. Event likelihoods determined at baseline by individual patient characteristics

2. Whichever event has shortest time to event occurs first

5. Next shortest time to event occurs and cycle restarts

KEY
£ Cost accrued
♥ QALY accrued/lost



3. Costs and QALYs estimated and stored when event happens, considering time passed since last event

4. Patient demographics, disability status, treatment, total costs and QALYs updated at each event

6. Results aggregated over time to get summary experience for whole cohort

Difference from Markov model

- Uses individual patient not cohort data
- No cycles→ progresses according to time to event data instead of probabilities
  - ❖ Allows events to occur at any time rather than regular intervals (assumed in Markov model)
- Allows modelling of treatment sequencing

QALY, quality-adjusted life year

Key real-world evidence from MS Registry

Background

- MS registry data used to address data paucity in previous TAs
- 3 populations: people with confirmed diagnosis of:
  - RRMS
  - SPMS

  } 1 or more prior DMT
  - Active RRMS → 2 or more prior DMTs
- Rate of events calculated using exponential survival and continuous-time multistate models fit to interval censored data
- Covariate effect to represent treatment → only used for baseline natalizumab rates (SC or IV) to which NMA treatment effects applied

Natural history data from MS Registry

Time to event	All RRMS	HA RRMS	SPMS
EDSS increase	✓	✓	✓
EDSS decrease	✓	x	x
EDSS increase or decrease	✓	x	✓
Relapse	✓	✓	✓
Progression to SPMS	✓	✓	x

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; HA, highly active; IV, intravenous; MS, multiple sclerosis; NMA, network meta-analysis; RRMS, relapsing-remitting MS; RR, rate ratio; SAEs, severe adverse events; SC, subcutaneous; SPMS, secondary progressive: TA, technology appraisal

Link to main slides: MS Registry data

Key results of UK MS Registry analysis

Log rates estimated by the MS Registry using exponential survival model, a) with treatment dependence, b) without treatment dependence

a.	Time to:							
	EDSS Increase, HA RRMS		EDSS Increase, All RRMS		Relapse, HA RRMS		Relapse, All RRMS	
	Rate	N	Rate	N	Rate	N	Rate	N
Intercept	-0.93 (-1.94, 0.07)	-	-2.25 (-2.63, -1.86)	-	-2.13 (-2.95, -1.3)	-	-2.63 (-3.08, -2.18)	
EDSS	-0.18 (-0.33, -0.03)	-	-0.17 (-0.25, -0.1)	-	-0.02 (-0.2, 0.17)	-	-0.07 (-0.16, 0.01)	
Alemtuzumab	-0.34 (-1.49, 0.81)	12	0.05 (-0.68, 0.78)	41	0.02 (-2.07, 2.12)	1	0.18 (-0.58, 0.93)	9
Cladribine	-3.29 (-5.44, -1.14)	23	-1.17 (-2.35, 0)	35	-0.79 (-2.87, 1.29)	1	0.37 (-1.05, 1.79)	2
Fingolimod	-2.38 (-3.53, -1.23)	65	-0.53 (-1.05, -0.01)	158	-0.21 (-1.1, 0.68)	13	0.13 (-0.34, 0.6)	34
Glatiramer Acetate	-1.04 (-2.23, 0.16)	20	-0.3 (-0.81, 0.2)	158	-0.52 (-1.49, 0.45)	11	0.04 (-0.39, 0.48)	44
Natalizumab	-1.26 (-2.5, -0.02)	23	0.28 (-0.17, 0.72)	177	-0.74 (-1.92, 0.43)	7	0.4 (-0.1, 0.9)	28
Ocrelizumab	-1.05 (-2.09, 0)	43	0.37 (-0.06, 0.8)	203	-0.17 (-1.4, 1.05)	4	0.29 (-0.36, 0.93)	15
Ofatumumab	-1.81 (-3.24, -0.38)	25	-0.02 (-0.72, 0.67)	69	-1.03 (-3.11, 1.05)	1	-0.1 (-1.53, 1.32)	2
Ponesimod	-1.43 (-3.58, 0.72)	4	-0.51 (-2.49, 1.48)	7	-0.38 (-2.46, 1.7)	1	0.23 (-1.76, 2.22)	1

b.	Time to:				
	EDSS Decrease (All RRMS)*	EDSS Increase (SPMS)	Relapse (SPMS)	SPMS Conversion (RRMS Highly Active)	SPMS Conversion (All RRMS)
Sample size	793	181	164	66	222
Rate	-3.51 (-3.94, -3.08)	-1.89 (-3.15, -0.63)	-4.83 (-6.66, -3.01)	-2.58 (-3.89, -1.26)	-2.81 (-3.52, -2.1)
EDSS	0.14 (0.04, 0.23)	-0.2 (-0.42, 0.01)	0.07 (-0.22, 0.36)	0.01 (-0.21, 0.23)	0.04 (-0.08, 0.15)

No patients in MS Registry with highly active RRMS decreased in EDSS → analysis could not be conducted

EDSS, Expanded Disability Status Scale; HA, highly active; MS, multiple sclerosis; N, number; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS

Link to main slides: MS Registry data

MS Registry

Patient years at risk

Group	Treatment (if relevant)	N	Patient years at risk	Mean follow-up time
Time to EDSS Increase (RRMS Highly Active)	Natalizumab	23	87	3.79
Time to EDSS Increase (All RRMS)	Natalizumab	177	582	3.29
Time to EDSS Decrease (All RRMS)	Any Treatment	613	1,965	3.20
Time to EDSS Decrease (SPMS)	Any Treatment	138	597	4.32
Time to EDSS Increase (SPMS)	Any Treatment	135	560	4.15
Time to Relapse (SPMS)	Any Treatment	130	2,419	18.61
Time to Relapse (RRMS Highly Active)	Any Treatment	33	387	11.72
Time to Relapse (All RRMS)	Any Treatment	143	2,007	14.03
Time to SPMS Conversion (RRMS Highly Active)	Any Treatment	44	468	10.64
Time to SPMS Conversion (All RRMS)	Any Treatment	180	2,195	12.19

- Natalizumab group used for time to EDSS increase and relapse in RRMS populations
- Data for relapse in only natalizumab group can be provided on request but similar to that for EDSS increase

EDSS, Expanded Disability Status Scale;; N, number; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS

Link to main slides: MS Registry data

MS Registry

Sample size and patient years at risk (PYAR) by EDSS

EDSS	Time to EDSS Increase (RRMS Highly Active - natalizumab only)		Time to EDSS Decrease (All RRMS)		Time to Relapse (RRMS Highly Active)		Time to SPMS Conversion (RRMS Highly Active)		Time to SPMS Conversion (All RRMS)	
	N	PYAR	N	PYAR	N	PYAR	N	PYAR	N	PYAR
0	3	6.77	37	129.63	5	40.34	1	0.42	1	0.42
1	1	1.00	11	41.66	2	18.08	1	7.16	3	27.75
1.5	4	15.16	5	9.66	2	8.42	1	0.42	4	63.84
2	1	5.95	87	248.30	1	9.59	2	9.17	4	30.26
2.5	3	8.04	67	204.78	7	53.76	3	37.67	1	0.42
3	2	10.91	92	300.35	1	15.16	2	40.75	7	55.92
3.5	2	11.58	47	178.40	5	63.18	1	18.42	6	84.33
4	1	5.90	69	205.80	2	43.92	11	106.00	13	167.16
4.5	2	7.21	29	99.12	1	11.41	19	206.75	3	53.50
5	4	14.54	41	128.12	1	5.00	1	18.83	34	359.35
5.5			11	32.19	6	117.91	2	22.76	69	907.43
6			37	135.66					15	167.43
6.5			64	195.97					17	237.26
7			9	31.37					3	39.67
7.5			5	20.19						
8			2	3.36						

EDSS, Expanded Disability Status Scale; HA, highly active; MS, multiple sclerosis; N, number; PYAR, patient years at risk; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS

MS Registry

Mean time to event calculated at EDSS=3 (for illustration)

	Times to EDSS Increase (RRMS Highly Active)	Times to EDSS Increase (All RRMS)	Time to Relapse (RRMS Highly Active)	Time to Relapse (All RRMS)
Intercept	2.53	9.49	8.41	13.87
Alemtuzumab	6.11	21.12	9.12	16.44
Cladribine	89.12	2.97	2.03	0.30
Fingolimod	293,607.76	561.16	62.80	0.12
Glatiramer Acetate	95,798.28	61.56	10.59	0.35
Natalizumab	862.64	5.75	34.81	0.48
Ocrelizumab	354.25	0.23	80.64	0.10
Ofatumumab	502.70	0.12	13.74	0.17
Ponesimod	2724.39	1.27	298.87	0.98

- This calculation ignores skew from uncertainty, hence the high implied mean for time to EDSS in RRMS highly active.
- See probabilistic estimates from the model for more accurate time to event assessment

EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting MS

Link to main slides: Cost effectiveness section

Utilities in the EAG's model

EAG includes EDSS specific utilities for RRMS, SPMS and carer disutilities

Background: Utilities for EDSS and SPMS from previous TAs and literature

- Base case utilities from UK MS Survey 2005 (Orme et al): cross-sectional study of 2048 MS patients
  - ❖ self-reported EQ-5D & resource use
- ANOVA models used to generate mean utility by EDSS score → stratified by key covariates
- One off disutility (-0.07) for relapse

Utility values used in the EAG base case and scenarios

	Orme et al		Other RRMS utilities		Carer disutility	
EDSS	RRMS	SPMS	OPERA	CLARITY	Acaster et al	Loveman et al
0	0.87	0.825	0.8809	0.906	-0.002	0.000
1	0.799	0.754	0.8438	0.845	-0.002	-0.001
2	0.705	0.66	0.7699	0.804	-0.045	-0.003
3	0.574	0.529	0.7048	0.701	-0.045	-0.009
4	0.61	0.565	0.6438	0.655	-0.142	-0.009
5	0.518	0.473	0.6003	0.565	-0.16	-0.020
6	0.458	0.413	0.4909	0.573	-0.173	-0.027
7	0.297	0.252	0.4387	0.573	-0.03	-0.053
8	-0.049	-0.094	-	0.573	-0.095	-0.107
9	-0.195	-0.24	-	0.573	-0.095	-0.140
EAG's	Base case		Scenario	Scenario	Base case	Scenario
Used in	TA767, TA699, TA533, TA312, TA254 and TA127. TA127 (natalizumab) used amended values		TA533: with Orme et al. (EDSS 6-9)	TA616: with Hawton et al. (EDSS 6-8) and Orme et al (EDSS 9)	Various including TA767, TA616 and ongoing ID6263 (cladribine)	Alzheimer's utilities used in TA127 (natalizumab)

ANOVA, analysis of variance; EDSS, Expanded Disability Status Scale; HA, highly active; MS, multiple sclerosis; N, number; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS; TA, technology appraisal

Are the EAG's base case utilities appropriate?

Serious adverse event costs and utilities

EAG models natalizumab specific serious AE and utility values only

Link to main slides: Cost effectiveness section

Background: EAG modelled serious SAEs as single natalizumab specific cost and utility, based on weighted average of occurrence in AFFIRM.

- % experiencing PML from TOP study
- Resource use for SAEs based on past TAs

Company: Biogen: concerned only SAEs associated with originator natalizumab from AFFIRM included in the model.

- Acknowledge pragmatic and consistent with past TAs but doesn't capture known SAEs associated with other therapies.
- Alemtuzumab use restricted due to CV and immune-related disorders.

Costs for PML differ across past appraisals

Sandoz: SAE costs in EAG's model lack face validity

EAG: general approach aligned with prior TAs.

- Amended costs for UTI, depression, anaphylactic reaction and hypersensitivity reaction in response to company comments
- Errors in PML costing in past MS TAs – maintain pre-consultation cost
- Clarified that costs/disutilities not included for some SAEs in model

Are the costs and disutilities included in the EAG's model appropriate?

Costs for SAEs used in EAGs model

SAE	Cost	Annual disutility
Cholelithiasis	£9,006	-
Rehabilitation therapy	£618	-
Urinary tract infection	£4,757	-0.10
Depression	£10,942	-0.56
Anaphylactic reaction	£911	-1.00
Hypersensitivity reaction	£320	-1.00
Breast cancer	£14,213	-0.1160
Gastritis	£707	-
PML	£14,333	-0.30

CV, cardiovascular; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; SAE, serious adverse event; TA, technology appraisal; UTI, urinary tract infection

Key issue: Costs for anti-JCV testing

Link to main slides: anti-JCV testing

Current testing recommendations for serum anti-JCV antibody:

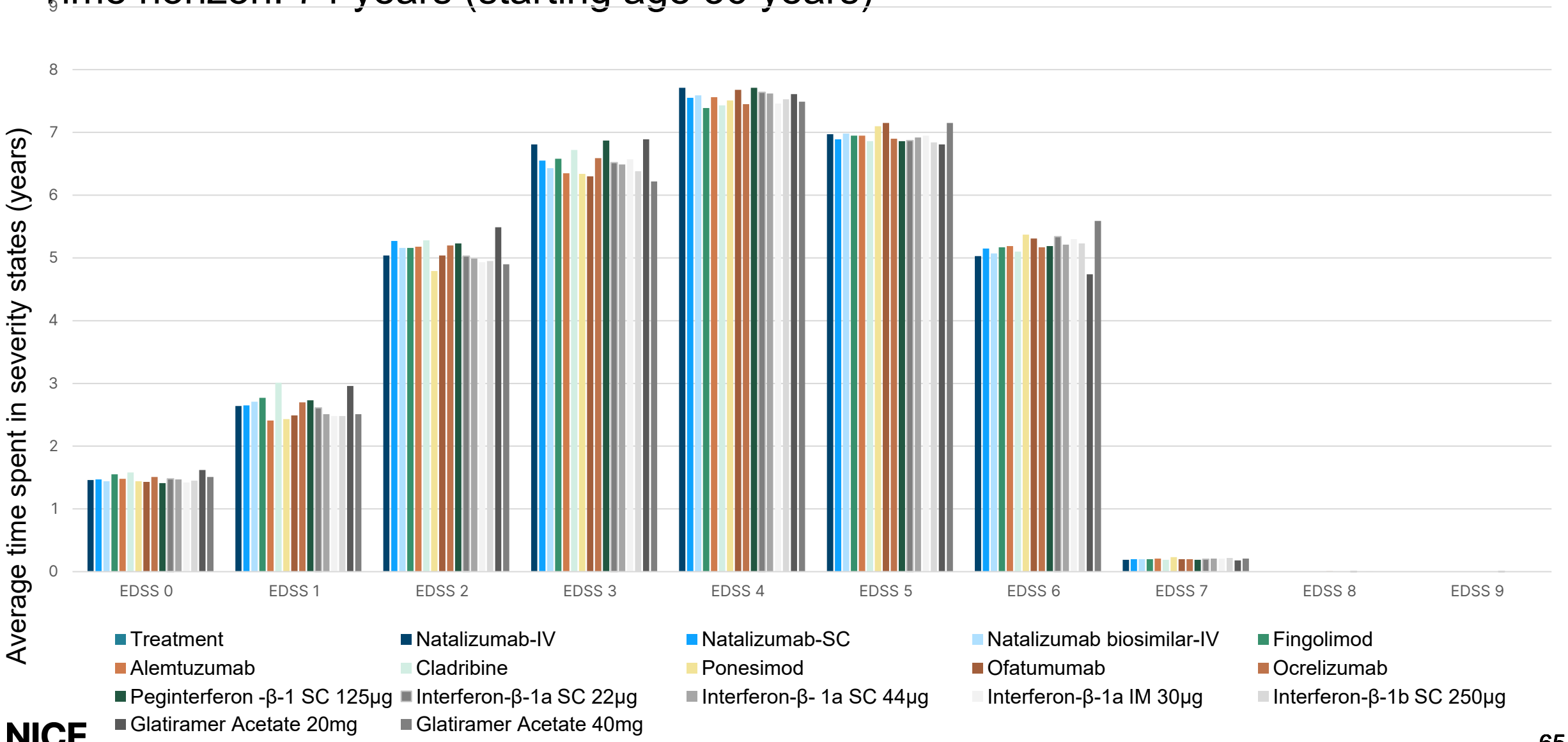
- Prior to initiating or in patients receiving natalizumab-TYS with unknown antibody status
- 6 monthly for anti-JCV antibody negative patients → risk of PML from new JCV infection, fluctuating antibody status or false negative test result
- 6 monthly for low index patients with no prior immunosuppressant after 2-year treatment point

Abbreviations: JCV, John Cunningham virus; PML, progressive multifocal leukoencephalopathy

Link to main slides: Model outputs

Average time (years) spent in severity states

Time horizon: 74 years (starting age 36 years)



EDSS, Expanded Disability Status Scale; IM, intramuscular; IV, intravenous; mg, milligram; µg, microgram; SC, subcutaneous

Average time in years spent on treatment lines

N.B. Treatment costs are capped as per re-treatment schedule EAG Report

Treatment	2nd Line	3rd Line	4th Line
Natalizumab-IV	9.62	2.59	1.10
Natalizumab-SC	9.81	2.55	1.10
Natalizumab biosimilar-IV	9.75	2.70	1.22
Fingolimod	9.79	2.67	1.17
Alemtuzumab	9.61	2.61	1.10
Cladribine	9.92	2.56	1.06
Ponesimod	9.67	2.52	1.17
Ofatumumab	9.65	2.64	1.18
Ocrelizumab	9.63	2.58	1.06
Peginterferon -β-1 SC 125µg	9.85	2.68	1.14
Interferon-β-1a SC 22µg	9.73	2.71	1.14
Interferon-β- 1a SC 44µg	9.48	2.67	1.10
Interferon-β-1a IM 30µg	9.47	2.55	1.16
Interferon-β-1b SC 250µg	9.48	2.49	1.06
Glatiramer Acetate 20mg	9.81	2.71	1.13
Glatiramer Acetate 40mg	9.67	2.66	1.11
Mean	**9.67**	**2.66**	**1.11**

IM, intramuscular; IV, intravenous; mg, milligram; µg, microgram; SC, subcutaneous

Average time (years) to progression and relapse per treatment

Highly Active RRMS (MS Registry data)

Treatment	Time to progression	Time to relapse
Natalizumab-IV	10.32	10.91
Natalizumab-SC	10.37	11.01
Natalizumab biosimilar-IV	10.42	10.96
Fingolimod	10.21	11.08
Alemtuzumab	10.40	10.85
Cladribine	10.61	11.06
Ponesimod	10.38	10.66
Ofatumumab	10.64	10.94
Ocrelizumab	10.45	11.05
Peginterferon -β-1 SC 125µg	10.34	10.96
Interferon-β-1a SC 22µg	10.42	11.06
Interferon-β- 1a SC 44µg	10.27	10.68
Interferon-β-1a IM 30µg	10.26	10.85
Interferon-β-1b SC 250µg	10.42	10.76
Glatiramer Acetate 20mg	10.10	10.98
Glatiramer Acetate 40mg	10.20	10.83
Mean	**10.36**	**10.92**

NICE

IM, intramuscular; IV, intravenous; mg, milligram; µg, microgram; SC, subcutaneous

EAG amendments at consultation

Area	Description
NMA	NMA amended to include correct HRs and updated sources for cladribine
Annual treatment costs	List price costs for cladribine and fingolimod amended
	Dose of ofatumumab corrected
Treatment administration costs	Cost of nurse time removed for ofatumumab for year 2 onwards
Cost of SAEs	Amended costs for UTI, depression, anaphylactic reaction and hypersensitivity reaction
Utilities	Disutility for gastritis set to 0
Resource use	Resource use for ofatumumab corrected
Stopping treatment	Introduced stopping rule at EDSS7

EDSS, Expanded Disability Status Scale; HR, hazard ratio; NMA, network meta-analysis; QoL, quality of life; RRMS, relapsing-remitting MS; SAEs, severe adverse events; UTI, urinary tract infection

Model inputs compared with previous TAs

Factor	Ponesimod (TA767)	Ofatumumab (TA699)	Cladribine (TA493/TA616)	Cladribine (ID6263)	Natalizumab and biosimilar (ID6369)
Health state structure	20 health states	21 health states	11 health states	11 health states	Discrete event simulation
Source of natural history EDSS	BCMS for EDSS transitions (RRMS). London Ontario for transitions from RRMS to SPMS	BCMS for EDSS transitions (RRMS). London Ontario and EXPAND for RRMS to SPMS and during SPMS	BCMS	BCMS	MS Registry
Source of natural history relapse	Patzold et al. (1982) combined with UK MS survey data	Patzold et al. (1982) combined with UK MS survey data	Placebo arm of CLARITY combined with BCMS data from Tremlett et al. (2010)	Placebo arm of CLARITY combined with BCMS data from Tremlett et al. (2010)	MS Registry
Source of MS mortality	Pokorski (1997) extrapolated for EDSS states	Pokorski (1997) extrapolated for EDSS states	Jick et al. (2014)	Jick et al. (2014)	Jick et al. (2014)
Application of treatment effect	• ARR • CDP-3M	• ARR • CDP-6M	• ARR • CDP-6M	• ARR • CDP-6M	• ARR • CDP-6M

Abbreviations: RR/RRMS, relapsing-remitting multiple sclerosis; SP/SPMS, secondary progressive multiple sclerosis; EDSS, expanded disability status scale; BCMS, British Columbia Multiple Sclerosis (registry); ARR, annualised relapse rate; CDP, confirmed disease progression; MS, multiple sclerosis

Model inputs compared with previous TAs

Factor	Ponesimod (TA767)	Ofatumumab (TA699)	Cladribine (TA493/TA616)	Cladribine (ID6263)	Natalizumab and biosimilar (ID6369)
Treatment effect waning	25% after 2 years and 50% after 5 years	Not applied; all-cause treatment discontinuation acts as a proxy for waning	Cladribine: • 0% years 0-4 • 25% years 4-5 • 50% years 5+ Comparators: • 0% in years 0-2 • 25% years 2-5 • 50% years 5+	Cladribine and comparators: • 0% years 0-4 • 25% years 4-5 • 50% years 5+	Baseline rates of discontinuation due to AEs used as a proxy
Treatment discontinuation	Trial data sourced from NMA, constant annualised rates	Trial data sourced from NMA, constant annualised rates	Trial data sourced from NMA, constant annualised rates	Trial data sourced from NMA, constant annualised rates	Trial data sourced from NMA, constant annualised rates
Stopping rule	EDSS ≥7.0 SPMS transition	EDSS ≥7.0 SPMS transition	EDSS ≥7.0	EDSS ≥7.0	EDSS ≥7.0
Source of patient utilities	Orme et al. (2007)	Pooled trial data and Orme et al. (2007)	EQ-5D in CLARITY study for EDSS 0-5, Hawton et al. (2016) for EDSS 6-8 and Orme at al. (2007) for EDSS 9	EQ-5D in CLARITY study for EDSS 0-5, Hawton et al. (2016) for EDSS 6-8 and Orme at al. (2007) for EDSS 9	Orme et al. (2007)

Abbreviations: AE, adverse event; NMA, network meta-analysis; RRMS, relapsing-remitting multiple sclerosis; EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis; EQ-5D, EuroQoL five dimension (questionnaire).

Model inputs compared with previous TAs

Factor	Ponesimod (TA767)	Ofatumumab (TA699)	Cladribine (TA493/TA616)	Cladribine (ID6263)	Natalizumab and biosimilar (ID6369)
Source of relapse disutility	Orme et al. (2007)	Pooled ASCLEPIOS trials	Orme et al. (2007)	Orme et al. (2007)	Orme et al. (2007)
Source of caregiver disutility	Acaster et al. (2013)	Loveman et al. (2006) and UK MS survey data	Acaster et al. (2013)	Acaster et al. (2013)	Acaster et al. (2013)
Source of EDSS cost	Tyas et al. (2007), inflated to 2019 for direct medical costs	UK MS survey data with values inflated to cost year	Hawton et al. (2016)	Hawton et al. (2016); Tyas et al. (2007) in sensitivity analysis	Tyas et al. (2007)
Source of relapse cost	Tyas et al. (2007), inflated to 2019	Hawton et al. (2016)	Hawton et al. (2016)	Hawton et al. (2016)	Hawton et al. (2016)

Abbreviations: RRMS, relapsing-remitting multiple sclerosis; EDSS, expanded disability status score.