Slides for public – Part 1 (contains no ACIC data)

NICE National Institute for Health and Care Excellence

Peginterferon beta-1a for treating relapsing-remitting multiple sclerosis

Lead team presentation

1st appraisal committee B meeting

Chair: Amanda Adler

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ERG: Warwick Evidence

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Company: Biogen Idec

26th November 2019

Key issues

- Positioning of peginterferon beta-1a:
  - would peginterferon beta-1a only be used at first-line?
  - what are the relevant comparators?
- ADVANCE trial:
  - are patients from ADVANCE generalisable to NHS patients likely to be treated with peginterferon beta-1a?
  - is peginterferon beta-1a clinically effective compared with existing treatments?
- Economic model:
  - should treatment waning be included in the model?
  - how should stopping treatment for any reason be modelled?
  - which utility values should be used?

[redacted]

History of appraisal

27th June 2018	Originally in, but then removed, from NICE Multiple Technology Appraisal TA527 on beta interferons and glatiramer acetate; a single technology appraisal eventually deemed more appropriate. Peginterferon not in committee's preferred effectiveness source for TA527, the UK MS Risk Sharing Scheme (see next slide).
7th June 2019	**Company submission**: target population is subgroup of marketing authorisation. Positioning is in line with current use in NHS – first-line treatment (since August 2015)
27th Sep to 24th Oct 2019	**Technical engagement**: draft technical report including questions (based on company submission and ERG report)
24th October 2019	**Stakeholder feedback to technical engagement** • Company: new scenario analyses • 1 clinical expert nominated by MS Trust • 1 clinical organisation (Association of British Neurologists) • 2 patient organisations (MS Society, MS Trust) • 1 comparator company (Novartis)
	Final technical report: updated based on stakeholder feedback

History of the MS risk sharing scheme (introduced 2002)

- Allowed NHS funding for the following drugs initially considered cost-ineffective by NICE:
  - Interferon beta-1a (Avonex, Rebif)
  - Interferon beta-1b (Betaferon)
  - Glatiramer acetate (Copaxone)
- To enter scheme companies:
  - Monitored effectiveness, ultimately over 10 years for >5,000 patients
  - Reduced prices to levels considered cost effective by NICE, with agreement to further reduce price if outcomes worse than predicted
- TA527 stated “all the technologies offered in the RSS delayed disease progression compared with best supportive care”

[redacted]

EMA update on alemtuzumab

- September 2013: Alemtuzumab recommended for:
  - adults with “relapsing remitting multiple sclerosis with active disease defined by clinical or imaging features”
- April 2019: European Medicines Agency (EMA) recommended its use was restricted whilst it reviewed rare but potentially serious reported side effects relating to heart, blood vessels, liver and immune system. Interim restriction:
  - “relapsing-remitting multiple sclerosis that is **highly** active despite treatment with **at least two disease-modifying therapies** or **where other disease-modifying therapies** cannot be used”
- November 2019: Restriction endorsed with wording amendment by EMA’s Committee for Medicinal Products for Human Use (CHMP). CHMP opinion recommendation:
  - “relapsing remitting multiple sclerosis that is **highly** active despite **adequate** treatment with **at least one disease-modifying therapy** or if **the disease is worsening rapidly with at least two disabling relapses in a year and brain-imaging showing new damage**”

⊙ ***Is alemtuzumab an appropriate comparator?***

[redacted]

Disease background: multiple sclerosis

- Chronic, lifelong, neurological disease. No cure. Results in progressive, irreversible disability. Affects central nervous system:
  - Immune system mistakenly attacks myelin sheath (layer that surrounds and protects nerves), disrupting signals travelling along the nerves
- 85% relapsing-remitting (RRMS): episodes of relapses (neurological worsening) separated by remission (periods of stability)
- Associated with pain, disturbance to muscle tone, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment
- Affects approximately 110,000 people in UK, and 5,000 newly diagnosed annually
- Onset typically between 25 and 35 years of age
- Treatment (disease-modifying therapies): decrease frequency and severity of relapses, reduce accumulation of lesions, slow accumulation of physical and mental disability, maintain or improve patient quality of life

Types of multiple sclerosis

Primary progressive MS
- 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% to 60% in 15 to 20 years

Secondary progressive MS (SPMS)
- Steady progression of neurological damage with or without relapses
- Treatment might be restricted to secondary progressive disease *with relapses*

Subgroups of RRMS

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

Patient and clinical perspectives

- Patients value range of treatment options to meet individual circumstances
- Peginterferon beta-1a is an established drug that has:
  - similar efficacy to other beta interferon drugs
  - well-known risk/benefit profile; possibly better tolerated than other beta interferon drugs
  - additional benefits may include fewer injections, easily self-administered, can be stored at home, resulting in improved quality of life
- Likely to be used in a small number of people with RRMS
- Not a step change in management but improved method of delivery of pre-existing molecule

Peginterferon beta-1a (Plegridy)

- Marketing authorisation: “adult patients for the treatment of relapsing remitting multiple sclerosis” (obtained July 2014)
- Mechanism of action: man-made version of naturally produced beta interferons, which help to reduce nerve inflammation. Reduces disease activity similar to non-pegylated interferon beta-1a. Pegylation increases circulation time of interferon (less frequent dosing) and decreases immunogenicity (reduced neutralising antibodies linked to treatment waning)
- Administration and dose: prefilled syringe/autoinjector administered subcutaneously every 2 weeks. 63µg dose 1, 94µg dose 2, 125µg dose 3+
- Cost: standard pack 2 injections £654. Annual cost: £8,502. No patient access scheme
- Currently commissioned by NHS England for RRMS first-line, not highly active (disease activity despite previous therapy) or rapidly evolving severe MS
- Originally included but removed from NICE TA527 on beta interferons and glatiramer acetate (see previous slide)

NHS England treatment algorithm and company positioning

RRMS: 1 relapse in last 2 years & radiological activity	RRMS: 2 significant relapses in last 2 years	Rapidly evolving severe MS (RES)

1st line therapy (and *alternative for intolerance to first-line therapy*)

• ***Interferon beta-1a*** • ***Glatiramer acetate*** • Alemtuzumab(?) or ocrelizumab	• ***Interferon beta-1a*** • ***Interferon beta-1b (Extavia)*** • ***Dimethyl fumarate*** • ***Glatiramer acetate*** • ***Teriflunomide*** • Alemtuzumab(?) or ocrelizumab	• ***Alemtuzumab(?) or ocrelizumab*** • ***Cladribine*** • ***Natalizumab*** • ***Fingolimod (only used for intolerance)***

PEGINTERFERON BETA-1A?
currently commissioned by NHS England

Drugs in *bold italics* are those that are also used as alternatives for intolerance

Second-line therapy

• Alemtuzumab or ocrelizumab • Cladribine • Fingolimod *Patients developing RES receive second-line therapy for RES*	• Alemtuzumab or ocrelizumab • Cladribine • Natalizumab

Third-line therapy

• Alemtuzumab or ocrelizumab • Cladribine • Autologous haematopoietic stem cell treatment (AHSCT) *Patients developing RES receive third-line therapy for RES*	• Alemtuzumab or ocrelizumab • Cladribine • Natalizumab • AHSCT

Issue 1: Positioning of peginterferon beta-1a in treatment pathway and comparators

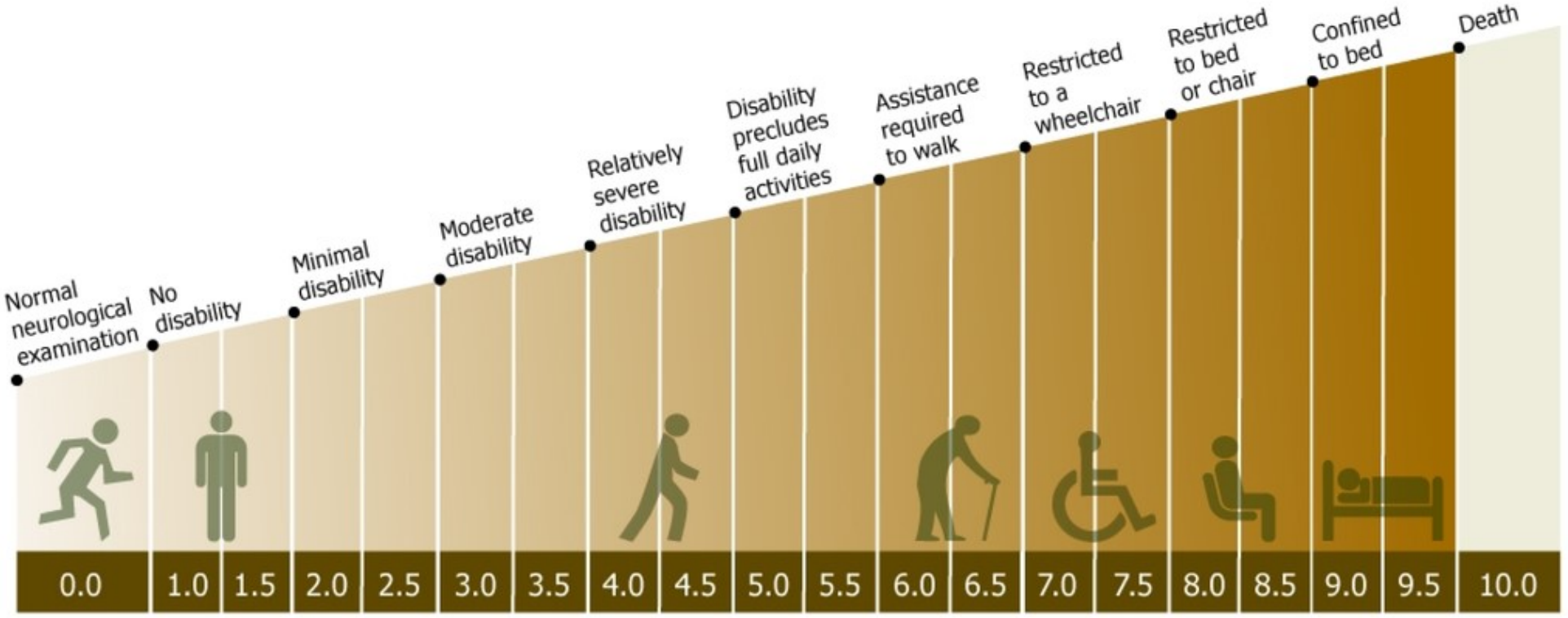
Background	Stakeholder responses	Technical team consideration
Company and current NHS use: 1st-line, but NOT 'highly active' and 'rapidly evolving' subgroups	• Will be used as in current NHS practice, 1st-line, and alternative 1st-line because of intolerance • May be considered for efficacy switch • Should be option for highly active and rapidly evolving subgroups if desired	• Likely to be used as 1st-line and alternative 1st-line therapy • Unclear whether alemtuzumab is a comparator

- ***Would peginterferon beta-1a only be used at 1st-line?***
- ***What are the relevant comparators?***

[redacted]

Aim of disease-modifying therapies

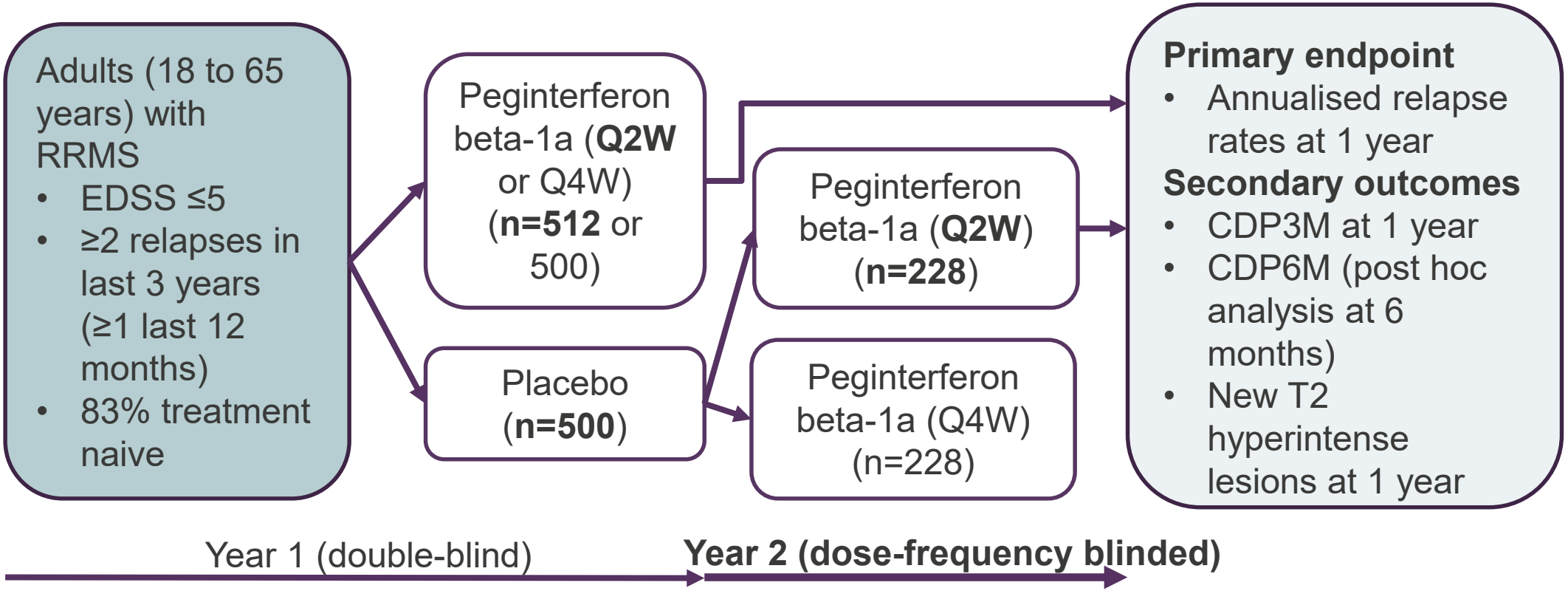
- Reduce frequency of relapse and slow disability
  - Relapse: new or recurrent neurological symptoms lasting ≥24 hours without fever or infection; separate events are at least 30 days apart
  - Disability: assessed using Expanded Disability Status Scale (EDSS)



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

Clinical trials

ADVANCE: Double-blind, randomised, 2-year, international (UK site, n=14), superiority, phase 3



ATTAIN: 2 year dose-frequency blinded extension study of ADVANCE. Peginterferon beta-1a Q2W (n=376) or Q4W (n=354)

- ADVANCE trial used in economic model for base case population, stopping treatment and adverse events. Also used for annualised relapse rate and CDP6M (via mixed treatment comparison results). ATTAIN not used in economic model

CDP3M or CDP6M, confirmed disability progression at 3 or 6 months;
EDSS, Expanded Disability Status Scale; Q2W or Q4W, every 2 or 4 weeks

Issue 2: Minimum clinically significant reduction

Background	Stakeholder responses	Technical team consideration
Main clinical effectiveness outcomes in economic model were • annualised relapse rates (ARR) and • confirmed disability progression However, no information regarding their minimum clinically significant reduction between treatments	• Any reduction in these outcomes is clinically significant • One stakeholder suggested 30% reduction in ARR was clinically significant, but did not provide supporting evidence	• Likely that any reduction in outcomes is clinically meaningful

⊙ ***What are clinically meaningful changes in annualised relapse rates and confirmed disability progression?***

[redacted]

ADVANCE: baseline characteristics

Characteristic		Peginterferon beta-1a every 2 weeks (Q2W; n = 512)	Placebo (n = 500)
Age, mean ± SD		36.9 ± 9.8	36.6 ± 9.8
Female, n (%)		361 (71)	358 (72)
Race, n (%)	White	416 (81)	412 (82)
Region, n (%)	India	58 (11)	56 (11)
	North America	19 (4)	17 (3)
	Western Europe	41 (8)	38 (8)
	Eastern Europe	355 (69)	354 (71)
	Rest of world	39 (8)	35 (7)
Body mass index (kg/m^2), mean ± SD		24.6 ± 5.1	24.6 ± 4.9
EDSS, mean ± SD		2.5 ± 1.3	2.4 ± 1.2
Relapses in previous year, mean ± SD		1.6 ± 0.7	1.6 ± 0.7
Relapses in previous 3 years, mean ± SD		2.6 ± 1.0	2.6 ± 1.0
Time since MS diagnosis, years ± SD		4.0 ± 5.1	3.5 ± 4.63
Previous treatment, n (%)	Glatiramer acetate	27 (5)	24 (5)
	Interferon beta-1b	8 (2)	6 (1)
	Interferon beta-1a	4 (< 1)	5 (1)
	Other	58 (11)	58 (12)
Number of lesions, mean ± SD	T2	48.7 ± 36.8	50.6 ± 35.7
	Gd+	1.2 ± 3.4	1.6 ± 3.8

EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; SD, standard deviation

Issue 3: Generalisability of ADVANCE trial population

Background	Stakeholders	Technical team
69% from Eastern Europe. ERG noted differences in efficacy based on geographical location. There may be differences in clinical practice, treatments and standards of care across regions. Should economic model instead use baseline characteristics of cohort from UK MS Risk Sharing Scheme?	• Mixed views: ADVANCE eligibility criteria reflect NHS patients (company and patient organisations) vs does not completely represent NHS (clinical expert and clinical organisation) • Use baseline characteristics from ADVANCE cohort	• ADVANCE broadly generalisable and relevant for this appraisal. • Use baseline characteristics from ADVANCE

⊙ ***Should the economic model use baseline characteristics from people in ADVANCE or UK MS Risk Sharing Scheme?***

[redacted]

ADVANCE: key results at 1 year

Outcome	Peginterferon beta-1a every 2 weeks (Q2W; n = 512)	Placebo (n = 500)	Peginterferon beta-1a Q2W vs placebo
Annualised relapse rate (95% CI)	0.26 (0.21 to 0.32)	0.40 (0.33 to 0.48)	Rate ratio: 0.64 (0.50 to 0.83); p=0.0007
Confirmed disability progression at 3 months (estimated proportion)	0.07	0.12	Hazard ratio: 0.62 (0.40 to 0.97); p=0.04
Confirmed disability progression at 6 months	-	-	Hazard ratio: 0.46 (0.26 to 0.81); p=0.007

CI, confidence interval; Q2W or Q4W, every 2 or 4 weeks

Subgroup analysis of annualised relapse rate showed efficacy of peginterferon beta-1a was similar in all patients regardless of sex, age, body weight or disease status
Statistically significant if $p<0.05$

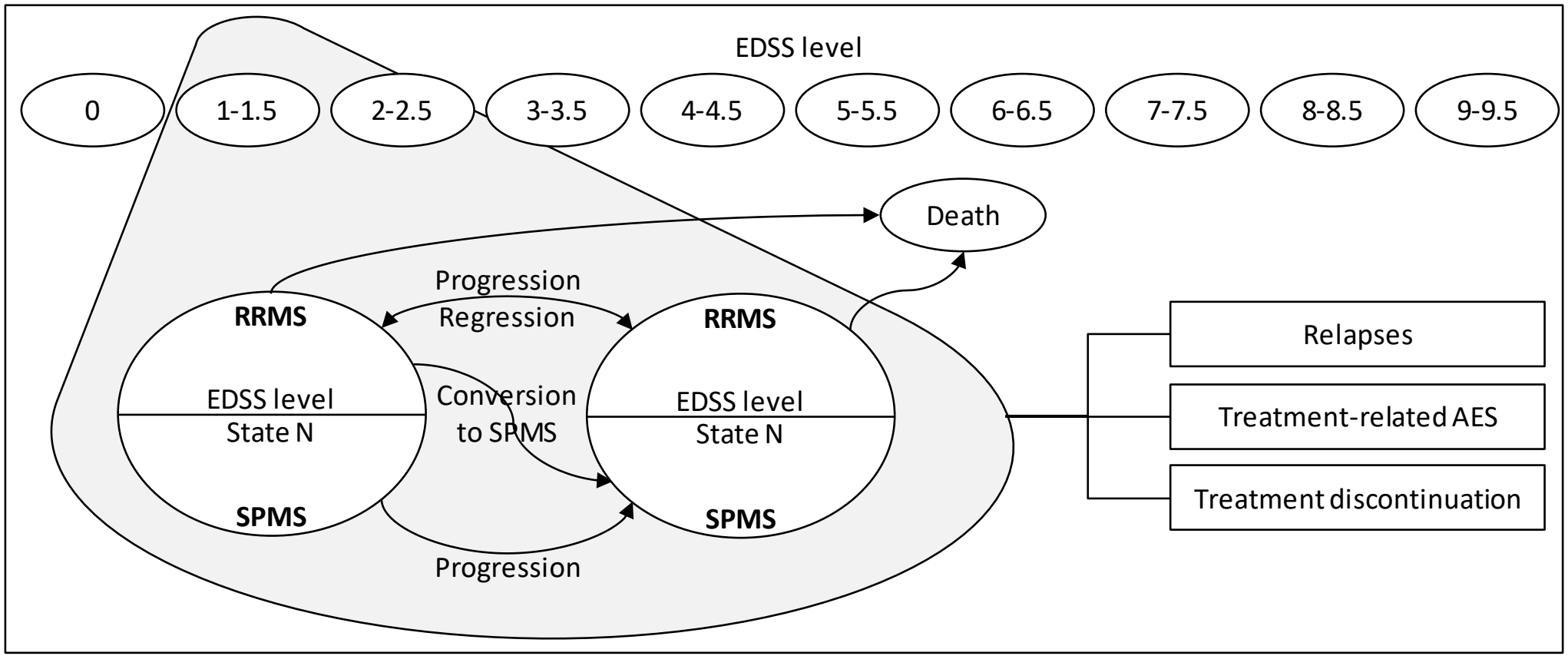
Network meta-analysis: key results reported by company

- **Annualised relapse rates (Company submission, Document B, Figure 15)**
  - XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
  - XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
  - XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
- **Confirmed disability progression at 3 months (CDP3M; Company submission, Document B, Figure 17)**
  - XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
- **Confirmed disability progression at 6 months (CDP6M; Company submission, Document B, Figure 19)**
  - XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
  - XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

⊙ ***Is peginterferon beta-1a clinically effective?***

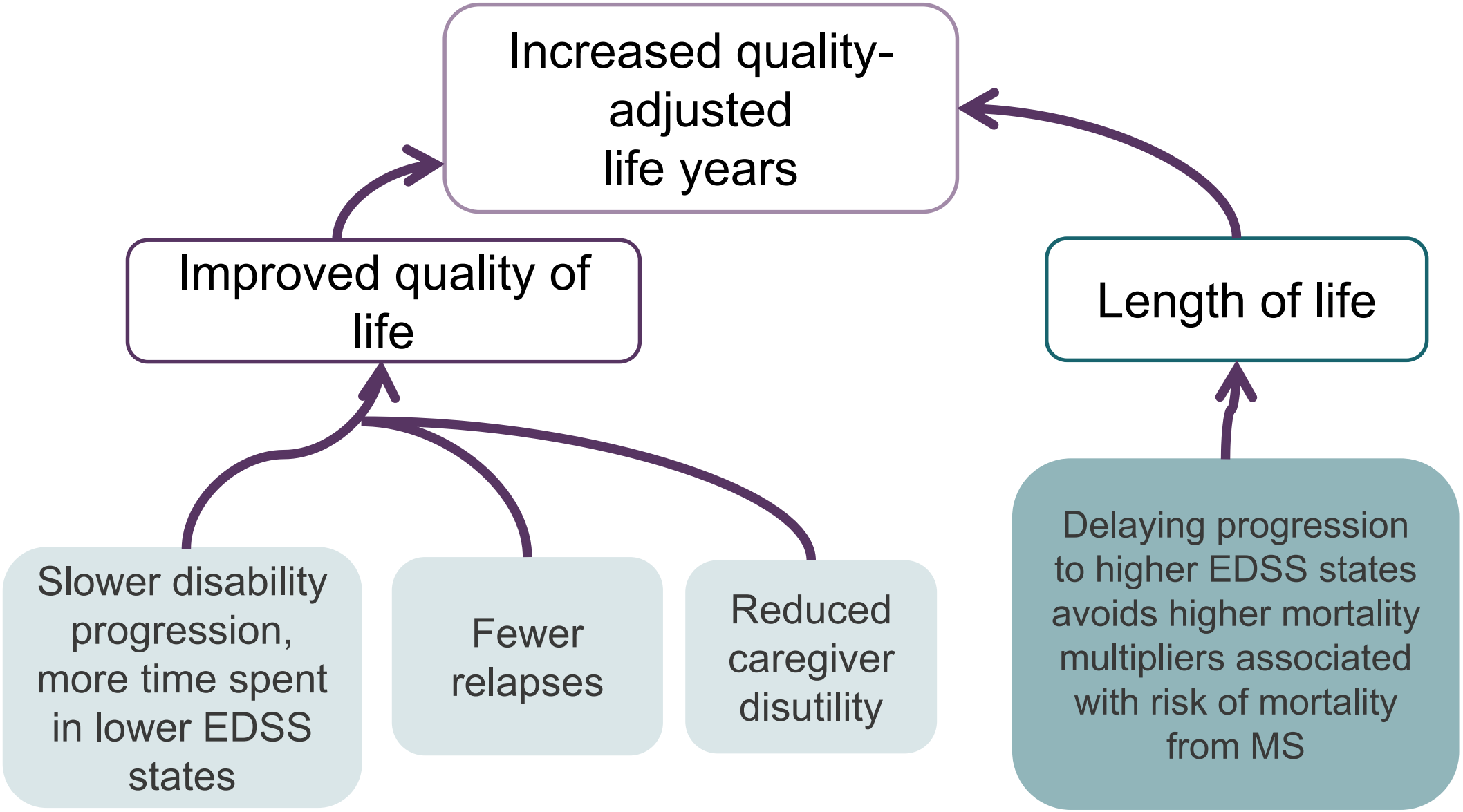
Statistically significant p<0.05
Note: The clinical significance of the results will be considered in more detailed by committee

Company's model structure



- Markov cohort model
- 20 EDSS health states (RRMS, SPMS)
- Annual cycle, 50-year time horizon
- Starting age 36 years; 29% men
- NHS/PSS perspective, 3.5% discount
- On-treatment effects (annualised relapse rates, disability progression, adverse events) taken from network meta-analyses
- Patients stop treatment after progression to EDSS ≥ 7 or on conversion to SPMS. Overall stopping risk applied for all treatments over lifetime horizon
- After stopping treatment, patients follow natural disease progression course based on British Columbia MS data set (n=898)

Overview of how quality-adjusted life years accrue in the model



Company key model assumptions (1)

Parameter	Base-case assumption	Justification
Disability progression	Disability progression and relapses modelled independently, with treatment effects applied to each	In line with previous appraisals. EDSS progression is a key driver of cost-effectiveness. Avoids double counting.
	Treatments indirectly change risk of progression to SPMS and dying	Delaying progression to higher EDSS levels avoids higher risk of mortality from MS and avoids higher probabilities of progression to SPMS.
	Transition probabilities within RRMS: patients can improve to a lower EDSS level in this phase. **Transition probabilities within SPMS**: patients cannot improve to a lower EDSS level in this phase.	Patients can improve (demonstrated in the British Columbia MS data set). For SPMS, patients cannot improve (aligned with London, Ontario data set).
	After stopping treatment, patients follow the natural disease progression course.	In line with previous appraisals. This approach underestimates cost-effectiveness estimates for treatments with the highest stopping rates as they are likely to transition to drugs that work better

Company key model assumptions (2)

Parameter	Base-case assumption	Justification
Mortality	Same rate ratios for RRMS and SPMS	Lack of data (conservative assumption)
Treatment waning	Treatment effect wanes over time; same decline for all disease-modifying therapies. • Years 1-2: no waning of full treatment effect • Years 3-5: 75% • Year 6 onwards: 50%	In line with previous appraisals.
Health related quality of life	Fatigue, injection-site reaction not associated with a disutility.	Lack of data.
	Patient who received treatment would incur the risk of disutility and costs associated with adverse effects for each year.	Lack of data. This approach may overestimate impact of adverse effects, because patients with severe/frequent events likely to stop treatment early.
	Caregiver disutility values by EDSS and disease phase (RRMS or SPMS) are the same in both RRMS and SPMS phases	Lack of data (conservative assumption)
Costs	Non-serious fatigue, injection-site reactions and nasopharyngitis have no costs associated with them.	Injection-site reactions often do not lead to any resource use, particularly from NHS/PSS perspective.

[redacted]

Issue 5: Treatment waning

Background	Stakeholder responses	Technical team consideration
Company: assumed same waning effects for all treatments (in line with some previous NICE technology appraisals) • Years 1-2: no waning • Years 3-5: 75% of full treatment effect • Year 6 onwards: 50% of full treatment effect. Unclear whether waning effects for newer disease modifying therapies may be different.	• General view that waning likely to be different for various disease modifying therapies • One stakeholder suggested inclusion of treatment waning plus stopping treatments result in double counting because of lack of efficacy	• Likely that waning effects of peginterferon beta-1a may be different to treatments such as alemtuzumab and ocrelizumab. • However, in absence of evidence, same waning effects should be applied to all disease modifying therapies.

- ***Should treatment waning be included in the model?***
- ***If yes, should the same waning effects be applied to all disease modifying therapies?***

Issue 6: Stopping treatment for any reason

Background	Stakeholder	Technical team
Company: applied probability of stopping treatment for any reason for each disease-modifying therapy based on annualised stopping rates from 18 trials, weighted on *sample size*. **ERG**: stopping risk weighted by *person time* more appropriate. Annualised stopping rate would not capture changes over time. Trial may not reflect true rate over longer time period (ERG report, page 147). Better to use estimates from epidemiological studies e.g. UK MS Risk Sharing Scheme. ERG used stopping rate in base case of 5% (NICE TA527 - beta interferons and glatiramer acetate for MS) for all treatments.	• General consensus: not plausible to apply same probability of stopping treatment for all therapies because side effects differ substantially and some may be time-dependent • Probability of stopping treatment varies over lifetime, relatively high initially because of side effects and then because of disease progression to SPMS, probability of stopping treatment after several years will increase.	• More plausible that individual disease modifying therapies would have specific stopping rates, and would vary over time.

Issue 6: Stopping rates for individual treatments (trial data)

Treatment	Annual probability of stopping treatment for any reason	
	Weighted by sample size (company base case)	Weighted by person time (ERG's preferred approach for calculation)
Peginterferon beta-1a	15.6%	15.6%
Avonex (interferon beta-1a)	7.9%	8.3%
Rebif 22 mcg (interferon beta-1a)	6%	6%
Rebif 44 mcg (interferon beta-1a)	10.5%	9.7%
Extavia (interferon beta-1b)	6.9%	7.5%
Copaxone 20 mg (glatiramer acetate)	11%	8.1%
Copaxone 40 mg (glatiramer acetate)	8.9%	8.9%
Generic glatiramer acetate 20 mg	11%	8.1%
Generic glatiramer acetate 40 mg	8.9%	8.9%
Teriflunomide	18.6%	18.5%
Dimethyl fumarate	18%	18%
Alemtuzumab	2.6%	2.6%
Ocrelizumab	6.7%	6.7%

- ***Should the same probability of stopping treatment be applied to all disease modifying therapies? If yes, is 5% plausible?***
- ***If no, should stopping rates from trial data be used, weighted by sample size or by person time?***

Issue 7: Utility values

Background	Stakeholder responses	Technical team consideration
Company: utility values from Orme et al. (2007) consistent with previous appraisals. **ERG**: provided scenario using Thompson et al. (2017) which collected resource use, cost and health-related quality of life (EQ-5D) data in cross-sectional retrospective study, 779 UK patients with MS. Includes more recent disease-modifying therapies, but fewer and older participants than in Orme. Generally utility values similar but some health states have more pronounced differences e.g. EDSS 7.	• General consensus: Use Orme because of larger sample size and consistency with other appraisals	• Utility values broadly similar between 2 studies, and Orme is consistent with previous appraisals.

Issue 7: Utility values from Orme and Thompson studies

EDSS	Orme et al. (2007)				Thompson et al. (2017) – difference compared to Orme et al.			
	No relapse		Relapse		No relapse		Relapse	
	RRMS	SPMS	RRMS	SPMS	RRMS	SPMS	RRMS	SPMS
0	0.870	0.825	0.799	0.754	0.028	0.028	0.028	0.028
1-1.5	0.799	0.754	0.728	0.683	-0.012	-0.012	-0.012	-0.012
2-2.5	0.705	0.660	0.634	0.589	-0.01	-0.01	-0.01	-0.01
3-3.5	0.574	0.529	0.503	0.458	-0.001	-0.001	-0.001	-0.001
4-4.5	0.610	0.565	0.539	0.494	-0.005	-0.005	-0.005	-0.005
5-5.5	0.518	0.473	0.447	0.402	0.051	0.051	0.051	0.051
6-6.5	0.460	0.415	0.389	0.344	-0.004	-0.004	-0.004	-0.004
7-7.5	0.297	0.252	0.226	0.181	0.076	0.076	0.076	0.076
8-8.5	-0.049	-0.094	-0.120	-0.165	0.206	0.206	0.206	0.206
9-9.5	-0.195	-0.240	-0.266	-0.311	0.085	0.085	0.085	0.085

⊙ ***Which study should be used? Orme or Thompson?***

Company's base case

Parameter	Base-case assumption
Disability progression	Disability progression and relapses modelled independently, with independent treatment effects applied to each
	Treatments had indirect effect on risk of progression to SPMS and mortality
	Transition probabilities in RRMS: patients can improve to lower EDSS level **Transition probabilities in SPMS**: patients cannot improve to a lower EDSS level
	After stopping treatment, patients follow natural disease progression course
Mortality	Same rate ratios for RRMS and SPMS phases. Pokorski et al. 1997 standardised mortality ratio (SMR) by EDSS level used to adjust all-cause mortality risks in general population where SMR increases with higher EDSS states
Treatment waning	Treatment effect wanes over time; same decline for all treatments • Years 1-2: no waning • Years 3-5: 75% of full treatment effect • Year 6 onwards: 50% of full treatment effect
Health related quality of life	Fatigue, injection-site reaction (erythema, pain, pruritus) not related to disutility
	Patient who received treatment would incur risk of disutility and costs related to adverse effects for each year
	Caregiver disutility values by EDSS and disease phase (RRMS or SPMS) are same for disease phases. Data from **Acaster et al. (2013)**
Costs	Non-serious type of fatigue, injection-site reaction (erythema, pain, pruritus) and nasopharyngitis have no costs associated with them

ERG changes to company base case

	Company	ERG	ERG comment/ justification for preferred source
Disease progression: RRMS relapse frequency	UK MS Survey and Patzold 1982	TA527	ERG preferred TA527 as values have decrease in relapse frequency with worsening EDSS state*
Disease progression: SPMS relapse frequency			As above, plus rates by EDSS state in SPMS are lower than RRMS* ERG considered company assumption to overestimate rates.
Mortality	Pokorski, 1997	Pokorski interpolated	Previous appraisals noted Pokorski overestimated risk. Interpolated values better reflect mortality risk vs general population as EDSS levels increase
All-cause discontinuation risk	Treatment specific, data from 18 trials, weighted by sample size	5% for all treatments using RSS	'Real world' data likely to be more realistic than trial. NICE TA527 used 5% based on RSS. Unclear why company assumed pegIFNβ-1a rate is higher vs other inteferons
HRQoL: Caregiver utility decrements	Acaster et al. (2013)	Gani et al. (2008)	Values from Gani et al. (2008) provide more plausible utility decrements, that is, utility decrements increase as EDSS levels rise*

*Whereas this is sometimes but not always true in company base case.

[redacted]

See ERG report tables 45 to 49 for specific rates by EDSS state

Results

All results shown in Part 2 because of commercial arrangements of comparators [interferon beta-1a (Avonex, Rebif), interferon beta-1b (Extavia), glatiramer acetate (Copaxone), dimethyl fumarate (Tecfidera), teriflunomide and ocrelizumab]