Natalizumab (originator and biosimilar) for treating highly active relapsing–remitting multiple sclerosis after disease-modifying therapy [ID6369]

For projector – contains noCON information

Technology appraisal committee B – 4th June 2025

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Natalizumab (originator and biosimilar) for treating highly active relapsing–remitting multiple sclerosis after disease-modifying therapy [ID6369]

- ✓ **Recap to background and key issues**
- ❑ Summary of consultation comments
- ❑ New evidence

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RECAP

Types of multiple sclerosis

Natalizumab already recommended for RES RRMS but not HA RRMS

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

50%-60% in 15-20 yrs

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)**

Originator natalizumab not recommended in HA RRMS (TA127), so MTA required to assessed originator and biosimilar natalizumab (NICE's biosimilar position statement: *"biosimilars will only be appraised together with the reference products as part of a MTA.")*

DMT, disease-modifying therapy; MRI, magnetic resonance imaging; MS, multiple sclerosis; MTA, multiple technology appraisal; RRMS, relapsing-remitting multiple sclerosis; TA, technology appraisal. Link to supplementary appendix: background to RRMS, previous natalizumab appraisals

Originator (Tysabri, Biogen) & biosimilar natalizumab (Tyruko, Sandoz)

RECAP

Originator licenced as SC and IV, biosimilar IV only; 6 weekly extended interval dosing possible

	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: Decision problem at ACM1

Summary of appraisal to date (1)

Recommendation after ACM 1: Natalizumab (originator and biosimilar) should not be used to treat relapsing–remitting multiple sclerosis (MS) that is highly active despite a full and adequate course of at least 1 disease-modifying therapy in adults.

Issue	Committee conclusion	Further info provided	Resolved?
Comparator	Ocrelizumab (SC & IV), ofatumumab, ublituximab, cladribine	Updated in EAG base case (SC ocrelizumab in scenario only)	Yes
ITC	Appropriate to use EAG's NMA in all RRMS population. • Insufficient evidence to support equal effectiveness (cost comparison) for natalizumab, ocrelizumab and ofatumumab	Scenario: equal clinical effectiveness for natalizumab, ocrelizumab and ofatumumab	Yes
Natural history data	MS Register most recent and relevant data source for natural history data → captures gradual progression of HA RRMS	DataSAT for MS Register	For discussion
Progression to SPMS	MS Register data may overestimate % moving to and time to SPMS	% with SPMS at 5, 10 and 15 years in the EAG's model	For discussion
Efficacy	Equal effectiveness for originator and biosimilar natalizumab	Updated in EAG base case	Yes

ACM, appraisal committee meeting; HA, highly active; IV, intravenous; MS, multiple sclerosis; NMA, network meta-analysis; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous; SPMS, secondary progressive MS. Link to supplementary appendix: treatment pathway at ACM1

Summary of appraisal to date (2)

Issue	Committee conclusion	Further info provided	Resolved
Dosing	60% of people having natalizumab have extended interval dosing (EID) in clinical practice	Updated EAG base case includes 60% having EID	Yes: see supplementary appendix
Treatment waning	Discontinuation for AEs inappropriate proxy for waning (many stop treatment due to risk of PML)	Scenario with alternative approach to treatment waning	For discussion
Subsequent treatment	• Subsequent treatments in NHS: ocrelizumab, ofatumumab, ublituximab, cladribine • Inappropriate to model equal chance of having any available subsequent treatment	Data on subsequent treatments used in NHS from MS Register	For discussion
Stopping treatment	Stopping rule at EDSS 7 appropriate	-	Yes
Mortality	• EAG's preferred SMR for excess mortality (Jick et al.) inappropriate → mortality increases with disability • Prefer granular EDSS states from Harding et al. but likely overestimate SMRs, especially in high EDSS states	• Base case using relative difference between SMRs for EDSS states from Harding et al. calibrated to Jick et al. • Survival curves	For discussion
SC vs IV	Equal resource use for SC and IV originator natalizumab appropriate	Scenario with reduced costs for SC route	For discussion

EDSS, Expanded Disability Status Scale; PML, Progressive Multifocal Leukoencephalopathy; MS, multiple sclerosis; SMR, Standardized Mortality Ratio. Link to supplementary appendix: Key issue: EID, company/EAG response to DG

Equality considerations

Inequality in pregnancy and older people at higher risk of infection

The following equalities issues were raised at ACM1:

- Natalizumab has proven safety data in pregnancy → addresses unmet need in population: High efficacy DMTs (ocrelizumab, ofatumumab) not recommended in people who are pregnant or planning pregnancy
- A negative recommendation in HA RRMS means people would need a 2nd, potentially disabling relapse to meet RES criteria for escalation to natalizumab.
- MS affects 3 times more women than men → disproportionate impact of negative recommendation in this population

Stakeholders raised the following potential equality issues during consultation:

- Most stakeholders reiterated that no effective treatments that can be used during pregnancy and breastfeeding → natalizumab may be only option in these people
- People with MS who are older have higher risk of infections or have comorbidities that complicate management decisions would benefit more from natalizumab's non-immunosuppressive mechanism of action.

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

Key issues

Issue
Natural history data: Has evidence provided at consultation reduced uncertainty around the generalisability of the MS Register data to the NHS population with RRMS? • Is the proportion of people progressing to SPMS with different treatments clinically plausible?
Treatment waning and sequencing: How should treatment waning be modelled for natalizumab originator, biosimilar and comparators?
Subsequent treatments: Is the EAG's modelling of subsequent treatments appropriate?
Mortality: How should mortality be modelled? Are the EAG's updated base case SMRs appropriate for decision making?
SC/IV administration: Are subcutaneous and intravenous natalizumab appropriately modelled? • Should home administration costs for subcutaneous natalizumab be included in the model? • What proportion of people are expected to have SC vs. IV in clinical practice?
Cost comparison: Is a cost comparison appropriate? If yes, is Sandoz's model appropriate for decision making?

IV, intravenous; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous; SPMS, secondary progressive MS; SMR, standardised mortality rate

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Consultation responses to draft guidance summary (1)

Disappointment in negative recommendation, especially given unmet need for new treatments: clinical experts, ABN, MS Society

- Negative recommendation causes *"irreversible disability for some people living with MS"* and:
  - ❖ Means no highly effective treatment after disease activity on 1st line therapy (antiCD20 or cladribine) until 2nd relapse → only options long-term immunosuppression or HSCT
  - ❖ Is based on lack of direct comparative data and model inability to capture real world complexity and need
- Natalizumab available for HA RRMS during COVID-19 (reduced risk of severe COVID vs other DMTs) → highly valued by patients and clinicians
- Recommendation in HA RRMS would increase patient choice and reduce geographical disparity (natalizumab recommended in other UK countries)

Treatment pathway: MST, MS Society

- MS classifications meaningless to patients and limited clinical use → depend on effectiveness of previous DMTs
- Treatment response more about match between treatment and personal physiology, not disease activity
  - Should not limit access until more known about response to DMTs
  - Negative recommendation for HA RRMS could complicate future use of AI to personalise DMTs (delayed prescription accuracy, increased use of ineffective treatments with side effects and NHS spending).
- MS course uncertain and choosing DMT personal → balancing risks and benefits.
- More available treatments = greater patient choice

AI, artificial intelligence; ABN, Association of British Neurologists; DMT, disease modifying therapy; HA, highly active; HSCT, Hematopoietic Stem Cell Transplantation; ; MS, multiple sclerosis; MST, MS Trust; RRMS, relapsing-remitting multiple sclerosis. Link to supplementary appendix: classifications of MS

Consultation responses to draft guidance summary (2)

Natalizumab address inequality in pregnancy: Web comments, clinical expert, ABN, MS Society, Biogen

- Currently no effective treatment with safety record in pregnancy for breakthrough disease on antiCD20s
- Women who are wishing to conceive:
  - cannot have fingolimod (teratogenic) or alemtuzumab/cladribine (induction therapies with long washout)
  - must chose to expose foetus to drug with side effects, take no DMT and risk permanent disability, or not get pregnant.
- Significant issue as women 3 x as likely to get RRMS, many of whom are diagnosed at child-bearing age
  - ❖ NHS England considered a patient and public participation policy to address inequality
- Natalizumab proven safety record in pregnancy and continuation recommended during conception and pregnancy in UK and international guidance

Costs: Web comments

- Treating MS aggressively may slow brain atrophy → reduction in lost productivity costs and resource savings as people access care through hospital/GP services

ABN, Association of British Neurologists; DMT, disease modifying therapy; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis

Link to supplementary appendix: further consultation comments 1 and 2

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Link to supplementary appendix: key clinical evidence, trial results, NMA results , model structure; model inputs, costs and utilities in the model, inputs compared with other TA 1, 2 and 3

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Treatment effectiveness in the EAG's model

Link to supplementary appendix: MS Register overview and results

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

Background: EAG model applies treatment effects from NMA and AFFIRM to natural history data from MS Register.

- Previous RRMS TAs used natural history data from old Canadian databases BCMS or London Ontario which led to implausibly high % of people in high EDSS health states

RECAP: Sources of clinical effectiveness evidence in EAG's model

Event rates

Natural history data from MS register

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

Events in SPMS not treatment specific

Committee conclusion: Some issues with missing data and generalisability of MS Register but most recent and relevant data source

- DataSAT form requested for MS Register, BCMS and London Ontario
- Rates of progression to SPMS may be treatment specific → requested % with SPMS at 5, 10 & 15 years in model

AE, adverse event; ARR, annualised relapse rate; BCMS, British Columbia Multiple Sclerosis; CDP6, confirmed disability progression at six months; DataSAT, Data Suitability Assessment Tool; EDSS Expanded Disability Status Scale; HA, highly active; NMA, network meta-analysis; RRMS, relapsing-remitting multiple sclerosis; SAE, serious adverse event; SPMS, secondary progressive MS; TA, technology appraisal

Key issue: Natural history data

EAG provided additional information to support use of MS Register data for natural history of RRMS

Stakeholder comments: MST: Model may underestimate chance of progressing to high EDSS states:

- Many people living with advanced and complex symptoms of MS not under care of Neurology teams but cared for directly by GP and District Nursing, or Palliative Care or residential care homes.
- MST research: up to 40,000 people with advanced MS in the UK → exact number uncertain (poor recording on Neurology caseloads and coding issues in GP records)

Table: % with SPMS in EAG model

	5 yrs	10 yrs	15 yrs
Natalizumab originator IV	27.7%	42.3%	50.6%
Natalizumab originator SC	27.7%	42.3%	50.5%
Natalizumab biosimilar IV	27.6%	42.1%	50.2%
Cladribine	27.6%	41.9%	49.7%
Ublituximab	27.6%	42.2%	50.3%
Ofatumumab	27.7%	42.2%	50.4%
Ocrelizumab	27.6%	42.0%	49.9%

EAG: maintains preference for MS Register data in base case

- Provided requested DataSAT form for MS Register (see supplementary appendix) but not BCMS or London Ontario datasets and updated average time spent in EDSS states
- Recognises associated limitations of using MS Register data to inform progression to advanced MS (SPMS)

- Has evidence provided at consultation reduced uncertainty around the generalisability of the MS Register data to the NHS population with RRMS?
- Is the proportion of people progressing to SPMS with different treatments in the model clinically plausible?

BCMS, British Columbia Multiple Sclerosis; DataSAT, data Suitability Assessment Tool; EDSS Expanded Disability Status Scale; MS, multiple sclerosis; MST, MS Trust; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive MS; yrs, years

Key issue: Treatment waning

EAG base case: discontinuation for AEs as proxy to waning; EAG scenarios vary approach

Background ACM1: EAG used discontinuation from AEs as proxy for waning. Rates from AFFIRM (originator natalizumab), ANTELOPE (biosimilar natalizumab), NMA effects applied to baseline AFFIRM rates (comparators)

Committee conclusion: Discontinuation due to AEs may not be appropriate proxy for waning as most stop natalizumab because they become JCV positive or are concerned about PML risk, not because of AEs

- Requested alternative waning approaches using same source for originator and biosimilar natalizumab.

Company: Sandoz: waning not appropriate → clinical expert states DMT response binary (either works or not)

EAG: EAG's clinical experts: consider 'breakthrough' disease, not waning

- Treatment failure detected via routine scan or due to relapse
- Would allow 6 months before defining treatment failure
- Recent audit showed stable rate of breakthrough activity of 5% to 10% up to 5 years on DMT

Base case: maintain discontinuation rates due to AEs as proxy (AFFIRM rates for natalizumab originator and biosimilar, with treatment specific rates from NMA applied for comparators)

***Scenario*:** assuming 10% waning over 5 years (2% waning per year) for natalizumab and comparators in line with clinical expert audit

- How should treatment waning be modelled for natalizumab originator, biosimilar and comparators?
- Is the EAG's base case or scenario most appropriate for decision making?

AE, adverse event; DMT, disease modifying therapy; NMA, network meta-analysis; JCV, John Cunningham virus; PML, Progressive Multifocal Leukoencephalopathy

Key issue: Subsequent treatments

EAG updates base case to include data on subsequent treatment usage from MS Register

Background, ACM1: EAG modelled treatment switching using:

- basket of subsequent treatments at 3rd line+ based on those available in NHS algorithm (except ofatumumab)
- equal likelihood of having any available subsequent treatment when switch

Committee conclusion: EAG's approach simplification → subsequent treatments influenced by previous therapy.

- Subsequent treatments: ocrelizumab, ofatumumab, ublituximab or cladribine
- More information on sequencing from real-world evidence or clinician surveys would be useful

Company: Sandoz: ublituximab newly recommended (December 2024) so reliable data on NHS subsequent treatments unavailable

EAG: Obtained data from MS Register on subsequent treatments in NHS

- No efficacy or safety data on ublituximab → assume equivalent to ocrelizumab
- No use of ublituximab in MS Register so not a subsequent treatment in the model
- Natalizumab used at 2nd line (19%) in MS Register, despite not recommended by NICE in HA RRMS - EAG model aligned with MS Register

Base case: MS Register usage data from UK population with HA RRMS

Scenarios: 100% that swich have a) ocrelizumab, b) ofatumumab, c) ublituximab

Usage data from MS Register in HA RRMS

2nd line therapies	
Natalizumab	19%
Cladribine	19%
Ocrelizumab	37%
Ofatumumab	25%
3rd line therapies	
Natalizumab	8%
Cladribine	19%
Ocrelizumab	35%
Ofatumumab	15%

Is the EAG's modelling of subsequent treatments appropriate?

ACM1, appraisal committee meeting; HA, highly active; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis

Key issue: Mortality (1)

Company: appropriate to use EDSS specific SMRs but Harding et al. values overestimate mortality in high EDSS states

Background, ACM1: EAG used single all cause excess SMR for MS vs. general public from Jick et al 2014

Committee conclusion: mortality risk increases with disability → prefer EDSS specific mortality rates

- Considered EDSS specific SMRs from Sadovnick at al (1992; reported in Pokorski [1997]) and Harding et al (2018)
- Preferred granularity of EDSS scores from Harding, but SMRs likely overestimated, especially for high EDSS scores. Requested alternative ways to model mortality, including:
  - using data from MS Register to verify SMRs by Sadovnick et al. and Harding et al.
  - using the SMRs from Harding et al. as indication of relative difference between EDSS scores but calibrating to a more plausible overall MS SMR

Company: Biogen: agree that EDSS-specific mortality appropriate

- Cladribine (ID6263): Harding et al. considered best available source of SMR data. Appropriate for SMRs to be at least partially informed by Harding et al.

Sandoz: Clinical expert to company suggested Harding data gives unrealistic increases in mortality rate for high EDSS scores.

- Other data sets suggest higher EDSS scores have 2–3 times higher risk of death vs lower EDSS scores
- Suggest committee consider calibrating between sources to derive SMRs that increase with EDSS by a more realistic amount than Harding.

ACM, appraisal committee meeting; EDSS Expanded Disability Status Scale; MS, multiple sclerosis; SMR, standardised mortality rate

Key issue: Mortality (2)

EAG updates base case to use EDSS specific SMR from a Jick et al. and Harding et al. mix

EAG: *Base case:* updated approach uses average SMR across EDSS levels from Jick 2014 with differences between EDSS categories matched to Harding 2018 (see supplementary appendix).

- SMRs calculated relative to EDSS 4 based on model simulation that showed highest % time spent in EDSS 4
  - ❖ Approach pragmatic but produces SMRs that increase less rapidly than Harding 2018
  - ❖ Treatments affect mortality indirectly through reducing time spent in high EDSS states only
- SMR from Jick 2014 for EDSS<4 → not reported in Harding 2018
- SMR for EDSS 7 used for EDSS 8 and 9 → avoids extreme values from Harding. Unlikely impacts results as few people in high EDSS categories.

EAG also provided survival curves as requested by committee at ACM1 (see supplementary appendix)

Illustration of SMR calculations using both Jick 2014 and Harding 2018

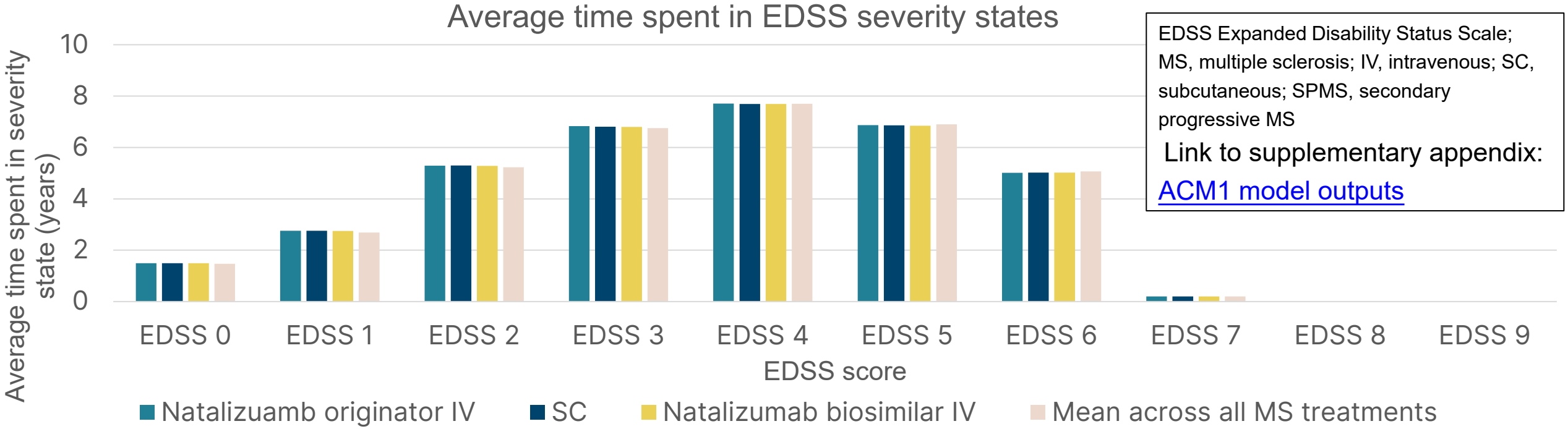
EDSS	0	1	2	3	4	5	6	7	8	9
Sources considered at ACM1										
Sadovnick et al. (1992; reported in Pokorski [1997])	1.6	1.6	1.6	1.6	1.84	1.84	1.84	4.44	4.44	4.44
Jick 2014 (ACM1 base case)	1.68	1.68	1.68	1.68	1.68	1.68	1.68	1.68	1.68	1.68
Harding for EDSS≥4 and Jick for EDSS<4	1.68	1.68	1.68	1.68	2.02	2.02	3.86	4.76	22.17	60.74
New sources for ACM2										
Harding relative to EDSS=4 HR	0.83	0.83	0.83	0.83	1.00	1.00	1.91	2.36	10.98	30.07
Jick/Harding mix SMR (ACM2 base case)	**1.40**	**1.40**	**1.40**	**1.40**	**1.68**	**1.68**	**3.21**	**3.96**	**18.44***	**50.52***

Are the EAG's updated base case SMRs appropriate for decision making?

ACM, appraisal committee meeting; EDSS Expanded Disability Status Scale; SMR, standardised mortality rate

* Not used in model (apply SMR for EDSS7 for these states)

Key outputs from the EAG's model



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

Link to supplementary appendix: ACM1 model outputs

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 to SPMS	9.77	9.78	9.76	9.76
Relapse	10.44	10.43	10.41	10.43
Average time spent on treatment (years)				
2nd line	9.99	10.01	9.98	9.97
3rd line	2.74	2.73	2.73	2.72
4th line	1.04	1.05	1.03	1.04

Key issue: Costs and benefits of SC natalizumab

Company estimate considerable savings with SC administration

Background, ACM1: Natalizumab originator licensed as SC or IV, biosimilar licensed for IV only

- EAG at ACM1 assumed equal administration costs for SC and IV natalizumab (13 x day case costs per year) based on clinical advice that no resource use difference by formulation in clinical practice.
- Clinical experts: minimal overall time saving with SC natalizumab.

Committee conclusion: data on resource requirements for IV vs SC should be submitted at consultation

Company: Biogen: EAG does not capture reduction in workload and patient burden with SC originator natalizumab:

- Benefits of SC vs IV (in secondary care): reduced HCP time, infusion chair time, equipment costs, waiting times
- Patient preference for SC vs IV natalizumab reported in studies because less time in clinic
- Swansea survey shows SC saves time: average minutes per administration + surveillance = 142 min. for IV vs 61 min. for SC
- Company estimates total costs savings of [redacted] per year in 500 patients, assuming all switch from IV to SC ([redacted] less administration and observation nursing time per year, [redacted] less IV consumables, [redacted] more nursing capacity)
- DG incorrectly states that SC use declining → unit sales of SC increasing

ACM, appraisal committee meeting; DG, draft guidance; HCP, health care practitioner; IV, intravenous; SC, subcutaneous

Key issue: Costs and benefits of SC natalizumab

EAG base case: same admin costs for IV and SC. EAG scenario: 50% reduction in admin costs for SC

EAG: clinical advice: company's potential cost savings plausible

- Admin costs in model based on HRG4+ grouper cost per patient visit (as per other MS TAs) → Biogen's costs do not align with use of HRG4+ grouper codes

Base case: no change (equal administration costs for SC and IV)

Scenario: Reduced administration/ observation day case cost for SC natalizumab. Equal monitoring time for IV and SC (based on clinical advice).

Administration costs in the EAG base case and scenario

	Route	Admins	Cost/ admin	Source
Base case	IV	13	£626.13	AA30F Medical care of patients with MS, with CC score 0-1. Day case - NHS England. HRG4+ 2024/25 Local Payment Grouper
	SC	13	£626.13	Same as IV
Scenario	IV	13	£626.13	Same as base case
	SC	13	Year 1: £313.07	50% reduced costs for IV admin
			Year 2+: £0	Assumes 100% company funded home administration (See key issue: THIS)

ABN; Association of British Neurologists; HCP, health care practitioner; HRG, Healthcare Resource Group; IV, intravenous; MS, multiple sclerosis; SC, subcutaneous; TA, technology appraisal; THIS, Tysabri Home Injection Service

- What % of people would have SC vs IV natalizumab in clinical practice?
- Does the EAG's base case or scenario better represent expected costs for SC natalizumab in the NHS?

Stakeholder comments: ABN: most SC natalizumab given in hospital → reduced staff and administration time in safe environment.
Web comment: Model should capture reduced consumables, time in hospital (more patients treated), waiting time with SC vs IV

- Reduced admin time and treatment burden in practice with SC

Key issue: Modelling Tysabri Home Injection Service, THIS

EAG scenario: reduced costs for SC from home administration. No costs for THIS in base case.

Background, ACM1: Company funds home administration by nurse for originator SC natalizumab only

- Clinical experts: Home administration rarely used due to concerns about continuality of funding and need for regular monitoring

Committee conclusion: more data on frequency of home administration for SC natalizumab useful

Company: Biogen: Benefits: care closer to home, less patient travel time, helps address inequalities and reduce patient costs and administration time (e.g. transport, childcare, lost productivity).

- Uptake of THIS [redacted] rapidly – predict up to [redacted]% future use.
- Ongoing monitoring during home administration includes robust measures to monitor for risk of PML

Sandoz: appropriate to model equal resource use for SC and IV routes of administration

Stakeholder comments: MST: important to consider benefits of home administration if unable or unwilling to travel long distances → due to comorbidities (common in MS), disabling symptoms, cost.

- Patients may choose DMT based on travel → greater benefit of THIS in people with lower household income

EAG: *scenario:* no costs for SC natalizumab after year 1 → assumes 100% people have THIS (see key issue: costs and benefits of SC natalizumab). THIS not included in base case.

- Should company funded home administration be included in the model?
- If yes, in what proportion of people having SC natalizumab?
- Is the assumption in EAG's scenario of 100% THIS uptake after year 2 plausible?

ACM, appraisal committee meeting; DMT, disease modifying therapy; MST, MS Trust; PML, Progressive Multifocal Leukoencephalopathy; IV, intravenous; SC, subcutaneous

Key issue: Cost comparison

Sandoz provides cost comparison with ocrelizumab, ofatumumab, ublituximab at consultation

Background, ACM1: Sandoz consider cost comparison appropriate

Clinical experts: natalizumab may have sightly improved efficacy vs comparators as works more quickly.

Committee conclusion: lack of evidence to confirm equal effectiveness but cost comparison at consultation useful

Company: Sandoz: cost comparison avoids uncertain natural history data, treatment waning, stopping rule.

EAG: Cost comparison limited by short time horizon and does not consider:

- Mortality
- Treatment switching and discontinuation
- Differences in costs for events (relapses, EDSS progression)
- Differences in costs and treatments for progression to SPMS
- Monitoring costs → clinical advice suggests patients routinely monitored in tertiary care for relapse & side effects

Similar number of visits assumed → cost mostly align with EAGs except:

- EAG assumes higher number of doses of ublituximab
- EAG assumes a higher day care cost (£513 vs £626) and extra annual monitoring visit
- No consideration of time saving from SC formulation in cost comparison

Details of Sandoz's cost comparison

Input	Assumption
Interventions	Natalizumab (originator, biosimilar) IV (SC not included)
Comparators	Ocrelizumab, ofatumumab, ublituximab
Time horizon	3 years
Costs	Acquisition & administration
EID	a) 100%, b) 60% or c) 0% for originator and biosimilar

- Are there differences in mortality, treatment switching, event rates and monitoring between natalizumab originator/biosimilar and ocrelizumab, ofatumumab and ublituximab?
- Is a cost comparison appropriate? If yes, is Sandoz's model appropriate for decision making?

ACM, appraisal committee meeting; EID, extended interval dosing; IV, intravenous; SC, subcutaneous

Key issue: Cost comparison

Differing administration costs and dosing regimens in Sandoz's cost comparison vs EAG model

Treatment	Sandoz cost comparison			EAG model		
	N admins/ year	Cost/year	Source	N admins/year	Cost/year	Source
Natalizumab originator + biosimilar IV - 60% on EID	Year 1: 13 Year 2+: 8.67	Year 1: £6,665 Year 2+: £4,443	AA30F. Medical care of patients with MS, with CC score 0-1. Day case. Updated to latest 2023/24.	[redacted]	£5,635	AA30F Medical care of patients with MS, with CC score 0-1. Day case
Ocrelizumab	Year 1: 3 Year 2+: 2	Year 1: £1,538 Year 2+: £1,025		Year 1: 3 Year 2+: 2	Year 1: £1,878 Years 2+: £1,252	
Ublituximab	As per ocrelizumab			Year 1: 4 Year 2: 2	Year 1: £2,505 Years 2+: £1,252	
Ofatumumab	Year 1: 15 Year 2: 12	Year 1: £186 Years 2+: £0	1 up-front initial training cost for guidance at first injection (3 hours Band 7 nurse time, PSSRU (2023) as per NICE TA706). Then self-administered → no costs.	15	Year 1: £204 Years 2+: £0	3 hours Band 7 nurse time, PSSRU Sandoz
Cladribine	Not included as comparator			12 to 14	£0	TA616

NICE

- Are the administration costs and frequency of administrations in Sandoz's cost comparison plausible?

CC, Complication/Comorbidity; EID, extended interval dosing; IV, intravenous; MS, multiple sclerosis; N, number; PSSRU, Personal Social Services Research Unit.; TA, technology appraisal

EAG base case after consultation

EAG update base case to align with committee preferred assumption at ACM1

Area	EAG base case ACM1	EAG base case ACM2
Comparators (2nd line)	Glatiramer acetate, interferon beta 1a and 1b, alemtuzumab, cladribine, fingolimod, ocrelizumab, ofatumumab, ponesimod, HSCT	Cladribine, ofatumumab, ocrelizumab, ublituximab
Clinical effectiveness	EAG base case NMA	Same as ACM1
	IV originator and biosimilar separate technologies	Equal efficacy and safety of IV originator and biosimilar
Natural history	MS Register time to event data	Same as ACM1
Treatment waning	Discontinuation due to AEs (proxy)	Same as ACM1
Subsequent treatments	• As per NHS England algorithm except ofatumumab • Equal chance of any available subsequent treatment when switch	• Same available treatments as for 2nd line • Treatments not repeated after switching • Distribution across 3rd line therapies: MS Register data • Distribution across 4th line+ treatments: equal chance of having all available therapies
Mortality	Single SMR from Jick et al	SMR from Jick 2014, with differences between EDSS state SMRs based on Harding 2018.
EID	No EID	6-weekly EID in 60% of people having natalizumab
Anti-JCV tests	For originator and biosimilar	None included
IV vs SC	Equal costs and resource use	Same as ACM1

AE, adverse events; ACM, appraisal committee meeting; EID, extended interval dosing; EDSS, Expanded Disability Status Scale; IV, intravenous; JCV, John Cunningham virus; NMA, network meta-analysis; RRMS, relapsing-remitting MS; SC, subcutaneous; SMR, standardised mortality rate

EAG scenarios

	Analysis	Description
1	**Reduction in natalizumab-SC administration costs**	50% reduced administration cost for natalizumab-SC vs IV to explore company's assumption of reduced resource use (nurse administration hours per year) in year 1. 100% have home administration (no administration costs) from year 2
2	**Equal clinical effectiveness for natalizumab, ocrelizumab and ofatumumab**	Only cladribine has different treatment effect (ublituximab assumed equal to ocrelizumab) for CDP6, ARR, discontinuation due to SAEs, SAEs.
3	**Treatment waning**	Reduced treatment effects on EDSS increase for RRMS patients by 10% waning over 5 years (2% waning per year) for natalizumab and comparators
	All patients on subsequent treatments (3rd line) have:	
4	**ocrelizumab**	4th line+ = patients equally distributed across all available therapies.
5	**ofatumumab**	
6	**ublituximab**	
7	**Jick/Harding mix for SMRs EDSS 8/9**	No capping of SMR at EDSS7 → greater uncertainty on EDSS 8 and 9.
8	**Lowest MPSC prices**	Scenarios including the highest and lowest nationally available prices for comparators with regional MPSC pricing
9	**Highest MPSC prices**	
10	**Including SC ocrelizumab**	Including costs for SC ocrelizumab from TA1025 (ublituximab)

ARR, annualised relapse rate; CDP6, confirmed disability progression at six months EDSS Expanded Disability Status Scale; MPSC, Medicines Procurement and Supply Chain; IV, intravenous, RRMS, relapsing-remitting multiple sclerosis; SAE, serious adverse event; SC, subcutaneous; SMR, standardised mortality rate; TA, technology appraisal.

Link to supplementary appendix: EAG scenarios at ACM1

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: provided ICERs and incremental net monetary benefits for comparators vs natalizumab originator IV → decision making should focus on incremental net benefits not ICERs to better capture high degree of uncertainty

ICER, incremental cost-effectiveness ratio; IV, intravenous; MPSC, Medicines Procurement and Supply Chain

Key issues

Issue
Natural history data: Has evidence provided at consultation reduced uncertainty around the generalisability of the MS Register data to the NHS population with RRMS? • Is the proportion of people progressing to SPMS with different treatments clinically plausible?
Treatment waning and sequencing: How should treatment waning be modelled for natalizumab originator, biosimilar and comparators?
Subsequent treatments: Is the EAG's modelling of subsequent treatments appropriate?
Mortality: How should mortality be modelled? Are the EAG's updated base case SMRs appropriate for decision making?
SC/IV administration: Are subcutaneous and intravenous natalizumab appropriately modelled? • Should home administration costs for subcutaneous natalizumab be included in the model? • What proportion of people are expected to have SC vs. IV in clinical practice?
Cost comparison: Is a cost comparison appropriate? If yes, is Sandoz's model appropriate for decision making?

IV, intravenous; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous; SPMS, secondary progressive MS; SMR, standardised mortality rate

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

RECAP

Relapsing remitting multiple sclerosis (RRMS)

Chronic, lifelong, neurological disease with no cure; results 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): 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

Link to main slides: types of MS

Decision problem at ACM1

RECAP

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

Link to main slides: technology

RECAP

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: types of MS

Treatment pathway at ACM1

NHS England algorithm defines treatments used for HA RRMS

RECAP

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.

Link to main slides: new evidence

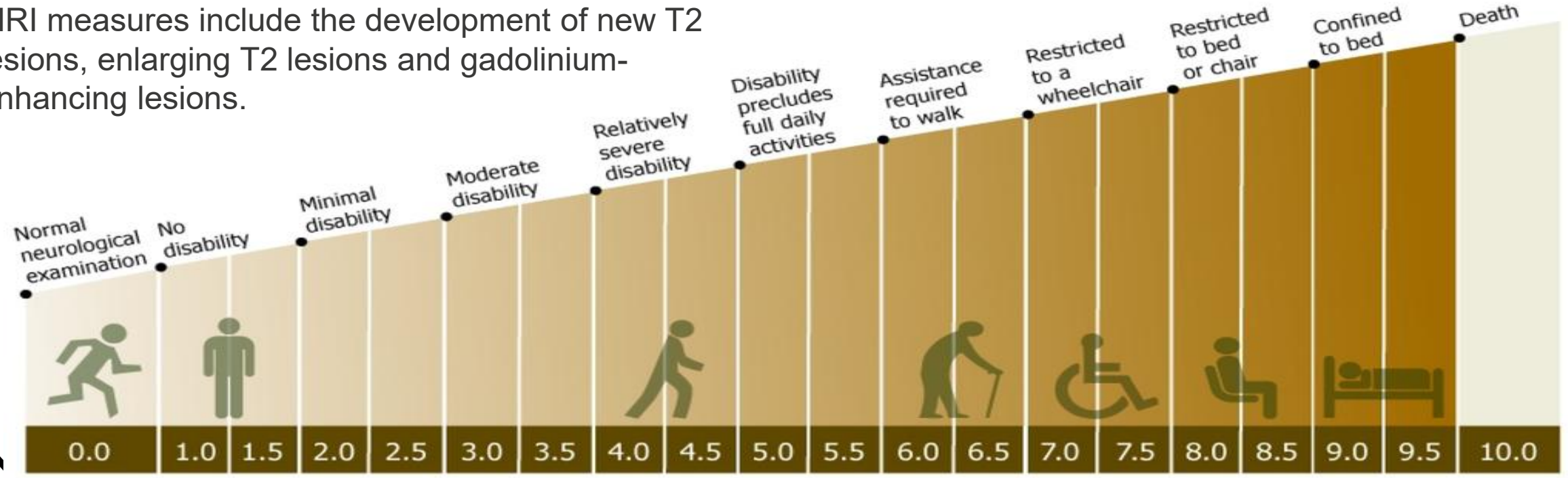
Definition of outcomes in trials

Link to main slides: new evidence

RECAP

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/*

Classification of RRMS

Variation in definition of highly active RRMS across NICE TAs

RECAP

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)**

Link to main slides: consultation comments

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

Overview of clinical effectiveness data in EAG's model

No RCTs in HA RRMS, similar effectiveness of high efficacy DMTs for key NMA outcomes in all RRMS population

Key data for natalizumab:

RCT: AFFIRM & Saida 2017 (originator vs placebo), ANTELOPE (originator vs biosimilar) – all RRMS. No RCT data in HA RRMS.

Summary of EAG's NMA:

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

Outcomes: ARR; MRI measurements (Gd+ enhancing & T2 weighted lesions); disease progression (CDP3, CDP6, combined CDP3/6); AEs; HRQoL

Results: Natalizumab and ocrelizumab greatest improvements for most efficacy outcomes of committee preferred comparators

- SAEs: No difference between all treatments in network
- Limited results in HA RRMS subgroup show similar trend

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 main slides: new evidence RECAP

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%

Non-RCT data:

- **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 Q4W): ARR, CDP3, PK, PD, safety outcomes comparable

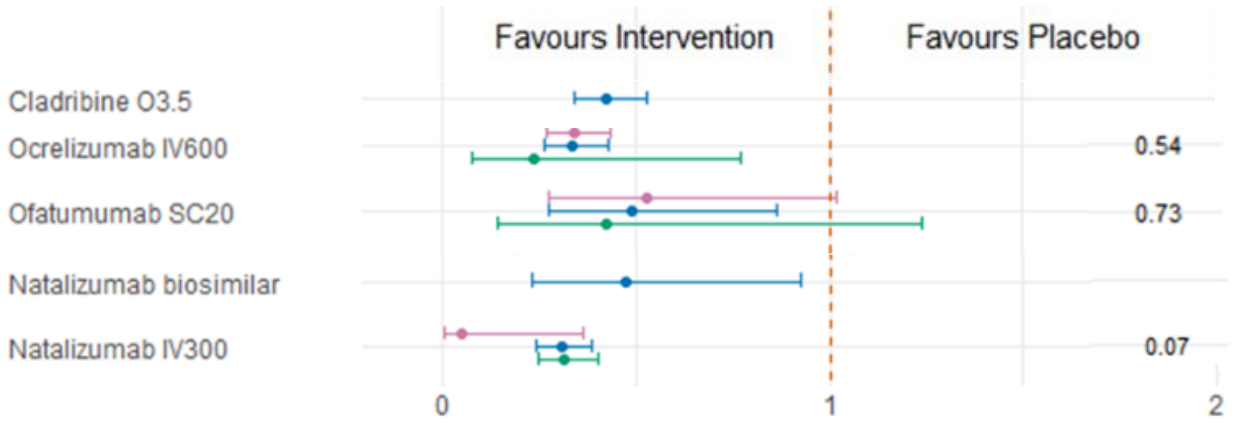
ARR, annualised relapse rate; CDP, confirmed disease progression at 3/6 months; DMT, disease-modifying therapy; HA, highly active; HR, hazard ratio; N, number; NR, not reported; RCT, randomised controlled trial; Q4W, 4 weekly RR, rate ratio; RRMS, relapsing-remitting MS; SAEs, severe adverse events

NMA results (1)

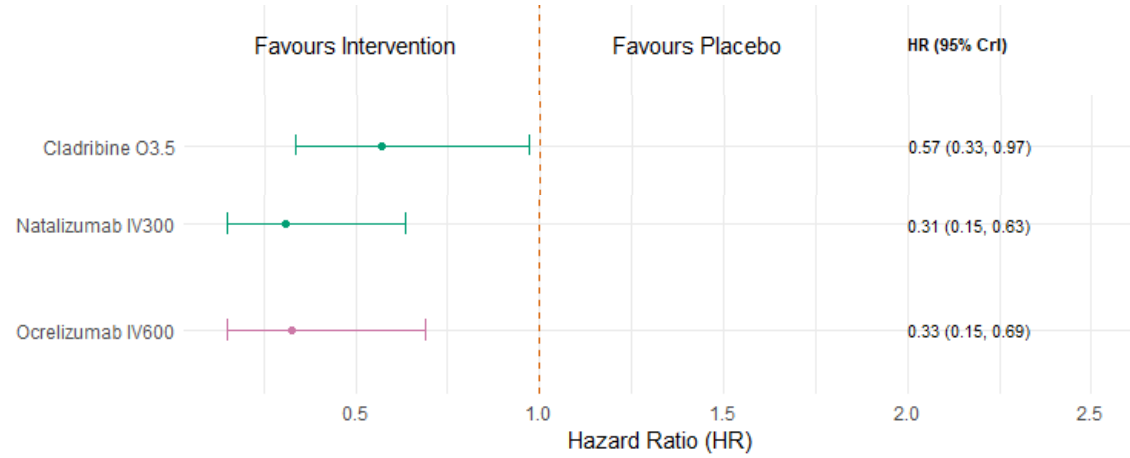
Link to main slides: new evidence

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

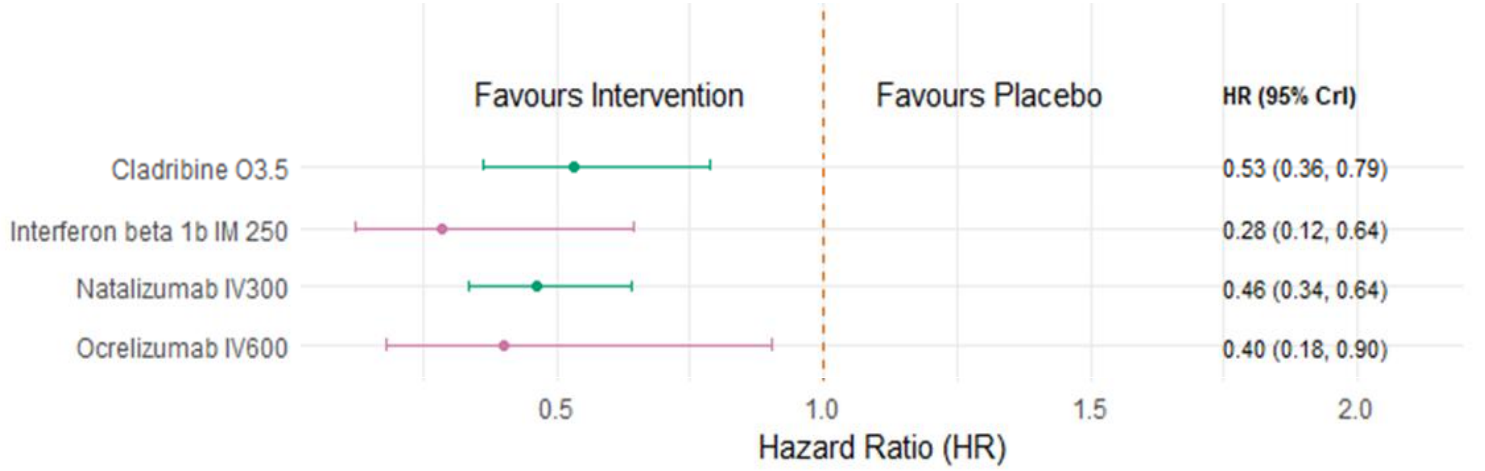
Full RRMS population



HA RRMS population



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

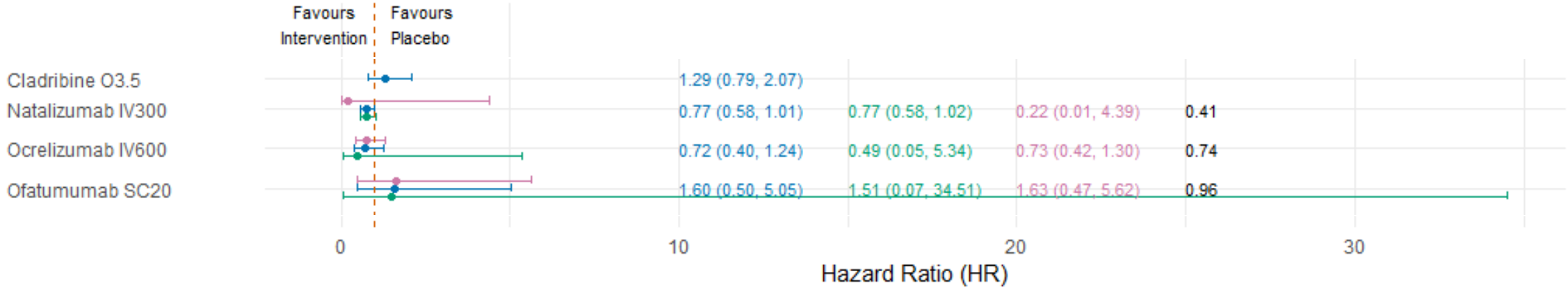


ARR, annualised relapse rate; CrI, confidence interval; HA, highly active; HR, hazard ratio; IM, intramuscular; IV, intravenous; NMA, network meta-analysis; RRMS, relapsing-remitting MS; SC, subcutaneous

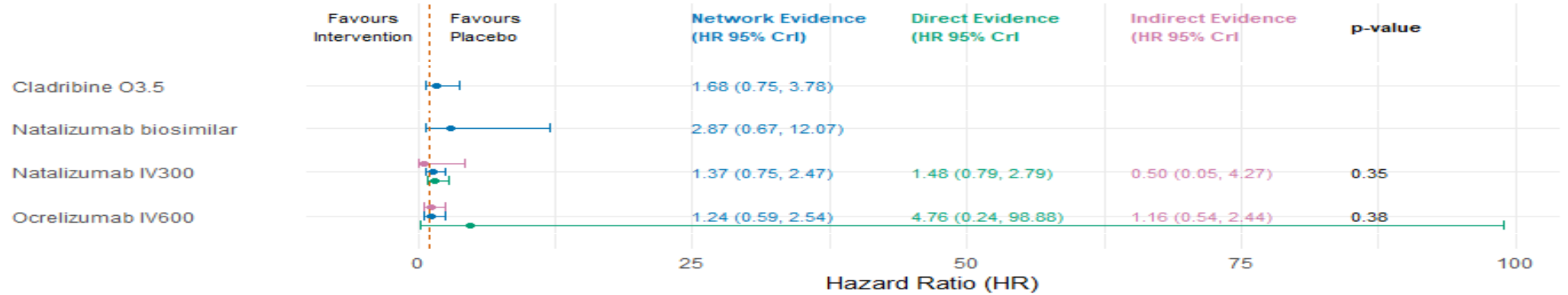
NMA results (2)

Link to main slides: new evidence

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



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; SAE, serious adverse event; SC, subcutaneous

Company/EAG response to draft guidance

Link to main slides: summary of ACM1

Requested by committee	Provided?
Information on clinical equivalence of natalizumab originator and biosimilar	Company comment
Scenario assuming equal clinical effectiveness for natalizumab, ocrelizumab & ofatumumab	Cost comparison provided by Sandoz
Additional information on quality and relevance of MS Register data, including completed DataSAT tool for all potential natural history sources	Yes
% with SPMS in model at 5, 10 and 15 years	Yes
Exploring alternative ways to model treatment waning	Yes
Data on subsequent treatments in NHS clinical practice	Yes
Exploring alternative ways to model mortality, including but not limited to: – using data from MS Register to verify data by Sadovnick et al. and Pokorski et al. – using the SMRs from Harding et al. as indication of relative difference between EDSS scores but calibrating to a more plausible overall MS SMR	Yes
Survival curves from the model	Yes
Data on % having 6-weekly dosing with natalizumab for each formulation in NHS	Company comment

Further data provided at consultation:

- **Biogen:** data to support additional benefits with SC vs IV formulation

DataSAT, data Suitability Assessment Tool; EDSS Expanded Disability Status Scale; IV, intravenous, MS, multiple sclerosis; SC, subcutaneous; SPMS, secondary progressive MS; SMR, standardised mortality rate

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: natural history 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

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

DataSAT questionnaire, MS (Multiple Sclerosis) Register (1) [43]

Data provenance

Link to main slides: natural history data

Item	Response
Data sources	UK MS Register (UKMSR), self-reported data extracted August 2024.
Data linkage and data pooling	No external datasets were linked for this analysis. All analyses based on data collected within the UKMSR.
Type of data source	Longitudinal patient-reported outcome data.
Purpose of data collection	The UKMSR is a research based disease registry linking clinical and self-reported outcomes to help improve understanding MS disease progression, treatment outcomes, and general quality of life for people with MS.
Data collection	• Treatment data: DMT types, treatment dates • MS Phenotype and progression dates • Relapse dates and severity • EDSS (Leddy S, Hadavi S, McCarren A, Giovannoni G, Dobson R. Validating a novel web-based method to capture disease progression outcomes in multiple sclerosis. J Neurol. 2013 Oct;260(10):2505-10. doi: 10.1007/s00415-013-7004-1. Epub 2013 Jun 27. PMID: 23807152.)
Care setting	Direct patient reporting via our secure online portal and NHS Neurology clinics
Geographical setting	The UKMSR is proportionally represented by participants from all of the constituent countries of the United Kingdom
Population coverage	The UKMSR has >25,000 participants with MS which covers a broad population with some selection bias due to being an online registry, however efforts to diversify the cohort via active recruitment on the lifespan of the registry has led to more proportional representation.
Time period of data	Data collection has been ongoing since April 2011.

DMT, disease modifying therapy; EDSS Expanded Disability Status Scale; MS, multiple sclerosis

DataSAT questionnaire, MS (Multiple Sclerosis) Register (2)

Data preparation	Data extracted using R version 4.4.0 programming language with DBI and ODBC packages, pre-processed using the tidyverse packages, and EQ5D scores processed using the eq5d package. Instruments that used by the UK MS Register were pre-processed as follows: Participants – Register users had to contain the following info to be considered: • MS at Diagnosis recorded as either RRMS or SPMS, • Current MS Type recorded as either RRMS or SPMS, • Year of birth must be present, • Gender must be provided and either Male or Female. Those who recorded “Prefer not to say” on Gender were excluded due to low counts. • Age at time of study (2024) had to be between 18-100, • Date of Current MS Type must be recorded and valid (i.e after onset/diagnosis dates, after year of birth), • Have at least 1 DMT recorded in their medications, • Have at least 2 web EDSS readings. For dates of MS Onset, Diagnosis, and Current MS, users can indicate that they do not know the month/year of the date in question. In cases where the month is unknown, the month is inferred to be January. WebEDSS – In the event that users made multiple webEDSS submissions on the same day, the latest webEDSS entry made on that day was used, with other entries discarded. Self-Reported Medications – Medications were grouped into main DMT components, and on initial filtering, any entries which: • Were flagged as having started after August 15th, 2024, • Started after the date the medication entry was filled in on the register website, • Had a zero day duration (Start date being equal to end date) were excluded and filtered out of the medications. In the event that multiple DMTs were logged with no stop date with the potential to cause a clash with another DMT, a timeline was constructed where a stop date was inferred based on the next DMT’s start date minus 1 day to ensure that only DMT was in use at a time. Relapses – Users on register can indicate if they had any relapses in the last 6 months and identify the month of most recent relapse. Pre-processing was performed on these responses to check that the month reported on the relapse corresponds to being within 6 months of the completion of the relapse survey. EQ5D – EQ5D-5L responses were gathered to link to the latest webEDSS readings from users. To calculate the index score from the EQ5D components, the 5L UK Crosswalk algorithm was used in the eq5d package.

DBUI, database interface; DMT, disease modifying therapy; EDSS Expanded Disability Status Scale; MS, multiple sclerosis; ODBC, Open Database Connectivity; RRMS, relapsing-remitting MS; SMPS, secondary progressive MS

Link to main slides: natural history data

DataSAT questionnaire, MS (Multiple Sclerosis) Register (3)

Item	Response
Data governance	UK MS Register is managed and maintained by Swansea University Medical School and is primarily funded by MS Society. The UKMS Register has ethical approval from South West Central Research Ethics Service 21/SW/0085 It operates under strict governance protocols where data is made pseudonymously available to accredited researchers after suitable review. The platform has high security standards being ISO 27001 accredited with regular external security audits with annual penetration testing. The system benefits for extensive network segmentation and data protection backups. For researchers to access these data there is a formal process where an expression of interest leads to a feasibility meeting with register team. This then moves on to a formal collaboration request which is then assessed by the governance review board. If the project is approved then data assess agreements are signed and relevant training is assign. Only then are the data provisioned. The register is fully compliant with GDPR/Data Protection Act 2018
Data specification	A data dictionary sufficient to data provided for each project is provided as needed.

GDRP, General Data Protection Regulation; ISO, International Organization for Standardization

Link to main slides: natural history data

DataSAT questionnaire, MS (Multiple Sclerosis) Register (4)

Data management plan and quality assurance methods

Secure eResearch Platform (UKSeRP), achieved ISO27001 accreditation, as a consequence of the audit level required to attain this. All host systems servers and software, electronic and physical security are maintained to these standards. To that end we use the term UKSeRP below

This network covers the data networks, LAN-attached servers and personal computers (stand-alone or network- enabled), located at company offices and company production related locations, where these systems are the responsibility of UKSeRP, and any personal computers, laptops, mobile device and or servers authorised to access the company's data networks. Data are backed up to a schedule as agreed with the UKSeRP tenant. Typically this takes the form of daily entire system backups and hourly transaction log shipping from databases.

All backups are fully documented – covering configuration and usage instructions.

All backups are stored securely onsite within UKSeRP access-controlled areas / secure perimeter (but remote from backup infrastructure location) on the main Swansea University campus.

Access to data stored in SeRPs is approved by an information governance committee who will review project access. This is typically made up of a team member, several people affected by the conditions, academics from outside of Swansea University and clinicians from the NHS.

Access to anonymised data is then granted and users must sign a data sharing agreement, similar to this one:
https://redcap.ukmsregister.org/surveys/?s=8HRC4KLCW9

They must also complete a GDPR course from a recognised provider and present this and a CV to the research team.

Data are provided to researchers via the SeRP. Comprising the security and governance layer then 2 factor remote access to anonymised data via SPSS/R/SAS/Stata as appropriate. Line level data are not allowed out and all requests for data are reviewed by a senior analyst.

Data are retained for the duration of the research unless participants elect to leave the study. In this case all identifiable data are purged although the research data will remain. This is due to publications/analyses potentially having been based on these data. The terms for this are clear to participants should they choose to leave the study.

Typically, most data is kept for 21 to 25 years or for the duration of the study should it be longer. Data reside in databases as laid out in the data dictionaries for the project. Where it is linked to other data sources – Such as SAIL documentation for that are kept. All accesses, user rights, requests for data out and ultimately publications will be logged by the system.

GDRP, General Data Protection Regulation; LAN, Local Area Network; SAS, Statistical Analysis System

Link to main slides: natural history data

DataSAT questionnaire, MS (Multiple Sclerosis) Register (5)

Data quality

Link to main slides: natural history data

Study variable	Target concept	Operational definition	Quality dimension	How assessed	Assessment result
What type of variable (for example, population eligibility, outcome)	Define the target concept (for example, myocardial infarction [MI])	Define operational definition. For example, MI defined by an ICD-10 code of I21 in the primary diagnosis position	Choose: accuracy or completeness	Describe how quality was assessed. Provide reference to previous validation studies if applicable.	Provide quantitative assessment of quality if available. For example, 'positive predictive value 85% (75% to 95%)'
MS Type at diagnosis	Diagnosis		completeness		100%
MS Type Now	Diagnosis		completeness		100%
Self-reported medication	Drug		completeness	Selected self-reported disease modifying therapies (DMTs) of interest	At least 1 per patient
Web EDSS	PRO assessment		completeness		At least 2 per patient
Self-reported Relapse	PRO assessment		completeness	Users report any relapses as they occur. If none reported then assumption that no relapse occurred	
EQ5D	PRO assessment		Completeness	QoL Index linked to webEDSS	

EDSS Expanded Disability Status Scale; ICD, International Classification of Diseases; PRO, patient reported outcome; QoL, Quality of Life

DataSAT questionnaire, MS (Multiple Sclerosis) Register (6)

Data relevance

Link to main slides: natural history data

Item	Response
Population	The UKMSR population is representative of the population of people with MS being treated at NHS neurology clinics (Middleton, et al. 2018). Self-reported treatments have been validated using linked data from partner NHS treatment centres where the patient has consented to do so.
Care setting	See above, our population and treatment pathways are representative of NHS treatment protocols at UK neurology centres.
Treatment pathway	See above, all participants in the UKMSR have a confirmed diagnosis of MS. All treatments over the course of the disease are self-reported via our online secure portal.
Availability of key study elements	See data preparation section. Data selected such that each participant had a valid entry for MS type at diagnosis and current MS Type, Date of birth, Sex, have record of at least one DMT and at least 2 EDSS scores.
Study period	The study period ranged from first EDSS visit of 03/01/2015 and last recorded EDSS visit 13/08/2024, DMTs could be any treatment available on the NHS during this time period.
Timing of measurements	All measures were self-reported and generally recorded after the fact. For example each questionnaire window is every 6 months and we ask if there were any relapses in the last 6 months, number and severity of latest. Date of SPMS progression is recorded after a diagnosis from a clinician so it can range from being recorded on the same day to many years after the fact. EDSS is recorded when the participant does the online assessment.
Follow up	Note how the follow-up period available in the dataset is sufficient for assessing the outcomes. The median number of EDSS assessments for this cohort were 5 and the mean follow up time was 3.84 years.
Sample size	2140 participants in the UKMSR met all the inclusion criteria described above.

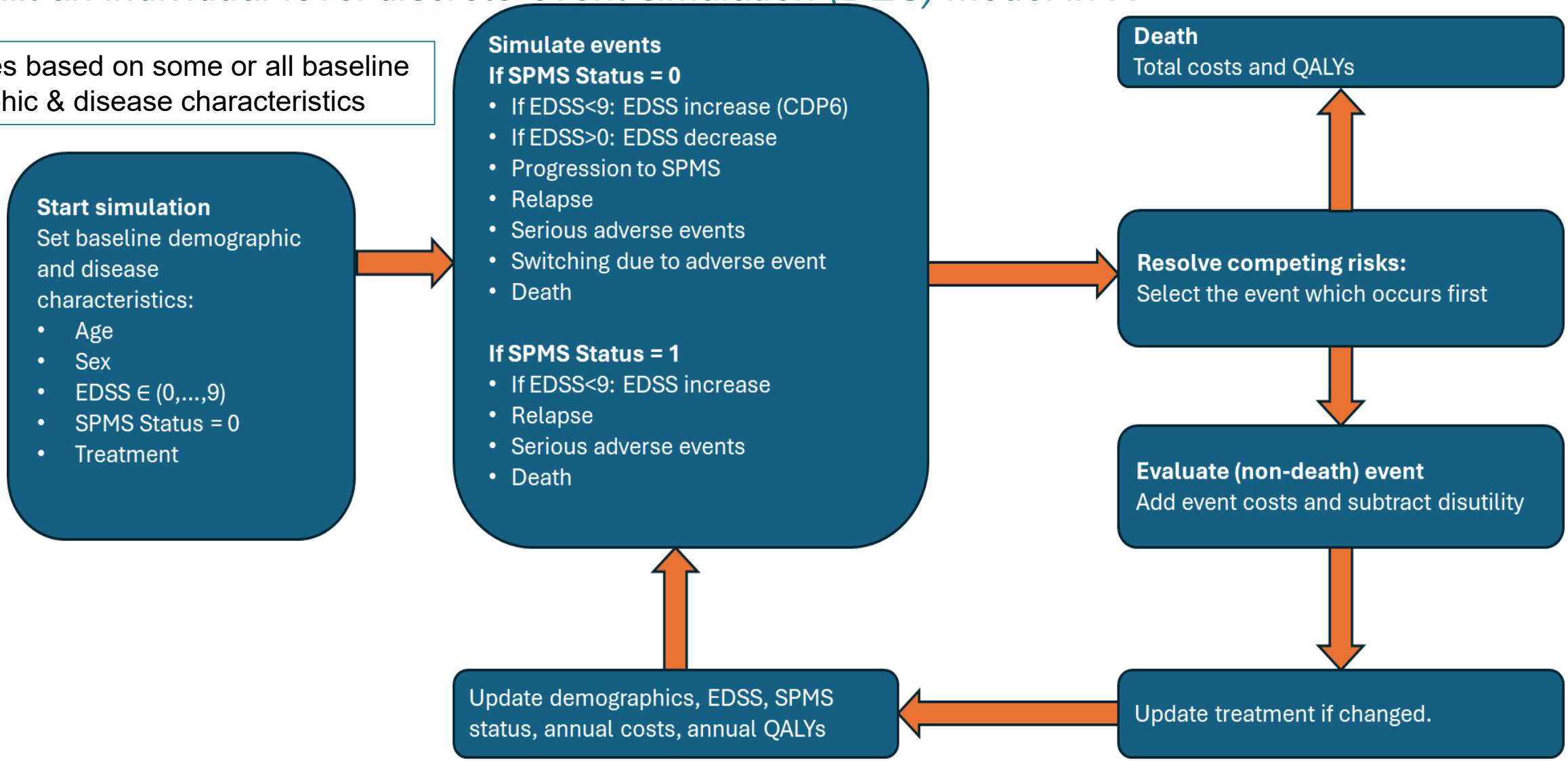
DMT, disease modifying therapy; EDSS Expanded Disability Status Scale; UKMSR, UK MS Register; SPMS, secondary progressive MS

EAG's clinical effectiveness model

Link to main slides: new evidence

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

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



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 at ACM1

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

Link to main slides: new evidence

Validity of model outputs, ACM1

Link to main slides: key model outputs

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

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: extended interval dosing (EID) (1)

EAG base case updated to include committee preferred EID frequency (60% model population)

Background, ACM1: 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 PML

Committee conclusion: Prefer 6-weekly dosing in 60% of people to reflect expected use in clinical practice

Company: both support 60% having EID in clinical practice

Biogen: Clinical experts suggest EID routine in clinical practice → allows flexibility in determining appropriate treatments, especially for high-risk groups

- Supported by average number doses of originator natalizumab in NHS ([redacted] per patient per year)
- FDG should reflect value of EID to NHS and patients including reduced: a) costs (less HCP time for administration); 2) exposure during pregnancy; 3) risk of PML; 4) travel and in-clinic time for patients and carers
- No data to suggest different efficacy and safety between formulations → proportions having EID likely equal
- Natalizumab observational programme: similar efficacy when switch from IV to SC with 4 and 6 weekly dosing.
- 8 weekly dosing available for further flexibility (e.g. maintaining outcomes in pregnancy)

Sandoz: Clinical expert option to company suggests EID likely to become more common in future.

NICE technical team: SmPC for natalizumab does not limit EID to 6 weekly: Highlights average dosing interval of approximately 6 weeks may be associated with lower risk of PML based frequency on retrospective analysis of US anti-JCV antibody positive patients having natalizumab originator IV (TOUCH Prescribing Program)

EID, extended interval dosing; FDG, final draft guidance; HCP, healthcare practitioner; IV, intravenous, JCV, John Cunningham virus; MS, multiple sclerosis; PML, Progressive Multifocal Leukoencephalopathy; SC, subcutaneous; SmPC, summary of product characteristics. Link to main slides: summary of ACM1

Key issue: extended interval dosing (EID) (2)

EAG base case updated to include committee preferred EID frequency (60% model population)

EAG: clinical advice → EID use differs by centre
Base case: EID used in 60% as per committee preference

Stakeholder comments: ABN: Many centres now use mostly 6-weekly dosing due reduce risk of PML and increase infusion suite capacity.

- EID: 33% reduction vs SID in drug and NHS infusion-associated costs, possible safety monitoring cost savings.

MST: people having natalizumab and clinicians confirm EID common and widely accepted → EAG's costs overestimated

- EID allows pregnant women to time infusions to avoid third trimester (when natalizumab may influence baby) whilst still protecting mother from relapse → avoids potential risk of post-birth rebound activity from poor control during pregnancy

Web comment: decision at ACM1 driven by incorrect modelling of natalizumab administration (no EID)

ABN, Association of British Neurologists; ACM, appraisal committee meeting; EID, extended interval dosing; MST, MS Trust; PML, Progressive Multifocal Leukoencephalopathy; SID, standard interval dosing

EAG's updated mortality calculations

1) Calculate log (SMR) for Jick 2014 and Harding 2018 stratified by severity

EDSS	0-4	4-5.5	6-6.5	7-7.5	8-8.5	9-9.5
SMR Jick 2014	1.68 (95% CI 1.38, 2.05)					
Log SMR (log SD) Jick 2014	0.52 (0.10)					
SMR (95% CI) Harding 2018	-	2.02 (0.98, 3.71)	3.86 (2.63, 5.47)	4.76 (2.82, 7.56)	22.17 (18.20, 26.75)	60.74 (47.62, 76.41)
Log SMR (log SD) Harding 2018	-	0.70 (0.34)	1.35 (0.19)	1.56 (0.25)	3.10 (0.10)	4.11 (0.12)

2) Calculate proportion of total time at risk spent in each EDSS category across modelled treatments calculated to determine EDSS state where most time spent (EDSS4).

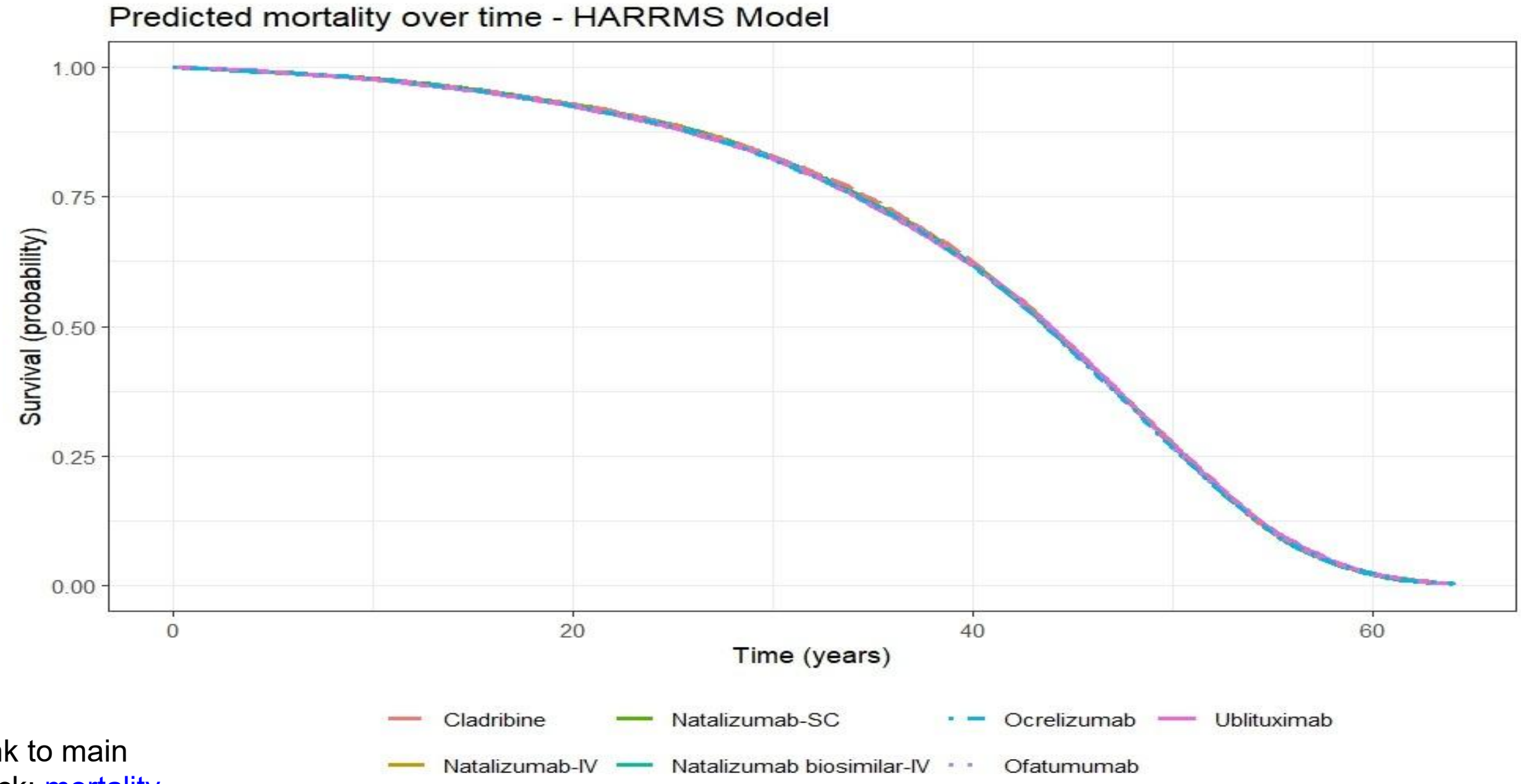
Jick (EDSS 0-9)	EDSS 0	EDSS 1	EDSS 2	EDSS 3	EDSS 4	EDSS 5	EDSS 6	EDSS 7	EDSS 8	EDSS 9
Natalizumab originator IV	0.039	0.071	0.143	0.187	0.216	0.192	0.146	0.006	0.000	0.000
Natalizumab originator SC	0.040	0.072	0.143	0.188	0.214	0.195	0.143	0.005	0.000	0.000
Natalizumab biosimilar IV	0.043	0.078	0.142	0.181	0.212	0.193	0.144	0.005	0.000	0.000
Cladribine	0.043	0.069	0.142	0.179	0.205	0.201	0.154	0.006	0.000	0.000
Ofatumumab	0.042	0.075	0.146	0.181	0.217	0.190	0.143	0.006	0.000	0.000
Ocrelizumab	0.043	0.076	0.147	0.182	0.213	0.188	0.144	0.005	0.000	0.000

3) Calculate SMRs from Harding relative to EDSS health state 4 (see main deck: mortality)

4) Combine data from Jick and Harding et al to get a mixed SMR by severity (see main deck: mortality)

CI, confidence interval; EDSS, Expanded Disability Status Scale; IV, intravenous; SC, subcutaneous; SD, standard deviation; SMR, standardised mortality rate

Survival curves with EAG/committee preferred base case



Link to main deck: mortality

IV, intravenous; SC, subcutaneous; HA RRMS, highly active relapsing-remitting multiple sclerosis

Costs and utilities in the EAG's model

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

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

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

Link to main slides: new evidence

Further consultation comments (1)

	Stakeholder comment	EAG comment
Comparators	**Sandoz:** Cladribine not relevant comparator. Accept licenced for population but: • market access data suggests rarely used in NHS. • MSBase cohort analyses: less effective than most potent IV MS therapies, including natalizumab → supports case for cost comparison (see key issue) • contraindicated in pregnancy & breastfeeding	Cladribine included in scope and committee preferred assumptions → included in EAG base case
Model	**Sandoz:** model overly complex, lacks transparency and computationally inefficient to run	DES allows treatment sequencing and waning • Markov model inflexible and leads to high % with high EDSS states. • R code & data available for transparency
Starting treatment	**ABN:** natalizumab can be started more rapidly than other highly effective RRMS treatments, without the need for pre-screening and potential vaccination → benefit when switch needed urgently due to clinical deterioration	Clinical advice: delays at multiple stages of pathway (often due to local issues): • infusion bed access delays (prefer non-IV treatments such as cladribine, ofatumumab or SC natalizumab) • JCV tests and time to consider risk of PML can also delay starting natalizumab Pre-treatment vaccinations and TB screening rare

ABN, Association of British Neurologists; DES, discrete event simulation; EDSS, Expanded Disability Status Scale; IV, intravenous; JCV, John Cunningham virus; PML, Progressive Multifocal Leukoencephalopathy; RRMS, relapsing-remitting MS; SC, subcutaneous; TB, tuberculosis

Link to main slides: consultation comments

Further consultation comments (2)

Link to main slides: consultation comments

	Stakeholder comment	EAG comment
Clinical equivalence	**Sandoz**: Guidance on licensing of biosimilar products states that that biosimilar considered interchangeable with their RMP → expect to achieve the same therapeutic effect • NICE's position statement: "[Recommendations] will not differentiate between the originator and biosimilar products…. the issue of switching and interchangeability will not be considered within the technology appraisal." **Web comment:** Biosimilar natalizumab has approved by MHRA → regulatory responsibility for determining equivalence. • Following approval, biosimilar considered equivalent (reflects how already used in NHS). Basis for committee's uncertainty unclear.	No new info that could inform appraisal
NMA	**Sandoz:** accepting EAG's NMA is practical conclusion but NMA open to criticism.	None
Costs	**MST**: NHS costs for advanced MS care (e.g. admissions for UTIs) should be captured	Model does not cover full complexity of advanced stages of MS → simplification but attempts to capture most important impacts on costs and effects

ACM, appraisal committee meeting; MS, multiple sclerosis; MST, MS Trust; NMA, network meta-analysis; UTI, urinary tract infection; RMP, reference medicinal product

EAG scenarios at ACM1

Link to main slides: 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

Model inputs compared with previous TAs (1)

Link to main slides: new evidence

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) , with differences between EDSS state SMRs based on Harding 2018.
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 (2)

Link to main slides: new evidence

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 (3)

Link to main slides: new evidence

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.