No AIC or CIC

Lead team presentation

Baricitinib for treating moderate to severe rheumatoid arthritis

Single Technology Appraisal

Clinical effectiveness

1st Appraisal Committee Meeting: 16th May 2017

Committee C

Evidence Review Group: School of Health and Related Research (ScHARR), The University of Sheffield

Lead Team: Andrew Renehan and David Chandler

For the public observers

Abbreviations

ABA	Abatacept
ACR20	20% improvement in American College of Rheumatology Criteria
ADA	Adalimumab
AE	Adverse event
BARI	Baricitinib
bDMARD	Biological DMARD
BSRBR	British Society for Rheumatology Biologics Register
cDMARD	Conventional DMARD
CTZ	Certolizumab pegol
DAS28	Disease activity score in 28 Joints
DMARD	Disease-modifying anti-rheumatic drug
ETN	Etanercept
EULAR	European League against Rheumatism

GOL	Golimumab
HAQ	Health Assessment Questionnaire
IFX	Infliximab
IR	Insufficient response
JAK	Janus kinase
MTX	Methotrexate
Q2W	Every 2 weeks
QD	Once daily
QW	Weekly
RA	Rheumatoid arthritis
RTX	Rituximab
TCZ	Tocilizumab
TNF	Tumour necrosis factor
TNFi	Tumour necrosis factor inhibitor
TOFA	Tofacitinib

Shaded rows contain comparator technologies

Key issues: Clinical effectiveness

- Innovation, including that baricitinib is oral rather than subcutaneous or i.v. administration
- Is baricitinib comparable to the bDMARDs in clinical effectiveness in moderate and severe rheumatoid arthritis?
- Is baricitinib effective as a monotherapy?
- The ERG considered that the company's network meta-analysis results should be treated with caution
  - Are the Committee comfortable that the conclusions of the company NMA and the ERG NMA are broadly similar?

Background to rheumatoid arthritis

- Autoimmune disease that causes inflammation in multiple joints resulting in pain and stiffness
- Can lead to irreversible joint damage, deformities and loss of function
- Disease severity measured using the composite DAS28 score
  - Swelling/tenderness in 28 joints, patient reported 'global assessment of health' and erythrocyte sedimentation rate or C-reactive protein
- For most patients, disease remains mild with occasional flare-ups. For some patients, disease may be active and progressive, significantly compromising quality of life
  - Approximately 15% of patients in the UK have severe disease
- Management of rheumatoid arthritis aims to suppress disease activity and induce remission, prevent the development of irreversible joint damage, maintain quality of life and address comorbidities associated with the condition

Patient perspective – 1
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*
- 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
What patients want from treatments

- Reduction in pain
- Reduction in inflammation
- Prevent and stop permanent damage to joints
- Aim to avoid permanent disability
- Reduction in fatigue – *major issue to patients*
- Maintain independence and the ability to work
- Treatments need to have low adverse events
  - Patients report that current biologic therapies generally have fewer adverse events than methotrexate and other standard DMARDs
- Need for a range, as response varies – *even in same class/target*
- No disadvantages were identified by the patient group for baricitinib

Relevant NICE technology appraisals

TA	Treatment	Population
415 2016	CTZ + MTX	Inadequate response to, or intolerance of, other DMARDs including at least 1 TNF inhibitor, only if: • disease activity is severe and RTX is contraindicated or not tolerated
	CTZ monotherapy	As above but only if: • RTX therapy cannot be given because MTX is contraindicated or not tolerated
375 2016	ADA, ETN, IFX, CTZ, GOL, TCZ, ABA (all + MTX)	Severe disease with inadequate response to intensive therapy with a combination of cDMARDs
	ADA, ETN, CTZ, TCZ monotherapy	As above but only if MTX contraindicated or not tolerated

TA	Treatment	Population
247 2012	TCZ + MTX	Inadequate response to DMARDs and a TNF inhibitor and RTX contraindicated or not tolerated, and TCZ used as described for TNF inhibitor treatments in TA195, specifically the recommendations on disease activity **or** disease responded inadequately to 1 or more TNF inhibitor treatments and to RTX
225 2011	GOL + MTX	Inadequate response to other DMARDs, including a TNF inhibitor, if GOL used as described for other TNF inhibitor treatments in TA195
195 2010	RTX + MTX	Severe active RA with inadequate response to, or intolerance of, other DMARDs, including at least 1 TNF inhibitor
	ADA, ETN, IFX, ABA (all + MTX)	As for RTX + MTX but only if RTX contraindicated or not tolerated
	ADA, ETN monotherapy	As for RTX + MTX but only if MTX contraindicated or not tolerated

Details of the technology

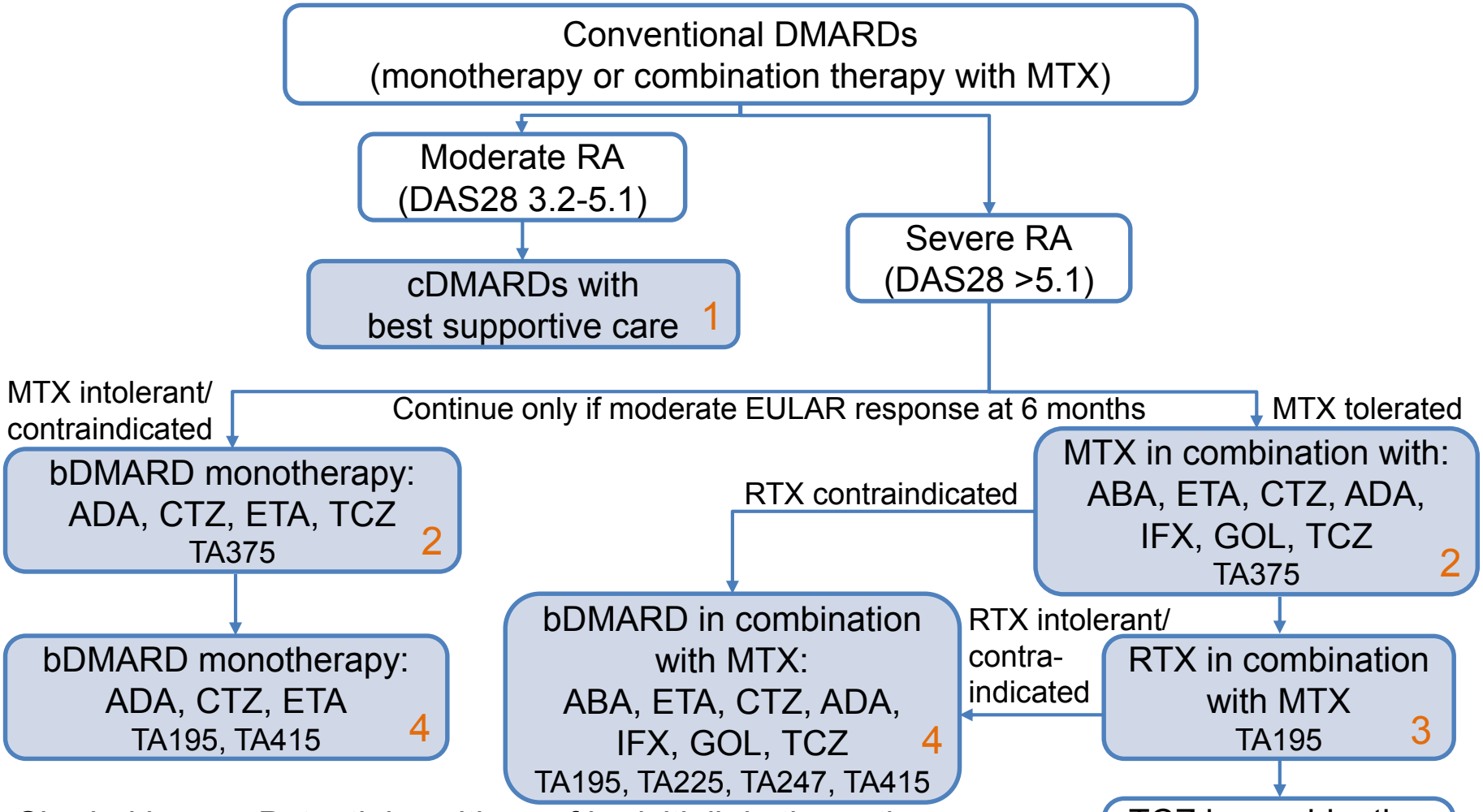
Technology	Baricitinib (Olumiant; Lilly)	
Marketing authorisation	Treatment of moderate to severe active RA in adult patients • who have responded inadequately to, or • who are intolerant to one or more DMARDs – used as monotherapy or in combination with MTX	
Mechanism of action	Reversible janus kinase (JAK) inhibitor; selective for JAK1 and JAK2. Disrupts cytokine signalling, cellular activation and proliferation of key immune cells involved in RA, reducing inflammation	
Administration	Oral, 4 mg once daily. 2 mg once daily for people aged ≥ 75 years (may be appropriate if history of chronic or recurrent infections). Treatment continuous (no stopping rule), but dose reduction to 2 mg once daily may be considered for people with sustained control of disease activity	
Acquisition cost	List price per pack: 2 or 4 mg x 28 tab: £805.56 2 or 4 mg x 84 tab: £2,416.68 Annual per patient: £10,501	PAS price per pack: 2 or 4 mg x 28 tab: £[redacted] 2 or 4 mg x 84 tab: £[redacted] A[redacted]

Confidential

Innovation

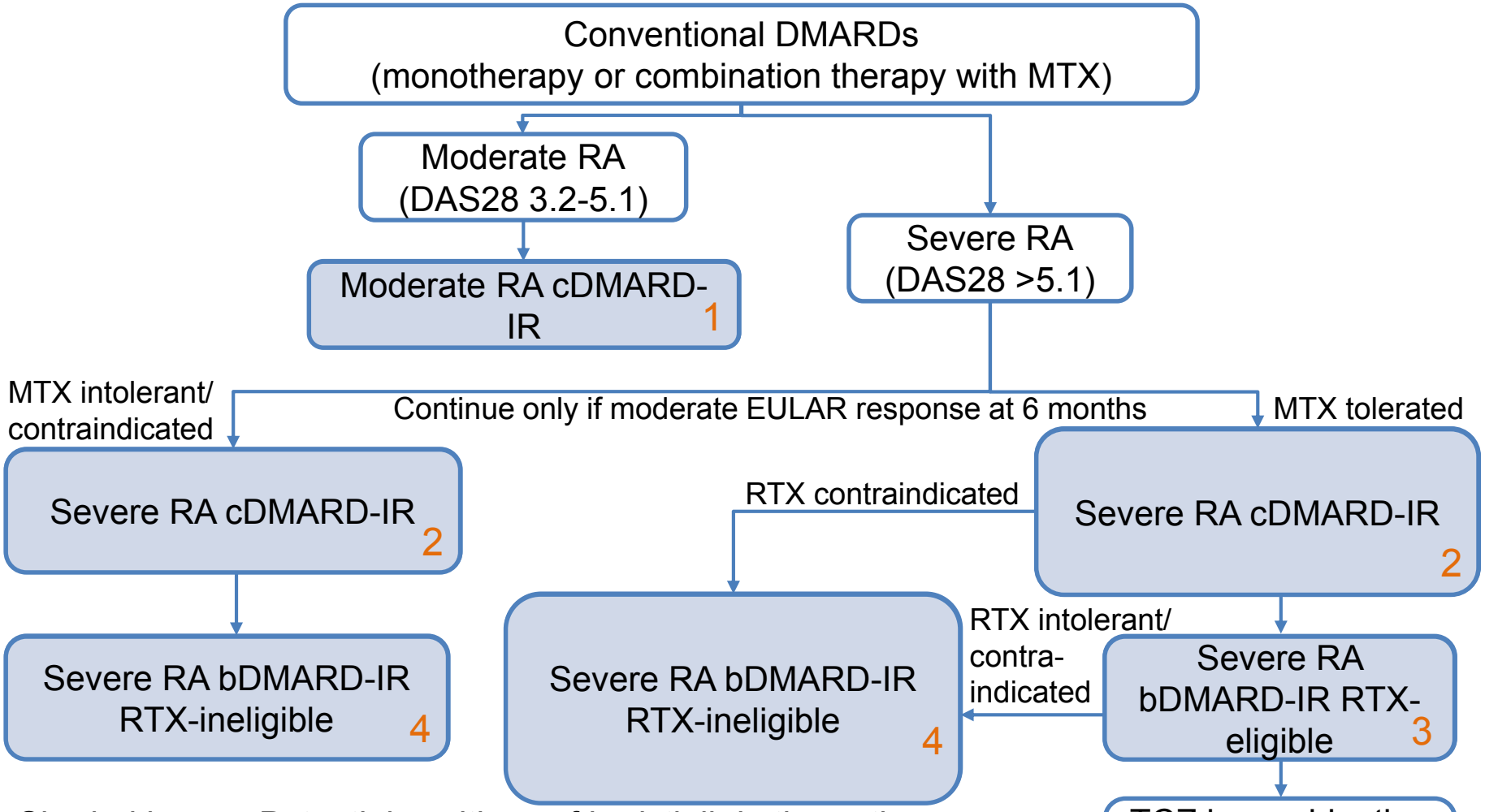
- First JAK1/2 inhibitor licenced in Europe
- Oral rather than subcutaneous or i.v. administration
  - Eliminates injection site reactions which can result in discontinuation of bDMARDs
  - Offers treatment for people who don't like needles
- Small molecule rather than a biologic
  - Does not induce the production of anti-drug antibodies seen with TNF inhibitors, which cause efficacy to decline over time
- Selective for JAK1/2 with low affinity for JAK3
  - Off-target effects limited

Treatment pathway – Comparators



- Shaded boxes=Potential positions of baricitinib in the pathway
- 1-4=Patient populations referred to in the company submission
- Tofacitinib is currently being appraised by NICE at the same positions as baricitinib in the treatment pathway

Treatment pathway – Populations



- Shaded boxes=Potential positions of baricitinib in the pathway
- 1-4=Patient populations referred to in the company submission
- Tofacitinib is currently being appraised by NICE at the same positions as baricitinib in the treatment pathway

EULAR Criteria

- No EULAR response
  - Change ≤0.6 in DAS28 from baseline OR
  - Change of >0.6 and ≤1.2 in DAS28 from baseline AND DAS28 >5.1 at baseline
- Moderate EULAR response
  - Change >0.6 and ≤1.2 in DAS28 from baseline AND DAS28 >3.2 and ≤5.1 or DAS28 ≤3.2 at endpoint OR
  - Change of >1.2 in DAS28 from baseline AND DAS28 >3.2 at baseline
- Good EULAR response
  - change of >1.2 in DAS28 from baseline AND DAS28 of ≤3.2 at endpoint

Company's decision problem - 1

Population	Adults with moderate to severe, active RA whose disease has responded inadequately to, or who are intolerant of 1 or more DMARDs, including conventional or biologic DMARDs	
Intervention	Baricitinib monotherapy or in combination with methotrexate	
Comparators	See treatment pathway (slide 9) Insufficient data to allow comparison between baricitinib monotherapy and bDMARDs + methotrexate	
Outcomes	• Disease activity • Physical function • Joint damage • Pain • Mortality	• Fatigue • Radiological progression • Extra-articular manifestations • Adverse effects of treatment • Health-related quality of life

Company's decision problem - 2

Economic analysis	• Cost-effectiveness expressed as incremental cost/QALY • Time horizon sufficiently long to reflect differences in costs or outcomes between the technologies • Costs considered from NHS perspective only, consistent with the Assessment Group's model in TA375 • Patient access schemes for the intervention or comparator accounted for • Availability and cost of biosimilar products accounted for
Subgroups	• Primary endpoint (ACR20 response at week 12) presented for: - Moderate disease activity - Severe disease activity • Economic analysis presents results: - Separately for moderate and severe disease activity in the cDMARD-IR population - For severe patients only in the bDMARD-IR population

Submissions from clinical experts

- cDMARDs are insufficient for a significant proportion of people
- Many patients don't respond adequately to their first biologic and there are few tools available to predict response, or to help decide which biologic to use
- Baricitinib is novel; there are no other JAK inhibitors available in the UK and the oral formulation has benefits for the system and patients. The EULAR 2016 update recommends that JAK inhibitors are considered as an alternative to bDMARDs in poor prognosis patients after failure of cDMARDs
- Use as a monotherapy is an advantage as many people don't tolerate methotrexate, which leads to poor adherence.
- The people in the trials broadly reflect those in the UK and are comparable to those in trials for other NICE approved RA treatments. Trial outcomes are appropriate and relevant to routine clinical practice
- There are no new safety signals, and the overall benefit/risk profile is favourable and broadly comparable to other bDMARDs

Clinical effectiveness systematic review and network meta-analysis

- Company systematic review identified 4 RCTs and 1 long-term safety and tolerability study
  - RA–BEAM RCT: MTX-treated, bDMARD-naïve *vs* placebo *vs* adalimumab
  - RA-BUILD RCT: cDMARD-IR, bDMARD-naïve *vs* placebo
  - RA-BEACON RCT: bDMARD-IR *vs* placebo
  - RA-BEGIN RCT: DMARD-naïve (unlicensed) *vs* methotrexate
  - RA-BEYOND long-term study: Included patients from RA-BEAM, RA-BUILD, RA-BEACON and RA-BEGIN and a phase II study of baricitinib

- Network meta-analysis assessed the relative efficacy of baricitinib in the cDMARD-IR and bDMARD-IR populations

Study characteristics

Trial name	Population and number enrolled	Intervention	Comparators	Primary outcome
RA-BEAM	•MTX-IR, bDMARD-naïve adult patients with moderate to severe RA •1307 randomised (1305 at least 1 dose, included in mITT) • [redacted]	•BARI 4 mg, oral, QD (+ background MTX)	•ADA 40 mg, SC injection, Q2W (+ background MTX) •Placebo (+ background MTX)	% of patients achieving ACR20 response at week 12
RA-BUILD	•cDMARD-IR, bDMARD-naïve adult patients with moderate to severe active RA •684 randomised • [redacted]	•BARI 2 mg, oral, QD •Baricitinib 4 mg, oral, QD Patients on ≥1 cDMARDs (with or without MTX) continued to take background therapy during study	•Placebo •Patients on ≥1 cDMARDs (with or without MTX) continued to take background therapy during study	% of patients achieving ACR20 response at week 12

- Baseline patient characteristics within trials were balanced across trial arms

Study characteristics

Trial name	Population and number enrolled	Intervention	Compara-tors	Primary outcome
RA-BEA-CON	•bDMARD-IR adult patients with moderate to severe active RA •527 randomised • [redacted]	•BARI 2 mg, oral, QD (+ background cDMARDs) •BARI 4 mg, oral, QD (+ background cDMARDs)	•Placebo (+ background cDMARDs)	% of patients achieving an ACR20 response at week 12
RA-BEGIN	•DMARD-naïve adult patients with moderate to severe RA (unlicensed) •588 randomised •15 UK patients	•BARI 4 mg, oral, QD •BARI 4 mg, oral, QD (+ MTX)	•MTX oral, QW	% of patients achieving an ACR20 response at week 24
RA-BEY-OND	•Patients with moderate to severe RA who completed Phase 2b study, or RA-BEAM, -BUILD, -BEACON or -BEGIN • [redacted]	•BARI 2 mg, oral, QD •BARI 4 mg, oral, QD	Not applicable	Long-term safety and tolerability

- Baseline patient characteristics within trials were balanced across trial arms

Summary results: ACR20 and EULAR at 12 weeks

MTX-IR, bDMARD-naïve, moderate to severe RA (RA-BEAM)

	PBO (n=488)	BARI 4 mg + cDMARD (n=487)	ADA (n=330)
ACR20 (%)	40	70***+	61***
ACR20 odds ratio (95% CI)	-	BARI *vs* PBO	BARI *vs* ADA
		3.6 (2.7 to 4.7); p=0.001	1.5 (1.1 to 2.0); p=0.014
EULAR (good + moderate) response rate (%)	[redacted]	[redacted]	[redacted]
EULAR (good) response rate (%)	[redacted]	[redacted]	[redacted]
EULAR good and moderate response Odds ratio (95% CI)	-	BARI *vs* PBO	BARI *vs* ADA
		[redacted]	[redacted]
EULAR good response Odds ratio (95% CI)	-	[redacted]	[redacted]

***p≤0.001 versus placebo, and +p≤0.05, ++p≤0.01 ve
regression, without control for multiple comparisons

Summary results: ACR20 and EULAR at 12 weeks

cDMARD-IR, bDMARD-naïve, moderate to severe RA (RA-BUILD)

	PBO (n=228)	BARI 2 mg + cDMARD (n=229)	BARI 4 mg + cDMARD (n=227)
ACR20 (%)	39.5	65.9***	61.7***
ACR20 odds ratio (95% CI)	-	BARI 2 mg *vs* PBO 3.0 (2.0 to 4.4) p=0.001	BARI 4 mg *vs* PBO 2.5 (1.7 to 3.7) p=0.001
EULAR (good + moderate) response rate (%)	53.5	79.0***	79.3***
EULAR (good) response rate (%)	15.4	34.1***	38.3***
EULAR good and moderate response Odds ratio (95% CI)	-	BARI 2 mg *vs* PBO 3.3 (2.2 to 5.0) p=0.001	BARI 4 mg *vs* PBO 3.5 (2.3 to 5.4) p=0.001
EULAR good response Odds ratio (95% CI)	-	2.9 (1.8 to 4.6) p=0.001	3.6 (2.3 to 5.7) p=0.001

***p≤0.001 versus placebo

Summary results: ACR20 and EULAR at 12 weeks

bDMARD-IR moderate to severe RA (RA-BEACON)

	PBO (n=176)	BARI 2 mg + cDMARD (n=174)	BARI 4 mg + cDMARD (n=177)
ACR20 (%)	27.3	48.9***	55.4***
ACR20 odds ratio (95% CI)	-	BARI 2 mg *vs* PBO 2.7 (1.7 to 4.2) p=0.001	BARI 4 mg *vs* PBO 3.4 (2.2 to 5.4) p=0.001
EULAR (good + moderate) response rate (%)	42.6	66.1***	72.3***
EULAR (good) response rate (%)	8.5	24.1***	29.9***
EULAR good and moderate response Odds ratio (95% CI)	-	BARI 2 mg *vs* PBO 2.7 (1.8 to 4.2) p=0.001	BARI 4 mg *vs* PBO 3.6 (2.3 to 5.7) p=0.001
EULAR good response Odds ratio (95% CI)	-	3.6 (1.9, 6.8) p=0.001	4.8 (2.6, 9.0) p=0.001

***p≤0.001 versus placebo

Summary of adverse events from weeks 0 to 24 (RA-BEAM, -BUILD, -BEACON)

Trial	RA-BEAM			RA-BUILD			RA-BEACON		
Treatment (n)	PBO (n=488)	BARI 4 mg QD + cDMARD (n=487)	ADA + cDMARD (n=330)	PBO (n=228)	BARI 2 mg QD + cDMARD (n=229)	BARI 4 mg QD + cDMARD (n=227)	PBO (n=176)	BARI 2 mg QD + cDMARD (n=174)	BARI 4 mg QD + cDMARD (n=177)
Treatment exposure, patient-years (total/group)	197.7	215.0	141.9	89.8	97.7	96.4	65.8	69.9	73.3
Overall AE, n (%) [EAIR]	[redacted]	[redacted]	[redacted]	161 (71)	154 (67)	162 (71)	112 (64)	123 (71)	137 (77)
Serious AE, n (%) [EAIR]	[redacted]	[redacted]	[redacted]	11 (5)	6 (3)	12 (5)	13 (7)	7 (4)	18 (10)
Withdrawal because of AE, n (%) [EAIR]	[redacted]	[redacted]	[redacted]	10 (4)	10 (4)	12 (5)	7 (4)	7 (4)	11 (6)
Temporary interruption due to AE, n [EAIR]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
Death, n [EAIR]	[redacted]	[redacted]	[redacted]	2	0	0	0	0	1
Infection, n (%)	134 (27)	176 (36)	110 (33)	79 (35)	70 (31)	96 (42)	55 (31)	76 (44)	70 (40)
Serious infection, n (%)	7 (1)	5 (1)	2 (<1)	4 (2)	2 (<1)	4 (2)	5 (3)	4 (2)	6 (3)
Cancer, n (%)	3 (<1)	2 (<1)	0	0	0	1 (<1)	0	0	2 (1)
MACE	0	1 (<1)	0	2 (<1)	0	0	0	0	2 (1)

cDMARD-IR median EULAR response at 24 weeks follow-up: Company NMA results

- The median EULAR moderate + good response rates for baricitinib 4 mg and 2 mg (QD) were [redacted] and [redacted], respectively. The median EULAR good response rates were [redacted] and [redacted], respec

bDMARD-IR median EULAR response at 24 weeks follow-up: Company NMA results

- The median EULAR moderate or good response rates for baricitinib 4 mg and 2 mg (QD) were [redacted] and [redacted], respectively. The median EULAR good response rates were [redacted] and [redacted], respectively

ERG critique of the indirect comparison and/or multiple treatment comparison

- NMAs were performed separately for the cDMARD-IR and bDMARD-IR populations

- The ERG identified several issues with approaches taken by the company including:
  - The conversion of ACR data to EULAR data before synthesis
  - The use of simultaneous models for baseline and treatment effects
  - Not assessing goodness-of fit
  - Using a random effects model for the cDMARD-IR population and fixed effects model for the bDMARD-IR population

- The ERG noted that inappropriate pooling of the control arms means that all results should be treated with caution

Additional work carried out by the ERG

- ACR and EULAR outcomes at week 24 re-analysed for the cDMARD-IR and bDMARD-IR populations. All cDMARDs assumed to have equivalent efficacy and were grouped together
- EULAR data from van de Putte *et al*. (2004) amended so the moderate EULAR responders did not include good EULAR responders
- The ERG's ACR NMA used the same studies included in the company submission. The ERG's EULAR NMA only included studies that reported EULAR outcomes
- The ERG used the same model for the relative treatment as the NICE Decision Support Unit technical support document which did not assume a random effects model for the baseline for each study
  - The baseline and relative treatment effect models were run separately to ensure information in the baseline model did not propagate to the relative treatment effect model
- Random effects model used for both ACR and EULAR outcomes in both the cDMARD-IR and bDMARD-IR populations

cDMARD-IR median EULAR response at 24 weeks follow-up: ERG NMA results

Baricitinib 4 mg + cDMARD associated with statistically significant beneficial treatment effects relative to placebo and cDMARD. No statistically significant differences were found versus any other comparator, with the exception of tocilizumab + cDMARD, which was associated with statistically beneficial treatment effects relative to baricitinib 4 mg + cDMARD

bDMARD-IR median EULAR response at 24 weeks follow-up: ERG NMA results

Baricitinib 4 mg + cDMARD associated with statistically significant beneficial treatment effects relative to cDMARD. No statistically significant differences were found versus rituximab 1000 mg + cDMARDs with the effect favouring rituximab 1000 mg + cDMARDs, which was the only other comparator in the network

Key issues: Clinical effectiveness

- Innovation, including that baricitinib is oral rather than subcutaneous or i.v. administration
- Is baricitinib comparable to the bDMARDs in clinical effectiveness in moderate and severe RA?
- Is baricitinib effective as a monotherapy?
- The ERG considered that the company's network meta-analysis results should be treated with caution
  - Are the Committee comfortable that the conclusions of the company NMA and the ERG NMA are broadly similar?

No AIC or CIC

Lead team presentation

Baricitinib for treating moderate to severe rheumatoid arthritis

Single Technology Appraisal

Cost effectiveness

1st Appraisal Committee Meeting: 16th May 2017

Committee C

Evidence Review Group: School of Health and Related Research (ScHARR), The University of Sheffield

Lead Team: Steve O'Brien

For the public observers

Key issues: Cost effectiveness

- Is baricitinib comparable to the bDMARDs in both clinical effectiveness and cost effectiveness?

- Has the case for baricitinib monotherapy been made?

Cost effectiveness studies

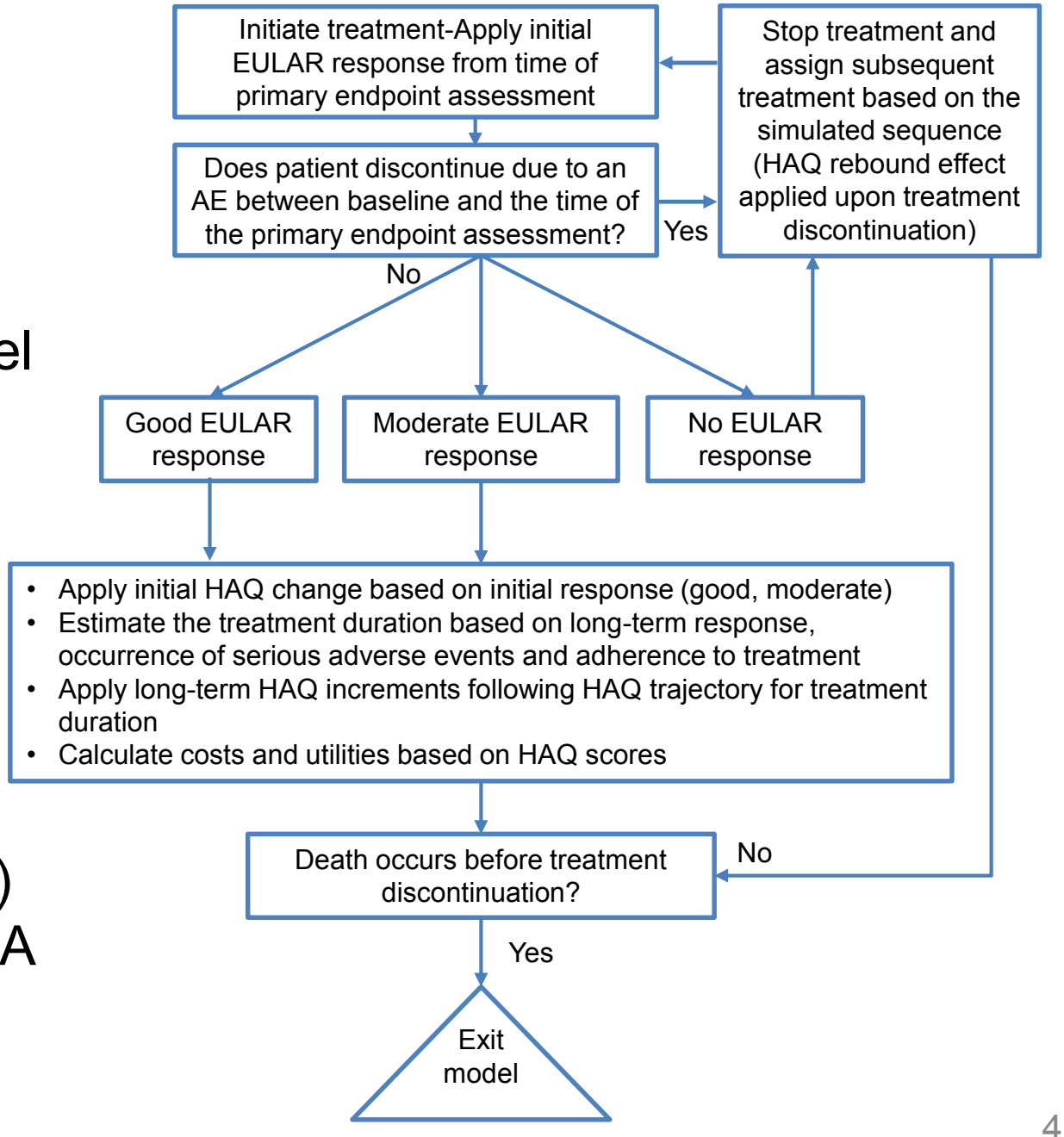
- The company identified 9 UK cost-effectiveness studies
  - 8 models used in NICE technology appraisals
  - 1 independent published review

- The company did not identify any models that included baricitinib
  - Therefore the company developed a *de novo* health economic model to assess the cost effectiveness of baricitinib

- The company based the model on the Assessment Group's model used in TA375

Model structure

- Discrete event simulation model based on AG model used in TA375
- Models individual patients
- Uses treatment sequences
- Estimated treatment effect (EULAR response) from company NMA
- 45 year time horizon



Company cost effectiveness model: Resources and costs

- Company model includes costs associated with drug acquisition, drug administration and monitoring, and hospitalisation
- Baricitinib has a confidential PAS
- PASs for certolizumab pegol and golimumab were incorporated (not confidential) but the confidential PASs for abatacept and tocilizumab were not included
- For weight-dependent dosing calculations, the average dose cost assumed all patients had the average weight of the population in the relevant baricitinib trials
- The company overestimated the number of doses and therefore the cost of infliximab
- Non-drug costs were largely based on TA375, inflated to 2016 prices

Company cost effectiveness model: Utilities

- EQ-5D-5L questionnaire used to collect HRQOL data in all 3 RCTs
  - Baseline at week 1
  - Every 4 weeks from week 4 onwards
    - To week 52 for RA-BEAM
    - To week 24 for RA-BUILD and RA-BEACON
- Patient-level EQ-5D-5L responses converted to utility index-based HAQ* scores using the UK-specific scoring algorithm as reported in Hernández Alava *et al*. (2012)
  - Approach not in line with TA375 which used the four-class mixture model by Hernández Alava *et al*. (2013)
  - The ERG does not consider that this changes the overall conclusions

*Health Assessment Questionnaire

Company base case: Treatment sequences for moderate RA, cDMARD-IR*

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment/ Rescue	Rescue
1	Baricitinib (4 mg or 2 mg QD)	Combination of cDMARDs	Methotrexate	Palliative care	Not applicable
2	Combination of cDMARDs	MTX	Palliative care	Not applicable	Not applicable

*Insufficient response

Company base case: Treatment sequences for severe RA, cDMARD-IR

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment/ Rescue	Rescue
1	Baricitinib (4 mg or 2 mg QD)+ methotrexate	Rituximab+ methotrexate	Tocilizumab+ methotrexate	Methotrexate	Palliative care
2	bDMARDs (excluding tocilizumab)+ methotrexate	Rituximab+ methotrexate	Tocilizumab+ methotrexate	Methotrexate	Palliative care
3	Tocilizumab+ methotrexate	Rituximab+ methotrexate	Adalimumab + Methotrexate	Methotrexate	Palliative care

Company base case: Treatment sequences for severe RA, bDMARD-IR

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment/ Rescue	Rescue
Rituximab-eligible patients					
1	Baricitinib (4 mg or 2 mg QD)+ methotrexate	Tocilizumab+ methotrexate	Methotrexate	Palliative care	Not applicable
2	Rituximab+ methotrexate	Tocilizumab+ methotrexate	Methotrexate	Palliative care	Not applicable
Rituximab-ineligible patients					
1	Baricitinib (4 mg or 2 mg QD)+ methotrexate	Tocilizumab+ methotrexate	Methotrexate	Palliative care	Not applicable
2	bDMARDs	Tocilizumab+ methotrexate	Methotrexate	Palliative care	Not applicable
3	Tocilizumab +methotrexate	Adalimumab+ methotrexate	Methotrexate	Palliative care	Not applicable

Cost-effectiveness analyses

- Cost-effectiveness results for **4 populations**:
  1. Moderate RA cDMARD-IR
  2. Severe RA cDMARD-IR
  3. Severe RA bDMARD-IR RTX-eligible
  4. Severe RA bDMARD-IR RTX-ineligible

- Deterministic results in the base case produced by simulating 27,500 patients

- Probabilistic sensitivity analyses for severe cDMARD-IR and bDMARD-IR, RTX-ineligible populations based on 500 patients simulated in each of the 1,000 iterations

1. Moderate RA cDMARD-IR

Company base-case cost effectiveness results: deterministic

Interventions	Total QALYs	Total LYG	Total costs (£)	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)
Intensive cDMARDs→ methotrexate→palliative care	[redacted]	16.04	[redacted]	[redacted]	[redacted]	-
Baricitinib+methotrexate→ intensive cDMARDs→ methotrexate→palliative care	[redacted]	16.03	[redacted]	[redacted]	[redacted]	37,420

- Providing baricitinib + methotrexate before cDMARDs results in [redacted] additional QALYs gained at an additional cost of [redacted] resulting in an ICER of £37,420 per QALY gained compared with current practice
- The company did not present probabilistic results for this population

2. Severe RA cDMARD-IR

Company base-case cost effectiveness results: deterministic

Interventions*	Total QALYs	Total LYG	Total costs (£)	Inc. QALYs	Inc. costs (£)	Inc. analysis
IFX-b+MTX	[redacted]	14.73	[redacted]	[redacted]	[redacted]	Dominated
ABA SC+MTX	[redacted]	14.73	[redacted]	[redacted]	[redacted]	Dominated
GOL+MTX	[redacted]	14.73	[redacted]	[redacted]	[redacted]	Dominated
ADA+MTX	[redacted]	14.73	[redacted]	[redacted]	[redacted]	Dominated
ETN-b+MTX	[redacted]	14.73	[redacted]	[redacted]	[redacted]	Dominated
TCZ IV+MTX	[redacted]	14.73	[redacted]	[redacted]	[redacted]	Dominated
BARI+MTX	[redacted]	14.73	[redacted]	[redacted]	[redacted]	Baseline
CTZ+MTX	[redacted]	14.73	[redacted]	[redacted]	[redacted]	£18,400

*All treatments followed by sequence RTX+MTX→TCZ IV+MTX→MTX→PALL except TCZ IV+MTX, which is followed by RTX+MTX→ADA+MTX→MTX→ PALL
Note: Does not include the confidential PASs for ABA and TCZ
Dominated: Treatment is less effective and more costly than an alternative

Confidential

2. Severe RA cDMARD-IR

Company base-case cost effectiveness results: probabilistic

Interventions*	Total QALYs	Total LYG	Total costs (£)	Inc. QALYs	Inc. costs (£)	Inc. analysis
IFX-b+MTX	[redacted]	14.71	[redacted]	[redacted]	[redacted]	Dominated
ABA SC+MTX	[redacted]	14.70	[redacted]	[redacted]	[redacted]	Dominated
ADA+MTX	[redacted]	14.71	[redacted]	[redacted]	[redacted]	Dominated
GOL+MTX	[redacted]	14.70	[redacted]	[redacted]	[redacted]	Dominated
ETN-b+MTX	[redacted]	14.70	[redacted]	[redacted]	[redacted]	Dominated
TCZ IV+MTX	[redacted]	14.70	[redacted]	[redacted]	[redacted]	Dominated
BARI+MTX	[redacted]	14.70	[redacted]	[redacted]	[redacted]	Baseline
CTZ+MTX	[redacted]	14.70	[redacted]	[redacted]	[redacted]	£18,414

*All treatments followed by sequence RTX+MTX→TCZ IV+MTX→MTX→PALL except TCZ IV+MTX, which is followed by RTX+MTX→ADA+MTX→MTX→ PALL
Note: Does not include the confidential PASs for ABA and TCZ

3. Severe RA bDMARD-IR rituximab-eligible

Company base-case cost effectiveness results: deterministic

Interventions*	Total QALYs	Total LYG	Total costs (£)	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)
Baricitinib+ methotrexate	[redacted]	13.49	[redacted]	[redacted]	[redacted]	Dominated
Rituximab+ methotrexate	[redacted]	13.51	[redacted]	[redacted]	[redacted]	-
*All treatments followed by sequence TCZ IV+MTX→MTX→PALL Note: Confidential PAS for TCZ IV not included						

- The company did not present probabilistic results for this population

Confidential

4. Severe RA bDMARD-IR rituximab-ineligible

Company base-case cost effectiveness results: deterministic

Interventions*	Total QALYs	Total LYG	Total costs (£)	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)	ICER *vs* BARI + MTX (£/QALY)
GOL+MTX	[redacted]	13.49	[redacted]	[redacted]	[redacted]	Dominated	Dominated
BARI + MTX	[redacted]	13.49	[redacted]	[redacted]	[redacted]	Baseline	
ABA SC+MTX	[redacted]	13.49	[redacted]	[redacted]	[redacted]	Dominated	484,782
IFX-b+MTX†	[redacted]	13.49	[redacted]	[redacted]	[redacted]	Dominated	34,942†
TCZ IV+MTX	[redacted]	13.49	[redacted]	[redacted]	[redacted]	Dominated	36,757
ADA+MTX†	[redacted]	13.49	[redacted]	[redacted]	[redacted]	Dominated	27,008†
ETN-b+MTX†	[redacted]	13.49	[redacted]	[redacted]	[redacted]	Extendedly dominated	19,874†
CTZ+MTX†	[redacted]	13.49	[redacted]	[redacted]	[redacted]	16,201	16,201†

*All treatments followed by sequence TCZ IV+MTX→MTX→PALL except TCZ IV+MTX, which is followed by ADA+MTX→MTX→ PALL. Does not include the confidential PASs for ABA and TCZ. †Efficacy estimates assumed to be equal to those for the severe cDMARD-IR population. Extendedly dominated: The intervention has an ICER greater than an ICER of a more effective intervention

Confidential

4. Severe RA bDMARD-IR rituximab-ineligible

Company base-case cost effectiveness results: probabilistic

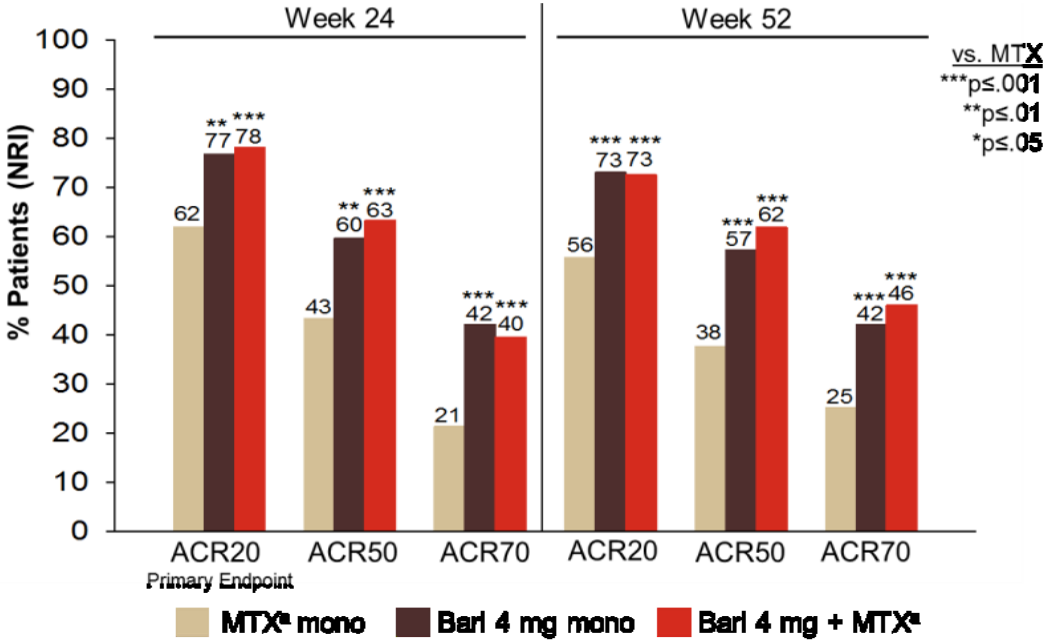
Interventions*	Total QALYs	Total LYG	Total costs (£)	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)	ICER *vs* BARI + MTX (£/QALY) ‡
GOL+MTX	[redacted]	13.53	[redacted]	[redacted]	[redacted]	Dominated	20,824§¶
TCZ IV+MTX	[redacted]	13.52	[redacted]	[redacted]	[redacted]	Dominated	19,962§¶
ADA+MTX†	[redacted]	13.53	[redacted]	[redacted]	[redacted]	Dominated	19,947†§¶
ETN-b+MTX†	[redacted]	13.53	[redacted]	[redacted]	[redacted]	Baseline	19,457†§¶
IFX-b+MTX†	[redacted]	13.52	[redacted]	[redacted]	[redacted]	Extendedly dominated	5,367†¶
BARI + MTX	[redacted]	13.52	[redacted]	[redacted]	[redacted]	Extendedly dominated	
ABA SC+MTX	[redacted]	13.52	[redacted]	[redacted]	[redacted]	Dominated	442,044
CTZ+MTX†	[redacted]	13.52	[redacted]	[redacted]	[redacted]	18,738	17,149†

*All treatments followed by sequence TCZ IV+MTX→MTX→PALL except TCZ IV+MTX, which is followed by ADA+MTX→ MTX→PALL. Does not include the confidential PASs for ABA and TCZ; †Efficacy estimates assumed to be equal to those for the severe cDMARD-IR population. ‡ Approximate ICERs calculated by the ERG based on total costs and QALYs reported by the company; § These interventions are less effective than BARI + MTX and therefore the ICERs represent savings per QALY los
error in the PSA

Confidential

Baricitinib monotherapy

- The company did not make a case for baricitinib monotherapy
  - The ERG point out that data from RA-BEGIN showed that the addition of methotrexate to baricitinib 4 mg did not produce a marked improvement over baricitinib monotherapy



Cost effectiveness summary: Company estimates

Population	Summary (ICERs)
1. Moderate RA cDMARD-IR	• BARI + MTX *vs* intensive cDMARDs = £37,420
2. Severe RA cDMARD-IR	• BARI + MTX dominated all comparators • **Except** BARI + MTX *vs* CTZ + MTZ = £18,400
3. Severe RA bDMARD-IR RTX-eligible	• BARI + MTX dominated by RTX + MTX
4. Severe RA bDMARD-IR RTX-ineligible	• BARI + MTX less effective and less expensive than all comparators • **Except** BARI + MTX dominated GOL + MTX

- The confidential PASs for abatacept and tocilizumab were not included in these analyses.

Company scenario analyses: Scenario 1

Scenario

- Patients on cDMARDs or palliative care had a linear increase in their HAQ scores at an annual rate of 0.045 and 0.06, respectively (based on Malottki *et al*., 2011) instead of using the latent class approach

Impact on results

- For the moderate population, the ICER for baricitinib + methotrexate compared with intensive cDMARDs decreased from £37,420 to £20,965 per QALY gained
- Small impact on the severe populations, producing slightly lower ICERs for the most effective drugs

- The ERG states that the Malottki *et al*. 2011 mapping is as not as robust as that of Hernández Alava *et al*. 2013

Company scenario analyses: Other scenarios

- HAQ score for baricitinib + methotrexate deteriorates (increases) at half of rate assumed for cDMARDs
- HAQ score improvements for baricitinib calculated from trial data rather than BSRBR database
- Different time to treatment discontinuation for patients on baricitinib
- Alternative methods used to map HAQ scores to the EQ-5D
- Serious adverse events accounted for
- Tapering baricitinib from 4 mg QD to 2 mg QD
- Head-to-head comparison between baricitinib + methotrexate and adalimumab + methotrexate

- The ERG states that these scenarios are unlikely to change the conclusions of the cost-effectiveness analyses

ERG exploratory analyses

- ERG undertook few exploratory analyses
- ERG identified 2 programming errors that affected the company's PSA results and re-ran the PSA
  - 1. Error resulted in patients on golimumab, etanercept, adalimumab and infliximab (all with methotrexate) never achieving a good or moderate EULAR response
    - Also affects the sequence starting with tocilizumab + methotrexate, given that adalimumab + methotrexate is included in the sequence
  - 2. Error in the calculations of the CODA samples for moderate response probability for baricitinib + methotrexate in the severe cDMARD-IR population

Severe RA cDMARD-IR

ERG exploratory analyses: Error affected the PSA

Interventions*	Total QALYs	Total LYG	Total costs (£)	Inc. QALYs	Inc. costs (£)	Inc. analysis
IFX-b+MTX	[redacted]	14.72	[redacted]	[redacted]	[redacted]	Dominated
ABA SC+MTX	[redacted]	14.71	[redacted]	[redacted]	[redacted]	Dominated
ADA+MTX	[redacted]	14.71	[redacted]	[redacted]	[redacted]	Dominated
GOL+MTX	[redacted]	14.71	[redacted]	[redacted]	[redacted]	Dominated
TCZ IV+MTX	[redacted]	14.71	[redacted]	[redacted]	[redacted]	Dominated
ETN-b+MTX	[redacted]	14.71	[redacted]	[redacted]	[redacted]	Dominated
BARI+MTX	[redacted]	14.71	[redacted]	[redacted]	[redacted]	Baseline
CTZ+MTX	[redacted]	14.71	[redacted]	[redacted]	[redacted]	£18,135

*All treatments followed by sequence RTX+MTX→TCZ IV+MTX→MTX→PALL except TCZ IV+MTX, which is followed by RTX+MTX→ADA+MTX→MTX→PALL. Confidential PAS for TCZ IV not included.
Note: Does not include the confidential PASs for ABA and TCZ

- Minimal impact on the results

Confidential

Severe RA bDMARD-IR rituximab-ineligible

ERG exploratory analyses: Error affected the PSA

Interventions*	Total QALYs	Total LYG	Total costs (£)	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)	ICER *vs* BARI+MTX (£/QALY)
GOL+MTX	[redacted]	13.52	[redacted]	[redacted]	[redacted]	Baseline	18,805 §
BARI+MTX	[redacted]	13.52	[redacted]	[redacted]	[redacted]	Extendedly dominated	
ABA SC+MTX	[redacted]	13.52	[redacted]	[redacted]	[redacted]	Dominated	454,225
TCZ IV+MTX	[redacted]	13.52	[redacted]	[redacted]	[redacted]	Dominated	37,063
ADA+MTX †	[redacted]	13.52	[redacted]	[redacted]	[redacted]	Dominated	21,494†
ETN-b+MTX†	[redacted]	13.52	[redacted]	[redacted]	[redacted]	£15,527	10,197†
IFX-b+MTX†	[redacted]	13.52	[redacted]	[redacted]	[redacted]	Dominated	35,045†
CTZ+MTX†	[redacted]	13.52	[redacted]	[redacted]	[redacted]	£20,170	16,962†

*All treatments followed by sequence TCZ IV+MTX→MTX→PALL except TCZ IV+MTX, which is followed by ADA+MTX→MTX→ PALL. Does not include the confidential PASs for ABA and TCZ. †Efficacy estimates assumed to be equal to those for the severe cDMARD-IR population. § GOL+MTX is less effective than BARI+MTX; ICER represents savings per QALY lost compared with BARI+MTX

- Important impact in the sequences effected. Markedly higher costs and QALYs gained for tocilizumab, etanercept biosimilar, infli[redacted] and adalimumab (all with methotrexate)

Confidential

Cost effectiveness summary: ERG estimates

- In the moderate RA population, the AG in TA375 estimated that the median ICER of bDMARDs compared with cDMARDs was in the region of £50,000 per QALY gained
- In the severe cDMARD-IR population who can tolerate rituximab, [redacted]
- In severe cDMARD-IR patients and in bDMARD-IR patients for whom rituximab is contraindicated or not tolerated, [redacted]
- The ERG states that the results will also apply to baricitinib monotherapy

Impact of the confidential PASs

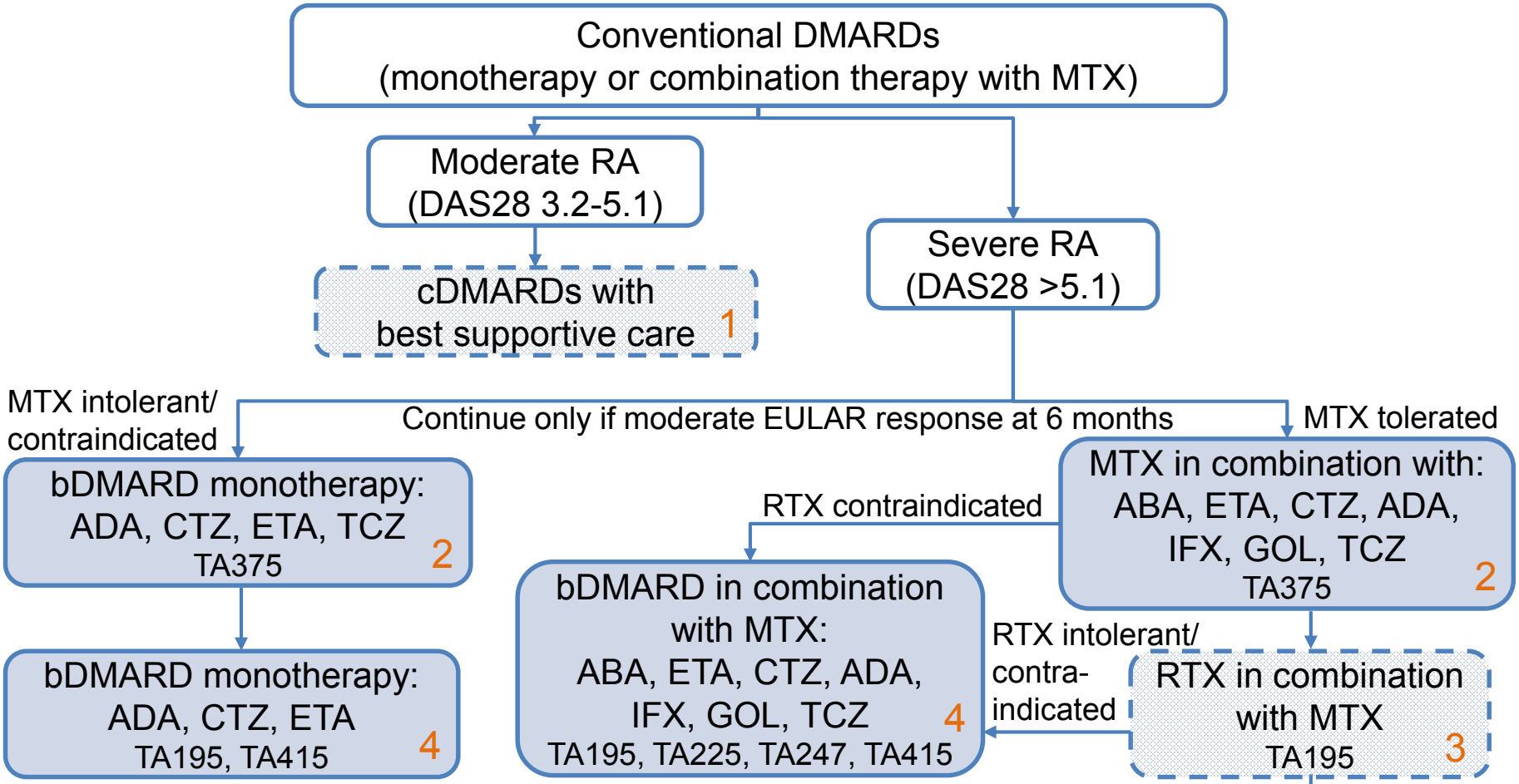
- Certolizumab pegol and golimumab have non-confidential PASs
  - Incorporated into the above analyses
- Abatacept and tocilizumab have confidential simple discount PASs
- ERG re-ran analyses for all 3 severe populations: cDMARD-IR, bDMARD-IR rituximab-eligible, and bDMARD-IR rituximab-ineligible
  - Neither abatacept nor tocilizumab are included as comparators in the severe, bDMARD-IR, RTX-eligible population
  - Tocilizumab is included in the sequence of both the cDMARD-IR and bDMARD-IR rituximab ineligible populations
- The analysis for the moderate population was not re-run, as it was not affected by the PAS of abatacept or tocilizumab
- All other sequences are affected by the tocilizumab PAS, as it is included either as first or last bDMARD in every sequence
- All the analyses were run using the original company model

Key issues: Cost effectiveness

- Is baricitinib comparable to the bDMARDs in both clinical effectiveness and cost effectiveness?

- Has the case for baricitinib monotherapy been made?

Treatment pathway



- Shaded boxes with solid line=Proposed positions in the pathway where the ERG state BARI is likely to be cost effective (assumed for BARI monotherapy based on TA375); shaded boxes with broken line=Proposed positions in the pathway where the ERG state BARI is unlikely to be cost effective.
- 1-4=Patient populations referred to in the company submission
- TOFA is currently being appraised by NICE at the same positions as BARI in the treatment pathway