Projector and public slides

Lead team presentation

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs

Cost effectiveness

1st Appraisal Committee meeting, 26 July 2017

Committee D

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

Lead team: Rachel Elliott

Key issues: Cost effectiveness

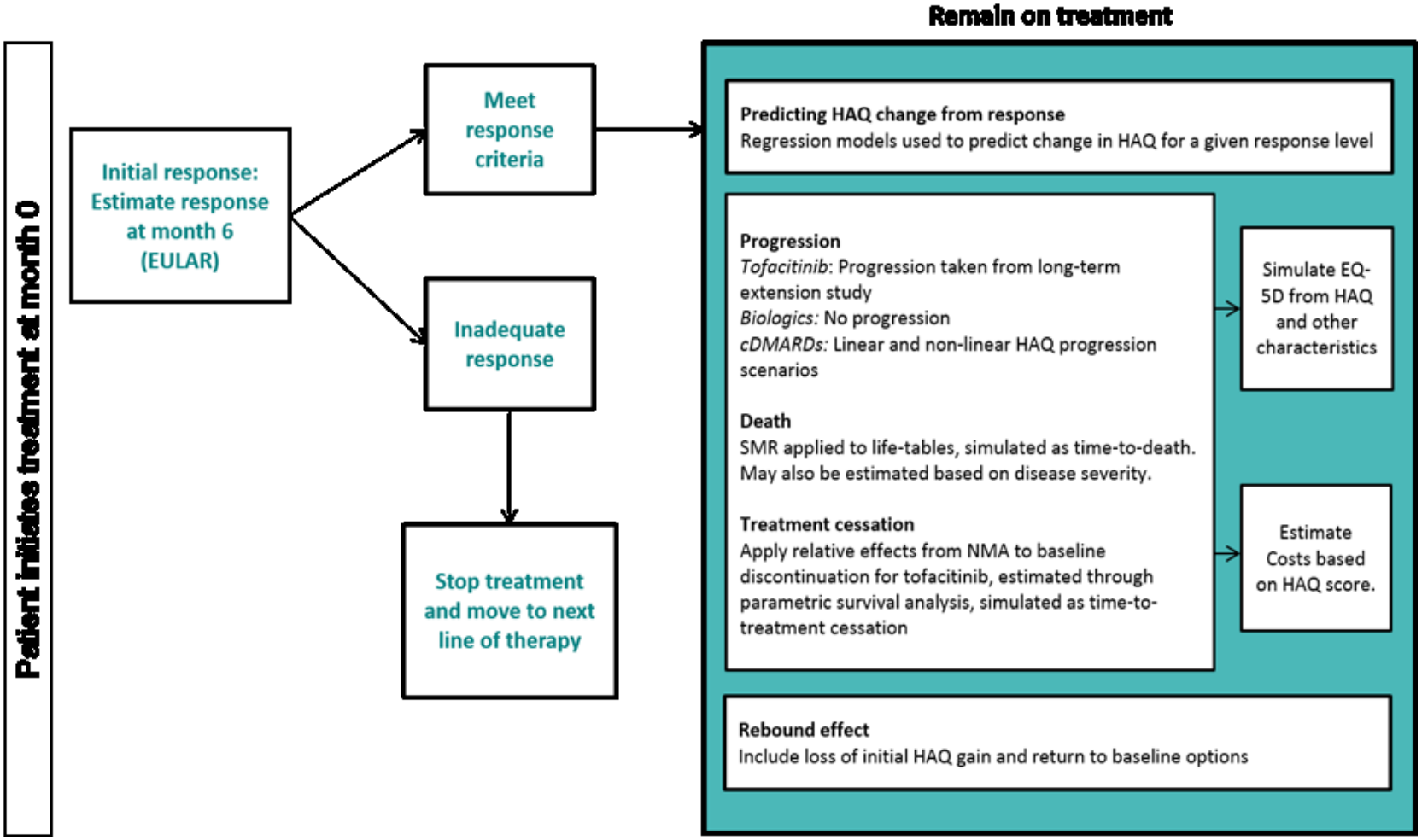
- Is tofacitinib comparable to the bDMARDs in both clinical effectiveness and cost effectiveness?
- Has the case for tofacitinib monotherapy been proven?
- Do the ERG's sequences better reflect the clinical practice than the ones developed by the AG for TA375 (and accepted in BARI appraisal)?
- Are the deterministic results (and not probabilistic) appropriate for decision making?

Company's model structure (I)

- Patient-level simulation model, in line with TA375 and BARI appraisal
- Models individual patients, using TOF-specific data (TA375 used BSRBR data)
- Uses treatment sequences (sequences different from BARI appraisal)
- Estimated treatment effect (EULAR response) from regression model fitted to ORAL trials (TOF, TOF + MTX) and company NMA (comparators) (EULAR response directly from trials in BARI)
- Lifetime time horizon with a maximum age of 100 years (45 years in BARI appraisal)

BSRBR: British Society for Rheumatology Biologic Register

Company's model structure (II)



Resources and costs

- Company model includes costs associated with drug acquisition, drug administration and monitoring, and hospitalisation and serious infections
- TOF has a confidential PAS
- PASs for CTZ and GOL were incorporated in the CS (complex PASs – not confidential). Confidential simple discount PASs for ABA and TCZ could not be included. All PAS analyses are included only in PART 2
- Palliative care cost was taken from Pfizer Rheumatoid Arthritis Model, rather than TA375; the different monthly prices (£44 compared with £60) not expected to affect the ICER significantly
- Non-drug costs were largely based on TA375, inflated to 2014/15/16 prices

Clinical assumptions (I)

Model outcome	Company submission and *ERG critique*	TA375 and BARI appraisal
EULAR response at Month 6	TOF + MTX (from ORAL trials): regression model *ERG: TOF efficacy assumed equal TOF+MTX* Comparators: applying ORs from NMA to probabilities of EULAR responses for TOF+MTX *ERG: SSZ+HCQ efficacy assumed equal placebo*	EULAR responses from NMA, or mapped from ACR to EULAR response (when EULAR response not available)
Treatment duration	For patients who achieved good or moderate EULAR response and stay on treatment: • Individual parametric survival curve fitted to trial data, independent of treatment • Baseline characteristics as predictive covariates • Best statistical fit with log-normal distribution For patients who fail to achieve a moderate or good response: • Discontinue treatment at 6 months and start the next treatment in the sequence.	•Same approach, with BSRBR data •No baseline characteristic •Gamma distribution (TA375) •Weibull distribution (BARI appraisal)

Clinical assumptions (II)

Model outcome	Company submission and *ERG critique*	TA375 BARI appraisal
Changes in HAQ-DI from the long-term extension studies	***HAQ improvement upon treatment response:*** Patients assumed to have a reduction in HAQ score when achieved a moderate (-0.317) or good (-0.672) response at 6 months. Remain on treatment until loss of efficacy, incidence of AEs or death	Same approach, with BSRBR data
	HAQ trajectory following initial response: Base case: • bDMARD and TOF: no HAQ progression, assumed constant • cDMARD: (1) HAQ change for average patients (Norton *et al*.); (2) HAQ change for 'rapid progressor' patients (NICE DSU) *ERG: 'rapid progressor' group not considered because couldn't be identified in advance* • Scenario analysis: linear HAQ progression for cDMARD, yearly rate increases of 0.045 for LEF, and 0.06 for PALL *ERG disagrees with the scenario analyses as HAQ-DI progression has been proven to be non-linear in TA375. Corrected by company at clarification.*	Base case: • same approach • (1) Norton *et al* used and modified
	HAQ trajectory prior to treatment cessation: Linear loss of the HAQ improvement over 6 months: resulting values rounded to nearest valid HAQ score *ERG disagrees with the rounding to the nearest score, this was not addressed by company at clarification. ERG assessed the impact of this change in exploratory analyses.*	HAQ loss occurred at time of discontinuation, HAQ-DI scores rounded to higher or lower valid HAQ-DI score

ERG critique on company's assumptions

- Relevant comparators recommended by NICE not included in the analyses*
- SC formulations of ABT and TCZ as well as RTX biosimilar Truxima have not been included in the analyses
- Errors in the company's sequencing*
- Efficacy of TOF assumed to be the same as TOF+MTX; ERG notes that ORAL Strategy showed that TOF monotherapy was shown not to be non-inferior to TOF + MTX and ADA + MTX and NMA results show that TOF monotherapy results in slightly lower probabilities of response than TOF + MTX (assumption likely to have relatively low impact) *[addressed by ERG, and company when they corrected their submission error]*
- Efficacy for SSZ+HCQ was assumed to be the same as placebo (likely to underestimate the ICER for TOF *vs* SSZ)
- Rounding the HAQ-DI values to the nearest valid HAQ-DI score (rather than allowing the valid HAQ-DI score to be sampled based on the continuous HAQ-DI value) might lead to biased estimations of HAQ-DI scores, as values might be rounded up more often than rounded down or vice versa, depending on the size of changes *[addressed by ERG]*

*The company addressed the comparators and sequencing issues in the clarification response but didn't provide the full set of analyses for their revised base case

Company's error

- On 17 July 2017, the company informed NICE that they had identified an error (impacting NMA and cost-effectiveness results) in their submission.
- Further, the company increased the level of PAS discount.
- The company provided revised results including the ERG's preferred assumption of ORs calculated compared to TOF+MTX[1]. The other ERG's preferred assumption (probabilistic HAQ-DI rounding) was not incorporated due to time constraints.
- The ERG noted that the sequences evaluated in the company's corrected submission of 20 July included sequences that were not recommended by NICE, these had been amended in the ERG analyses
- Results presented in the next slides are as follows:

Results	Analysis
Company's corrected base case (not presented)	• Analysis provided at clarification stage (Norton *et al.* progression for all cDMARD incl. palliative care, activating 'prior_bdmard' flag after the 1st biologic or JAK inhibitor when calculating the probabilities of EULAR response) • OR calculated compared to TOF + MTX
ERG's corrected base case	Same as company's corrected base case + • correction of sequencing (use sequence recommended by NICE) • probabilistic HAQ-DI rounding

[1] The ERG has not verified this due to time constraint and note that "It is believed that the results presented by the company have incorporated the ERG change removing the assumption that TOF monotherapy was of equal efficacy to TOF+MTX".

ERG additional analyses - sequences for severe RA, cDMARD-IR

Lines	1st	2nd	3rd	4th	5th	6th	7th	8th	9th
Seq.	Combination therapy (MTX-eligible)								
	MTX	***ABT+ MTX***	***ADA+ MTX***	***CTZ+ MTX***	***GOL+ MTX***	***TCZ+ MTX***	***TOF+ MTX***	***ETNb+ MTX***	***INFb+ MTX***
1	MTX	ABT+ MTX	ADA+ MTX	CTZ+MTX	GOL+ MTX	TCZ+ MTX	TOF+ MTX	ETNb+ MTX	INF+ MTX
2	NBT	RTX+ MTX	RTX+ MTX	RTX+MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX
3		TCZ+ MTX	TCZ+ MTX	TCZ+ MTX	TCZ+ MTX	MTX	TCZ+ MTX	TCZ+ MTX	TCZ+ MTX
4		MTX	MTX	MTX	MTX	NBT	MTX	MTX	MTX
5		NBT	NBT	NBT	NBT		NBT	NBT	NBT

	Monotherapy (MTX-ineligible)				
Seq.	***SSZ***	***TCZ***	***TOF***	***ETNb***	***ADA***
1	SSZ	TCZ	TOF	ETNb	ADA
2	NBT	ETNb	ETNb	ADA	ETNb
3		SSZ	SSZ	SSZ	SSZ
4		NBT	NBT	NBT	NBT

ERG additional analyses - sequences for severe RA, bDMARD-IR

Sequence	1st	2nd	3rd	4th
Rituximab-eligible patients				
Sequence	***RTX, TCZ***	***RTX, TOF***	***RTX, TOF, TCZ***	***RTX, TCZ, TOF***
1	RTX+MTX	RTX+ MTX	RTX+MTX	RTX+MTX
2	TCZ+MTX	TOF+ MTX	TOF+MTX	TCZ+MTX
3	MTX	MTX	TCZ+MTX	TOF+MTX
4	NBT*	NBT*	MTX	MTX
5			NBT*	NBT*
Rituximab-ineligible patients				
Sequence	***TOF+MTX***	***ABT+MTX***	***TCZ+MTX***	***GOL+MTX***
1	TCZ+MTX	TCZ+MTX	GOL+MTX	TCZ+MTX
2	MTX	MTX	MTX	MTX
3	NBT*	NBT*	NBT*	NBT*

*NBT: non-biologic treatment

ERG additional analyses - sequences for moderate RA, cDMARD-IR

	1st	2nd	1st
Sequence	**Moderate†**		**Severe**
	MTX	***TOF+MTX***	***ETNb+MTX***
1	MTX	TOF+MTX	ETNb+MTX
2	NBT	MTX	RTX+MTX
3		NBT	TCZ+MTX
4			DMC‡
5			NBT

Abbreviations: cDMARD, conventional disease modifying anti-rheumatic drug; DMC, DMARD combination; NBT, non-biologic treatment; TOF, tofacitinib. ETNb, etanercept biosimilar; MTX, methotrexate; RTX, rituximab; TCZ, tocilizumab.

†Current NICE guidance for patients with moderate disease recommends offering a combination of DMARDs, to include methotrexate and at least one other DMARD plus short-term glucocorticoids. ‡Combination therapy will still be possible with cDMARD but will not include MTX.

Severe RA, cDMARD-IR, MTX-eligible

ESTIMATE 1*

	Total		Incremental		Deterministic ICER (£/QALY)	
Sequences	QALYs	Costs	QALYs	Costs	Incremental	Pairwise vs TOF+MTX
MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	£32,826†
TCZ+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£19,521†
IFXb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£30,883	-
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£1,041,718
CTZ+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£225,613
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£165,231	£165,231

*Estimate 1 is based on company's NMA
†ICERs in the south-western quadrant, representing cost savings per QALY lost.
TOF: tofacitinib; ABT: abatacept; TCZ: tocilizumab; ADA: adalimumab; CTZ: certolizumab pegol, ETNb: etanercept biosimilar; GOL: golimumab; IFXb: infliximab biosimilar; RTX: rituximab; MTX: methotrexate;

ERG's corrected base case
with PAS for TOF (new), GOL, CZP

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Severe RA, cDMARD-IR, MTX-eligible

ESTIMATE 2*

	Total		Incremental		Deterministic ICER (£/QALY)	
Sequences	QALYs	Costs	QALYs	Costs	Incremental	Pairwise vs TOF+MTX
MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	£29,098†
TCZ+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£15,372†
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£29,098	-
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£197,881
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Ext.dominated	£118,648
CTZ+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£107,436	£107,436

*Estimate 2 is based on NMA requested at clarification stage
†ICERs in the south-western quadrant, representing cost savings per QALY lost.
TOF: tofacitinib; ABT: abatacept; TCZ: tocilizumab; ADA: adalimumab; CTZ: certolizumab pegol, ETNb: etanercept biosimilar; GOL: golimumab; IFXb: infliximab biosimilar; RTX: rituximab; MTX: methotrexate;

Severe RA, cDMARD-IR, MTX-ineligible

ESTIMATE 1*

	Total		Incremental		Deterministic ICER (£/QALY)	
Sequences	QALYs	Costs	QALYs	Costs	Incremental	Pairwise vs TOF
SSZ	[redacted]	[redacted]	[redacted]	[redacted]	-	£31,996†
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£31,996	-
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£149,411
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£117,875
TCZ	[redacted]	[redacted]	[redacted]	[redacted]	£38,406	£64,070

ESTIMATE 2*

	Total		Incremental		Deterministic ICER (£/QALY)	
Sequences	QALYs	Costs	QALYs	Costs	Incremental	Pairwise vs TOF
SSZ	[redacted]	[redacted]	[redacted]	[redacted]	-	£32,427†
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£32,427	-
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£112,745
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£127,182
TCZ	[redacted]	[redacted]	[redacted]	[redacted]	£63,663	£63,663

*Estimate 1 is based on the company's NMA; Estimate 2 is based on NMA requested at clarification stage.
†ICERs in the south-western quadrant, representing cost savings per QALY lost.
TOF: tofacitinib; TCZ: tocilizumab; ADA: adalimumab; ETNb: etanercept biosimilar

Severe RA, bDMARD-IR, RTX-eligible

ESTIMATE 1*

	Total		Incremental		Deterministic ICER (£/QALY)	
Sequences	**QALYs**	**Costs**	**QALYs**	**Costs**	**Incremental**	**Pairwise vs RTX,TCZ‡**
RTX,TOF	[redacted]	[redacted]	[redacted]	[redacted]	-	£80,442†
TOF,TCZ	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
RTX,TCZ‡	[redacted]	[redacted]	[redacted]	[redacted]	Ext dominated	-
RTX,TOF,TCZ	[redacted]	[redacted]	[redacted]	[redacted]	£44,452	£25,642
RTX,TCZ,TOF	[redacted]	[redacted]	[redacted]	[redacted]	£985,635	£33,442

ESTIMATE 2*

only the "RTX, TCZ" sequence is recommended by NICE

	Total		Incremental		Deterministic ICER (£/QALY)	
Sequences	**QALYs**	**Costs**	**QALYs**	**Costs**	**Incremental**	**Pairwise vs RTX,TCZ‡**
TOF,TCZ	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
RTX,TOF	[redacted]	[redacted]	[redacted]	[redacted]	-	£137,483†
RTX,TCZ‡	[redacted]	[redacted]	[redacted]	[redacted]	Ext dominated	-
RTX,TOF,TCZ	[redacted]	[redacted]	[redacted]	[redacted]	£43,530	£27,941
RTX,TCZ,TOF	[redacted]	[redacted]	[redacted]	[redacted]	£59,237	£32,845

**Estimate 1 is based on the company's NMA; Estimate 2 is based on NMA requested at clarification stage. RTX, TOF and TCZ are provided with concomitant MTX. †ICERs in the south-western quadrant, representing cost savings per QALY lost; ‡ Currently recommended sequences, RTX: rituximab; TOF: tofacitinib; TCZ: tocilizumab; MTX: methotrexate

Severe RA, bDMARD-IR, RTX-ineligible

ESTIMATE 1*

	Total		Incremental		Deterministic ICER (£/QALY)	
Sequences	QALYs	Costs	QALYs	Costs	Incremental	Pairwise vs TOF+MTX
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	-
TCZ+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£73,446	£74,940

ESTIMATE 2*

	Total		Incremental		Deterministic ICER (£/QALY)	
Sequences	QALYs	Costs	QALYs	Costs	Incremental	Pairwise vs TOF+MTX
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	-
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£705,993
TCZ+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£134,099
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£38,017	£50,811

**Estimate 1 is based on the company's NMA; Estimate 2 is based on NMA requested at clarification stage. †ICERs in the south-western quadrant, representing cost savings per QALY lost.

TOF: tofacitinib; TCZ: tocilizumab; GOL: golimumab; ABT: abatacept; MTX: methotrexate; ETNb: etanercept biosimilar

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Moderate RA, cDMARD-IR

ESTIMATE 1*

	Total		Incremental		Deterministic ICER (£/QALY)
Sequences	**QALYs**	**Costs**	**QALYs**	**Costs**	**Incremental**
MTX	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£39,044

ESTIMATE 2*

	Total		Incremental		Deterministic ICER (£/QALY)
Sequences	**QALYs**	**Costs**	**QALYs**	**Costs**	**Incremental**
MTX	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£41,701

*Estimate 1 is based on the company's NMA; Estimate 2 is based on NMA requested at clarification stage.
TOF: tofacitinib; MTX: methotrexate;

ICER summary (with TOF new PAS and CZP, GOL PASs)		
Populations	**TOFACITINIB (ERG's corrected analysis)**	**BARICITINIB* (Committee)**
Severe, cDMARD-IR, MTX-eligible	• TOF+MTX dominated IFXb, ADA, ABT (+MTX) • GOL, ETNb, CTZ (+MTX) *vs* TOF+MTX >£100k • Cost saving produced by MTX, TCZ+MTX	• BARI + MTX dominated all comparators **except** BARI + MTX *vs* CTZ + MTZ = £18,400
Severe, cDMARD-IR, MTX-ineligible	• ETNb, ADA, TCZ *vs* TOF >£60k • Cost saving produced by SSZ • CTZ excluded	*Not assessed*
Severe, bDMARD-IR RTX-eligible	Cost saving produced by "RTX, TOF"	BARI + MTX dominated by RTX + MTX
	BARI submission did not look at other sequences with BARI elsewhere	
Severe, bDMARD-IR RTX-ineligible	• TOF + MTX less effective and less expensive than all comparators (estimate 2) **except** TOF + MTX dominated GOL + MTX • ADA, IFX, CTZ (+MTX) excluded	• BARI + MTX less effective and less expensive than all comparators **except** BARI + MTX dominated GOL + MTX
Severe, bDMARD-IR MTX ineligible	*Not assessed*	*Not assessed*
Moderate, cDMARD-IR*	TOF + MTX *vs* MTX >35k£	BARI + MTX *vs* intensive cDMARDs = £50,000
	BARI submission did not progress moderate patients onto bDMARDs when they became severe	

*Baricitinib isn't a comparator in the scope but this information is included for reference

Innovation

- New mechanism of action JAK inhibitor, offers new class of innovative therapy that could be positioned post DMARD failure or post first TNF failure
- Oral treatment rather than SC or IV - imply no cost associated to administration (e.g., infusion, sub-cut route, home care delivery)
- Additional option to biologic therapy

Equality and diversity

- No issues identified

Key issues: Cost effectiveness

- Is tofacitinib comparable to the bDMARDs in both clinical effectiveness and cost effectiveness?
- Has the case for tofacitinib monotherapy been proven?
- Do the ERG's sequences better reflect the clinical practice than the ones developed by the AG for TA375 (and accepted in BARI appraisal)?
- Are the deterministic results (and not probabilistic) appropriate for decision making?