Certolizumab Pegol in Rheumatoid Arthritis after inadequate response to a TNF inhibitor

1st Appraisal Committee C meeting – 15 June 2016

Background and Clinical Effectiveness

Lead team: Anna O'Neill, David Chandler

Slides for Public only – contains noAiC

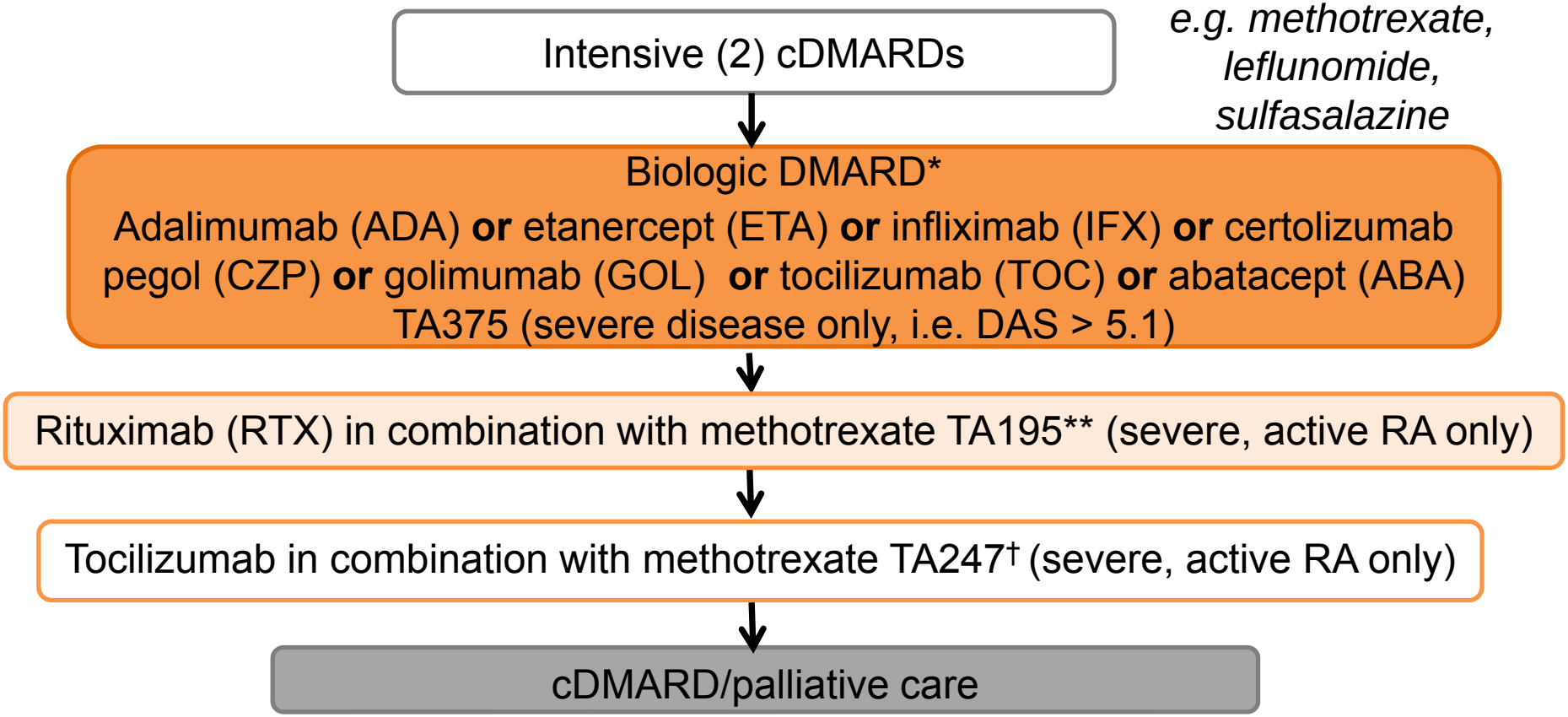
Rheumatoid Arthritis (RA)

- An inflammatory auto immune chronic disease, characterised by relapses with patterns of flare up, can also be constantly progressive
- 0.8% of the UK population affected by RA, approximately 20,000 new cases annually
  - 580,000 estimated people in England with RA, 2-3.5% have severe disease 2-3 times more prevalent in women, can develop at any age, usual onset age 40-50 years
- Pain, fever, joint swelling / inflammation
- Severe impact on Quality of life (QoL), around 1/3rd stop work within 2 years
- No cure, treatment aims to improve QoL and prevent or reduce joint damage

Response criteria

- American College of Rheumatology response criteria (ACR 20, 50 or 70) refers to a 20, 50 or 70% improvement measure in tender or swollen joints in at least 3 of the following parameters: patient or physician assessments, pain scale, disability and circulating inflammatory markers such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
  - Higher ACR rates indicate greater improvement
- Disease activity score (DAS28) - alternative scoring system developed in Europe. It is calculated using a formula that includes counts for tender and swollen joints, an evaluation of general health by the person, and erythrocyte sedimentation rate or C-reactive protein
  - A DAS28 score greater than 5.1 indicates high disease activity
  - between 3.2 and 5.1 moderate disease activity
  - Between 2.6 and 3.2 low disease activity
  - less than 2.6 indicates disease remission
- EULAR European League Against Rheumatism - uses the degree of change in DAS28 and the DAS28 reached to determine good, moderate or non-response
- The Stanford Health Assessment Questionnaire (HAQ) comprises one component of the ACR criteria and scores the ability to perform daily activities; it ranges from 0 (least disability) to 3 (most severe disability).

NICE recommended biologics for RA



*Certolizumab pegol, etanercept, adalimumab or tocilizumab monotherapy if methotrexate (MTX) is inappropriate (TA375); adalimumab or etanercept monotherapy after initial failure with TNFi (TA195)

**If rituximab is contraindicated or withdrawn due to adverse events then the following can be used: adalimumab or etanercept or infliximab or abatacept all in combination with MTX (TA195) or golimumab in combination with MTX (TA225)

†Would not be used if tocilizumab has been used previously in the sequence

Clinical expert perspective (1 of 2)

Statement in-line with British Society of Rheumatology (BSR) patient statement which include the following:

- Certolizumab pegol offers an additional therapy option for patient who do not respond to a TNF inhibitor first-line
- Safety and efficacy profile related to other approved TNF inhibitors
- Difficulty of not knowing who will respond to which biologic therefore need a range of biologic options
- Inconsistency that CZP is unavailable as an option when RTX + MTX in contra-indicated as there is minimal variation over the biologics

Clinical expert perspective (2 of 2)

- Ability to assess at 3 months rather than 6 may inform clinical prescribing decisions

- REALISTIC trial is the key study that reflects clinical practice and has a patient population similar to that of the UK with a high number of patients with prior TNF inhibitor use

- Although outcomes were assessed at 12 weeks, long-term efficacy is more important than short-term

Patient perspective (1 of 2)
Living with rheumatoid arthritis

- A chronic disease with no cure
- Debilitating effect – *relentless pain, fatigue*
- Life-changing – *diagnosis can be at any age post 16*
  Although "...being diagnosed today has significantly better potential outcomes..."
- High impact on quality of life
  - Psychologically
    future plans, aspirations, life plans
  - Employment
    anxiety about job loss and ability to work
  - Social life
    developing relationship, isolation, loss of confidence

Patient perspective (2 of 2)
Treatments

- Reduction in pain and inflammation
- Prevent and stop permanent damage to joints and avoid disability
- Reduction in fatigue – major issue for patients
- Maintain independence and the ability to work
- Need for treatments with no, or few adverse events - patients report that biologic therapies generally have fewer adverse events (AEs) than methotrexate and other conventional DMARDs
- Access to relevant staff and treatment is variable
- Need options, as response varies – even in same class/target
- Sero-negative patients may benefit more with access to a second anti-TNF
- Certolizumab provides similar benefits as other biologics

  But "...is slightly different..." and may provide further clinical options
- No disadvantages were identified by the patient group

Treatment being appraised

Technology and mode of action	Certolizumab pegol solution for injection (Cimzia, UCB Pharma). A recombinant, humanised antibody Fab' fragment against tumour necrosis factor alpha (TNFα), a pro-inflammatory mediator that is partly responsible for damage to the joints in rheumatoid arthritis
Marketing Authorisation	"Cimzia, in combination with methotrexate (MTX), is indicated for: • The treatment of moderate to severe, active rheumatoid arthritis (RA) in adult patients when the response to disease-modifying anti-rheumatic drugs (DMARDs) including MTX, has been inadequate. Cimzia can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate • The treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs" "MA extension for 'adults with moderate to severe active rheumatoid arthritis whose disease has not responded adequately to a tumour necrosis factor (TNF) inhibitor (TNFi). Moderate to severe disease activity is defined as disease activity score 28 (DAS28)>3.2"
List Price	200-mg prefilled syringe = £357.50 (British National Formulary)
Dosage (sub-cutaneous 200mg prefilled syringe)	Loading doses at week 0, 2 and 4 of 400mg and maintenance doses of 200mg every 2 weeks or 400mg every 4 weeks once clinical response is confirmed = (first year) £6793 (PAS) and £9295 (after first year PAS)

Source certolizumab pegl SmPC and company's submission

Company's decision problem

Population	Adults with moderate to severe active rheumatoid arthritis whose disease has not responded adequately to a tumour necrosis factor (TNF) inhibitor (TNFi). Moderate to severe disease activity is defined as disease activity score 28 (DAS28)>3.2
Intervention	CIMZIA® (certolizumab pegol, CZP) monotherapy or in combination with methotrexate (MTX)
Comparator	Treatment sequences are used: **Population A** - adults previously treated with other DMARDs including at least 1 TNFi: CZP is inserted into the sequence before rituximab (RTX) in combination with MTX **Population B** - adults for whom RTX is contraindicated or withdrawn: the first line of therapy is either CZP or one of the other comparators in the scope: abatacept (ABA), adalimumab (ADA), etanercept (ETA), golimumab (GOL), infliximab (IFX) and tocilizumab (TOC) each in combination with MTX **Population C** - adults for whom RTX therapy cannot be given because MTX is contraindicated or withdrawn: first line of therapy in the sequence is either CZP, ADA, ETA or TOC, all as monotherapy
Outcomes	Disease activity, Physical function, ~~Joint damage~~, Pain, Mortality, Fatigue, ~~Radiological progression~~, ~~Extra-articular manifestations the disease~~, Adverse effects of treatment, Health-related quality of life

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Relevant RCTs (1 of 2)

Trial	Reference	Interventions	Patient population	Duration of study	Primary outcome(s)
Moderate to severe disease activity population					
REALISTIC (NCT00717236)	Weinblatt 2012	• CZP 200 mg Q2W +/- MTX/cDMARDs* • PBO +/- MTX/cDMARDs	Active RA with an inadequate response to >1 prior cDMARD, having received treatment with ≤ 2 TNFis	28 weeks	• ACR20 response at 12 weeks
DOSEFLEX (NCT00580840)	Furst 2015	• CZP 200 mg Q2W + MTX≠ • CZP 400 mg Q4W + MTX≠ • PBO + MTX≠	Active RA receiving MTX for ≥3 months, including patients with prior TNFi exposure	34 weeks≠	• ACR20 response at 34 weeks
PREDICT (NCT01255761)	Curtis 2015	• CZP 200 mg Q2W +/- MTX/cDMARDs*	Active RA with unsatisfactory response or intolerance to ≥1 DMARD, having received treatment with ≤2 TNFis	52 weeks	• CDAI and RAPID-3 scores at 12 and 52 weeks • DAS28(ESR) at 52 weeks

CZP; certolizumab, MTX; methotrexate, PBO; placebo, Q2W; every 2 weeks, Q4W; every 4 weeks, cDMARDs; coverntional DMARDs, DAS28(ESR);disease activity score in 28 joints (erythrocyte sedimentation rate), ACR20; American College of Rheumatism score of 20%, TNFi; tumor necrosis factor alpha inhibitor

Relevant RCTs (2 of 2)

Trial	Reference	Interventions	Patient population	Duration of study	Primary outcome(s)
SWITCH (NCT01147341)	Schiff 2014	• CZP 200 mg Q2W + cDMARDs* • PBO + cDMARDs	Active RA having had inadequate response or intolerance to a TNFi other than CZP	24 weeks	ACR20 response at 12 weeks
J-RAPID (NCT00791999)	Yamamoto 2014	• CZP 100 mg Q2W + MTX ** • CZP 200 mg Q2W + MTX * • CZP 400 mg Q2W + MTX * • PBO + MTX	Active RA with an inadequate response to MTX, including patients with prior exposure if they received 1 TNFi as a non-primary failure (only Japanese patients)	24 weeks	ACR20 response at 12 weeks
HIKARI (NCT00791921)	Yamamoto 2014	• CZP 200 mg Q2W +/- non-MTX cDMARDs[Ŧ] • PBO +/- non-MTX cDMARDs	Active RA with an inadequate response to ≥1 prior DMARDs (including MTX), including patients with prior exposure if they received 1 TNFi as a non-primary failure (only Japanese patients)	24 weeks	ACR20 response at 12 weeks

CZP; certolizumab, MTX; methotrexate, PBO; placebo, Q2W; every 2 weeks, Q4W; every 4 weeks, cDMARDs; coverntional DMARDs, DAS28(ESR);disease activity score in 28 joints (erythrocyte sedimentation rate), ACR20; American College of Rheumatism score of 20%, TNFi; tumor necrosis factor alpha inhibitor. *Source Company's submission*

Results of the primary outcome (ACR20) for the pop. with prior TNF inhibitor use

Trial	Treatment Group	Treatment arms for which data extraction performed (n)	Assessment time point	% achieving ACR20 response
REALISTIC	TNFi-experienced	PBO *******	Week 12	**** (27.5%)
		CZP **********	Week 12	**** (47.2%) p=<0.01
	TNFi-experienced (NRI), CZP monotherapy	*******	*******	*******
		*******	*******	*******
		*******	*******	*******
		*******	*******	*******
	TNFi-experienced (NRI), CZP+MTX	*******	*******	*******
		*******	*******	*******
		*******	*******	*******
		*******	*******	*******

CZP;certolizumab pego, MTX;methotrexate,Q2w, every 2 week, PBO; placebo, OLE; open label extension, p; statistical significance, NRI; non-responder imputation, NR; not reported. *Source Company's submission*

Results for EULAR responses at 3 months for the pop. with prior TNF inhibitor use

Trial	Treatment Group	Treatment arms for which data extraction performed (n)	Assessment time point	% achieving EULAR response Good	% achieving EULAR response Moderate	% achieving EULAR response None
REALISTIC	TNFi-experienced (LOCF)	*******	*******	*******	*******	*******
		*******	*******	*******	*******	*******
		*******	*******	*******	*******	*******
	TNFi-experienced (LOCF) monotherapy	*******	*******	*******	*******	*******
		*******	*******	*******	*******	*******
		*******	*******	*******	*******	*******
	TNFi-experienced (LOCF) +MTX	*******	*******	*******	*******	*******
		*******	*******	*******	*******	*******
		*******	*******	*******	*******	*******

PBO;placebo, CZP; certolizumab pegol, MTX; methotrexate, Q2W; every 2 weeks, OLE; open label extension, LOCF; last observation carried forward. *Source ERG report*

HAQ-DI score from REALISTIC at 3 months for pop. with prior TNF inhibitor use

Source Company's submission

Direct meta-analysis for comparing certolizumab in combination with methotrexate and certolizumab monotherapy in prior TNF inhibitor patients

- To pool data from REALISTIC, J-RAPID and SWITCH
  - Compare sub-populations of patients for CZP + MTX and PBO + MTX

- To pool data from REALISTIC and HIKARI
  - Compare sub-population of patients that receive certolizumab monotherapy

- Higgins (I^2) test used to detect heterogeneity therefore company used both fixed and random effects models

Results of direct meta-analysis for certolizumab (combination with methotrexate) vs methotrexate and for certolizumab (monotherapy) vs placebo, at 3 months (week 12): showing relative risks (RRs over 1 favour the intervention)

	ACR20 response at 3 months RR (95% CI)	**ACR50 response at 3 months RR (95% CI)**	**ACR70 response at 3 months RR (95% CI)**	**EULAR (good)**	**EULAR (good to moderate)**
Fixed effect model **(Combination)**	*******	*******	*******	*******	*******
Random effects model **(Combination)**	*******	*******	*******	*******	*******
Fixed effect model **(Monotherapy)**	*******	*******	*******	*******	*******
Random effects model **(Monotherapy)**	*******	*******	*******	*******	*******

ACR, American College of Rheumatology criteria; CI, confidence interval; RR, relative risk.

Indirect comparisons for certolizumab versus other bDMARDs

- Company used an adjusted indirect comparison (ITC) and Bayesian network meta-analysis (NMA) method

- Adjusted method chosen over NMA when the evidence network included *not* more than two competing interventions and vice versa

- Higgins (I^2) test used to detect heterogeneity between trials of the same agent. Company assumed that trials of different agents were sufficiently similar to pool

Results from the indirect comparisons for certolizumab vs comparators showing EULAR (good/moderate) responses at 3 months: showing relative risks (RRs) with 95% confidence intervals

Source Company's submission

EULAR response probabilities from the network meta-analysis

- Summary statistics, effect size estimates and cut-off statistics from NMA used to gain EULAR response probabilities

- A series of assumptions had to be made for comparative efficacy between bDMARD in order to do this

- Lack of comparative data available between biologics

Estimated EULAR response probabilities from NMA for pop. A: *patients eligible for rituximab and methotrexate*

Source Company's submission

Evidence Review Group critique

- Fixed effect model used in the meta-analyses do not adequately capture heterogeneity between studies
- Frequently p-values were not reported and caution needed in interpreting the wide credible intervals (true effect uncertain)
- Clarification required regarding omission of Kang et al in the submission
- Absence of data for radiological progression, joint damage and extra articular manifestations

Key issues for consideration

- **Is certolizumab pegol clinically effective compared with other bDARMDs?**

  Is the network meta-analysis a reliable estimate of the relative effect?

- **Should Certolizumab pegol be considered at the same point in the pathway as rituximab?**

Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF inhibitor [ID824]

1st Appraisal Committee C meeting – 15/06/2016

Cost-Effectiveness

Lead team: Paul Miller

Slides for Public only – contains noACiC

Company's decision problem

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Outcomes	Disease activity, Physical function, ~~Joint damage~~, Pain, Mortality, Fatigue, ~~Radiological progression~~, ~~Extra-articular manifestations~~ the disease, Adverse effects of treatment, Health-related quality of life

Source Company's submission

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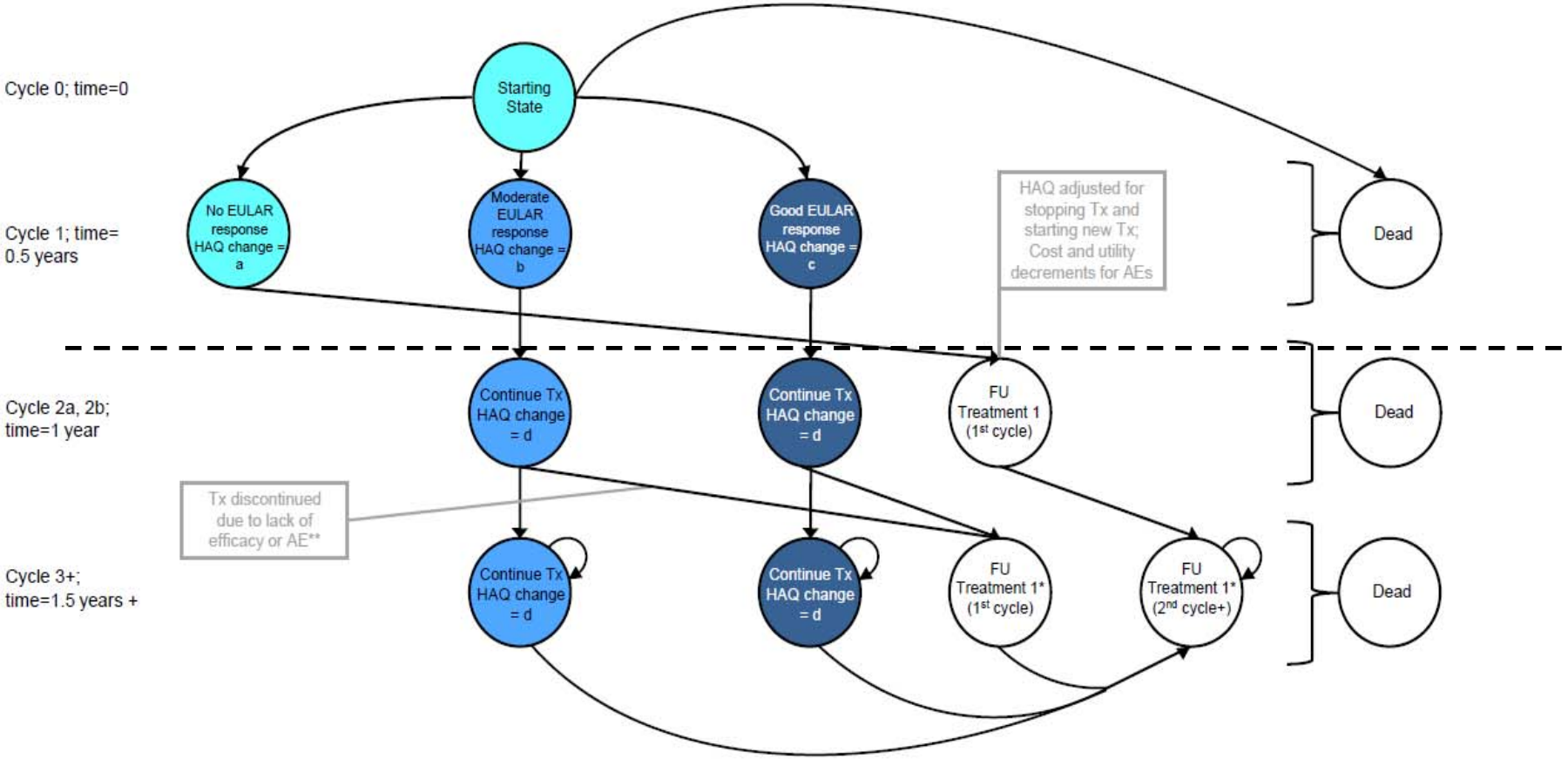
L’Abbe plot: RCT evidence for ACR20/50 at 3 months in patients that were previously exposed to TNFi

Model structure



Source Company's submission

Company base case: treatment sequence for population A (where RTX and MTX is an option)

A) Adults previously treated with other DMARDs including at least one TNFi

Line of therapy	Intervention	Comparator
1st	→ CZP + MTX	RTX + MTX
2nd	RTX + MTX	TOC + MTX
3rd	TOC + MTX	ABA + MTX
4th	ABA + MTX	MTX+HCQ+SSZ
5th	MTX+HCQ+SSZ	NBT
6th	NBT	Palliative care
7th	Palliative care	-

Company base case: treatment sequence for population B (where RTX is contraindicated or withdrawn)

Line of therapy	Intervention	Comparator
1st	CZP + MTX	Comparator Biologic + MTX
2nd	MTX+HCQ+SSZ	MTX+HCQ+SSZ
3rd	Leflunomide	Leflunomide
4th	Gold injection	Gold injection
5th	Ciclosporin	Ciclosporin
6th	Azathioprine	Azathioprine
7th	Palliative care	Palliative care

NBT; non-biological therapy, HCQ; hydroxychloroquine, SSZ; sulfasalazine

Company base case: treatment sequence for population C (where MTX is contraindicated or withdrawn)

Line of therapy	Intervention	Comparator
1st	CZP	Comparator Biologic
2nd	Leflunomide	Leflunomide
3rd	Gold injection	Gold injection
4th	Ciclosporin	Ciclosporin
5th	Azathioprine	Azathioprine
6th	Palliative care	Palliative care

Baseline characteristics in the model

The characteristics of the modelled population are based on the population with prior anti-TNF use in REALISTIC, except baseline EQ-5D which is from PREDICT

Characteristic	**All patients in the study (CZP and PBO) who are TNFi-IR**
Sample	*******
Mean age, years	*******
Gender, % female	*******
Baseline HAQ score, (0-3)	*******
Baseline Pain score on visual analogue scale, (0-100)	*******
Baseline EQ-5D (from PREDICT)	*******
Disease duration, years	*******
At least one prior TNFi One Prior TNFi Two or more prior TNFi	*******

Treatment assumptions in company model

- For each treatment, patients are assumed to go through a six-month treatment period and then discontinue treatment unless they achieve a good or moderate EULAR response

- For the first treatment considered in the model (the second line bDMARD), EULAR response probabilities are modelled using the results of the NMA
  - *The NMA includes results of trials for CZP, TOC, ABA, RTX and GOL in combination with MTX. In the absence of data, the efficacy of ETA, ADA and IFX is assumed to be equal to GOL (TNFi class equivalence)*

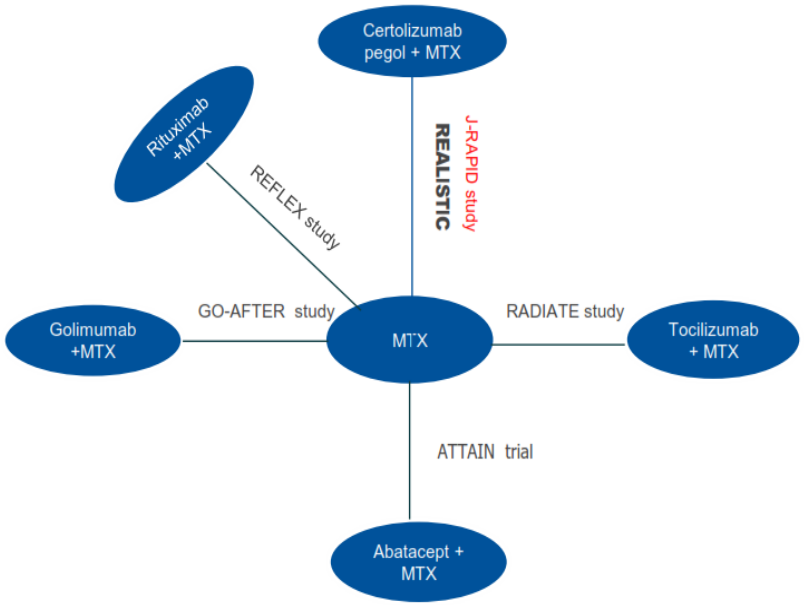
- For follow up treatments, the probabilities of EULAR response were derived from the results of RADIATE; the results of TOC + MTX are extrapolated to other bDMARDs and those of MTX to cDMARDs
  - *Patients also discontinue follow-up treatments at six-months if no EULAR response is observed*
  - *Patients who discontinue treatment are assumed to start the next treatment in the sequence immediately*

How the clinical data were incorporated into the model (1 of 4)

Key Parameters	Method
1) Clinical response to first treatment	Based on EULAR response measured at 6 month estimated from a Bayesian NMA: • CZP+MTX: uses week 28 OLE from REALISTIC study; MTX (PBO): uses wk12 REALISTIC data mapped to 6 months (mapping matrix derived from RAPID 1 & 2) • Comparator TNFi & MTX: uses GO-AFTER (GOL TNF-IR study), assumes class effect and ADA, ETA and IFX have same 6 month response • CZP monotherapy: uses REALISTIC • TOC monotherapy: estimated from relative effects observed in combination • TNFi monotherapy : GOL monotherapy estimated from relative effects observed in combination + ADA and ETA assumed to have same response

How the clinical data were incorporated into the model (2 of 4)

Network of evidence map for NMA (J-RAPID only included in company's sensitivity analysis)



Source Company's submission

Forest plot results of NMA showing treatment effect on the probit scale (EULAR response at six months) comparing biologic versus CZP

How the clinical data were incorporated into the model (3 of 4)

Key Parameters	Method
2) Change in HAQ score associated with first treatment	estimated for each EULAR response status through a linear regression model fitted to patient-level data from the REALISTIC study
3) Discontinuation of treatment after response to first therapy	modelled based on discontinuation data from patients with prior TNF inhibitor use; registered to the British Society For Rheumatology (BSRBR; as used in TA195)

How the clinical data were incorporated into the model (4 of 4)

Key Parameters	Method	
4) Efficacy and discontinuation of ***subsequent*** lines of therapy	**EFFICACY** • 1st subsequent biologic: -0.39 mean change in HAQ in next 6 month (based on TOC 8mg/kg arm in RADIATE (50% 2 or more TNFi-IR), + assumes other biologics same) • 1st subsequent cDMARD: -0.05 mean change in HAQ in next 6 month (based on PBO/MTX arm in RADIATE) • 2nd subsequent + biologic: assumes no further change in HAQ • 2nd subsequent + cDMARD: assumes HAQ scores increase at a rate of 0.045 p.a (based on previous NICE appraisals), + capped ceiling value	**DISCONTINUATION** • 1st subsequent biologics: modelled using the treatment effect parameters in the NMA, applied to the trial-specific baseline effects from the RADIATE study (RTX+MTX 46.6%, TOC+MTX 34.5%, ABA+MTX 61.2%) • 1st subsequent cDMARDs: modelled using response data from the PBO and MTX arm of RADIATE (83.7%) • For all subsequent six monthly cycles of therapy, treatment discontinuation was modelled based on discontinuation data from the BSRBR (biologics, 15.6%) and from data in Edwards et al (cDMARDs, 3.8-11.3%)
5) Mortality associated with RA	• Probabilities of death are assumed to increase with increasing age & disability status (in terms of HAQ score)	

Health States and Utility Values

- Health utilities are modelled according to HAQ score progression
  - Baseline utility = ******* (mean EQ-5D utility from PREDICT study)
- HAQ score improves following a positive response to first treatment, and after response the HAQ score is assumed to stay constant for the duration of bDMARD treatment
  - Non-responder utility = *******
  - Moderate responder utility = *******
  - Good responder utility = *******
- HAQ score is assumed to increase linearly for patients on cDMARDs until a maximum value is reached

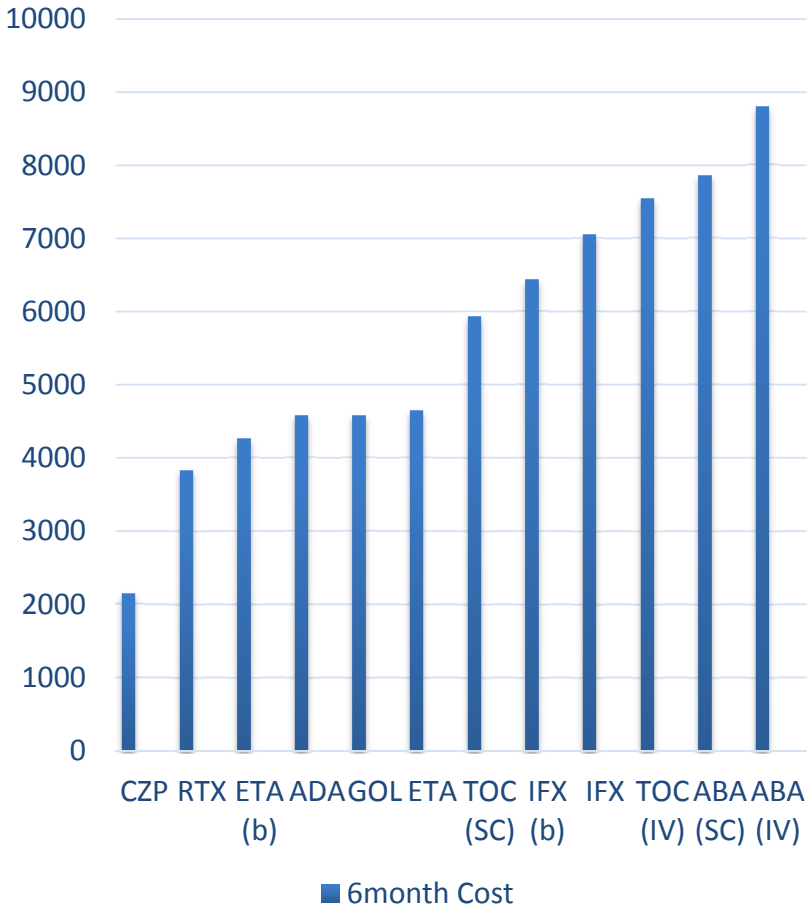
Resources and costs

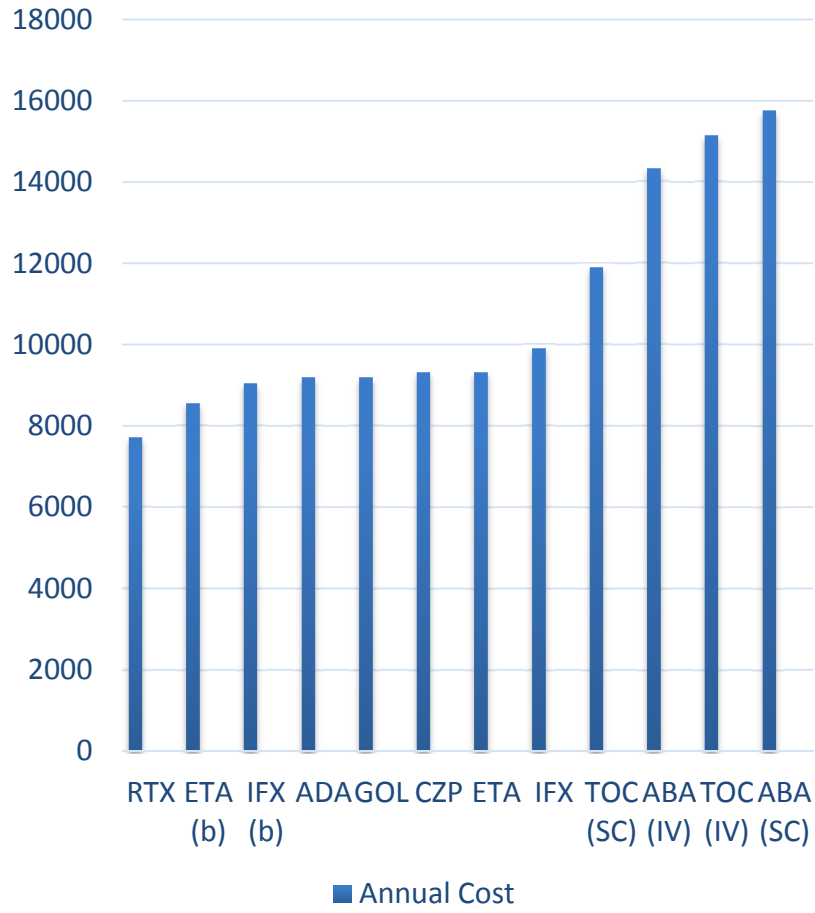
- Resource use estimates were based on previous NICE Technology Appraisals and the views of an expert clinician

- Unit costs were taken from the British National Formulary, the Personal Social Services Unit and NHS Reference Costs 2014 to 2015

- Adverse events are assumed not to have an impact on the relative Health-Related Quality of life (HRQoL) and costs

Drug costs





Note: Includes the non confidential PAS schemes for CZP and GOL, but not confidential discount schemes

Company's base case results pop. A: *(where RTX and MTX are an option)*

Sequences	**Total QALYs**	**Total costs**	**Inc. QALYs**	**Inc. costs**	**ICER (£/QALY)**	Probability (%) of cost effectiveness at a threshold of	
						£20,000 /QALY	£30,000 /QALY
DETERMINISTIC RESULTS:							
RTX	7.000	£138,520	-	-	-		
CZP before RTX	**7.286**	**£148,361**	**0.286**	**£9,842**	**£34,378**		
PROBABILISTIC RESULTS:							
RTX	7.031	£139,933	-	-	-	97.80	63.02
CZP before RTX	**7.321**	**£149,579**	**0.290**	**£9,647**	**£33,222**	2.20	36.98

Source ERG report

Company's base case results pop. B: *(where RTX is contraindicated or withdrawn) – Deterministic results*

First therapy of the sequence	Total QALYs	Total costs	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)
IFX + MTX	6.048	£101,484	-	-	Dominated
ETA + MTX	6.048	£97,606	-	-	Dominated
ADA + MTX	6.048	£97,183	-	-	-
GOL + MTX	6.048	£97,183	-	-	-
ABA(IV) + MTX	6.095	£115,555	0.047	£18,373	Dominated
CZP + MTX	**6.308**	**£98,100**	**0.260**	**£918**	**£3,527**
TOC(IV) + MTX	6.507	£125,112	0.199	£27,011	£135,953

Source ERG report

Company's base case results pop. B: *(where RTX is contraindicated or withdrawn) – probabilistic results*

First therapy of the sequence	Total QALYs	Total costs	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)	Probability(%) of cost effectiveness at a threshold of	
						£20,000/ QALY	£30,000/ QALY
IFX + MTX	6.038	£102,242	-	-	Dominated	0.00	0.00
ETA + MTX	6.070	£98,360	-	-	Dominated	0.0	0.7
GOL + MTX	6.071	£97,964	-	-	-	0.3	1.5
ADA + MTX	6.076	£98,015	-	-	Extendedly dominated	0.2	1.7
ABA (IV)+ MTX	6.119	£116,232	-	-	Dominated	0.00	0.00
CZP + MTX	**6.327**	**£98,848**	**0.256**	**£884**	**£3,461**	**99.5**	**96.0**
TOC (IV)+ MTX	6.528	£125,507	0.201	£26,659	£132,783	0.00	0.00

Source ERG report

Company's base case results pop. C: *(where MTX is contraindicated or withdrawn)*

First therapy of the sequence	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER (£/QALY)	Probability (%) of CE at a threshold of	
						£20,000/ QALY	£30,000/ QALY
DETERMINISTIC RESULTS:							
ADA	5.880	£95,632	-	-	-		
ETA	5.880	£96,036	-	-	Dominated		
CZP	**6.141**	**£97,249**	**0.260**	**£1,617**	**£6,213**		
TOC (IV)	6.346	£123,592	0.206	£27,960	£127,955		
PROBABILISTIC RESULTS:							
ETA	5.899	£96,270	-	-	Dominated	0.04	0.92
ADA	5.902	£95,918	-	-	-	0.18	1.16
CZP	**6.162**	**£97,254**	**0.260**	**£1,336**	**£5,151**	**99.78**	**97.48**
TOC(IV)	6.358	£123,433	0.196	£26,179	£133,655	0.00	0.00

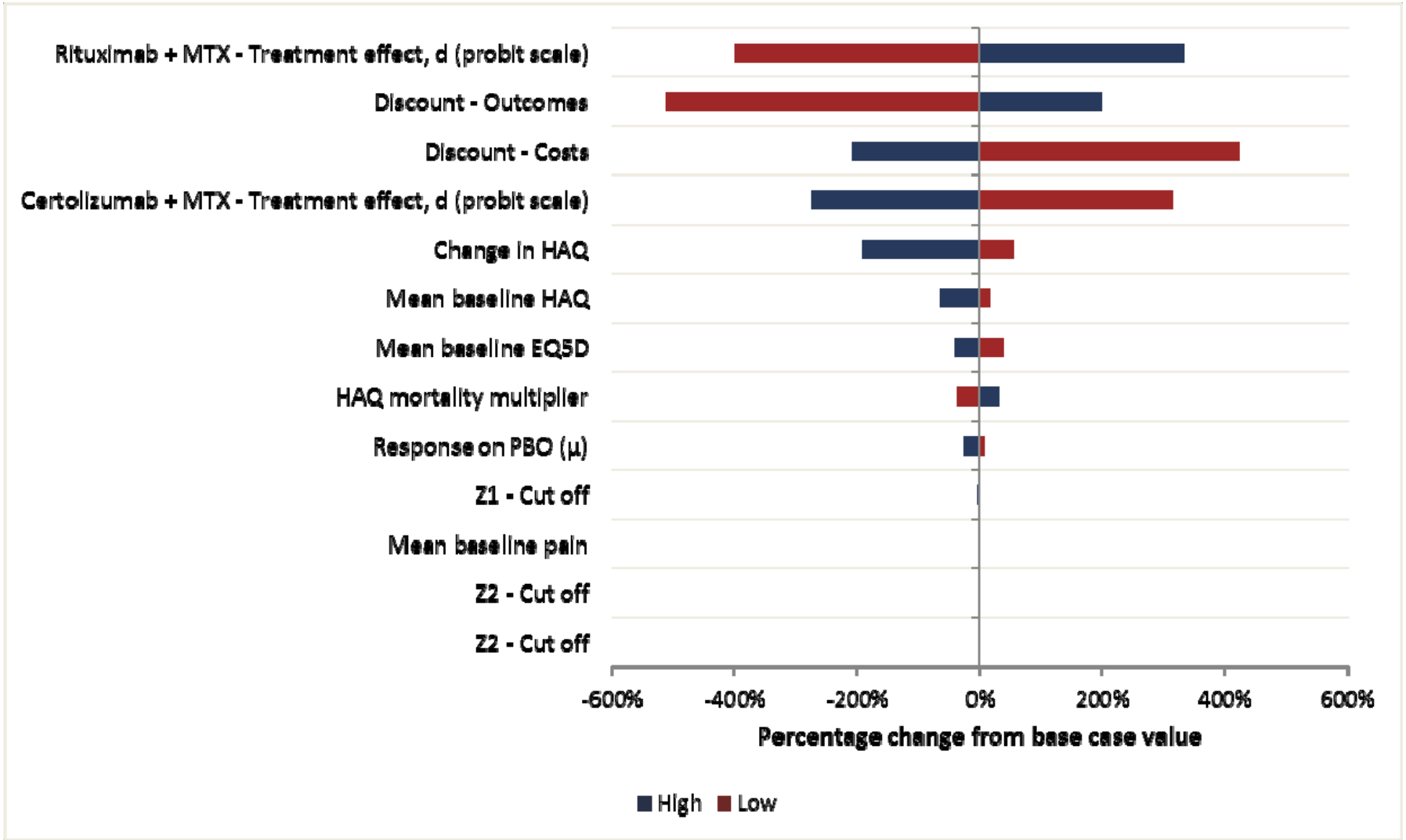
Company's one-way sensitivity analyses

	Parameter	Variation
1	Discount rates for costs and effects	0-6%
2	Mean baseline HAQ	30 % variation
3	Mean baseline pain	30 % variation
4	Mean baseline EQ-5D	30 % variation
5	Trial-specific baseline effects in the NMA model[a]	95% CrI
6	Cut-off statistics (Z) in the NMA model (see Section 5.2.6.1)[b]	95% CrI
7	HAQ mortality hazard ratio	95% CrI
8	Coefficient of HAQ for the mapping to EQ-5D	30% variation
9	Effect of CZP treatment on probability of EULAR response	95% CrI
10	Effect of comparator treatment on probability of EULAR response	95% CrI

a: Assumed by the ERG to mean the "No response" rate from the NMA for the reference treatment in the REALISTIC study

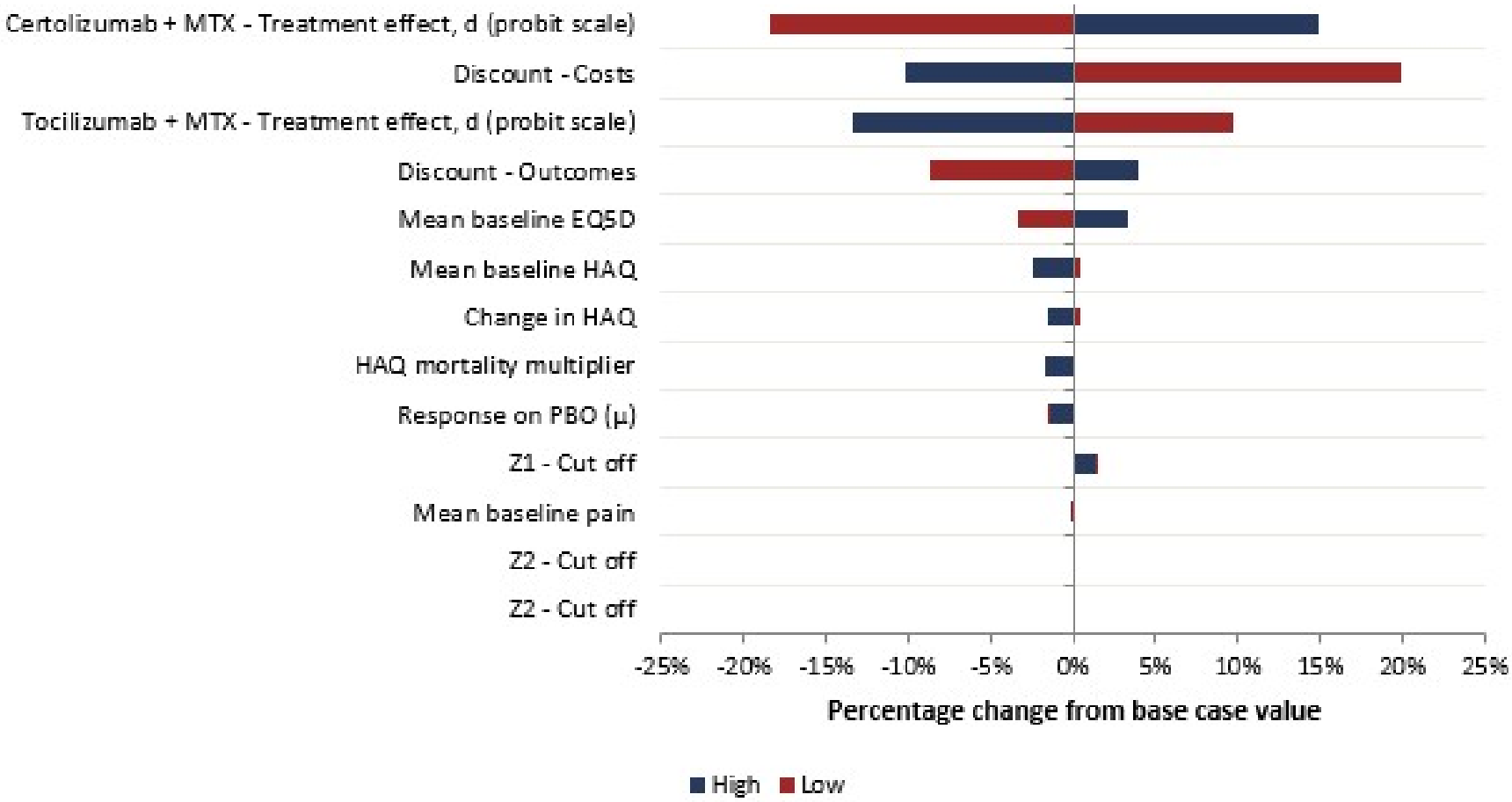
b: Assumed by the ERG to mean the common value across studies included in the NMA that splits responders between moderate and good responders for the reference treatment

Company's sensitivity analyses: results pop. A: *patients eligible for rituximab and methotrexate*



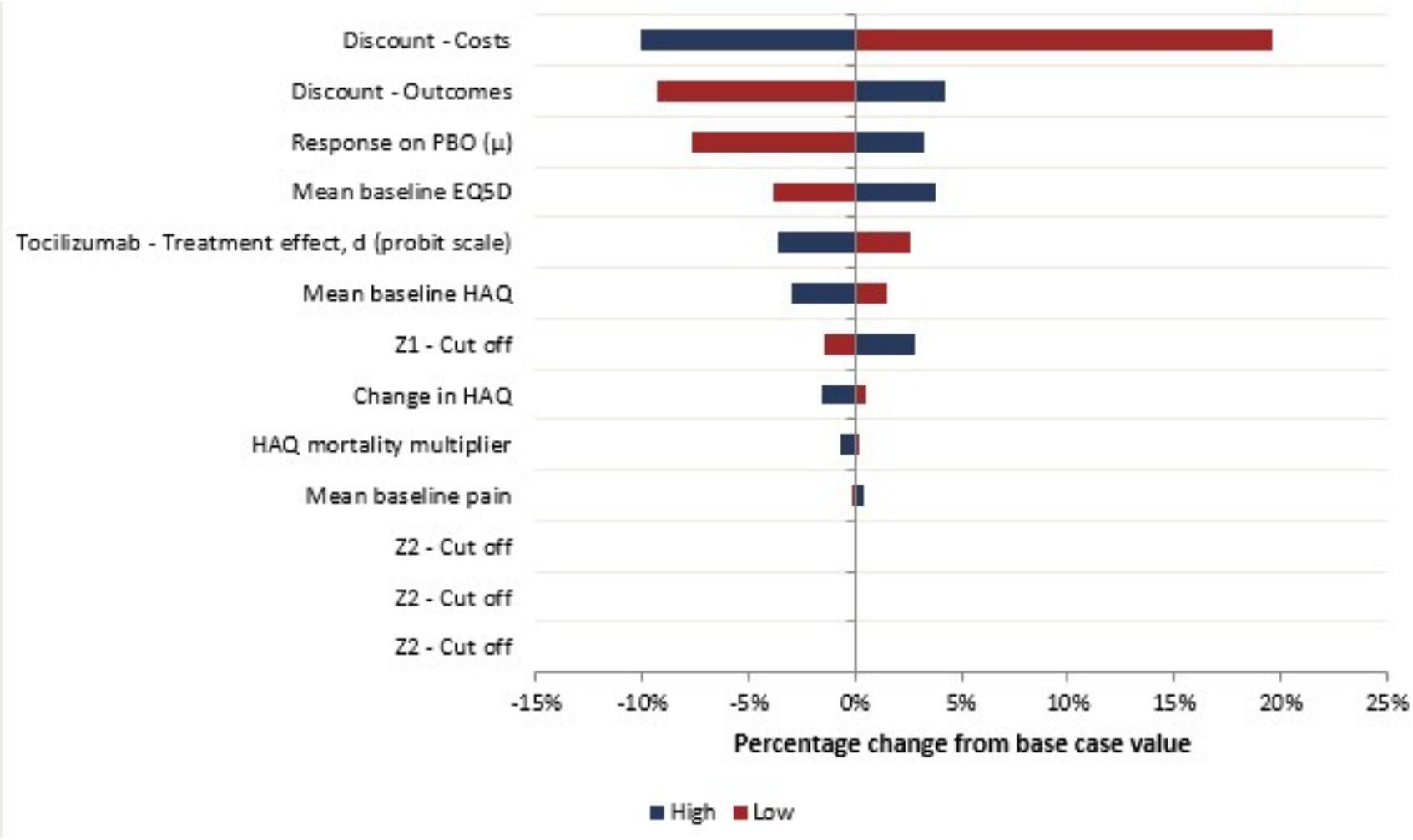
Source ERG report

Company's sensitivity analyses: results pop. B: *patients whom rituximab is inappropriate*



Source ERG report

Company's sensitivity analyses: results pop. C: *patients for whom methotrexate is inappropriate*



Source ERG report

Company's scenario analyses

	Parameter		Base case assumption	Alternative assumption(s)
1	Efficacy of CZP		Using results from the NMA (Efficacy of CZP taken from the REALISTIC study)	For Populations A and B, assume CZP has same efficacy as the rest of TNFis. For Population C, assume ADA and ETA have same efficacy as CZP
				Including J-RAPID in the NMA
2	Retreatment interval of RTX		6 months	9 months
3	Mapping from HAQ to EQ-5D		Using coefficient (-0.2102) attributed to Brennan et al.	Using pain and HAQ, based on Hernández Alava et al.
4	Estimates of utility improvements on initial response to first-line treatment		Linear regression model fitted to data from the PREDICT study	Change from baseline utility mapped from change in HAQ score
5	% of patients enjoying full utility gains after six weeks of first treatment		100%	25%
6	Time to treatment discontinuation of first therapy (scale parameter of Weibull distribution)	Non-TNFi	0.4416	0.2208
		TNFi	0.4416	0.3003
7	Perspective		NHS/PSS	Societal
8	HAQ progression on cDMARDs		0.045 increase per year	0.000 increase per year
9	HAQ progression on palliative care		0.06 increase per year	0.000 increase per year

Source ERG report

Company's scenario analyses – results (1 of 2)

Parameter	Base case	Scenario analysis	A	B*		C*	
			CZP + MTX vs RTX + MTX	CZP + MTX	TOC + MTX	CZP	TOC
Base case analysis			£34,516	£3k	£129k	£5k	£123k
Source of utility for first treatment Response	Linear regression (PREDICT)	HAQ score from REALISTIC mapped to EQ-5D	£33,199	£6k	£204k	£8k	£189k
% patients enjoying utility gain at 6 weeks	100%	25%	£34,430	£3k	£132k	£5k	£126k
Efficacy of CZP	Based on NMA	Pop A and B = other TNFi and pop C = ADA and ETA	£169,690	-	£62k	-	£793k
		Incl. J-RAPID in NMA	£29,613	£4k	£182k	£7k	D

Source ERG report. *other comparators not shown remain same as base case

Company's scenario analyses – results(2 of 2)

Parameter	Base case	Scenario analysis	A	B*		C*	
			CZP + MTX vs RTX + MTX	CZP + MTX	TOC + MTX	CZP	TOC
Duration of TNF therapy (scale parameter, Weibull)	0.4416	0.3003	£19,673	£7k	£2M	£7k	D
Vial wastage	Yes	No	£34,110	£4k	£98k	£5k	£94k
RTX retreatment interval	6 months	9 months	£49,618	NA	NA	NA	NA
Perspective	NHS/PSS	Societal	£4,729	-	£118k	£5k	£135k
HAQ progression on cDMARDs	0.045 p.a	0 per annum	£53,578	£5k	£140k	£5k	£133k
HAQ progression on palliative care	0.06 p.a	0	£57,156	£7k	£155k	£10k	£155k
Maximum mean HAQ	2.76	3.0	£34,183	£4k	£130k	£5k	£123k

Source ERG report. *other comparators not shown remain same as base case.

Company's additional scenario analyses – results: pop. B use of subcutaneous (SC) formulations of TOC and ABA, and IFX biosimilars (inflectra and remsima)

First therapy of the sequence	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER (£/QALY)
CZP + MTX	6.286	£98,575	0.270	£981	£3,641
TOC (SC) + MTX	6.491	£112,716	0.205	£14,141	£68,953

Company's additional scenario analyses results: Pop. C use of subcutaneous (SC) formulations of TOC

First therapy of the sequence	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER (£/QALY)
CZP	6.115	£97,292	0.271	£1,349	£4,985
TOC (SC)	6.328	£123,695	0.213	£26,403	£123,915

Evidence Review Group comments

1. Deviations from the NICE Reference Case
2. Appropriateness of sequences compared for Population A
3. Appropriateness of including ABA + MTX therapy after TOC + MTX
4. Appropriateness of the methods used for the NMA
5. Exclusion of the J-RAPID trial from the NMA
6. Modelling of HAQ progression on cDMARDs and palliative care
7. Modelling of HAQ to EQ-5D mapping
8. Retreatment interval of RTX
9. Appropriateness of assuming treatment duration of TNFis is equal to that of other bDMARDs
10. Appropriateness of assuming changes in HAQ score affect mortality
11. Failure to age-adjust utilities
12. Modelling of HAQ improvement in responders for subsequent therapies
13. Modelling of treatment discontinuation for subsequent therapies
14. Inaccuracy in TOC (IV) dosing
15. Approximation of the weight distribution of the population using weight bands
16. Inconsistency in benefits of treatment response during the first cycle
17. Exclusion of AEs
18. Inaccuracies in the number of doses per cycle
19. Appropriateness of using EQ-5D data from the PREDICT study
20. Perceived model errors and other issues surrounding model implementation

ERG's exploratory base case analysis – 12 changes made:

1	Correction of technical programming errors in the company's model
2	Adding two other sequences to be compared for Population A (see slide 34)
3	Removing ABA treatment from the intervention and comparator sequences for Population A
4	Using the results of the NMA including J-RAPID
5	Setting RTX retreatment interval to 7.35. The Appraisal Committee for TA195 concluded that the average retreatment interval was between 6 and 8.7 months. The ERG used the midpoint between these two figures: (6+8.7)/2= 7.35
6	Using different HAQ improvement for subsequent therapies. Instead of the -0.39 and -0.05 mean change in HAQ score for responders to subsequent bDMARD and cDMARD treatments respectively values of -0.576 for bDMARD responders and -0.303 for cDMARD responders
7	Using the Weibull parameters reported in TA195 for RTX (see Table 56) instead of assuming the same time to discontinuation as for TNF inhibitors

ERG exploratory base case changes (2)

8	Assume that mortality is only affected by the baseline HAQ score, and that changes in the HAQ score do not affect mortality
9	Using constant discontinuation rates for subsequent bDMARD treatments that would match the mean treatment duration estimated by the Weibull distribution used for the first treatment line considered in the model (see Table 56)
10	Including the 80 mg dose of TOC (IV) and 800 mg limit for people with a body weight greater than 100 kg
11	Using amended numbers of administrations per cycle for IFX (3.25) and TOC IV (7 in the first cycle)
12	Including the SC formulations of ABA and TOC, IFX biosimilars and Benepali (a new ETA biosimilar) as comparators in its analyses. Benepali is administered weekly as a 50mg/ml solution for injection in a pre-filled syringe or pre-filled pen. The cost to the NHS of each dose reported in MIMS86 (in May 2016) is £164.00

Additional treatment sequences in ERG exploratory base case (population A only)

	Sequence name			
	Certolizumab <u>before</u> rituximab	**Certolizumab <u>after</u> rituximab**	**Certolizumab <u>instead of</u> rituximab**	**Rituximab**
First	CZP + MTX	RTX + MTX	CZP + MTX	RTX + MTX
Second	RTX + MTX	CZP + MTX	TOC + MTX	TOC + MTX
Third	TOC(SC) + MTX	TOC(SC) + MTX	M + H + S	M + H + S
Fourth	M + H + S	M + H + S	NBT	NBT
Fifth	NBT	NBT	Palliative care	Palliative care
Sixth	Palliative care	Palliative care		

NBT = Non-biologic treatment: a weighted mix of leflunomide, gold, ciclosporin, azathioprine (25% each)
M + H + S = MTX + HCQ + SSZ

ERG exploratory base case results for population A (where RTX + MTX is an option)

Sequences	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER (£/QALY)	Probability (%) of cost-effectiveness at a threshold of	
						£20,000/ QALY	£30,000/ QALY
DETERMINISTIC RESULTS:							
CZP instead of RTX‡	7.719	£125,364	-	-	Dominated	-	-
CZP before RTX‡	8.239	£133,780	-	-	Dominated	-	-
RTX‡	8.378	£122,451	-	-	-	-	-
CZP after RTX‡	**8.649**	**£130,016**	**0.271**	**£7,565**	**£27,946**	**-**	**-**
PROBABILISTIC RESULTS:							
CZP instead of RTX‡	7.796	£128,376	-	-	Dominated	0.00	0.00
CZP before RTX‡	8.347	£136,751	-	-	Dominated	0.00	0.20
RTX‡	8.461	£125,189	-	-	-	71.46	45.64
CZP after RTX‡	**8.732**	**£132,692**	**0.271**	**£7,504**	**£27,700**	**28.52**	**54.26**

†Rest of the sequence: TOC(SC)+MTX, MTX + HCQ + SSZ, NBT, PC
‡CiC PAS not included;

ERG exploratory base case results for population B (where RTX is contraindicated or withdrawn)

First therapy of sequence	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER (£/QALY)	Probability (%) of cost-effectiveness at a threshold of	
						£20,000/ QALY	£30,000/ QALY
DETERMINISTIC RESULTS:							
CZP + MTX‡	**7.176**	**£95,197**	**0.279**	**£3,562**	**£12,773**	**-**	**-**
TOC(SC) + MTX ‡	7.697	£118,338	0.520	£23,141	£44,479	-	-
PROBABILISTIC RESULTS:							
CZP + MTX	**7.213**	**£95,899**	**0.280**	**£3,392**	**£12,116**	**96.22**	**92.30**
TOC(SC) + MTX	7.725	£119,171	0.571	£23,272	£45,414	0.000	0.0028

Source ERG report. *Only showing those therapies that are not dominated

ERG exploratory base case results for population C (where MTX is contraindicated or withdrawn)

First therapy of sequence	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER (£/QALY)	Probability (%) of cost-effectiveness at a threshold of	
						£20,000/ QALY	£30,000/ QALY
DETERMINISTIC RESULTS:							
CZP	**7.024**	**£93,807**	**0.279**	**£3,953**	**£14,185**	**-**	**-**
TOC(SC)	7.528	£117,033	0.505	£23,226	£46,018	-	-
PROBABILISTIC RESULTS:							
CZP	**7.070**	**£94,311**	**0.289**	**£3,988**	**£13,784**	**95.36**	**93.48**
TOC	7.561	£117,142	0.491	£22,832	£46,501	0.00	0.16
TOC(IV)	7.566	£126,323	0.005	£9,181	£1,945,969	0.00	0.00

Source ERG report. *Only showing those therapies that are not dominated

ERG comparative assumption scenario analysis for pop. B (deterministic)

- Assumed IFX, ETA and ADA in combination with MTX are as effective as CZP + MTX

First therapy of the sequence†	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER (£/QALY)
GOL + MTX	6.897	£93,524	-	-	-
ETA(bio) + MTX	7.176	£94,943	0.279	£1,418	£5,085
CZP + MTX	**7.176**	**£95,197**	**-**	**-**	**Dominated**
IFX(bio) + MTX	7.176	£96,619	-	-	Dominated
ADA + MTX	7.176	£97,193	-	-	Dominated
ETA + MTX	7.176	£97,694	-	-	Dominated
IFX + MTX	7.176	£99,719	-	-	Dominated
ABA(IV) + MTX‡	7.237	£121,272	-	-	Dominated
ABA(SC) + MTX‡	7.237	£125,187	-	-	Dominated
TOC(SC) + MTX‡	7.697	£118,338	0.520	£23,395	£44,967
TOC(IV) + MTX‡	7.697	£127,749	-	-	Dominated

†Rest of the sequence: MTX + HCQ + SSZ, LEF, GLD, CIC, AZA, PC, ‡CiC PAS not included, bio = biosimilar. *Source ERG report*

ERG comparative assumption scenario analysis for pop. C (deterministic)

- Assumed ETA and ADA monotherapies are as effective as CZP monotherapy

First therapy of the sequence†	**Total QALYs**	**Total costs**	**Inc. QALYs**	**Inc. costs**	**ICER (£/QALY)**
ETA(bio)	7.024	£93,629	-	-	-
CZP	**7.024**	**£93,807**	**-**	**-**	**Dominated**
ADA	7.024	£95,816	-	-	Dominated
ETA	7.024	£96,304	-	-	Dominated
TOC(SC) ‡	7.528	£117,033	0.505	£23,404	£46,371
TOC(IV) ‡	7.528	£126,262	-	-	Dominated

† Rest of the sequence: LEF, GLD, CIC, AZA, PC, ‡ CiC PAS not included, bio = biosimilar. *Source ERG report*

Further Evidence Review Group comments

- Treatment sequences compared for Population A - because they include TOC + MTX followed by ABA + MTX after RTX + MTX
- Lack of evidence on the efficacy of IFX, ADA and ETA in combination with MTX (& TOC, ADA and ETA monotherapies) in patients with inadequate response to a TNFi
- Assumption of the same treatment duration for all bDMARDs, despite suggesting different treatment durations for different bDMARDs
- Simple approach to map changes in HAQ score to changes in EQ-5D utility

Summary of ERG critique and analyses

- Population A (where RTX + MTX is an option)
  - 2 sequences added to consider CZP *after or instead of* RTX + MTX
  - ERG conclude that CZP is not cost effective before or instead of RTX
  - ICER for CZP after RTX is £27,946
  - However, the model results are not credible – elongated treatment sequences compared with standard treatment sequences

- Population B (where RTX is contraindicated or withdrawn)
  - Comparable results to the company's submission

- Population C (where MTX is contraindicated or withdrawn)
  - Comparable results to the company's submission

- Remaining uncertainty around data for the comparative analysis and for bDMARDs in general in the population with prior TNF inhibitor use

Decision problem logic: comments from the ERG

- As **********
- **********

Key issues for consideration

- Should certolizumab pegol (with or without methotrexate) be recommended as an option at the same point as rituximab? i.e. should it be given as a second anti-TNF after the first one has failed?
- Should certolizumab pegol plus methotrexate be an option where rituximab plus methotrexate is contra-indicated?
- Should certolizumab pegol monotherapy be an option where methotrexate is contra-indicated?