NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pre-meeting briefing
Rheumatoid arthritis - tofacitinib citrate

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

COMMON ABBREVIATIONS (shaded rows contain comparator technologies)

ABA or ABT	Abatacept
ACR	American College of Rheumatology
ACR 20/50/70	20/50/70% improvement in the ACR score
ADA	Adalimumab
AE	Adverse event
AIC	Akaike information criterion
bDMARD	Biologic disease-modifying anti-rheumatic drug
BNF	British National Formulary
BSR	British Society for Rheumatology
BSRBR	British Society for Rheumatology Biologics Register
cDMARD	Conventional DMARD
CG	Clinical guideline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CZP	Certolizumab pegol
DAS	Disease activity score
EAM	Extra-articular manifestation
EQ-5D	EuroQol five-dimension questionnaire
ERG	Evidence Review Group

ESR	Erythrocyte sedimentation rate
ETN	Etanercept
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
GOL	Golimumab
HAQ-DI	Health Assessment Questionnaire–Disability Index
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
INF or IFX	Infliximab
IR	Insufficient response
JAK	Janus Kinase inhibitor
MTX	Methotrexate
NMA	Network Meta-analysis
QALY(s)	Quality adjusted life year(s)
SSZ or SFZ	Sulfasalazine
TNFi	Tumour necrosis factor inhibitor
TOC or TCZ	Tocilizumab
TOF	Tofacitinib

Key issues: Clinical effectiveness

- Is tofacitinib comparable to the bDMARDs in clinical effectiveness in moderate and severe rheumatoid arthritis?
  - Is the network meta-analysis a reliable estimate of the relative effect?
- Is tofacitinib effective as a monotherapy?
- Is the EULAR response derived from DAS 28 acceptable ?
- For the EULAR response outcome, does the true treatment effect lie between estimates 1 and 2, but closer to estimate 1 than 2?
- Have the crossover issues been addressed appropriately?
- Is the safety profile of tofacitinib acceptable?

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?

Rheumatoid arthritis

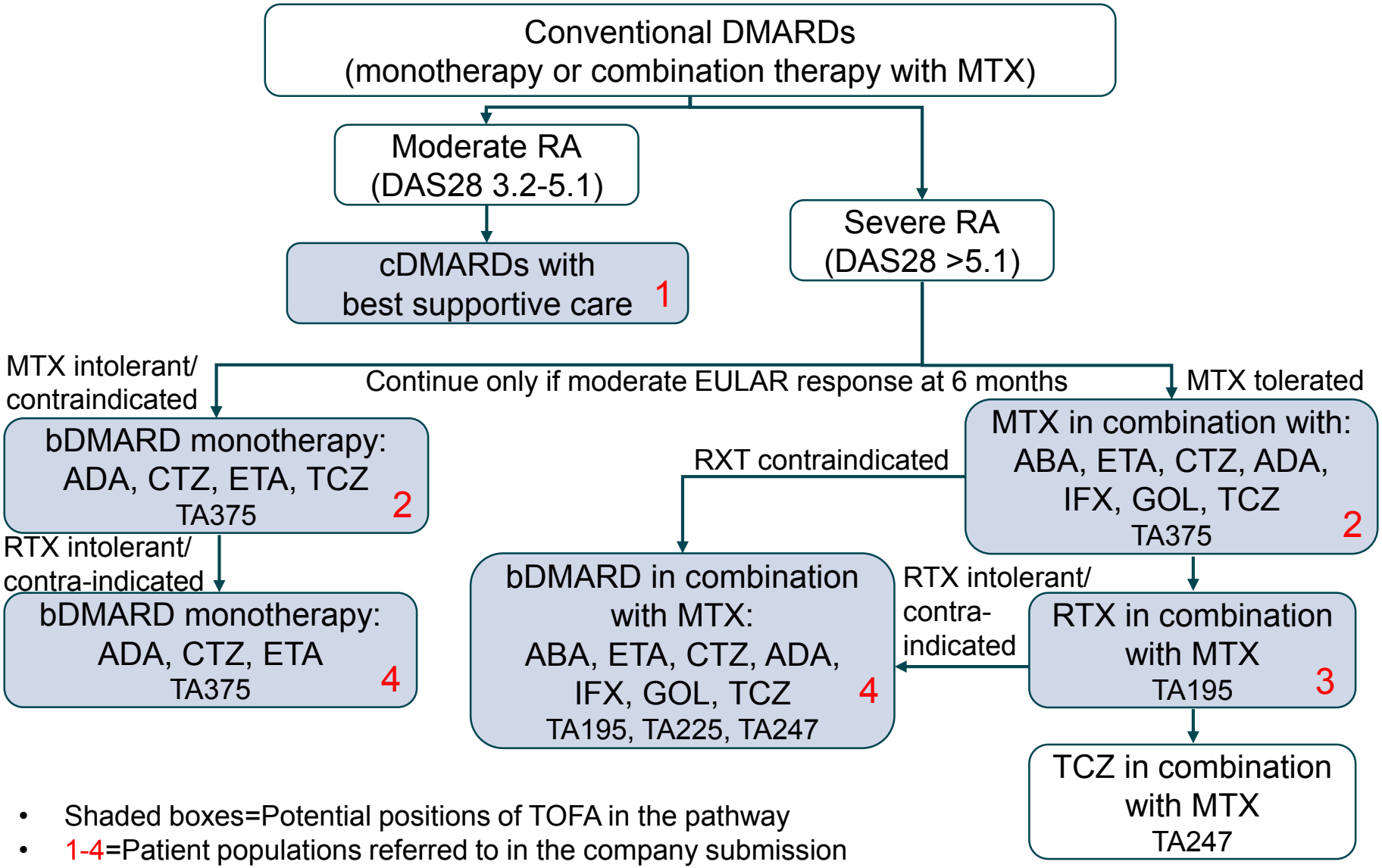
- An inflammatory autoimmune disease that typically affects the synovial tissue of the small joints of the hands and feet but can affect any synovial joint, causing swelling, stiffness, pain and progressive joint destruction.
  - Systemic disease that can affect the whole body, including the lungs, heart and eyes.
  - A chronic relapsing condition which has a pattern of flare-ups followed by periods of lower disease activity; however, for some people, the disease is constantly progressive.
- Disease severity measured using the composite disease activity score (DAS28), includes assessment of 28 joints for swelling/tenderness, the patient's assessment of health and erythrocyte sedimentation rate or C-reactive protein
  - DAS28 <3.2 indicates low disease activity, DAS28 ≥3.2 and ≤5.1 indicates moderate activity, and DAS28 >5.1 indicates high activity
- Associated with increased mortality and increasing disability, which has a severe impact on quality of life.
- No cure, treatment aims to improve quality of life and prevent or reduce joint damage

Relevant NICE technology appraisals

TA	Treatment	Population
415 2016	CTZ + MTX	Adults whose disease has responded inadequately to, or who cannot tolerate, 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)	Disease is severe (disease activity score [DAS28] >5.1) and has not responded to intensive therapy with a combination of cDMARDs
	ADA, ETN, CTZ, TCZ monotherapy	As above but for people who cannot have MTX because of contraindications or intolerance
247 2012	TCZ + MTX	Disease has responded inadequately to DMARDs and a TNF inhibitor and the person cannot have RTX because it is contraindicated or not tolerated, and TCZ is used as described for TNF inhibitor treatments in TA195, specifically the recommendations on disease activity or the disease has responded inadequately to 1 or more TNF inhibitor treatments and to RTX
225 2011	GOL + MTX	Adults whose RA has responded inadequately to other DMARDs, including a TNF inhibitor, if it is used as described for other TNF inhibitor treatments in TA195
195 2010	RTX + MTX	Adults with severe active RA with an inadequate response to, or are intolerant of, other DMARDs, including at least 1 TNF inhibitor.
	ADA, ETN, IFX, ABA (all + MTX)	As for RTX + MTX but for people who cannot have RTX because of contraindications or intolerance
	ADA, ETN monotherapy	As for RTX + MTX but for people who cannot have RTX because they have a contraindication to, or intolerance of MTX

Details of the technology	
Technology	Tofacitinib (Xeljanz, Pfizer)
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. Tofacitinib prevents full activation of lymphocytes interrupting the inflammatory process
Administration	Oral, 5 mg twice daily. Treatment is continuous (no stopping rule), but dose reduction to 5 mg once daily may be considered for people severe renal impairment (creatinine clearance <30mL/min) or moderate hepatic impairment
Acquisition cost	• List price: 5 mg x 56 tab: £690.03 (6-month treatment: £4,500.60 per patient; subsequent annual cost: £9,001.19 per patient) • **Simple PAS scheme** (discount to the list price) • **Patient funding scheme** in place to provide tofacitinib free-of-charge to the NHS during the period where reimbursement is not yet available in England and Wales.
Additional information	Tofacitinib was added to the EMA's list of medicines under additional monitoring in April 2017

Positons of tofacitinib in the treatment pathway



- Shaded boxes=Potential positions of TOFA in the pathway
- 1-4=Patient populations referred to in the company submission
- BARI is currently being appraised by NICE at the same positions as TOFA in the treatment pathway (FAD available June 2017, guidance to be published August 2017)

Potential positions for tofacitinib in the treatment pathway

Population	Comparators
1. Moderately active RA that has not responded adequately to therapy with cDMARDs (Moderate RA **cDMARD-IR**)	• Combination therapy with cDMARDs (including MTX and at least 1 other DMARD, such as sulfasalazine and leflunomide) • cDMARD monotherapy with dose escalation • Best supportive care (only where cDMARDs are not appropriate due to intolerance)
2. Severely active RA that has not responded adequately to therapy with cDMARDs (Severe RA **cDMARD-IR** MTX-eligible and MTX-ineligible)	• ADA, ETN, CTZ or TCZ only (each as monotherapy) • Biologic DMARDs in combination with MTX (ADA, ETN, IFX, CTZ, GOL, TCZ, ABA)
3. Severely active RA that has not responded adequately to therapy with bDMARDs, including at least 1 TNFi (Severe RA **bDMARD-IR** RTX-eligible)	• RTX in combination with MTX
4. As in 3, when RTX is contraindicated or withdrawn due to adverse events (Severe RA **bDMARD-IR** RTX-ineligible, MTX-eligible and MTX-ineligible)	• ADA, ETN and CTZ (each as monotherapy) • ADA, ETN, IFX, ABA, GOL, TCZ or CTZ each in combination with MTX

Decision problem (I)

	Final scope issued by NICE	Company submission	ERG's comment
Comparator(s)	Severe RA **cDMARD-IR**: • bDMARDs in combination with MTX (ADA, ETN, INF, CZP, GOL, TOC, ABA) • ADA, ETN, CZP, or TOC (each as monotherapy) Severe RA **bDMARD-IR** RTX-eligible: • RTX in combination with MTX Severe RA **bDMARD-IR** RTX-ineligible: • ABA, ADA, CZP, ETN, INF, TOC, or GOL, each in combination with MTX • ADA, ETN or CZP (each as monotherapy) Moderate RA **cDMARD-IR**: • Combination therapy with cDMARDs (including MTX and ≥1 DMARD) • cDMARD monotherapy with dose escalation • Best standard of care (only where cDMARDs are not appropriate due to intolerance)	As per the final scope issued by NICE. ***BARI appraisal:*** *no analyses are presented for severe RA cDMARD-IR who cannot take MTX and for whom BARI would be used as monotherapy*	Currently unlicensed, unapproved or yet to be assessed by NICE were excluded in the CS (anakinra, baricitinib, sarilumab, sirukimab). Baricitinib is currently under assessment by NICE* for treating moderate to severe RA and, like tofacitinib, is an orally administered JAK inhibitor (4mg once per day).

* FAD available, publication due August 2017

Decision problem (II)

	Final scope issued by NICE	Company submission	ERG's comment
Outcomes	The outcome measures to be considered include: • Disease activity • Physical function • Joint damage, pain • Mortality • Fatigue • Radiological progression • Extra-articular manifestations of disease (EAM) • Adverse effects of treatment • HRQoL	As per the final scope issued by NICE, with the exception of extra-articular manifestations (EAMs). Patients with EAMs were not specifically excluded from participation in the ORAL clinical trial programme. We are not aware, however, of sub analyses of efficacy and safety based on the presence or absence of these above mentioned EAMs. Therefore, Pfizer is unable to provide specific information regarding the use of tofacitinib in this population.	No comment

- Population, intervention and economic analysis were in line with the final scope

Clinician perspective
Oral therapy and safety profile

- Oral therapy: significant benefit to patients in terms of no risk of immunogenicity, no site reactions, and less wastage; patients are unlikely to develop antibody
- Similar safety profile to TNF-inhibitors
- May necessitate more frequent drug monitoring for toxicity.
- Cost-effectiveness evaluation should include monitoring costs
  - ERG confirmed these were included
- Dose adjustment only in patients with moderate hepatic impairment or with severe renal impairment, or when co-prescribed with CYP3A4 and CYP2C19 inhibitors.

Comments from UK Clinical Pharmacy Association

Clinician perspective
Outcomes and trial generalisability

- Differences in local treatment pathways for RA because lack of recommendations on the choice of therapy (NICE TA375: “it should be guided by cost-effectiveness”)
- Very few data on tofacitinib vs. biological therapy
- Tofacitinib + MTX should be reserved for patients with TNF-IR
- DAS28 better outcome than ACR20
- Limitations on the generalisability of evidence from RA study populations in general including:
  - Comorbidities may not be well represented
  - Durations of trials are too short
  - Increased incidence of cardiovascular events and raised lipids may be of concern in the long-term sustained use of the drug

Comments from UK Clinical Pharmacy Association and British Society for Rheumatology

Patient perspective
Living with rheumatoid arthritis

- A chronic and painful disease with no cure
- Distressing, life-changing – *diagnosis can be at any age post 16*
- Impact on several aspects of quality of life
  - Physically – *not being able to travel or look after children*
  - Emotionally – *anxiety, job-less*
  - Relationship – *RA can make people feel less desirable, less confident*
- What patients expect from treatments
  - Wanting their life back
  - Reduction of pain and fatigue– *2 most common symptoms*
  - Prevent permanent disability
  - Maintain independence and ability to work

Comments from patient carer expert and National Rheumatoid Arthritis Society

Patient perspective
Advantages of tofacitinib

- JAK-inhibitor is a new class of innovative therapy, additional therapeutic option for people who have refractory disease and who have been through all the biologics available
- Use at different places in the current pathway, i.e. After cDMARD failure and after TNF failure
- Oral treatment
  - Potential cost-saving for the NHS (by not having to bring people into day case care for infusions or have home healthcare companies delivering drugs)
  - More convenient for individual (may have difficulty getting to hospital appointments, injecting themselves due to disease/disability in their hands)

Comments from National Rheumatoid Arthritis Society

CLINICAL EFFECTIVENESS

Clinical effectiveness systematic review and network meta-analysis

- Company systematic review identified 4 RCTs relevant to the decision problem
  - ORAL Standard: cDMARD experienced, MTX-IR *vs* MTX + ADA *vs* MTX + placebo (combination)
  - ORAL Scan: cDMARD experienced, MTX-IR *vs* placebo + MTX (combination)
  - ORAL Sync: DMARD-IR* *vs* placebo + MTX (combination)
  - ORAL Solo: DMARD-IR* *vs* placebo (monotherapy)
- Network meta-analysis (NMA) assessed the relative efficacy of TOF in the cDMARD-IR and bDMARD-IR populations
- Clinical effectiveness data feeding into the model: ORAL trials (probabilities of EULAR response for TOF) and NMA (probabilities of EULAR response for the comparators)

*c-DMARD include MTZ or bDMARD

Clinical effectiveness - systematic review

- In their systematic review, the company identified:

4 pivotal Phase 3 trials	2 additional Phase 3 trials	3 supporting studies

• MTX-IR, cDMARD experienced:
  • **ORAL Standard** ▲
  • **ORAL Scan** ▲
• DMARD-IR (cDMARD including MTX or bDMARD)
  • **ORAL Sync** ▲
  • **ORAL Solo** ▲
 	
The trials met the decision problem
	• **ORAL Start**: MTX naïve
	  • Within TOF license
	  • Considered less relevant given the main 2nd line positioning
	• **ORAL Step**: TNFi-IR ▲
	  • Outside TOF license
	  • Shows significant impact on radiographic progression
		• **ORAL Strategy**:
		  • Completed Phase IIIb/IV
		  • MTX-IR, cDMARD experienced
		• **ORAL Sequel**:
		  • Ongoing open-label
		  • Long-term extension (LTE) safety and efficacy
		• **A3921041**:
		  • Open-label, LTE safety
		  • Only include Japanese

"**Early escape design**": patients in the placebo arm, who did not respond at month 3 or 6, were able to crossover to receive TOF 5 mg or 10 mg ('PBO to TOF', see slides 26-29)

▲ studies included in model

Early escape design (I)
A way to adjust for cross over

- In **ORAL Scan, Sync and Standard trials**, patients receiving placebo that did not respond at Month 3 crossover to receive TOF after early escape, which leads to confounding results.
- In **ORAL Step and Solo trials**, all patients receiving placebo were switched to TOF at Month 3, regardless of response, which lead to substantial underestimation of treatment effect (since the ITT analysis was done at Month 6)
- 2 non-responder imputation (NRI) approaches were applied
  - Estimate 1 of treatment effect was calculated by applying NRI to Month 3 non-responders from the placebo arm (termed NRI without advancement penalty).
  - Estimate 2 of treatment effect was calculated by applying NRI to Month 3 placebo non-responders as well as the Month 3 TOF non-responders (termed NRI with advancement penalty).
  - **The primary analysis for the ORAL Standard, Scan and Sync trials was based on NRI with advancement penalty (Estimate 2).**
- In the BARI appraisal, no crossover issues were discussed.

Early escape design (II)
2 methods to address crossover in EULAR response

	Estimate 1 of treatment effect: NRI without advancement penalty	**Estimate 2 of treatment effect: NRI with advancement penalty**
Description	NRI only to placebo group who received alternative treatments after early escape	• NRI to non-responders in the placebo group (at month 3) • NRI to non-responders in the TOF group at month 3 **(=advancement penalty)**
Advantage	Allow TOF-treated patients to produce a response to treatment at month 6 as per clinical practice, as well as the month 3 placebo responders	
Disadvantage	Unequal exposure to treatment between arms and assumes that placebo non-responders (at month 3) do not subsequently develop a response (between month 3 and 6)	Exclude TOF-treated patients as well as placebo-treated patients that have not responded at month 3 to develop a response to treatment between month 3 and 6

Key: NRI, Non-responder imputation

Estimate 1 was used in the base case of the NMA (see slide 21)

Early escape design (III)

Company favoured Estimate 1 & used in base case for all trials in the NMA

- The company favoured Estimate 1 as the base case for all trials included in the NMA for the following reasons:
  - Pooled trial analyses (ORAL Scan, Sync, Standard) showed that [redacted] of non-responders treated with TOF at Month 3 subsequently developed a EULAR response at Month 6.
  - Taking into account the prior exposure to methotrexate, clinical opinion indicates that less then 10% of non-responders at Month 3 in the placebo-treated arm would have subsequently developed a EULAR response by Month 6.
  - Estimate 2 is likely to underestimate the actual treatment benefit of TOF. Scenario analyses were presented with Estimate 2.

ERG believes that estimate 1 overestimates the relative treatment effect of TOF and estimate 2 underestimates the treatment effect of TOF, therefore it believes that the true treatment effect lies between these two estimates, but closer to estimate 1 than to estimate 2 .

Study characteristics (I)

Pivotal trials

Trial name	Population	Intervention	Comparators	Primary outcomes
ORAL Standard n=717	Adult patients with active moderate-to-severe RA who are cDMARD experienced and MTX-IR	• MTX+TOF 5 • MTX+TOF 10	• MTX + ADA* • MTX+ pbo to TOF 5† • MTX+ pbo to TOF 10†	• Proportion of patients who met ACR20 criteria at Month 6 (Month 3 for ORAL Solo) • Mean change from baseline in HAQ-DI at Month 3 • Proportion of patients with DAS28(ESR) <2.6 at Month 6 (Month 3 for ORAL Solo) • *Only for ORAL Scan*: Mean change from baseline in mTSS score at Month 6
ORAL Scan n=797			• MTX+ pbo to TOF 5† • MTX+ pbo to TOF 10†	
ORAL Sync n=792	Adult patients with active moderate-to-severe RA who are DMARD-IR (cDMARD including MTX or bDMARD)	• ≥1 cDMARD + TOF 5 • ≥1 cDMARD + TOF 10	• ≥1 cDMARD + pbo to TOF 5‡ • ≥1 cDMARD + pbo to TOF 10‡	
ORAL Solo n=610		• TOF 5 • TOF 10	• pbo to TOF 5‡ • pbo to TOF 10‡	

Key: ADA, adalimumab; TOF 5, tofacitinib 5 mg; TOF 10, tofacitinib 10 mg

*All patients self-administered injections of either ADA or placebo once every 2 weeks and took a TOF or placebo pill twice daily.

†Patients receiving placebo advanced to a predetermined dose of TOF (5 mg or 10 mg) at Month 3 if trial response criteria were not met (defined as 20% reduction in number of tender and swollen joints) or Month 6 regardless of response. ‡All patients receiving placebo advanced to a predetermined dose of TOF (5 mg or 10 mg) at Month 3.

Study characteristics (II)

ORAL strategy

Trial name	Population	Intervention	Comparators	Primary outcomes
ORAL Strategy n=1,080	Adult patients with active moderate-to-severe RA who are cDMARD experienced and MTX-IR	•ADA + MTX	•TOF 5 •TOF 5 + MTX	Proportion of patients who met ACR50 criteria at Month 6

Key: ADA, adalimumab 40 mg subcutaneously every other week; TOF 5, tofacitinib 5 mg.

- [redacted]

Baseline characteristics (I)

Heterogeneity in previous line of therapies

Study name	ORAL Standard	ORAL Scan	ORAL Sync	ORAL Solo	ORAL Step
Study duration	1 year	2 years	1 year	6 months	6 months
N	717	797	792	610	399
Background therapy	MTX	MTX	cDMARD	None	MTX
Severity of the disease					
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior lines of therapy %					
1	[redacted]	[redacted]	[redacted]	[redacted]	0
2	[redacted]	[redacted]	[redacted]	[redacted]	100
Prior biologics					
TNFi	7.1	15.9	6.6	16.2	99.2
Non-TNFi bDMARD	2.1	4.6	2.9	6.7	11.5

- All trials (except ORAL Step) included a mix of patients receiving 2nd and 3rd line therapies. ORAL Step only included patients receiving 3rd line therapy

Baseline characteristics (II)

Study name	ORAL Standard	ORAL Scan	ORAL Sync	ORAL Solo	ORAL Step
Positive rheumatoid factor test (%)					
PBO to TOF 5	71.4	79.7	73.1		N/A
PBO to TOF 10	60.8	75.3	72.2		
TOF 5	66.8	75.2	73.9		
TOF10	66.2	77.6	72.8		
ADA	68.2	-	-		
Positive anti-CCP test					
PBO to TOF 5	76.7	84.0			N/A
PBO to TOF 10	62.0	82.3			
TOF 5	71.3	85.9			
TOF 10	64.0	84.4			
ADA	74.8	-			

ERG: ORAL Solo reported groups that were not comparable at baseline

ACR20, HAQ-DI, and DAS-28

ORAL Standard: MTX-IR, cDMARD-experienced

Outcome		TOF 5 (licensed dose)	TOF 10	ADA	PBO to TOF
ACR20 at Month 6	N	196	196	199	106
	response rate, n (%)	101 (51.5)	103 (52.6)	94 (47.2)	30 (28.3)
	difference from PBO (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI score at Month 3	N	188	185	190	98
	change from baseline, (%)	- 0.55	-0.61	-0.49	-0.24
	difference from PBO (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
DAS28 (ESR) <2.6 at Month 6	N	177	176	178	92
	response rate, n (%)	11 (6.2)	22 (12.5)	12 (6.7)	1 (1.1)
	difference from PBO (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

***p≤0.001, +p≤0.05, ++p≤0.01 versus placebo

- TOF and ADA were significantly superior to placebo for the ACR20 and DAS28(ESR) at 6 months, and also HAQ-DI at 3 months

ACR20, HAQ-DI, DAS-28, mTSS
ORAL Scan: MTX-IR, cDMARD-experienced

Outcome		TOF 5 mg (licensed dose)	TOF 10 mg	PBO to TOF
ACR20 at Month 6	N	[redacted]	[redacted]	[redacted]
	response rate, n (%)	[redacted](51.5)	[redacted](61.8)	[redacted](25.3)
	difference from PBO (95% CI)	[redacted]	[redacted]	[redacted]
HAQ-DI score at Month 3	N	[redacted]	[redacted]	[redacted]
	change from baseline at (%)	-0.40±	-0.54	-0.15
	difference from PBO (95% CI)	[redacted]	[redacted]	[redacted]
DAS28 (ESR) <2.6 at Month 6	N	[redacted]	[redacted]	[redacted]
	response rate, n (%)	[redacted](7.2)	[redacted](16.0)	[redacted](1.6)
	difference from PBO (95% CI)	[redacted]	[redacted]	[redacted]
mTSS score at Month 6	N	[redacted]	[redacted]	[redacted]
	change from baseline (%)	0.12	0.06	0.47
	difference from PBO (95% CI)	[redacted]	[redacted]	[redacted]

***p≤0.001, +p≤0.05, ++p≤0.01 versus placebo; ± p-value not declared

- ACR20 was the only outcome where TOF 5 mg was significantly superior to placebo.

ACR20, HAQ-DI, and DAS-28

ORAL Sync: DMARD-IR (c-DMARD include MTZ or bDMARD)

Outcome		TOF 5 mg (licensed dose)	TOF 10 mg	PBO to TOF
ACR20 at Month 6	N	311	309	157
	response rate, n (%)	164 (52.7)	180 (58.3)	49 (31.2)
	difference from PBO (95% CI)	21.5 (12.4 to 30.7)***	27.0 (17.9 to 36.1)***	-
HAQ-DI score at Month 3	N	292	292	147
	change from baseline (%)	-0.46	-0.56	-0.21
	difference from PBO (95% CI)	-0.26 (-0.35, -0.16)***	-0.35 (0.44, -0.26)***	-
DAS28 (ESR) <2.6 at Month 6	N	263	270	148
	response rate, n (%)	24 (9.1)	36 (13.3)	4 (2.7)
	difference from PBO (95% CI)	6.4 (2.1, 10.8)$^{+}$	10.6 (5.8, 15.5)***	-

***p≤0.001, $^{+}$p≤0.05, $^{++}$p≤0.01 versus placebo

- TOF was significantly superior to placebo for ACR20 and DAS28(ESR) at 6 months and HAQ-DI at 3 months.

ACR20, HAQ-DI, and DAS-28
ORAL Solo: DMARD-IR (c-DMARD include MTZ or bDMARD)

Outcome		TOF 5 mg (licensed dose)	TOF 10 mg	PBO to TOF
ACR20 at Month 6	N	[redacted]	[redacted]	[redacted]
	response rate, n (%)	[redacted](59.8)	[redacted](65.7)	[redacted](26.7)
	difference from PBO (95% CI)	[redacted]	[redacted]	[redacted]
HAQ-DI score at Month 6	N	[redacted]	[redacted]	[redacted]
	change from baseline, n (%)	- 0.50	-0.57	-0.19
	difference from PBO (95% CI)	[redacted]	[redacted]	[redacted]
DAS28 (ESR) <2.6 at Month 6	N	232	229	114
	response rate	[redacted](5.6)	[redacted](8.7)	[redacted](4.4)
	difference from PBO (95% CI)	[redacted]	[redacted]	[redacted]

***p≤0.001, +p≤0.05, ++p≤0.01 versus placebo

- ACR20 and HAQ-DI at 3 months: TOF was statistically superior to placebo
- DAS28(ESR) at 3 months outcome TOF 5 mg BD is not significantly different from placebo.

Preliminary ACR50 results

ORAL Strategy: MTX-IR, cDMARD-experienced

Outcome		TOF 5 (N=384)	TOF 5 + MTX (N=376)	ADA 40+ MTX (N=386)
ACR50 response rate at Month 6, n (%)		147 (38.28)	173 (46.01)	169 (43.78)
Differences in ACR50 response rate				
Comparing with ADA 40 mg + MTX	Absolute difference (TOF – ADA), %	-5.50	2.23	-
	98.34% CI*	-13.98, 2.98	-6.40, 10.86	-
	Non-inferiority criteria met?	No	Yes	-
	p-value†	0.0512	<0.0001	-
Comparing with TOF 5 mg + MTX	Absolute difference (TOF mono – TOF+MTX), %	-7.73	-	-
	98.34% CI*	-16.29, 0.83	-	-
	Non-inferiority criteria met?	No	-	-
	p-value†	0.2101	-	-

Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; MTX, methotrexate; TOF, tofacitinib.
†p-values are from non-inferiority hypothesis testing. The p-values are multiplicity-adjusted and should be compared with 0.05.
* Non-inferiority between groups was shown if the lower bound of the 98·34% CI of the difference between comparators was larger than –13·0%

- TOF + MTX is non-inferior to ADA + MTX
- TOF monotherapy was shown not to be non-inferior to TOF + MTX and ADA + MTX

Health-related quality of life, fatigue and pain

- Across all Phase III trials, scores for pain (VAS) and fatigue (FACIT-F) were collected, as well as HAQ-DI.
- HAQ-DI scores were mapped to the EQ-5D (similar mapping method as used NICE TA375 and TA195) using an algorithm described by Hernandez Alava *et al.* (2013)
    - Approach not in line with TA375 which used the four-class mixture model by Hernández Alava *et al*. (2013)
    - in line with BARI appraisal
- **VAS, FACIT-F and quality of life (EQ-5D) were all significantly improved in the TOF group compared with placebo by Month 6** in all trials (except ORAL Start where EQ-5D was numerically improved *vs* placebo and pain was not recorded).

Key: FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue

Adverse events

Updated CS safety analysis on ORAL trials requested by ERG

Company did not provide (i) data for serious adverse events, (ii) data *vs* control arm (or odd ratios), (iii) requested data for hepatic enzymes elevation (see notes for detail)

Event Term (cut-off: January 2016, 6301 patients had received TOF)	**Total number of events**	**Number of patients affected**	**Incidence per 100 patient exposure years**
Serious Infection Events	[redacted]	[redacted]	[redacted]
Drug Induced Liver Injury (Cases meeting Hy's law†)	[redacted]	[redacted]	[redacted]
Gastrointestinal Perforation Events	[redacted]	[redacted]	[redacted]
Treatment discontinuations as a result of an Adverse Event	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]
Herpes Zoster infection	[redacted]	[redacted]	[redacted]
Interstital Lung Disease	[redacted]	[redacted]	[redacted]
Malignancies			
All Cancers (other than non-melanomatous cancers of the skin)	[redacted]	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]	[redacted]
Non-melanomatous cancers of the skin	[redacted]	[redacted]	[redacted]
Breast Cancer (Female patients only)	[redacted]	[redacted]	[redacted]
Lung Cancer	[redacted]	[redacted]	[redacted]
Melanoma	[redacted]	[redacted]	[redacted]

†prognostic indicator that a pure drug-induced liver injury (DILI) leading to jaundice, without a hepatic transplant, has a case fatality rate of 10% to 50%.

ERG critique on adverse events (I)

- The company's literature searches for adverse event data were not sufficient to identify all up-to-date relevant safety data for TOF: initial CS included pooled data up to March 2015
- Initial CS safety data showed lack of full and transparent safety due to pooling both combination and monotherapy trials - more informative to describe the relative occurrence of all AEs vs. the control arm
- Updated CS safety data showed highest incidence rates of AEs were for serious infections and herpes zoster.
- Updated CS safety data on Herpes zoster:
  - TOF infection rate is reported as [redacted] per 100 patient years whereas ERG' s review (based on a study by Winthrop* *et al*., 2014) reported 4.3 per 100 patient years and substantially higher within Asia (7.7 per 100 patient years).
  - Updated CS safety data did not report comparator's infection rates whereas Winthrop* *et al*. estimated a higher rates than bDMARDs (adalimumab: 2.8 per 100 patient years) and for placebo (1.5 per 100 patient years)
  - NMA by Curtis *et al.* (2016): incidence of herpes zoster was significantly higher in TOF than in bDMARDs
  - BARI appraisal: non-serious herpes zoster infections were more frequent in patients treated with BARI than placebo, but were not significantly higher than those seen with MTX or ADA. The majority of herpes zoster cases were mild to moderate in severity and complicated cases were uncommon
  - SPC of BARI and TOF report the same frequency estimate of Herpes Zoster (common: ≥ 1/100 to < 1/10)

*Winthrop *et al*., (2014) reviewed the tofacitinib RA development programme from the phase II, III and long-term extension studies; use a data cut from 2011.

ERG critique on adverse events (II)

ERG tabulated selected AE data for 4 ORAL trials

Number experiencing event/ Number of patients in tofacitinib (5 mg and 10 mg) treatment arms				
	ORAL Standard (combination)	ORAL Scan (combination)	ORAL Sync (combination)	ORAL Solo (monotherapy)
Treatment related SAEs between 0-6 months	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation due to AEs between 0-6 months	40/405 (9.9%)	53/637 (8.3%)	40/633 (6.3%)	14/488 (2.9%)
Deaths attributed to study treatment	1	5	3	0

- The 3 combination trials (ORAL Standard, Scan, Solo) have higher incidences of the selected treatment-related adverse events than the monotherapy trial (ORAL Solo).

Additional work on adverse events from the ERG

- The ERG conducted a specific search in MEDLINE of adverse events for TOF, from March 2015 to April 2017
  - Retrieved 152 citations
  - No relevant primary studies were identified
  - 1 NMA (including 10 TOF trials) highlighted a potentially different rate of AEs for TF + MTX *vs* TOF monotherapy, which is not drawn out by the safety analysis presented in the CS
  - 1 review by Boyce *et al.*(2016) echoed the sentiments of clinical advice to the ERG: it may require years of additional clinical studies and post marketing surveillance to fully characterize the benefit-to-risk ratio of TOF in a larger and diverse patient population.

EULAR response

EULAR response derived from DAS28 scores

- EULAR response was not collected from ORAL trials, therefore it was derived from DAS28
  - The CS estimated EULAR response criteria from DAS28 scores as a good or moderate EULAR response (described in the CS as an improvement in DAS28 from baseline) for ORAL Standard, ORAL Scan and ORAL Sync at 6 months and for ORAL Solo at 3 months.

DAS28 at time point	Improvement in DAS28 from baseline		
	>1.2	≤1.2 and >0.6	≤0.6
≤3.2	Good	Moderate	No response
≤5.1 and >3.2	Moderate	Moderate	No response
>5.1	Moderate	No response	No response

- In the BARI appraisal, EULAR response was collected directly from RCTs therefore no derivation of the data was required.

Description of the network meta-analysis

cDMARD-IR population	bDMARD-IR population
Adult patients with RA (as defined by the ACR criteria) who have had an inadequate response to at least one cDMARD or MTX	Adult patients with RA (as defined by the ACR criteria) who have had an inadequate response to at least one bDMARD

Interventions/comparators†

Only licensed doses of each treatment were included

- TNF-α-inhibitors: adalimumab, etanercept, infliximab, golimumab, certolizumab
- JAK-inhibitors: tofacitinib, baricitinib
- Anti-B-cell therapy: rituximab, co-stimulatory inhibitor molecules, abatacept
- Anti-IL-6 therapy: tocilizumab, sarukinumab, sirulimumab
- Anti-IL-1 therapy: anakinra
- Biosimilars

Outcomes of included studies

- **EULAR response** at month 6
- **Change from baseline in HAQ-DI** at month 6

Key: c/bDMARD, conventional/biological disease modifying anti-rheumatic drug; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire – disability index; IL, interleukin; JAK, Janus kinase; MTX, methotrexate; TNF-α, tumour necrosis factor-alpha.
†Interventions were considered alone or in combination with other conventional/biological DMARDs. There were no restrictions with regard to drug dose or formulation, mode of delivery, or duration of treatment. However, studies with at least one treatment arm with a licensed dose are of primary interest.

Trials included in the company's NMA

- NMA included 37 studies for the cDMARD-IR population and 8 for the bDMARD-IR population
- **bDMARD-IR population***: trials were largely the same as those in the NMA undertaken by AG in TA375, with some exceptions:
  - 10 trials in the CS were not included in TA375 (published after cut-off date in TA375: HERA; patients had received prior biologic therapy: Fleishmann *et al.* 2012, GO-AFTER, Kremer *et al.* 2012, RADIATE, LITHE, OPTION, RAPID 1, RAPID 2; separate 6-month data were not reported for those with concomitant cDMARDs and monotherapy: J-RAPID)
  - 19 trials included in TA375 were excluded from the CS for multiple reasons (see notes)
- To include etanercept (which did not share any common comparator with the rest of the network), the LARA trial was used (ETN + MTX versus cDMARD + MTX) to link ETN to the central node was, and it was assumed that the intensified DMARD arm is equivalent to the central DMARD node (see notes for the other option)
  - ERG was satisfied with the trials included in the NMA, however it noted that the inclusion of the LARA trial may not be an appropriate assumption because this would underestimate the treatment effect for ETN.

*cDMARD-IR population not included in TA375 which appraised ADA, ETN, IFX, CTZ, GOL, TCZ and ABA for RA not previously treated with DMARDs or after cDMARDs only have failed

ERG critique of the NMA

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

- Several issues with approaches taken by the company including:
  - Use of different models for EULAR response in the two populations (binomial and multinomial)
  - Use of a random effects (RE) model for the cDMARD-IR population (ordered categorical EULAR data were dichotomised, ignoring the natural ordering and correlations) and a fixed effects model was used for the bDMARD-IR population
  - Statistical assessments of heterogeneity I^2 suggested that a RE model would be more appropriate for EULAR response and HAQ-DI (cDMARD-IR population)
  - Use of LARA trial (may underestimate the treatment effect of ETN)
  - Use of a uniform prior in the RE model when data are sparse lead to implausible posterior uncertainty in the results
  - Unclear how odd ratios were calculated in bDMARD-IR population (because of use of probit model)

- Estimate 1 (NRI approach without penalty) was used in the base case NMA to calculate the relative treatment effect of TOF in ORAL trials, which overestimate the result. The ERG notes that, depending on the NRI approach (with or without penalty) applied to the TOF trials with early escape, the conclusions for the efficacy ranking of TOF among the bDMARDs varies markedly. NMA results should be interpreted with caution.

ERG request for NMA additional analysis

During clarification and based on the ERG's critique (see slide 39), it requested the company to perform additional analyses for EULAR response, in both populations:

Analysis	Original CS	Change requested by ERG
NMA	Different models for both populations	Same model for both populations (multinomial, fixed effect)
Prior used for the treatment effect relative to the reference treatment	Vague prior, uniform [0,5]	Informative prior, truncated log normal (-2.56, 1.74^2)
Non-responder imputation	Estimate 1	Estimate 2
Studies included in NMA	Include all studies following exclusion criteria	•Exclude studies which only reported DAS from the NMA and did not report EULAR[1] •Exclude studies with patients with prior bDMARD use[2]
Inclusion of etanercept	LARA trial (assuming intensified cDMARD was the same as cDMARD)	SWEFOT trial and LARA trial (without assuming intensified cDMARD was the same as cDMARD)
Reference treatment	placebo + cDMARD/cDMARD	No change

[1]In response to clarification letter, the company stated that "these original papers appear to have been using the term DAS when EULAR would have been more accurate. On the basis of both the review of the original publications, and their inclusion in previous technology appraisals in RA, it should be considered that all 7 of the publications have EULAR data readily available, and do not need to be excluded from the analysis." Hence, there were no changes to the data used regarding this point. [2]A sensitivity analysis of not excluding these studies was also requested. The results were similar.

EULAR response for cDMARD-IR (combination)

ESTIMATE 1

ESTIMATE 2

The analyses including patients with and without prior biologics provide very similar results for the cDMARD-IR population, except that the treatment effect of TCZ + cDMARD *vs* cDMARD reduced noticeably using the studies without prior biologics.

EULAR response for cDMARD-IR (monotherapy)

ESTIMATE 1

ESTIMATE 2

The analyses including patients with and without prior biologics use provide very similar results for the cDMARD-IR population, except that the treatment effect of ADA monotherapy became statistically significant without prior biologics.

EULAR response for bDMARD-IR (Estimate 2*)

*The company did not provide the results using Estimate 1

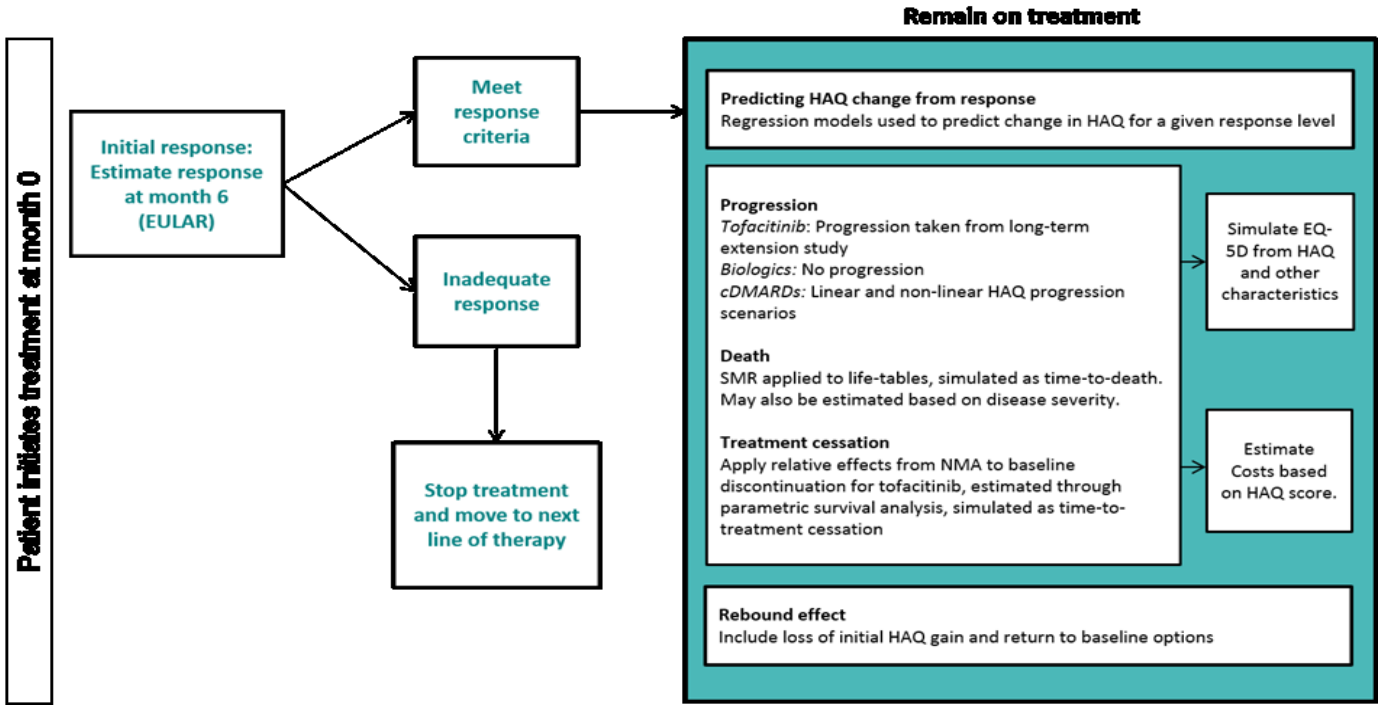
Key issues: Clinical effectiveness

- Is tofacitinib comparable to the bDMARDs in clinical effectiveness in moderate and severe rheumatoid arthritis?
  - Is the network meta-analysis a reliable estimate of the relative effect?
- Is tofacitinib effective as a monotherapy?
- Is the EULAR response derived from DAS 28 acceptable ?
- For the EULAR response outcome, does the true treatment effect lie between estimates 1 and 2, but closer to estimate 1 than to estimate 2?
- Has crossover been addressed appropriately?
- Is the safety profile of tofacitinib acceptable?

COST EFFECTIVENESS

Company's model structure

- 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)
- Lifetime time horizon with a maximum age of 100 years (45 yr in BARI appraisal)



BSRBR: British Society for Rheumatology Biologic Register

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 (not confidential as there were complex PASs) in the CS but the PASs for ABA and TCZ (confidential as there were simple) were not included (all PAS analyses are included only in PART 2)
- Palliative care cost was taken from Pfizer Rheumatoid Arthritis Model, rather than from the TA375, although the different monthly prices (£44 compared with £60) are not expected to affect the ICER to any large degree.
- 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	Probabilities of EULAR responses for: • TOF + MTX (from ORAL trials): multinomial regression model based on baseline characteristics *ERG: the efficacy of TOF was assumed to be the same as TOF+MTX* • Comparators: applying ORs from NMA to probabilities of EULAR responses for TOF+MTX *ERG: the efficacy for SSZ+HCQ was assumed to be the same as 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 for moderate and good response, independent of treatment • Used 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:*** Base case: Patients who achieved a moderate or good response at 6 months are assumed to have a reduction in HAQ score: • good response: - 0.672 • moderate response: - 0.317 Remain on treatment until loss of efficacy, incidence of AEs or death Sensitivity analysis: used ORAL data	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 did not consider the 'rapid progressor' group as this group 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 point was not addressed by company at clarification stage. 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

- The ERG noted further limitations related to:
  - 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*
  - Assuming the efficacy of the first bDMARD applies to all treatment lines (2nd and onwards) of bDMARDs in the cDMARD-IR population ●
  - Efficacy of TOF was 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) ●
  - 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 ●
  - Use of linear annual increase of HAQ-DI score for patients on palliative care is misrepresenting what was done in TA375 ●

*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;

● Corrected by the company at clarification stage; ● Addressed by ERG

Company's base case
with inclusion of PAS for TOF, GOL, and CZP*

Population	Summary (ICERs)
Severe, cDMARD-IR, MTX-eligible	• TOF + MTX vs MTX: ICER = £24–40k with rapid and Norton progression • TOF + MTX dominated or extendedly dominated all comparators (both assumptions) **Except** TOC + MTX and INF + MTZ (rapid progression only) • TOC + MTX vs TOF + MTX: ICER= £88–139k for both assumptions
Severe, cDMARD-IR, MTX-ineligible	• TOF + MTX vs MTX: ICER = £26–56k with rapid and Norton progression • TOF + MTX dominated or extendedly dominated all comparators (both assumptions) **Except** TOC • TOC vs TOF + MTX: ICER= £39–57k for both assumptions
Severe, bDMARD-IR RTX-eligible	• TOF + MTX not cost-effective
Severe, bDMARD-IR RTX-ineligible	• TOF + MTX dominated or extendedly dominated all comparators
Severe, bDMARD-IR MTX-ineligible	• TOF vs TOC: ICER=£25,932
Moderate, cDMARD-IR	• TOF+MTX vs cDMARD: ICER ranged from £29,186–51,693 (with TOF PAS price)

*Tofacitinib have confidential simple PAS discount, golimumab and certolizumab pegol have a complex non-confidential PAS; abatacept and tocilizumab have confidential simple PAS and therefore were not included, as recommended by NICE

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***	***ETN***	***ADA***
1	SSZ	TCZ	TOF	ETN	ADA
2	NBT	ETN	ETN	ADA	ETN
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	ETN+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.

Additional exploratory analyses undertaken by the ERG

Additional analysis (see details on slide 50)	
Company's correction at clarification stage	Corrected changes in HAQ-DI scores upon response
	Norton *et al.* progression is used instead of linear progression for palliative care (NBT)
	Activating the 'prior_bdmard' flag after the first biologic or JAK inhibitor when calculating the probabilities of EULAR response
ERG's additional changes	Calculating the ORs for all treatments including monotherapies compared to TOF+MTX
	Probabilistic rounding of HAQ-DI scores

- The results of the exploratory analyses carried out by the ERG were slightly different to those presented by the company but did not significantly impact the conclusions.

Cost effectiveness results

Subgroup analyses

Populations	PAS price*
Severe RA, cDMARD-IR, MTX-eligible	All the ICERs include the PAS for TOF (simple PAS - confidential) and for CZP and GOL (complex PAS - not confidential)
Severe RA, cDMARD-IR, MTX-ineligible	
Severe RA, bDMARD-IR, RTX-eligible	All the ICERs include the PAS for TOF (simple PAS - confidential), no comparator have a PAS
Severe RA, bDMARD-IR, RTX-ineligible	
Severe RA, bDMARD-IR, MTX-ineligible	No – analysis **not conducted** because the company did not identify evidence for any of the relevant comparators, namely ADA, ETN and CTZ
Moderate RA, cDMARD-IR	Analyses presented with PAS for TOF, no comparators have a PAS

*tofacitinib have confidential simple PAS discount, golimumab and certolizumab pegol have a complex non-confidential PAS

For each analysis, only deterministic results are presented using 2 sets of data :

- Estimate 1 (based on company's NMA)
- Estimate 2 (based on NMA requested at clarification stage)

Severe RA, cDMARD-IR, MTX-eligible

ESTIMATE 1

	Total		Incremental		ICER (£/QALY)	
Sequences*	QALYs	Costs	QALYs	Costs	Incremental	Pairwise vs TOF+MTX
MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	£32,883†
TCZ+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£31,163†
IFXb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£26,161†
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£32,883	-
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£563,148
CTZ+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£139,684
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£85,578	£85,578

*Treatments sequences as specified on slide 52.

†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-eligible

ESTIMATE 2

	Total		Incremental		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	£29,092†
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	-
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£6,572,401
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£32,481	£209
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£83,259
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£61,037	£49,988
CTZ+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£87,439	£57,326

*Treatments sequences as specified on slide 52.

†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		ICER (£/QALY)	
Sequences*	QALYs	Costs	QALYs	Costs	Incremental	Pairwise vs TOF
SSZ	[redacted]	[redacted]	[redacted]	[redacted]	-	£35,138†
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£35,138	-
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£99,795
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£79,288
TCZ	[redacted]	[redacted]	[redacted]	[redacted]	£51,488	£51,488

ESTIMATE 2

Note: for both estimate 1 and 2, relative effectiveness of TOF was calculated using odd ratios versus TOF+MTX

	Total		Incremental		ICER (£/QALY)	
Sequences*	QALYs	Costs	QALYs	Costs	Incremental	Pairwise vs TOF
SSZ	[redacted]	[redacted]	[redacted]	[redacted]	-	£35,095†
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£35,095	-
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£72,201
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£63,881
TCZ	[redacted]	[redacted]	[redacted]	[redacted]	£50,430	£50,430

*Treatments sequences as specified on slide 53. †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		ICER (£/QALY)	
Sequences*	QALYs	Costs	QALYs	Costs	Incremental	Pairwise vs RTX,TCZ‡
RTX,TOF	[redacted]	[redacted]	[redacted]	[redacted]	-	£67,852†
TOF,TCZ	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
RTX,TCZ‡	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	-
RTX,TOF,TCZ	[redacted]	[redacted]	[redacted]	[redacted]	£44,535	£32,426
RTX,TCZ,TOF	[redacted]	[redacted]	[redacted]	[redacted]	£704,235	£37,657

ESTIMATE 2

only the “RTX, TCZ” sequence is recommended by NICE

	Total		Incremental		ICER (£/QALY)	
Sequences*	QALYs	Costs	QALYs	Costs	Incremental	Pairwise vs RTX,TCZ‡
RTX,TOF	[redacted]	[redacted]	[redacted]	[redacted]		£90,846†
TOF,TCZ	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
RTX,TCZ‡	[redacted]	[redacted]	[redacted]	[redacted]	Ext dominated	-
RTX,TOF,TCZ	[redacted]	[redacted]	[redacted]	[redacted]	£43,530	£35,083
RTX,TCZ,TOF	[redacted]	[redacted]	[redacted]	[redacted]	£59,237	£36,202

*Treatments sequences as specified on slide 53. 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		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]	£75,070	£75,070

ESTIMATE 2

	Total		Incremental		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]	Ext. dominated	£12,624,118
TCZ+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£99,511
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£38,017	£38,017

*Treatments sequences as specified on slide 53.

†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

CONFIDENTIAL

Moderate RA, cDMARD-IR

ESTIMATE 1

	Total		Incremental		ICER (£/QALY)
Sequences*	QALYs	Costs	QALYs	Costs	Incremental
MTX	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£47,594

ESTIMATE 2

	Total		Incremental		ICER (£/QALY)
Sequences*	QALYs	Costs	QALYs	Costs	Incremental
MTX	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£50,708

*Treatments sequences as specified in slide 53.
TOF: tofacitinib; MTX: methotrexate;

ICER summary (with TOF PAS and CZP, GOL PASs)		
Populations	**TOFACITINIB (ERG analysis)**	**BARICITINIB* (Committee)**
Severe, cDMARD-IR, MTX-eligible	**Estimates 1 and 2:** • TOF+MTX dominates ADA+MTX; • TOF+MTX vs most comparators had favourable ICERs **Estimate 2:** TOF+MTX was extendedly dominated by MTX and IFXb+MTX	• BARI + MTX dominated all comparators • **Except** BARI + MTX *vs* CTZ + MTZ = £18,400
Severe, cDMARD-IR, MTX-ineligible	**Estimates 1 and 2:** • TOF *vs* all comparators <£50,000 • CTZ was not included in these analyses	*Not assessed*
Severe, bDMARD-IR RTX-eligible	**Estimates 1 and 2:** "RTX, TOF" is estimated to produce cost savings (ranging £67,852 to £90,846)	BARI + MTX dominated by RTX + MTX
	➢ *BARI submission did not look at other sequences with BARI elsewhere*	
Severe, bDMARD-IR RTX-ineligible	• TOF+MTX dominates GOL+MTX and ABT+MTX (**estimate 1**) and GOL+MTX (**estimate 2**) • TOF+MTX vs other comparators > £38,000 • ADA+MTX, IFX+MTX, CTZ+MTX were not included in the analyses	• 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*	**Estimates 1 and 2:** TOF + MTX *vs* MTX= 47-50k£	BARI + MTX *vs* intensive cDMARDs = £37,420
	➢ *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?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Rheumatoid arthritis - tofacitinib citrate [ID526]

Company evidence submission

Version: 1.0

Date of preparation: 1/04/2017

File name	Version	Contains confidential information	Date
		Yes/no	

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

List of Tables

List of Figures

Abbreviations

ABA or ABT	Abatacept
ACR	American College of Rheumatology
ADA	Adalimumab
AE	Adverse event
AIC	Akaike information criterion
ALDVMM	Adjusted limited dependent variable mixture models
ALT	Alanine aminotransferase
AQoL	Assessment of quality of life
AST	Aspartate aminotransferase
AWMSG	All Wales Medicines Strategy Group
BD	Twice-daily
bDMARD	Biologic disease-modifying anti-rheumatic drug
BHPR	British Health Professionals in Rheumatology
BIC	Bayesian information criterion
BIW	Twice-weekly
BMI	Body mass index
BNF	British National Formulary
BRAM	Birmingham rheumatoid arthritis model
BSR	British Society for Rheumatology
BSRBR	British Society for Rheumatology Biologics Register
CADTH	Canadian Agency for Drugs and Technologies in Health
CCP	Cyclic citrullinated peptide
CCS	Corticosteroid
CDAI	Clinical disease activity index
cDMARD	Conventional disease-modifying anti-rheumatic drug
CG	Clinical guideline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
COX-2	cyclooxygenase-2
CRP	C-reactive protein
CSR	Clinical summary report
CVD	Cardiovascular disease
CZP	Certolizumab pegol
DAS	Disease activity score
DMARD	Disease-modifying anti-rheumatic drug

DSU	Decision Support Unit
EAM	Extra-articular manifestation
EED	Economic Evaluation Database
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol five-dimension questionnaire
ERG	Evidence Review Group
ESR	erythrocyte sedimentation rate
ETN	Etanercept
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
FDA	Food and Drug Administration
GCC	Glucocorticoid
GI	Gastrointestinal
GOL	Golimumab
HAQ-DI	Health Assessment Questionnaire-disability index
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCQ	Hydroxychloroquine
HERC	Health eResearch Centre
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Appraisal
HUI	Health utility index
HZ	Herpes zoster
ICER	Incremental cost-effectiveness ratio
IgM	Immunoglobulin M
IM	Intramuscular
INAHTA	International Network of Agencies for Health Technology Assessment
INF or IFX	Infliximab
InR	Incidence rates
IR	Inadequate response
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention to treat
IV	Intravenous

IVR	Interactive voice response
JAK	Janus Kinase inhibitor
JSN	Joint space narrowing
LE	Linear extrapolation
LEF	Leflunomide
LOCF	Last observation carried forward
LS	Least squares
MC	Mental component
MI	Myocardial infarction
MOS-SS	Medical outcomes study sleep scale
MTA	Multiple technology appraisal
mTSS	van der Heijde modified total sharp score
MTX	Methotrexate
NIHR	National Institute for Health Research
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NMA	Network Meta-analysis
NMSC	Non-melanoma skin cancer
NRAS	National Rheumatoid Arthritis Society
NRI	Non-responder imputation
NRINAP	Non-responder imputation no advancement penalty
NRIWAP	Non-responder imputation with advancement penalty
NSAID	Non-steroidal anti-inflammatory drug
OCS	Oral corticosteroid
OI	Opportunistic infection
ORAL	Oral Rheumatoid Arthritis Phase 3 Trials
PAAP-VAS	Patient's assessment of arthritis pain – visual analogue scale
PAS	Patient access scheme
PASLU	Patient access scheme liaison unit
PBAC	Pharmaceutical Benefits Advisory Committee
PBT	Post-biologic therapy
PC	Physical component
PLS	Patient-level simulation
PPAS	Per protocol analysis set
PRAM	Pfizer rheumatoid arthritis model
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSL	Prednisolone
PSS	Personal and Social Services

PSSRU	Personal Social Services Research Unit
QALY(s)	Quality adjusted life year(s)
QS	Quality standard
QW	One weekly
Q2W	Every two weeks
Q4W	Every four weeks
RA	Rheumatoid Arthritis
RCT	Randomised controlled trial
RePEc	Research Papers in Economics
RF	Rheumatoid factor
ROW	Rest of world
RRR	Relative risk ratio
RTX	Rituximab
SAE	Serious adverse event
SAS	Safety analysis set
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SEER	Surveillance, Epidemiology, and End Results
SF-36	Short-form 36-item questionnaire
SG	Standard gamble
SIE	Serious infection event
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SMR	Standardised mortality rate
SR	Systematic review
SSZ or SFZ	Sulfasalazine
TA	Technology appraisal
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TNF	Tumour necrosis factor
TNFi	Tumour necrosis factor inhibitor
TOC or TCZ	Tocilizumab
TOF	Tofacitinib
TTO	Time trade off
UK	United Kingdom
ULN	Upper limit of normal
URTI	Upper respiratory tract infection

US	United States
VAS	Visual analogue scale
WLQ	Work limitation questionnaire

1 Executive summary

1.1 *Statement of the decision problem*

The decision problem for this appraisal asks if tofacitinib in combination with methotrexate (MTX) is clinically and cost-effective in line with its marketing authorisation, for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARD). Tofacitinib can also be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate. Further details of the decision problem, its alignment to the final scope issued by NICE (1), and how it has been addressed in this submission are presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderate-to-severe, active RA whose disease has responded inadequately to, or who are intolerant of ≥1 DMARD, including cDMARDs or bDMARDs.	As per the final scope issued by NICE.	N/A
Intervention	TOF in combination with MTX and as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate	As per the final scope issued by NICE.	N/A

Comparator(s)	People with severe active RA that has not responded adequately to therapy with cDMARDs only:
	• bDMARDs in combination with MTX (ADA, ETN, INF, CZP, GOL, TOC, ABA)
	• ADA, ETN, CZP, or TOC (each as monotherapy)
	People with severe active RA that have not responded adequately to therapy with DMARDs including ≥1 TNF inhibitor:
	• RTX in combination with MTX
	• When RTX is contraindicated or withdrawn due to AEs:
	  ○ ABA, ADA, CZP, ETN, INF, TOC, or GOL, each in combination with MTX
	  ○ ADA, ETN or CZP (each as monotherapy)
	People with moderate active RA:
	• Combination therapy with cDMARDs (including MTX and ≥1 DMARD, e.g. SSZ and LFM)
	• cDMARD monotherapy with dose escalation
	• Best standard of care (only where cDMARDs are not appropriate due to intolerance)
		As per the final scope issued by NICE.	N/A

Outcomes	The outcome measures to be considered include: • Disease activity	As per the final scope issued by NICE, with the exception of extra-articular	Patients with EAMs were not specifically excluded from participation in the ORAL clinical

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Physical function • Joint damage, pain • Mortality • Fatigue • Radiological progression • Extra-articular manifestations of disease • Adverse effects of treatment • HRQoL	manifestations (EAMs).	trial programme. We are not aware, however, of subanalyses of efficacy and safety based on the presence or absence of these above mentioned EAMs. Therefore, Pfizer is unable to provide specific information regarding the use of tofacitinib in this population.
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and PSS perspective. • The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. • The availability and cost of biosimilars should be taken into account.	As per the final scope issued by NICE.	N/A
Other considerations	If the evidence allows the following subgroups will be considered. These include people with moderate disease activity (DAS28 between 3.2 and 5.1) and severe active disease (DAS28 greater than 5.1). Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing	As per the comparator section above, people with moderate and severe RA are treated as separate populations, in line with TA375.	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	authorisation granted by the regulator.		

Abbreviations: ABA, abatacept; ADA, adalimumab; bDMARD, biologic disease-modifying anti-rheumatic disease; cDMARD, conventional disease-modifying anti-rheumatic disease; CZP, certolizumab pegol; DAS28, disease activity score in 28 joints; DMARD, disease-modifying anti-rheumatic disease; ETN, etanercept; GOL, golimumab; INF, infliximab; LFM, leflunomide; MTX, methotrexate; NHS, National Health Service; PSS, Personal Social Services; RA, rheumatoid arthritis; RTX, rituximab; SSZ, sulfasalazine; TNF, tumour necrosis factor; TOC, tocilizumab; TOF, tofacitinib.

1.2 *Description of the technology being appraised*

Tofacitinib citrate is an innovative, novel, orally administered Janus Kinase (JAK) inhibitor. JAK inhibitors were born out of a more complete understanding of the pathophysiology and underlying mechanisms responsible for the onset and progression of disease in rheumatoid arthritis (RA). A more sophisticated understanding of the complex streams of cytokine signalling shifted attention to intracellular pathways, and specifically the JAK family members, which are now recognised as processing hubs through which multiple cytokines work (2, 3). Tofacitinib and the JAK inhibitors represent a new class of immunomodulating agents, which the European League Against Rheumatism (EULAR) recognise as Targeted Synthetic Disease-Modifying Antirheumatic Drugs (tsDMARDs) (4, 5). Through an extensive clinical trial programme tofacitinib has been tested in a variety of patients with moderate -to -severe RA (6-9), which is also supplemented with use in the real world setting as tofacitinib is approved for use in moderate-to-severe RA in more than 50 countries worldwide, including the US, Canada, Japan, Switzerland, and Russia (10, 11). As of March 2015 6,194 patients received tofacitinib in the ORAL trial programme, which equates to19,400 patient years (12), and we estimate that over 70,000 patients have been treated with tofacitinib worldwide up to the end of 2016 (13).

The treat-to-target paradigm is now internationally accepted as best practice in the management of RA, and forms the basis of clinical guidelines from EULAR (14) and the American College of Rheumatology (15). The treat-to-target framework advocates rapid attainment of remission or low disease activity (LDA) to halt disease progression and maintain health related quality of life (HRQoL). It is widely accepted, however, that despite the availability of multiple biologic therapies for the treatment of moderate-to-severe RA, treatment failure and intolerance are common. It is therefore critically important for patients that alternative treatments are accessible under NHS care (2).

Tofacitinib is available as a 5 mg tablet taken twice daily. Hereafter, every mention of tofacitinib will infer a 5 mg twice-daily dose. A tofacitinib dose of 10 mg (unlicensed) was included in the main Phase III clinical trials for comparison and has been included in the dossier for completeness only; the dose frequency was also twice daily.

A summary of the technology being appraised is presented in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	UK approved name: Tofacitinib citrate Brand name: XELJANZ
Marketing authorisation/CE mark status	• Regulatory submission to EMA: The application was submitted on 23 March 2016. • CHMP positive opinion was received on 26 January 2017. • Marketing authorisation: 27 March 2017 • UK availability: 06 April 2017
Indications and any restriction(s) as described in the summary of product characteristics	Tofacitinib in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs. Tofacitinib can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.
Method of administration and dosage	Tofacitinib is available in 5 mg film-coated tablets for oral administration, twice daily.

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency.

1.3 *Summary of the clinical effectiveness analysis*

Evidence for the clinical efficacy and safety of tofacitinib (both in combination with MTX or as a monotherapy) for people with moderate (disease activity score in 28 joints [DAS28] 3.2–5.1) to severe (DAS28 >5.1) active RA has been demonstrated across six Phase III and one Phase IIIb/IV clinical trials which included a diverse set of sub-populations of RA patients. The trials most relevant to the population outlined in the decision problem are presented in Table 3 below.

Table 3: Tofacitinib ORAL clinical trial programme

Phase	Clinical Trials	Comparator(s)	Population
Phase III	ORAL Standard and Scan	Placebo + MTX	Participants with moderate-to-severe RA who were MTX-IR
	ORAL Sync	Placebo + MTX	Participants with moderate-to-severe RA who were cDMARD-IR or bDMARD-IR
	ORAL Solo	Placebo + cDMARD	
	ORAL Step	Placebo +MTX	Participants with moderate-to-severe RA who were TNFi-IR
	ORAL Start	Placebo +MTX	Participants with moderate-to-severe RA who were MTX naive
Phase IIIb/IV	ORAL Strategy	Adalimumab 40mg	Participants with moderate-to-severe RA who were MTX-IR

Abbreviations: bDMARD-IR, biologic disease-modifying anti-rheumatic disease inadequate responder cDMARD-IR, conventional disease-modifying anti-rheumatic disease inadequate responder; MTX-IR, methotrexate inadequate responder; RA, rheumatoid arthritis; TNF-IR, tumour necrosis factor inadequate responder.

1.3.1 *Efficacy of tofacitinib*

The data from the six Phase III and one Phase IIIb/IV clinical trials demonstrated that treatment with tofacitinib (both in combination with MTX/cDMARD or as a monotherapy) significantly improved a range of validated clinical and patient-reported outcomes. Owing to the substantive body of trial data available, the ORAL programme has demonstrated efficacy relevant both to American College of Rheumatology (ACR) response criteria and those consistent with treat-to-target recommendations adopted by EULAR guidelines (5). Against this background, we focus herein on data relating to disease activity and remission, to ensure consistency and maximum relevance to the final scope issued by NICE.

The ORAL clinical trials demonstrated that tofacitinib in combination with MTX significantly improves the rate of remission and low disease activity by Month 6 compared with placebo.

Disease remission (DAS28-4[ESR] <2.6) is an extremely important outcome used to treat patients in UK clinical practice with moderate to severe active RA. Disease remission was assessed in five of the six ORAL clinical trials relevant to the decision problem which involved n=1,897 patients randomised to tofacitinib (n=1,216) or placebo (n=681, 5mg=343 and 10mg=338).

The ORAL clinical trial programme demonstrated that tofacitinib, in combination with MTX (or cDMARD), resulted in significantly higher rates of disease remission compared to placebo, for (results presented tofacitinib vs placebo):

- Patients with moderate-to-severe RA who had an inadequate response to MTX (MTX-IR) in both ORAL Standard 6.2% vs 1.1% (p<0.015) and ORAL Scan 7.2% vs 1.6%, nominal p-value: 0.003[a] at 6 months;
- Patients with moderate-to-severe RA who had an inadequate response to cDMARDs (cDMARD-IR) in ORAL Sync 9.1% vs 2.7%, p<0.0038 at 6 months; and
- Patients with moderate-to-severe RA who are TNFi-IR in ORAL Step 6.7% vs 1.7%, p<0.0496 at 3 months.

Tofacitinib as monotherapy also resulted in a numerical improvement in the rate of remission in patients who are DMARD-IR compared with placebo in ORAL Solo 5.6% vs 4.4%, p<0.62 at 3 Months.

[a]Due to the lack of a significant difference in SHS score and the stepwise analysis of the primary endpoints (to preserve the type I error rate), improvement in HAQ-DI at Month 3 and DAS28-(ESR) <2.6 response rate at Month 6 could not be declared statistically significant for the tofacitinib 5 mg group compared with placebo. However, the differences were nominally significant.

Tofacitinib significantly increased the physical functioning of patients with moderate-to-severe active RA compared with placebo in all ORAL clinical trials.

Preventing physical functional disability has been noted as an important outcome for patients with RA. Disability can have a significant impact on patients' overall well-being and correlates with important personal consequences, such as inability to work (16). Physical function is universally measured by the health assessment questionnaire disability index (HAQ-DI) score, which has been found to closely correlate with patient reported outcomes (PRO) (17).

Tofacitinib in combination with MTX (or cDMARD) significantly improved HAQ-DI scores compared to placebo, for (results presented tofacitinib vs placebo):

- Patients with moderate-to-severe RA who are MTX-IR in both ORAL Standard –0.55 vs –0.24, p<0.001 and ORAL Scan –0.40 vs –0.15; nominal p-value: <0.001[b] at 3 months;
- Patients with moderate-to-severe RA who are DMARD-IR in ORAL Sync –0.46 vs –0.21, p<0.001, at 3 months; and
- Patients with moderate-to-severe RA who are TNFi-IR in ORAL Step –0.43 vs –0.18, p<0.001 at 3 months.

Tofacitinib monotherapy also significantly improved physical functioning as measured by HAQ-DI in patients who are DMARD-IR compared with placebo in ORAL Solo –0.50 vs –0.19, p<0.001 at 3 months

Tofacitinib significantly reduced the signs and symptoms in patients with moderate-to-severe RA by Month 6 compared with placebo, as measured by the American College of Rheumatology (ACR) response criteria.

Signs and symptoms, primarily measured in clinical trials by ACR response criteria, is a clinically important measure used worldwide to assess the impact RA treatments have in reducing patients' RA disease severity (18).

Tofacitinib in combination with MTX (or cDMARD) significantly reduced the signs and symptoms of RA as measured by ACR20 response rates (the primary endpoint in the ORAL clinical trial programme – except ORAL Strategy) for (results presented tofacitinib vs placebo):

- Patients with moderate-to-severe RA who are MTX-IR in both ORAL Standard 51.5% vs 28.3%, p<0.001 and ORAL Scan 51.5% vs 25.3%, p<0.001 by 6 months;

[b]Due to the stepwise analysis of the primary endpoints (to preserve the type I error rate), improvement in HAQ-DI at Month 3 and DAS28-4(ESR) <2.6 response rate at Month 6 could therefore not be declared statistically significant for the tofacitinib 5 mg group compared with placebo. However, the differences were nominally significant.

- Patients with moderate-to-severe RA who are DMARD-IR ORAL Sync 52.7% vs 31.2%, p<0.001 by 6 months; and
- Patients with moderate-to-severe RA who are TNFi-IR in ORAL Step 41.7% vs 24.4%, p=0.002 by 3 months.

Tofacitinib monotherapy also significantly improved signs and symptoms, as measured by ACR20 in patients who are DMARD-IR compared with placebo in ORAL Solo 59.8% vs 26.7%, p<0.001 by 3 months.

In ORAL Strategy, tofacitinib in combination with MTX also met its primary end point (% of ACR50 responders) in demonstrating non-inferiority compared to adalimumab 40 mg every-other-week in combination with MTX at Month 6, in patients who are MTX-IR. Tofacitinib monotherapy did not meet the same endpoint.

Tofacitinib was associated with a numerical delay in radiographic progression in patients with RA compared with placebo in ORAL Scan.

Radiographic progression (measured by the modified Sharp/van der Heijde score [SHS]) was assessed in patients with moderate-to-severe RA who are MTX-IR in ORAL Scan. At Month 6 the mean change from baseline in SHS score was 0.12 for tofacitinib vs 0.47 in placebo group (the difference from placebo was –0.34 [95% CI: –0.73, 0.04]). Although radiographic progression was more favourable for tofacitinib, the difference was not statistically significant (p=0.0792). The lack of statistical significance is in part a product of the slow rate of progression observed in the placebo group, which was approximately one-fifth of the rate predicted from the published literature. Consequently, the clinical trial was underpowered to detect a difference in the observed outcomes.

Radiographic progression was also assessed in ORAL Start (Section 4.7.4.2), which examined a population who were MTX naïve but over 1/3 of patients having previous cDMARD treatment, and therefore consistent with tofacitinib licensed indication. In this trial, a significant difference in the mean change from baseline in SHS score was observed between tofacitinib monotherapy (0.2) and the MTX group (0.8; p<0.001) at Month 6. Importantly, the vast majority of patients in both ORAL Scan and Start showed no progression, consistent with the efficacy expectations of an advanced DMARD.

Long-term follow up data of all patients enrolled in Phase I, II, and III clinical trials demonstrates that patients' who responded to treatment with tofacitinib experienced improvements in clinical outcomes relevant to UK clinical practice, which were maintained for up to 96 months.

As outlined above, tofacitinib treatment resulted in significant improvements in measures of physical function (i.e., HAQ-DI) and the signs and symptoms (i.e., ACR20) of RA from as early as two weeks, compared with placebo. Significant improvements in the number of patients achieving disease remission (DAS28-4[ESR]) were also observed in the tofacitinib group compared with placebo before Month 6.

Results from the tofacitinib long-term extension studies demonstrate that the efficacy of tofacitinib is maintained for up to 96 months with respect to physical functioning (HAQ-DI) and the signs and symptoms of RA (ACR20).

Tofacitinib also significantly improved levels of pain and fatigue, and health related quality of life for patients with moderate to severe active RA compared with placebo by Month 6.

Patient reported outcomes (PRO) are a vital component of RA clinical trials and clinical practice, as they capture implications beyond clinical metrics, and instead elicit patients' personal perspectives of living with moderate-to-severe RA (19, 20).

Across the Phase III clinical trials, tofacitinib (in combination with MTX and monotherapy) significantly reduced patients' levels of pain and fatigue, and improved overall quality of life in patients with moderate-to-severe RA who were MTX-IR, cDMARD-IR or TNF-IR. Scores for pain (VAS), fatigue (FACIT-F) and quality of life (EQ-5D) were all significantly improved in the tofacitinib group compared with placebo by Month 6 in all trials (except ORAL Start [a MTX naïve population] where EQ-5D was numerically improved vs placebo and pain [VAS] was not recorded).

The ORAL clinical trial programme (n=6 trials) demonstrates that treatment with tofacitinib is well-tolerated.

Across the ORAL Phase III clinical trial programme (including ORAL Standard, Scan, Sync, Solo, Start and Step) treatment with tofacitinib 5 mg was well tolerated. The most frequent adverse events (AE) reported throughout the Phase III trials were upper respiratory tract infections and nasopharyngitis (12).

Pooled safety data from across the ORAL clinical trial programme provided a maximum follow-up time of 8.5 years. For patients receiving a constant 5 mg dose of tofacitinib (n=2,342), the incidence rates (patient with events/100 patient-years) were:

- 153.1 (95% Confidence interval [CI]: 146.1, 160.4) for any AE.
- 9.2 (95% CI: 8.2, 10.3) for any serious AE (SAE).
- 7.2 (95% CI: 6.4, 8.2) for discontinuation due to AEs.
- 0.3 (95% CI: 0.2, 0.35) for mortality within 30 days of last dose of study drug.

Additionally, no unexpected safety issues were found in ORAL Strategy. The frequencies of treatment-emergent (TE) AE (TEAE), serious and severe AEs, discontinuation due to AEs were generally comparable across the tofacitinib (in combination with MTX and monotherapy) and adalimumab in combination with MTX treatment arms.

Our basecase network meta-analysis (NMA) demonstrates that tofacitinib (in combination with MTX and as monotherapy) is superior to cDMARDs (incl. MTX)/placebo and offers comparable efficacy to bDMARDs currently recommended by NICE.

To compare the short-term efficacy of tofacitinib (in combination with MTX and as monotherapy) with the comparators outlined in the NICE decision problem, we undertook a systematic literature review and performed a network meta-analysis (NMA) using a binomial logit model. The NMA assessed EULAR response criteria at Month 6, which informs treatment decisions made in UK clinical practice, and change in HAQ-DI at Month 6 for patients who attained a moderate or good EULAR response.

The basecase NMA demonstrated that tofacitinib (in combination with MTX and as monotherapy) is superior to cDMARDs (incl. MTX)/placebo at attaining at least a moderate, and at least a good EULAR response and change in HAQ-DI at Month 6.

The basecase NMA also permitted comparisons to bDMARDs currently recommended by NICE for people with moderate-to-severe active RA who are cDMARD-IR (TA375) and bDMARD-IR (TA195 and TA415). In the cDMARD-IR population, there were no statistical differences between tofacitinib in combination with MTX and currently recommended bDMARDs in attaining at least a moderate, and at least a good EULAR response, except for tocilizumab, which was statistically superior in attaining at least a good EULAR response.

In addition, we undertook multiple scenario analyses to explore how the NMA outputs varied when using an alternative configuration of the available clinical trials and an alternative modelling approach (i.e., multinomial probit). Overall, the NMA scenario analyses demonstrated that results were sensitive to the trials included in the basecase network, and less influenced by the modelling approach. The basecase ensured that we were able to compare tofacitinib to all comparators included in the NICE decision problem for patients with moderate-to-severe RA who have experienced an inadequate response to cDMARDs; however, in doing so, this approach favoured some comparators (e.g., certolizumab pegol, golimumab, and tocilizumab) over tofacitinib, which could influence cost-effectiveness results.

1.4 *Summary of the cost-effectiveness analysis*

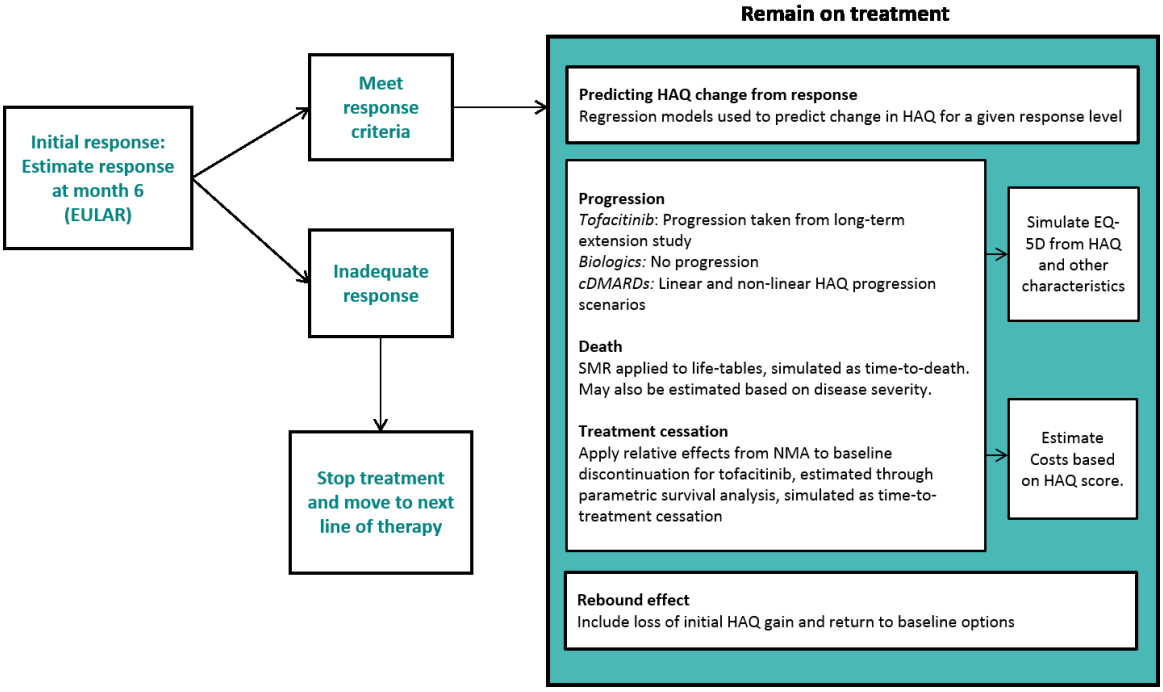
1.4.1 *Cost-effectiveness model*

Our patient-level simulation (PLS) approach aligned with the recent NICE multiple technology appraisal (MTA, TA375), and the modelled populations were considered generalisable to UK clinical practice and treatment sequences reflect current NICE Guidance – TA195, TA375, and TA415 (21-23).

A patient-level simulation (PLS) model was developed (in accordance with recent NICE Decision Support Unit guidance on PLS and statistical methods (24-27)) to compare tofacitinib in combination with MTX and as monotherapy against comparators relevant to the NICE decision problem.

The model utilises a two-stage approach (see Figure 1), to accurately reflect how patients with moderate-to-severe RA are treated in UK clinical practice. In the short-term, EULAR response criteria are used to assess treatment response at Month 6. Patients, who attain a moderate or good EULAR response, experience a reduction in HAQ-DI and remain on treatment, while those who have an inadequate response transition to the next treatment in the sequence. In the long-term, patients are exposed to a risk of treatment cessation, HAQ-DI progression, and death. On cessation of treatment, patients experience a worsening in HAQ-DI equal to their initial gain and then move on to the next treatment. This process is repeated for each treatment in the sequence until a patient moves to the final phase of the treatment pathway. Patients continue in the model until death.

Figure 1: Outline of model methods



The cost-effectiveness analysis utilized data from the ORAL clinical trial programme, which included a diverse population of participants across Europe, the Americas, and Asia. Comparing baseline characteristics such as age, disease severity (DAS-28 and HAQ-DI) and disease duration from the ORAL clinical trials with a recent extraction from the British Society of Rheumatology Biologics Registry (BSRBR) presented in TA375, suggests that participants are representative of patients treated in the UK.

To accurately reflect how people with severe RA are treated in UK clinical practice, we observed treatment sequences used in current NICE guidance, for patients who are cDMARD-IR (TA375) and bDMARD-IR (TA195 and TA415) and modelled additional sequences where clinically relevant.

Cost-effectiveness is reported in terms of incremental cost per quality-adjusted life year (QALY). Costs are considered from both a National Health Service (NHS) and Personal and Social Services (PSS) perspective, and default analyses use a lifetime time horizon and 3.5% annual discounting of costs and outcomes.

1.4.2 *Cost-effectiveness results*

Tofacitinib in combination with MTX (with Patient Access Scheme [PAS] applied) is a cost-effective treatment for patients with severe active RA who have experienced an inadequate response to cDMARDs (incl. MTX). Tofacitinib in combination with MTX dominated or extendedly dominated the majority of comparator treatments currently recommended by NICE in TA375 and available biosimilars.

The base case analysis for patients with severe active RA who have experienced an inadequate response to cDMARDs (incl. MTX) showed that tofacitinib in combination with MTX dominated or extendedly dominated all comparators recommended in TA375 with the exception of tocilizumab, which was more costly and more effective.

The incremental cost-effectiveness ratio (ICER) range for tofacitinib in combination with MTX (with PAS applied) compared with cDMARDs was comparable to the range that informed the NICE Appraisal Committee's decision in TA375. The ICERs for patients who experienced rapid HAQ-DI progression whilst on cDMARDs (incl. MTX), and for the whole severe cohort were £23,676 per QALY and £41,617 per QALY respectively. The ICER range for the more costly and more effective tocilizumab compared to tofacitinib was £88,129 to £139,113 per QALY for patients who experienced rapid HAQ-DI progression whilst on cDMARDs (incl. MTX), and for the whole severe cohort respectively.

Tofacitinib monotherapy (with PAS applied) is a cost effective treatment for patients who have experienced an inadequate response to cDMARDs who are contraindicated to, or intolerant of MTX. Tofacitinib extendedly dominated adalimumab, etanercept, and tocilizumab in this patient population.

For patients who are contraindicated to, or intolerant of MTX, tofacitinib monotherapy (with PAS applied) dominated or extendedly dominated relevant comparators considered in our analysis, with the exception of tocilizumab, which was more costly and more effective

The ICER range for tofacitinib monotherapy (with PAS applied) compared with cDMARDs (excl. MTX) was £25,807 to £56,231 per QALY for patients who experienced rapid HAQ-DI progression whilst on cDMARDs (incl. MTX), and for the whole severe cohort respectively.

Sensitivity analysis supported the robustness of the basecase results with the average probabilistic ICER range for tofacitinib in combination with MTX was £23,487 to £40,610 and monotherapy was £25,094 to £53,443 for severe RA patients who experience rapid HAQ progression whilst on cDMARDs (incl. MTX) and the whole severe cohort respectively. At a willingness-to-pay (WTP) threshold of £30,000, tofacitinib in combination with MTX and as monotherapy was the optimal treatment in 39% and 65% of scenarios, across the eight comparators included in the NICE decision problem (incl. MTX).

The stability of the basecase cost-effectiveness results for tofacitinib in combination with MTX or as monotherapy were further substantiated across a number of scenario analyses which explored alternate data sources and assumptions.

Consequently, we believe that tofacitinib (with PAS applied) in combination with MTX or as monotherapy demonstrates value for money to the NHS and represents a cost-effective treatment option for patients who have severe RA who have had an inadequate response to cDMARDs.

Tofacitinib (with PAS applied) dominated the majority of comparator treatments in the bDMARD-IR population when treatment with rituximab was not appropriate or for patients who experience an AE whilst receiving treatment with rituximab, or for patients who are contraindicated to, or intolerant of MTX.

The results of our analysis demonstrated that tofacitinib in combination with MTX dominated golimumab and tocilizumab, both in combination with MTX. The ICER for abatacept in combination with MTX vs tofacitinib in combination with MTX was

£1,544,810 per QALY. Additionally, tofacitinib monotherapy dominated golimumab and tocilizumab monotherapy for patients who are contraindicated to, or intolerant of MTX.

Tofacitinib in combination with MTX after treatment with rituximab in combination with MTX dominated all relevant comparators included in the NMA.

For patients who have experienced an inadequate response to both, a first line bDMARD and rituximab in combination with MTX, tofacitinib dominates golimumab, tocilizumab and abatacept, all in combination with MTX.

Results from PSA and scenario analyses were very stable across all subpopulations explored in the bDMARD-IR population. Consequently, we believe that tofacitinib (with PAS applied) demonstrates value for money to the NHS and represents a cost-effective treatment option for patients who have severe RA who have had an inadequate response to bDMARDs who are contraindicated to rituximab, or who experience an AE whilst receiving treatment with rituximab, or for patients who are contraindicated to, or intolerant of MTX

In addition to the severe active RA population, where NICE currently recommend bDMARDs, we also explored the cost-effectiveness of tofacitinib in combination with MTX for people with moderate-to-severe RA (DAS28 between 3.2 and 5.1), who have experienced an inadequate response to cDMARDs. Results for this population are uncertain and depend on the modelling approach and treatment sequence adopted. We explored two model designs, and several treatment sequences, which resulted in a range of plausible ICERs between £29,186 to 60,364 per QALY.

The cumulative cost of introducing tofacitinib to the NHS in England and Wales, is estimated to be [redacted] over 5 years. With the PAS applied, the introduction of tofacitinib is not expected to increase the cost incurred by the NHS of treating a patient with severe RA.

Concluding remarks

- Tofacitinib citrate is an innovative, novel, orally administered Janus Kinase (JAK) inhibitor.
- Tofacitinib and the JAK inhibitors represent a new class of immunomodulating agents, which the European League Against Rheumatism (EULAR) recognise as Targeted Synthetic Disease-Modifying Antirheumatic Drugs (tsDMARDs).
- Evidence for the clinical efficacy and safety of tofacitinib (both in combination with MTX or as a monotherapy) for people with moderate-to-severe active RA has been demonstrated across six Phase III and one Phase IIIb/IV clinical trials which included a diverse set of sub-populations of RA patients. As of March 2015, 6,194 patients received tofacitinib in the ORAL trial programme, which equates to19,400 patient years.
- Tofacitinib is approved for use for moderate-to-severe RA in more than 50 countries worldwide; approximately 70,000 patients have been treated with tofacitinib worldwide up to the end of 2016.
- The treat-to-target paradigm is internationally accepted as best practice in the management of RA, and forms the basis of clinical guidelines from EULAR and the ACR, which advocates rapid attainment of remission or low disease activity (LDA) to halt disease progression and maintain health related quality of life (HRQoL).
- It is widely accepted, however, that despite the availability of multiple biologic therapies for the treatment of moderate-to-severe RA, treatment failure and intolerance are common. It is therefore critical for patients that alternative treatments are accessible under NHS care.
- The ORAL clinical trials demonstrated that:
    - Tofacitinib in combination with MTX significantly improves the rate of remission and low disease activity by Month 6 compared with placebo.
    - Tofacitinib significantly increased the physical functioning of patients with moderate-to-severe active RA compared with placebo in all ORAL clinical trials.
    - Tofacitinib significantly reduced the signs and symptoms of patients with moderate-to-severe RA by Month 6 compared with placebo, as measured by the American College of Rheumatology (ACR) response criteria.
    - Tofacitinib was associated with a numerical delay in radiographic progression in patients with RA compared with placebo in ORAL Scan.
    - Tofacitinib also significantly improved levels of pain and fatigue, and health related quality of life for patients with moderate to severe active RA compared with placebo by Month 6.
    - Treatment with tofacitinib is well-tolerated.
- Our basecase network meta-analysis (NMA) demonstrates that tofacitinib (in combination with MTX and as monotherapy) is superior to cDMARDs (incl. MTX)/placebo and offers comparable efficacy to bDMARDs currently recommended by NICE.
- Tofacitinib in combination with MTX (with PAS applied) dominated or extendedly dominated the majority of comparator treatments currently recommended by NICE in TA375.
- For patients who have experienced an inadequate response to cDMARDs who are contraindicated to, or intolerant of MTX, tofacitinib monotherapy (with PAS applied) extendedly dominated adalimumab, etanercept, and tocilizumab in this patient population.
- Tofacitinib (with PAS applied) was also cost-effective in the bDMARD-IR population:
    - When treatment with rituximab was not appropriate or for patients who experience an AE whilst receiving rituximab, or for patients who are contraindicated to, or intolerant of MTX.
    - After treatment with rituximab in combination with MTX dominated all relevant comparators included in the NMA.
- We believe that tofacitinib in combination with MTX or as monotherapy (with PAS applied) demonstrates value for money to the NHS and represents a cost-effective treatment option for patients who have severe RA who have had an inadequate response to DMARDs
- With the PAS applied, the introduction of tofacitinib to the NHS in England and Wales, is not expected to increase the cost of treating a patient with severe RA.

2 The technology

2.1 *Description of the technology*

Brand name: Xeljanz

UK approved name: Tofacitinib citrate

Therapeutic class: Oral Janus kinase inhibitor

Mechanism of action: Tofacitinib offers a novel mechanism of action for treatment of RA through the potent, selective and reversible inhibition of the ATP binding site of JAK enzymes (4). The JAK family controls activation of signaling cascades for many cytokines important for the pathogenesis of immune-mediated inflammatory diseases, making them candidates for targeted therapeutic interventions for rheumatoid arthritis, psoriasis, psoriatic arthritis, and ulcerative colitis.

In enzymatic assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2. In contrast, tofacitinib is not thought to inhibit other kinases in the human genome. In human cells, tofacitinib preferentially inhibits signalling by heterodimeric cytokine receptors that associate with JAK3 and/or JAK1 with functional selectivity over cytokine receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib attenuates signalling of interleukins (IL-2, -4, -6, -7, -9, -15, -21) and type I and type II interferons, which will result in modulation of the immune and inflammatory response.

2.2 *Marketing authorisation/CE marking and health technology assessment*

2.2.1 *Marketing authorisation/CE marking*

The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on the granting of a marketing authorisation for tofacitinib on 26th January 2017. The European Commission granted marketing authorisation on the 27 March 2017.

2.2.2 *(Anticipated) indication(s) in the UK*

Tofacitinib in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs.

Tofacitinib can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.

2.2.3 *(Anticipated) restrictions or contraindications*

It is recommended not to initiate dosing in patients with haemoglobin <9 g/dL or an absolute neutrophil count <1,000 cells/mm^3 or an absolute lymphocyte count <750 cells/mm^3.

Contraindications for tofacitinib are:

- Hypersensitivity to the active substance or to any of the excipients listed below:
  - Tablet core:
    - microcrystalline cellulose
    - lactose monohydrate
    - croscarmellose sodium
    - magnesium stearate
  - Film coat:
    - hypromellose 6cP (E464)
    - titanium dioxide (E171)
    - lactose monohydrate
    - macrogol 3350
    - triacetin (E1518)
- Active tuberculosis, serious infections such as sepsis, or opportunistic infections.
- Severe hepatic impairment.
- Pregnancy and lactation

2.2.4 *SmPC/Information for use and (Draft) assessment report*

The Summary of Product Characteristics (SmPC) and European Public Assessment Report (EPAR) are provided in Appendix 1.

2.2.5 *Main issues discussed by regulatory authorities*

Clinical efficacy

The efficacy of tofacitinib 5 mg for radiographic progression was discussed extensively by the CHMP (see Section 4.13 for full discussion). Radiographic progression was assessed in cDMARD experienced and MTX-IR patients in ORAL Scan (NCT00847613); although more favourable results were observed in the tofacitinib 5 mg group, the difference was not significant compared with placebo (p=0.0792). Pfizer argued that the lack of significance may be explained by the slow rate of progression observed in the placebo group, which was approximately one-fifth of that predicted from the estimated mean annual radiographic progression in the published literature; the study had been powered based on this predicted rate of progression. Further data supporting the ability of tofacitinib to favourably affect radiographic progression were provided in a study of MTX-naïve patients in ORAL Start (NCT01039688). In this study, tofacitinib 5 mg as monotherapy significantly improved radiographic progression up to Month 24 compared with MTX.

[redacted]

[redacted]. Pfizer are currently assessing the relative safety and efficacy of tofacitinib 5 mg in combination with MTX and as monotherapy in a head-to-head trial (ORAL Strategy [NCT02187055]; Section 4.14).

Clinical safety

Between the first CHMP opinion in 2013 and the positive CHMP opinion received in January 2017, there was discussion around the safety of tofacitinib. [redacted] As of 31 March 2015, no new risks or safety signals were identified in a long-term safety database compared to those previously reported in the randomised controlled trials and long-term extension data from the tofacitinib RA development programme. Types and rates of AEs (including infections and malignancies) were similar to those observed in Phase III trials and were stable over time, with no evidence of directional trends with longer-term tofacitinib exposure through 8.5 years. With the exception of the rates for herpes zoster, the incidence of most AEs were generally comparable with that of biologics of RA (28). The CHMP concluded that [redacted]

2.2.6 *Anticipated date of availability in the UK*

Tofacitinib is expected to be available in the UK by April 2017.

2.2.7 *Regulatory approval outside the UK*

Tofacitinib was approved in the US by the Food and Drug Administration (FDA) in November 2012 to treat adults with moderately to severely active RA who have had an inadequate response to, or who are intolerant of, methotrexate (11). It may be used as monotherapy or in combination with methotrexate or other non-biologic DMARDs. Tofacitinib is approved for use in moderate-to-severe RA in more than 50 countries worldwide, including Australia, Canada, Japan, Switzerland, Russia, and the USA (10, 11). As of March 2015, 55,000 patients have been treated with tofacitinib worldwide (29).

2.2.8 *Ongoing HTAs in the rest of the UK*

A submission to the Scottish Medicines Consortium (SMC) is currently planned for 1st of May 2017. Pfizer is currently in discussions with All Wales Medicines Strategy Group

(AWMSG) in Wales over the need for a submission, but it is likely to be excluded from AWMSG appraisal as NICE intends to publish final guidance on the tofacitinib single technology appraisal [ID526] for the same indication within 12 months from the date of marketing authorisation.

2.3 *Administration and costs of the technology*

The administration and costs of the technology are shown in Table 4.

Table 4: Costs of the technology being appraised

	Information	Source
Pharmaceutical formulation	Oral tablet	SmPC
Acquisition cost (excluding VAT)	Anticipated tofacitinib list price: • List price: £690.03 per pack (56 x 5 mg tablets) • [redacted]	Data on file
Method of administration	Orally	SmPC
Doses	5 mg	SmPC
Dosing frequency	Twice daily	SmPC
Average length of a course of treatment	Tofacitinib is intended for long-term treatment. Decision to continue therapy is based on the level of disease control obtained.	SmPC
Average cost of a course of treatment	List price: • Month 0–6: £4,500.60 • Subsequent annual cost: £9,001.19 • [redacted]	Cost effectiveness model (Section 5.5.2)
Anticipated average interval between courses of treatments	No interval in normal use.	SmPC
Anticipated number of repeat courses of treatments	Intended for continuous use.	SmPC
Dose adjustments	Dose adjustments are only required to manage adverse events. Tofacitinib should be reduced to 5 mg once daily in: • patients with severe (creatinine clearance <30 mL/min) renal impairment • patients with moderate hepatic impairment	SmPC
Anticipated care setting	Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of RA. This is usually secondary care depending on the local service model.	SmPC

Abbreviations: SmPC, summary of product characteristics.

2.3.1 *Patient Access Scheme*

For the purposes of this submission and as agreed with the NICE appraisal team, Pfizer has also submitted a confidential Patient Access Scheme (PAS) appendix with a proposed PAS price for tofacitinib 5 mg, which is currently being processed by the Patient Access Scheme Liaison Unit (PASLU) as submitted on 16th of March to Department of Health, referred to PASLU on the 21st of March.

2.4 *Changes in service provision and management*

Tofacitinib is an orally administered treatment option for patients who may otherwise progress to a parenteral bDMARD. Patients are typically required to undergo thorough training in injection technique before self-administration of bDMARDs and the healthcare professional must also agree that self-administration is appropriate (30-32); where bDMARDs are administered via infusion, this should performed by a healthcare professional trained in detecting infusion-related issues (33). Therefore, tofacitinib may reduce the administrative burden associated with parenteral therapy and tofacitinib offers a choice for needle-phobic patients.

2.4.1 *Additional test/investigations*

No additional tests or investigations are required beyond those that are already part of current clinical practice for bDMARDs.

2.4.2 *Main resource use to the NHS associated with the technology*

In addition to outpatient contact, patients receiving tofacitinib will require resources dedicated to pre- and on-treatment monitoring. These are consistent with the requirements for cDMARDs and bDMARDs and include:

- Full blood count (pre- and on-treatment)
- Erythrocyte sedimentation rate (ESR; pre- and on-treatment)
- Biochemical profile (pre- and on-treatment)
- Chest X-ray (pre-treatment)
- C-reactive protein (CRP; pre-treatment)
- Tuberculosis test (pre-treatment)

The time between monitoring visits is typically two months for tofacitinib, bDMARDs and cDMARDs.

2.4.3 *Additional infrastructure requirements*

Not applicable.

2.4.4 *Patient monitoring requirements*

Currently, the SmPCs of all NICE recommended bDMARDs state that patients should be monitored for signs of infection (30-36). Similarly, patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with tofacitinib. The additional monitoring requirements of tofacitinib, beyond routine practice

for most bDMARDs, are similar to those stated in the SmPC for tocilizumab (34). These include monitoring of:

- neutrophils at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter
- lipid parameters after 8 weeks following initiation of therapy

Monitoring requirements specific to tofacitinib include monitoring of lymphocytes (at baseline and every 3 months thereafter) and haemoglobin (at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter).

2.4.5 *Need for concomitant therapies*

No concomitant therapies are required. Tofacitinib can be given as monotherapy in the case of intolerance to MTX or when treatment with MTX is inappropriate.

2.5 *Innovation*

Tofacitinib can be considered a step change in the management of RA. Tofacitinib has a novel mode of action through the reversible inhibitor of the ATP binding site of JAK enzymes with selectivity for JAK1 and JAK3. The efficacy of tofacitinib is supported by data from six phase III clinical trials. Results from the clinical programme, which included patients relevant to the population outlined in the decision problem, provides evidence for the use of tofacitinib at multiple points in the NICE RA treatment pathway. In particular, these include patients who are MTX intolerant or resistant. Rapid onset of treatment efficacy was observed as early as two weeks in the clinical trial programme and long-term extension studies demonstrated the maintained efficacy. In addition, tofacitinib provided significant improvements in patient reported outcomes, including pain, fatigue and sleep.

Tofacitinib provides a rapid onset and highly-efficacious, orally-administered treatment option for patients who may otherwise progress to a parenteral bDMARD. The mode of administration may be important in adherence to RA treatment (37), and patients with RA have reported a preference for oral administration over other routes, including subcutaneous injection (38) (see Section 3.7 for discussion of adherence to injectable therapy in RA).

3 Health condition and position of the technology in the treatment pathway

- RA is a progressive, destructive, and lifelong condition with no known cause, and has a substantial clinical and economic impact on patients, healthcare systems, and society as a whole **(39)**; approximately 441,000 people have RA in England (1), of whom 15% have severe disease (DAS28 >5.1) **(22)**.
- The disease manifests as a range of symptoms, which potentially impact many areas of health and quality of life over a patient's lifetime.
  - Patients with RA suffer with a range of debilitating symptoms and are predisposed to a range of comorbid conditions contributing to an increase in mortality **(40)**
  - RA has a substantial negative impact on patients' health-related quality of life (HRQoL).
    - People with RA are twice as likely to suffer from depression **(41)**, major fatigue **(42)** and sleep loss **(43, 44)**, which are all associated with pain **(41, 42, 45)**.
    - The symptoms of RA also affect the ability to perform activities of daily living **(46)** and prevent participation in some activities **(47)**, while almost 30% of patients stop working, leave employment, or switch jobs due to RA **(47)**.
- Patients with RA often require care from informal caregivers (mainly spouses or partners), which may be a life-long commitment and can result in a substantial burden in terms of forgone paid employment, leisure activity, and personal health **(48)**.
- A range of conventional and parenteral biologic therapies are available for the treatment of RA.
  - Treatment failure is common and patients often cycle between a number of cDMARDs, which may continue once they reach severe disease and are eligible for bDMARDs **(49)**.
  - Currently, patients are eligible for treatment with bDMARDs if **(22)**:
    - "disease is severe, that is, a disease activity score (DAS28) greater than 5.1 and
    - disease has not responded to intensive therapy with a combination of conventional disease-modifying anti-rheumatic drugs (DMARDs)"
  - 85% of patients with non-severe RA (22) must therefore exhaust cDMARD treatment options and wait until they transition to severe disease before accessing more effective treatments.
  - Patients with persistent moderate disease (defined as a DAS28 3.2–5.1) in early RA could benefit from more aggressive therapy (50).
- EULAR recommend a treat-to-target approach in RA, with the primary target being

a state of sustained clinical remission (14). Until the desired treatment target is reached, drug therapy should be adjusted at least every three months (14). As RA is a heterogeneous disease with differing responses to treatment between patients, a diverse portfolio of RA therapies is therefore necessary to meet this goal.

- There is an unmet need for a treatment with an alternative mechanism of action to current bDMARDs which can be used either in combination with MTX or as a monotherapy
- There is also an unmet need for a treatment which offers similar efficacy to bDMARDs but can be offered to patients with moderate RA earlier in the treatment pathway.
- The proposed positioning of tofacitinib is second line after cDMARDs and before bDMARDs or as an alternative to bDMARDs. The inclusion of tofacitinib at second line would provide a highly-efficacious, orally-administrated treatment option for patients who have responded inadequately to MTX and would otherwise require intensive therapy with a combination of cDMARDs prior to progression to a parenteral bDMARD. Tofacitinib can also be given as monotherapy to patients who are intolerant to MTX.

3.1 *Disease overview*

RA is a progressive, destructive, and lifelong condition, which is characterised by inflammation of the synovium (joint lining), progressive erosion, and the destruction of cartilage and bone tissue of symmetrical joints. The exact cause of RA is unknown. However, as with other autoimmune diseases, environmental and genetic factors are thought to influence the onset of the disease. RA begins with an invasion of the synovium by white blood cells, which leads to synovitis (51). Chronic inflammation of the synovium is the primary pathophysiological process in RA and is sustained by pro-inflammatory cytokine activity (2, 52).

The complex nature of the disease manifests as a range of symptoms, which have the potential to impact many areas of health and quality of life over a patient's lifetime. The most visible symptoms are those affecting the joints (most commonly the wrists, fingers, knees, feet, and ankles), which include pain, stiffness, and joint swelling. Irreversible joint destruction resulting from chronic inflammation can restrict movement and eventually lead to joint deformity and disability (53). These symptoms are usually accompanied by systemic symptoms, including fatigue, weight loss, malaise, and extra-articular manifestations (EAMs) (53, 54). EAMs occur in 18–41% of patients (55) and are caused by an increase in circulating inflammatory mediators (including cytokines) (55, 56). Patients with RA are also predisposed to a range of comorbid conditions (such as cardiovascular disease [CVD]), which contribute to an increase in mortality (40).

Overall, the clinical features of RA result in a reduction in patients' quality of life. Quality of life can be affected by the symptoms of RA, such as pain (57), and through the increased morbidity and mortality that result from the comorbid conditions experienced by patients with RA (40). Beyond the patient burden associated with RA, the disease has broader implications across society. These include the effect that the disease has on the

carers and family of patients and the substantial economic impact on healthcare systems and society as a whole (39).

3.2 *Burden to patients, carers and society*

There are estimated to be around 441,000 people with RA in England (1), of whom 15% have severe disease (22, 58). Based on UK guidance for the initiation of bDMARDs (NICE TA375), severe disease is defined as DAS28 >5.1 (22). Currently, only patients with a DAS28 >5.1 are eligible for treatment with bDMARDs (22). However, patients with persistent moderate disease (defined as a DAS28 3.2–5.1) in early RA have also been shown to experience functional decline (as measured by HAQ-DI), suggesting that these patients could benefit from more aggressive therapy (50). Overall, RA is twice as prevalent in women than in men (59) and prevalence increases with age. Patients with RA are typically diagnosed when they are of working age and 50% of patients with RA would typically be expected to remain in work for 10 years from the point of diagnosis (58). The incidence of RA is therefore expected to increase substantially due to an ageing population.

3.2.1 *Patient burden*

Patients with RA suffer with debilitating symptoms that include pain, fatigue, tenderness, morning stiffness, loss of movement, and redness and swelling of the peripheral joints. In many patients, symptoms of RA emerge over weeks to months; however, in approximately 15% of patients, onset of disease occurs rapidly over a period of days to weeks (60). Over time, sustained inflammation contributes to cartilage damage and bone erosion, affecting up to 80% of patients within one year of diagnosis (51, 56). Joint destruction can also occur within four months after disease onset (61). Consequently, deformity is common and can affect multiple sites, particularly the hands and feet (60, 62, 63). However, patients can have severe RA symptoms without any visible deformity (64).

EAMs are common manifestation in patients with RA and occur in 18–53% of patients (55, 65) which may be more associated with severe or highly active disease and can involve many different organ systems and tissues, causing swelling and inflammation.

Patients are predisposed to a range of comorbid conditions, due to the underlying disease pathology. In the UK, comorbidities are common, with 58% of patients having one comorbidity at the time of starting bDMARDs and 25% having ≥1 comorbidity. Specifically, patients with RA have an increased risk of CVD, certain cancers, and infections compared with the general population (40) (Table 5). The increased mortality seen in patients with RA is largely due to the effect of these comorbidities (40). The joint damage central to the pathophysiology of RA also compounds the problem by limiting physical exercise, thus increasing the risk of CV disease (53).

Table 5: Risk of comorbidities in RA compared with people without RA

Comorbidity	Relative risk compared to non-RA patient
Cardiovascular disease, ratio (95% CI) (66, 67)	
MI requiring hospitalisation	3.17 (1.16, 8.68)
Silent MI	5.86 (1.29, 26.64)
Heart failure (all RA patients)	1.87 (1.47, 2.39)
Heart failure (RF+ patients)	2.59 (1.95, 3.43)
Cancer, ratio (95% CI) (68)	
Lymphoma	2.08 (1.80, 2.39)
Lung cancer	1.63 (1.43, 1.87)
Any infection, ratio (95% CI) (69)	1.45 (1.29, 1.64)

Abbreviations: CI, confidence interval; MI, myocardial infarction; RA, rheumatoid arthritis; RF, rheumatoid factor.

RA has a substantial negative impact on patient health-related quality of life (HRQoL), including mental well-being (57). People with RA are subsequently twice as likely to suffer from depression (one of the most common comorbidities in RA affecting 15% of patients), often as a result of increased levels of pain (40, 41, 70). Depression may lead to reduced adherence and maladaptive behaviours which may exacerbate the risk of greater disease activity and comorbidities (71). Furthermore, over 80% of patients with RA suffer from major fatigue, which is also linked to pain and depression (42). Estimates of the burden of fatigue in RA suggest that 60–94% of patients suffer from sleep loss (43, 44); poor sleep quality is also associated with higher levels of depressive symptoms, greater pain severity, and greater functional disability (45).

As RA progresses, the increasing joint deformity, loss of mobility and reduced function have a negative impact on physical wellbeing and the ability to perform activities of daily living (46) such as washing and dressing, or social and leisure activities (47, 72-74). In a global study of patients with RA, 47% stated that they had stopped participating in some activities because of their disease (47). Furthermore, almost 30% had stopped working, left a job, or switched jobs because of difficulties with RA (47), which may cause a substantial economic burden given that 50% of patients with RA would typically be expected to remain in work for 10 years from the point that they are diagnosed when they are of working age (58). Together, the mental and physical burden of RA can negatively affect patients' relationships with their partners (75), including physical intimacy, predominantly due to fatigue and pain (75).

When HRQoL is quantified using the Short Form-36 (SF-36), RA negatively affects all eight domains of the questionnaire compared with the UK general population (57), with the greatest impact on the physical and pain domains of the questionnaire (76). RA patients also show consistently lower scores for physical SF-36 components (physical function, role physical, bodily pain and global health) than patients with hypertension, type 2 diabetes, myocardial infarction and clinical depression (57).

3.2.2 *Societal burden*

3.2.2.1 Caregivers and family members

Patients with RA often require care from informal caregivers, who are mainly spouses or partners. Caregiving can be a life-long commitment, with one study estimating that the mean duration of care was ≥11 years (77). This can result in a substantial burden on informal caregivers in terms of forgone paid employment, leisure activity, and personal health (48). Caregiving may result in absenteeism from work, switching from full-time to part-time work, and limited opportunities to advance careers (78). Consequently, caregivers may experience a reduction in income (78). Caregivers can also become isolated due to the time spent caring for the patient and their social network often becomes more limited, increasing their sense of isolation (78). In addition, caregivers may experience feelings of guilt that they either are not doing more for the patient or for their resentment of the patient, accompanied by depressive feelings (78). Caring for patients with RA can also negatively impact the health of the caregiver, which may be related to the severity of the disease (48). A study by Jacobi et al, 2003 observed that >20% of partners of patients with RA suffered from moderate or extreme anxiety/depression, while nearly 50% had moderate or extreme pain/discomfort (77); this may be related to the difficulties in providing long-term care (77). Furthermore, decreased functional abilities of the patient may be positively correlated with caregiver burden (77); greater caregiver burden may be associated with a lower patient health status, worse mental health and the expectations that patients have of symptom-control (77). The impact of caregiving on the partners of patients in the UK has been examined in the National Rheumatoid Arthritis Society (NRAS) survey (Table 6).

Table 6: Impact of RA on the partners of patients

Aspect	Impact on partner
Financial	• 57% reported a negative or very negative effect on their household income.
Domestic	• 92% reported changes in their responsibilities for household tasks, with 46% reporting significant changes. • 82% managed these without paid help or help from family and friends.
Social	• 60% agreed that their social life was restricted because of their partner's RA.
Mood and well-being	• 93% (22% often and 13% most of the time) reported that their partner's RA affected their own mood or mental wellbeing.
Relationship	• 41% said that they had had difficulties in their relationship as a result of RA. • 67% reported that their sex life had been negatively affected. • 32% felt that their partner having RA had brought them closer.

Abbreviations: RA, rheumatoid arthritis.
Source: NRAS survey 2012 (79).

3.2.2.2 Economic burden

RA has a substantial economic impact on patients, healthcare systems, and society as a whole (39). Overall, total healthcare costs for patients with RA are 2–3 times higher than for matched controls in the general population (80). The direct cost of RA is primarily a

result of long-term medical treatment and the high likelihood of surgery (81). Within the UK, direct costs were estimated to contribute 51% of the total annual cost of RA per person (82). However, indirect costs contribute a significant amount to the economic burden of RA and may even be greater than direct costs (83). Indirect costs result primarily from lost productivity (57% of indirect costs), absenteeism or disability (21% of indirect costs), job turnover or early retirement (21% of indirect costs) and work equipment adaptations for affected employees (84-86). In England, the estimated annual healthcare cost of RA in 2008 was £557 million, with estimated costs due to sick leave and work-related disability (lost employment) of £1.8 billion a year (58). Estimates of the total cost of RA to the UK economy are between £3.8 and £4.8 billion annually, which includes the cost of healthcare, carers, nursing homes, private expenditure, sick leave and work-related disability (58).

3.3 *Clinical pathway of care*

3.3.1 *NICE clinical guidance*

NICE guideline Clinical Guideline (CG)79 (87) and NICE technology appraisal 375 (22) provide recommendations on the clinical pathway of care in RA. Further recommendations are provided by EULAR guidelines (discussed in Section 3.6) (5).

Patients with active RA within three months of the onset of persistent symptoms should be offered MTX, ≥1 cDMARD and short-term Glucocorticoids (GCCs). If combination therapy with MTX is not appropriate because it is contraindicated or due to intolerance, cDMARD monotherapy should be initiated, placing a greater emphasis on fast escalation to a clinically effective dose rather than on the choice of cDMARD. Once disease control has been achieved, the dose should be cautiously reduced to levels that still maintain disease control. However, if symptoms return, the previous disease-controlling dose should be reinstated. GCCs can be used short-term to manage flares, or long-term in patients with established RA for whom all other treatment options have been offered.

Biologic DMARDs (adalimumab [ADA], etanercept [ETN], infliximab [INF], certolizumab pegol [CZP], golimumab [GOL], tocilizumab [TOC] and abatacept [ABA]), in combination with MTX, are recommended for patients who have severe RA (defined as a DAS28 score >5.1) and are cDMARD-IR. The first bDMARD should be the least expensive drug, taking into account administration costs, dose needed and product price per dose (22). For patients who are intolerant to MTX, or when MTX is contraindicated, only a subset of bDMARDs (adalimumab, etanercept, certolizumab pegol or tocilizumab) can be used as monotherapy, thereby reducing the treatment options available to these patients. Treatment with bDMARDs should be assessed for efficacy based on EULAR response criteria (Table 7) at Month 6 and withdrawn if a moderate EULAR response, or better, is not maintained.

Table 7: The EULAR response criteria

DAS28 at Month 6	Improvement in DAS28 from baseline		
	>1.2	≤1.2 and >0.6	≤0.6
≤3.2	Good	Moderate	No response
≤5.1 and >3.2	Moderate	Moderate	No response
>5.1	Moderate	No response	No response

Abbreviations: DAS28, Disease Activity Score in 28 joints; EULAR, EULAR, European League Against Rheumatism.
Source: Fransen et al, 2009 (88).

3.3.2 *Treat-to-target recommendations*

The NICE clinical pathway provides a framework for achieving and maintaining disease control. However, reaching the target of remission or low-disease activity is considered optimal by EULAR and is associated with improved outcomes in patients with RA (14). The treat-to-target recommendations provide a basis towards achieving these optimal therapeutic goals (14). The first and key overarching principle is that the treatment of RA should be based on shared decisions between the patient and the healthcare professional (14). This is in line with the NICE guidance on bDMARDs, which states that the guidance should be taken fully into account alongside the individual needs, preferences and values of patients (22). Overall, there are 10 recommendations on treating RA to target (Table 8). The sequence follows a hierarchical order, with the first (target of clinical remission) deemed the most important. Together, these recommendations help to guide treatment strategy and indicate the aspects of disease control that should be considered.

The key points from the treat-to-target guidelines that should be considered in clinical practice are:

- The primary target for treatment of rheumatoid arthritis should be a state of sustained clinical remission
- Until the desired treatment target is reached, drug therapy should be adjusted at least every three months

These recommendations therefore mean that a broad range of treatments with varying mechanisms of action are required for patients with RA to allow their treatment to be regularly adjusted and ensure they meet and maintain their treatment goal. It should be noted that the current restriction of bDMARDs in the UK to patients with severe RA (DAS28 >5.1) means that patients who currently have moderate RA (DAS28 ≤5.1 and >3.2) are restricted to cDMARDs when attempting to achieve these treatment targets. There is consequently an unmet need for a treatment with similar efficacy to bDMARDs which can be offered to patients with moderate RA to help them achieve their treatment goals.

Table 8: Recommendations on treating RA to target (2014 update)

1	The primary target for treatment of rheumatoid arthritis should be a state of clinical remission
2	Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity
3	While remission should be a clear target, low-disease activity may be an acceptable alternative therapeutic goal, particularly in long-standing disease
4	The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions
5	The choice of the (composite) measure of disease activity and the target value should be influenced by comorbidities, patient factors and drug-related risks
6	Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every six months) for patients in sustained low-disease activity or remission
7	Structural changes, functional impairment and comorbidity should be considered when making clinical decisions, in addition to assessing composite measures of disease activity
8	Until the desired treatment target is reached, drug therapy should be adjusted at least every three months
9	The desired treatment target should be maintained throughout the remaining course of the disease
10	The rheumatologist should involve the patient in setting the treatment target and the strategy to reach this target

Abbreviations: RA, rheumatoid arthritis.
Source: Smolen et al, 2015 (14).

3.3.3 *Proposed positioning of tofacitinib within the clinical pathway*

Patients with moderate RA (DAS28 ≤5.1 and >3.2) will currently receive therapy with cDMARDs (initially MTX) which will intensify if no treatment response is achieved until the patient has tried two different cDMARDs for 6-months each and has severe disease (DAS28>5.1) (Figure 2).

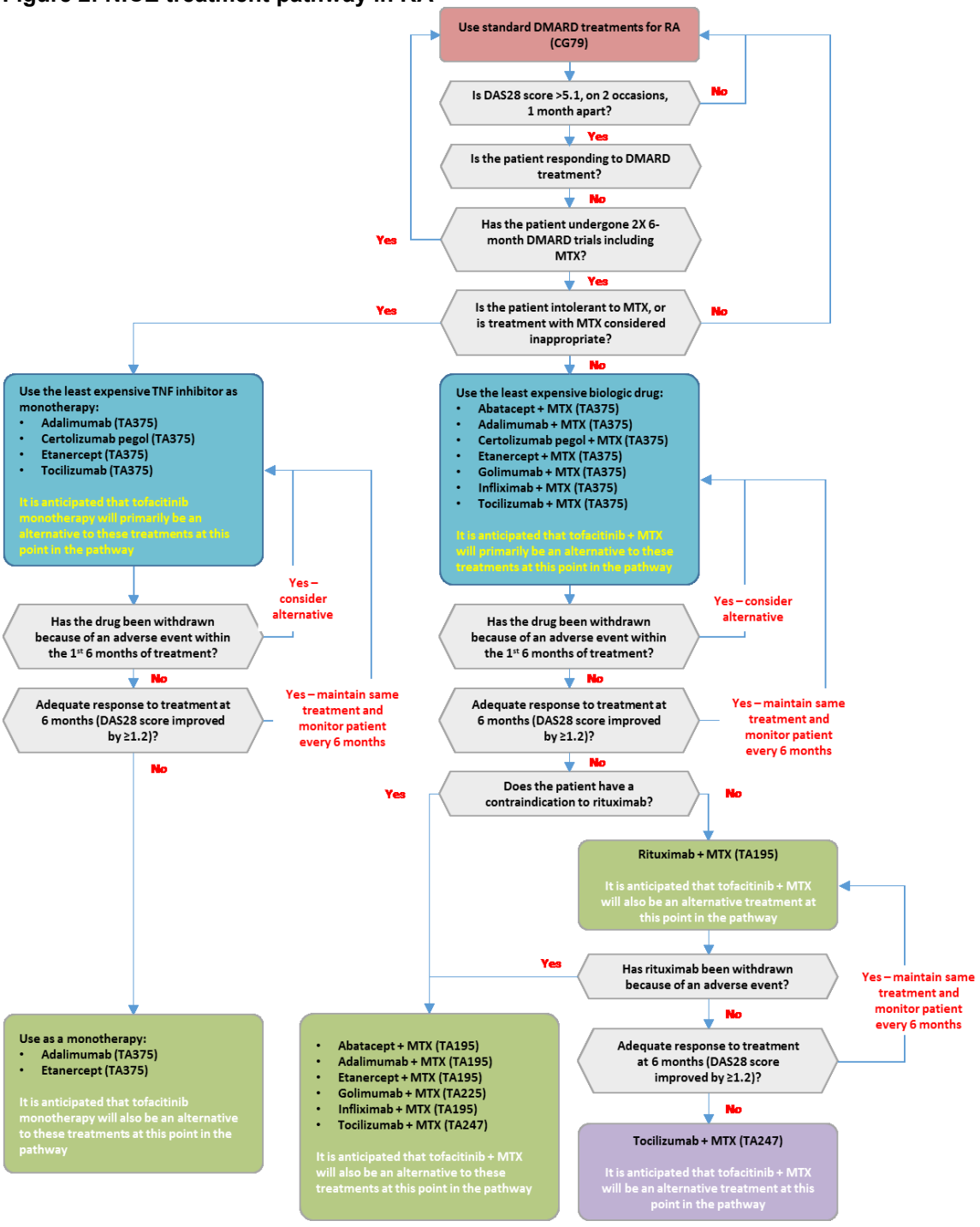
Once severe RA is reached patients will be offered a bDMARD, either in combination with MTX or as a monotherapy if intolerant to MTX (Figure 2). It should be noted that there are only four treatments available to patients who require a monotherapy, three of which have the same mechanism of action (TNF-inhibitor). If patients maintain their response to treatment, they will remain on their current bDMARD and will be monitored for treatment failure or AEs causing treatment withdrawal. Should an AE causing withdrawal occur another bDMARD will be offered; however, if an adequate response to therapy is not achieved within 6 months of initiation (DAS28 improved by ≥1.2), patients will be considered bDMARD-IR and (if not contraindicated to treatment) will be offered rituximab followed by tocilizumab if rituximab fails. If contraindicated to these treatments or intolerant to MTX an alternative bDMARD will be offered.

Based on the treat-to-target guidelines (Section 3.3.2) and the current pathway for severe RA, there is an unmet need for a treatment with an alternative mechanism of action to current bDMARDs which can be used either in combination with MTX or as a monotherapy to broaden the possible options for patients with RA to ensure they can achieve their treatment goals. A second unmet need is for a treatment which offers

similar efficacy to bDMARDs but can be offered to patients with moderate RA earlier in the treatment pathway.

The proposed positioning of tofacitinib is second line after cDMARDs and before bDMARDs or as an alternative to bDMARDs. The inclusion of tofacitinib at second line would provide a highly-efficacious, orally-administrated treatment option for patients who have responded inadequately to MTX and would otherwise require intensive therapy with a combination of cDMARDs prior to progression to a parenteral bDMARD. Tofacitinib can also be given as monotherapy to patients who are intolerant to MTX.

Figure 2: NICE treatment pathway in RA



3.4 *Life expectancy*

Mortality rates in patients with RA are 1.5–1.6-fold higher compared with the general population (89). Consequently, RA is associated with a reduction in life expectancy of 3 to 10 years (90). The risk of death also increases with disease severity (91). The causes of death in patients with RA is similar to the general population, with CVD reported as the most common cause (92). However, RA is not commonly recorded as a cause of death, or mentioned, on death certificates (89, 93). Without identifying RA as an underlying condition, the true mortality of the disease is therefore difficult to ascertain (93).

In the UK, the estimated standardised mortality rate (SMR) of patients with RA is 1.06–2.7 (94-98). A single-site study conducted in England assessed the mortality of patients (n=2,517) with RA across three cohorts depending on enrolment year (cohort 1: 1990–1994; cohort 2: 1995–1999; cohort 3: 2000–2004) (92). Overall, the SMR for patients who met the 2010 ACR/EULAR criteria (64) was 1.22 (95% CI: 1.07, 1.40) (92). The highest SMR (1.39; 95% CI: 1.18, 1.65) was observed in rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (CCP) positive patients (92). The SMR for these subgroups did not change significantly across the three cohorts (92). This indicates that mortality rates for patients with RA have not improved over the past 20 years in England, compared with the general population (92).

3.5 *Relevant NICE guidance, pathways or commissioning guides*

- **NICE guideline CG79** (87) covers the diagnosis and management of RA in adults (over 16 years). The guideline also provides guidance on pharmacological management of RA with cDMARDs and glucocorticoids. The key recommendations are summarised in Section 3.3.
- **NICE technology appraisal (TA) 375** (22) provides evidence-based recommendations for bDMARDs, including adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept. The key recommendations are summarised in Section 3.3. Additional NICE TAs include:
    - TA195 (21): Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of RA after the failure of a TNF inhibitor
    - TA225 (99): Golimumab for the treatment of RA after the failure of previous DMARDs
    - TA247 (100): Tocilizumab for the treatment of RA
    - TA415 (23): Certolizumab pegol for treating RA after inadequate response to a TNF-alpha inhibitor
- **NICE quality standard (QS) 33** (101) describes high-priority areas for quality improvement in a defined care or service area. The key quality statements (and rationale) relevant to this submission are:
    - **QS3**: People with newly diagnosed RA should be offered short-term GCCs and a combination of DMARDs by a rheumatology service within 6 weeks of referral.

Rapid initiation of treatment optimises the 'window of opportunity' within which effective treatment can improve long-term outcomes such as joint damage, joint function and quality of life.

  - **QS5**: People who have active RA should be offered monthly treatment escalation until the disease is controlled to an agreed low disease activity target. Monthly treatment escalation is important to achieving disease control rapidly, which results in a lower disease activity, and therefore reduced impact of the disease in terms of joint function and everyday living. The low disease activity target is agreed with the patient to maximise shared decision-making and patient satisfaction with their functional ability and suppression of symptoms.

- **RA NICE pathway** covers the guidance NICE has produced on RA, including the TA, CG and QS described above. The part of the pathway relevant to this submission is Drug treatment for rheumatoid arthritis (102).
- **NICE Clinical Knowledge Summary** (103) provides an overview of RA management in primary care. The key recommendations include:
  - Specialists will usually start a combination of DMARDs, plus a short-term corticosteroid. Ideally, treatment should be started within 3 months of the onset of symptoms. First-line treatment is usually MTX and ≥1 DMARD. DMARDs require regular monitoring with blood tests. This may be done in secondary care but can carried out in primary care under a shared care agreement.

3.6 *Clinical guidelines*

In addition to the NICE guidance and pathways described in Section 3.5, clinical guidelines and national policies of relevance are listed below:

- **EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying anti-rheumatic drugs: 2016 Update** (5). JAK inhibitors (referred to as targeted synthetic DMARDs [tsDMARDs] in the guideline) are now recommended for use as a second line therapy by EULAR. The guideline also states that '*in patients who cannot use cDMARDs as a comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other bDMARDs',* indicating a preference for use of these agents as monotherapy over bDMARDs. EULAR recommend a three-phase treatment algorithm:
  - Phase I: Therapy with DMARDs should be started as soon as the diagnosis of RA is made. Begin with MTX + GCC, or if the patient is MTX intolerant, initiate leflunomide (LEF) or sulfasalazine (SSZ) + GCC. If target (remission or low disease activity) is not achieved within 6 months (or no improvement is seen within 3 months) continue to phase II.
  - Phase II: If no prognostic factors are present, change to second cDMARD strategy: MTX, LEF, SSZ, alone or in combination. If target is not achieved within 6 months (or no improvement is seen within 3 months), add bDMARD or a JAK inhibitor to treatment regimen. If the patient has unfavourable prognostic factors (i.e. rheumatoid factor [Table 9]), add bDMARD or a JAK inhibitor to treatment regimen immediately. If target is not achieved within 6 months, or no improvement is seen within 3 months, continue to phase III.

- Phase III: In the case of failure for lack of efficacy and/or toxicity in phase II, change bDMARD and monitor for efficacy. If target is not achieved within 6 months, or no improvement is seen within 3 months, change to another bDMARD or a JAK inhibitor.

Table 9: Poor prognostic factors defined by EULAR

Poor prognostic factors
• Moderate (after csDMARD therapy) to high disease activity according to composite measures • High acute phase reactant levels • High swollen joint counts • Presence of RF and/or ACPA, especially at high level • Combinations of the above • Presence of early erosion • Failure of ≥2 csDMARDs

Source: EULAR recommendations 2016 update (5)
Abbreviations: ACR, American College of Rheumatology; ACPA, anti-citrullinated protein antibody; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; EULAR, European League Against Rheumatism; RF, rheumatoid factor.

- **British Society for Rheumatology (BSR)/British Health Professionals in Rheumatology (BHPR) guidelines** are available which cover different aspects of RA management. The relevant guidelines and their key points are as followed:
  - **BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs** (104). The guideline provides recommendations on the use of cDMARDs, with a particular focus on their toxicity profiles. The guideline does not cover the use of bDMARDs.
  - **BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy** (105). The guideline recommends bDMARDs for the treatment of adults who have active RA as measured by DAS28 >3.2 with ≥3 tender and ≥3 swollen joints and have undergone trials of two DMARDs, including MTX (unless contraindicated). A trial of DMARDs is defined as ≥2 DMARDs usually given concurrently over a 6-month period, with 2 months at standard doses, unless significant toxicity has limited the dose or duration of treatment. Treatment with bDMARDs in RA should be continued only if there is evidence of an adequate response (moderate EULAR response) to treatment following the first 6 months of continuous treatment.
- The BSR published a policy report in 2015 outlining recommendations for improving care in rheumatology (106). In particular, the report highlighted access to biologics:
  - UK health departments should commission a review of medicines approval processes, to improve access to biologics for all patients including those at the mild stage of the disease and those with rarer conditions.
  - Treatment with these specialist drugs at the mild stage of disease can prevent unnecessary disability.

3.7 *Issues relating to current clinical practice*

Due to the complex and chronic nature of RA, long-term treatment often involves a sequence of different therapies (107). Patients with RA may fail to respond or lose response to both cDMARDs and bDMARDs over time (108). Therefore, patients are required to cycle through different therapies in order to achieve remission or maintain disease control (49). As treatment failure may be due to a class effect, switching to a therapy with a different mode of action is a preferred option (49). Furthermore, patients may be intolerant to MTX; overall 8.6–10.5% of patients discontinue MTX due to AEs (109, 110). However, only four bDMARDs are currently recommended for use as monotherapy in the UK (Section 3.3.1), meaning that the options for these patients are currently limited. In order to meet these demands, a diverse portfolio of RA therapies and mechanisms of actions is therefore necessary (8). Tofacitinib is an effective new treatment option that expands upon the current treatment portfolio and offers a novel mechanism of action via an oral administration route. In addition to clinical measures of efficacy (such as disease activity), tofacitinib can provide improvements in patient-reported outcomes measuring physical functioning, pain and fatigue, which have been shown to be important outcomes from the patient's perspective (8). Furthermore, tofacitinib expands upon the limited treatment options for patients who are intolerant to MTX as tofacitinib can be given as monotherapy.

While bDMARDs have been shown to be effective in patients who do not respond or have lost response to cDMARDs (49), they all involve parenteral routes of administration. A recent study by Louder et al, 2016 suggested that patients with RA prefer oral administration over other routes, including subcutaneous injections (38). This may have important implications on adherence to bDMARDs as a study by Barton et al, 2009 demonstrated that mode of administration is central to uptake and adherence to medications in RA (37). Discontinuation of therapy in RA is also a substantial concern, with 21–35% of patients discontinuing anti-TNF therapy within the first year of treatment (111). A study by Bolge et al, 2015 reported that approximately 41% of patients receiving injectable bDMARDs discontinued treatment due to a negative injection experience (112). This included pain, burning or discomfort during and after injection, injection reactions (such as redness/swelling after injection), dislike of frequency of injection, fear of injections and a dislike of self-injection (112). A UK study of patients with RA also showed that many patients (typically older patients) are not confident about self-injecting their treatment (113), which could affect their adherence. Additionally, impaired hand function is commonly found in patients with RA and is often due to pain, reduced muscle strength and hand deformities (114). This may lead to problems with dexterity, which can present as a physical barrier to self-injection (115). As an easy-to-administer, highly-efficacious oral treatment, tofacitinib could therefore be a valuable option for patients who may otherwise progress to a parenteral bDMARD and could improve adherence compared with parenteral bDMARDs.

Finally, there is also a substantial unmet need for additional treatments for patients with moderate RA. Currently, only patients with a DAS28 >5.1 are eligible for reimbursement for treatment with bDMARDs (22). However, patients with persistent moderate disease (defined as a DAS28 3.2–5.1) in early RA have been shown to experience functional decline (as measured by HAQ-DI), suggesting that these patients could benefit from more aggressive therapy (50); UK clinical guidelines such as the BSR and BHPR RA

guidelines recommend the use of bDMARDs in moderate patients (105). Tofacitinib is licenced for use patients with moderate RA and could therefore be an important treatment option for these patients.

3.8 *Equality*

No equality issues are anticipated if tofacitinib is recommended for use in England and Wales.

4 Clinical effectiveness

The ORAL clinical trials demonstrated that tofacitinib 5 mg significantly improves the rate of remission and low disease activity by Month 6 compared with placebo.

Disease remission (DAS28-4[ESR] <2.6) is an extremely important outcome used to treat patients in UK clinical practice with moderate to severe active RA. Disease remission was assessed in five of the six ORAL clinical trials relevant to the decision problem which involved 1,897 patients randomised to tofacitinib 5 mg (n=1,216) or placebo (n=681, 5 mg=343 and 10 mg=338).

The ORAL clinical trial programme demonstrated that tofacitinib 5 mg, in combination with MTX (or cDMARD), resulted in significantly higher rates of disease remission compared to placebo, for:

- Patients with moderate-to-severe RA who are MTX-IR (tofacitinib 5 mg vs placebo) in both ORAL Standard (6.2% vs 1.1%; p<0.015) and ORAL Scan (7.2% vs 1.6%; nominal p-value: 0.003) at 6 months;
- Patients with moderate-to-severe RA who are cDMARD-IR (tofacitinib 5 mg vs placebo) in ORAL Sync (9.1% vs 2.7%; p<0.0038) at 6 months; and
- Patients with moderate-to-severe RA who are TNFi-IR (tofacitinib 5 mg vs placebo) in ORAL Step (6.7% vs 1.7%; p<0.0496) at 3 months.

Tofacitinib 5 mg as monotherapy also resulted in a numerical improvement in the rate of remission in patients who are DMARD-IR compared with placebo in ORAL Solo (5.6% vs 4.4%; p<0.62 at 3 Months).

Assessment of EULAR response (improvement in DAS28 from baseline; see Table 7) at Month 6 in ORAL Standard, Scan, and Sync demonstrated that [redacted]; therefore, these patients meet the EULAR criteria for maintenance of treatment.

Tofacitinib 5 mg significantly increased the physical functioning of patients with moderate to severe active RA compared with placebo in all ORAL clinical trials.

Preventing physical functional disability has been noted as important outcome for patients with RA. Disability can have a significant impact on patients' overall well-being and correlates with important personal consequences, such as inability to work (16, 116-119). Physical function is universally measured by the health assessment questionnaire disability index (HAQ-DI) score, which has been found to closely correlate with patient reported outcomes (PRO) (17).

Tofacitinib 5 mg in combination with MTX (or cDMARD) significantly improved HAQ-DI scores compared to placebo, for:

- Patients with moderate-to-severe RA who are MTX-IR (tofacitinib 5 mg vs placebo) in both ORAL Standard (–0.55 vs –0.24; p<0.001) and ORAL Scan (–0.40 vs –0.15; nominal p-value: <0.001) at 3 months;

- Patients with moderate-to-severe RA who are DMARD-IR (tofacitinib 5 mg vs placebo) in ORAL Sync (–0.46 vs –0.21; p<0.001) at 3 months; and
- Patients with moderate-to-severe RA who are TNFi-IR (tofacitinib 5 mg vs placebo) in ORAL Step (–0.43 vs –0.18; p<0.001) at 3 months.

Tofacitinib 5 mg also significantly improved physical functioning as monotherapy in patients who are DMARD-IR compared with placebo in ORAL Solo (–0.50 vs –0.19; p<0.001 at 3 months).

Tofacitinib 5 mg significantly reduced the signs and symptoms of patients with moderate to severe RA by Month 6 compared with placebo, as measured by the ACR response criteria

Signs and symptoms, primarily measured in clinical trials by ACR response criteria, is a clinically important measure used worldwide to assess the impact RA treatments have in reducing patients' RA disease severity (18).

Tofacitinib 5 mg in combination with MTX (or cDMARD) significantly reduced the signs and symptoms of RA as measured by ACR20 response rates for:

- Patients with moderate-to-severe RA who are MTX-IR (tofacitinib 5 mg vs placebo) in both ORAL Standard (51.5% vs 28.3%; p<0.001) and ORAL Scan (51.5% vs 25.3%; p<0.001) by 6 months;
- Patients with moderate-to-severe RA who are DMARD-IR (tofacitinib 5 mg vs placebo) ORAL Sync (52.7% vs 31.2%; p<0.001) by 6 months; and
- Patients with moderate-to-severe RA who are TNFi-IR (tofacitinib 5 mg vs placebo) in ORAL Step (41.7% vs 24.4%; p=0.002) by 3 months.

Tofacitinib also significantly improved the signs and symptoms of RA as monotherapy in patients who are DMARD-IR compared with placebo in ORAL Solo (59.8% vs 26.7%; p<0.001) by 3 months.

Tofacitinib 5 mg in combination with MTX also met its primary end point (% of ACR50 responders) in demonstrating non-inferiority compared to adalimumab 40 mg every-other-week via in combination with MTX in patients who are MTX-IR in ORAL Strategy Month 6. Tofacitinib 5 mg monotherapy did not meet the same endpoint.

Tofacitinib was associated with a numerical and clinically significant delay in radiographic progression in patients with RA compared with placebo. Tofacitinib inhibits radiographic progression in patients with moderate-severe RA

Radiographic progression, primarily measured in clinical trials by Modified Total Sharp Score, is a clinically important measure used worldwide to assess the impact RA treatments have in reducing signs of RA progression (120)

Tofacitinib 5 mg either in combination with MTX (or cDMARD) or as monotherapy numerically reduced the signs of radiographic progression, as measured by mTSS for:

- Patients with moderate-to-severe RA who are MTX-IR (tofacitinib 5 mg vs placebo) in ORAL Scan (mean change in mTSS 0.vs 0.47; p=0.0792) at 3 months.
- Rates of non-progression at 6 months in ORAL Scan (≤0.5-unit increase from baseline in mTSS) were 88.8% for tofacitinib 5 mg vs 77.7% placebo, p<0.05.

It should be noted that in ORAL Scan placebo patients did not progress at the rate assumed based on published literature (6 month mTSS 0.47 observed vs 1.4 expected); consequently, ORAL Scan was underpowered and did not reach statistical significance on the primary structural endpoint for the 5 mg dose.

Although less relevant to this submission, ORAL Start provides further evidence in an MTX naïve population for tofacitinib monotherapy:

- At month 6 mean change from baseline in mTSS was 0.2 for tofacitinib 5 mg monotherapy vs 0.8 for MTX; p<0.001
- At month 6 the rate of non-progression (≤0.5-unit increase from baseline in mTSS) was 87.1% for tofacitinib monotherapy vs 73.7% for MTX; p<0.001

Tofacitinib significantly improved levels of pain and fatigue, and overall health related quality of life of patients with moderate to severe active RA compared with placebo by Month 6

Patient reported outcomes (PRO) are vital component of RA clinical trials and clinical practice, as they capture data on the implications of living with RA beyond clinical metrics, and instead elicit patients' personal perspectives (19, 20).

Across the Phase III clinical trials, tofacitinib 5 mg significantly reduced patients' levels of pain and fatigue, and improved overall quality of life in patients with moderate-to-severe RA who were MTX-IR, DMARD-IR or TNF-IR. Scores for pain (VAS), fatigue (FACIT-F) and quality of life (EQ-5D) were all significantly improved in the tofacitinib 5 mg group compared with placebo by Month 6 in all trials (except ORAL Start [a MTX naïve population] where EQ-5D was numerically improved vs placebo and pain [VAS] was not recorded).

The ORAL clinical trial programme (n=6 trials) demonstrates that treatment with tofacitinib 5 mg is well-tolerated.

Across the ORAL Phase III clinical trial programme (ORAL Standard, Scan, Sync, Solo, Start and Step) treatment with tofacitinib 5 mg was well tolerated. The most frequent adverse events (AE) reported throughout the Phase III trials were upper respiratory tract infections and nasopharyngitis.

Pooled safety data from patients treated with tofacitinib across the ORAL clinical trial programme provided a maximum follow-up time of 8.5 years. For patients receiving a constant 5 mg dose of tofacitinib (n=2,342), the incidence rates (patient with events/100 patient-years) were:

- 153.1 (95% Confidence interval [CI]: 146.1, 160.4) for any AE.
- 9.2 (95% CI: 8.2, 10.3) for any serious AE (SAE).
- 7.2 (95% CI: 6.4, 8.2) for discontinuation due to AEs.
- 0.3 (95% CI: 0.2, 0.35) for mortality within 30 days of last dose of study drug.

Additionally, no unexpected safety issues were found in ORAL Strategy. The frequencies of treatment-emergent (TE) AE (TEAE), serious and severe AEs, discontinuation due to AEs were generally comparable across the two tofacitinib 5 mg (monotherapy and in

combination with MTX) and adalimumab in combination with MTX treatment arms.

The safety profile of tofacitinib is stable over time and consistent with biological therapies currently recommended by NICE for the treatment of severe active RA.

As of 31 March 2015, no new risks or safety signals were identified in the tofacitinib long-term safety database compared to those previously reported in the randomised controlled trials and long-term extension data from the tofacitinib RA development programme. Types and rates of AEs (including infections and malignancies) were similar to those observed in ORAL Phase III trials and were stable over time, with no evidence of directional trends with longer-term tofacitinib exposure through 8.5 years. With the exception of the rates for herpes zoster, the incidence of most AEs were generally comparable with that of biologics of RA (28).

To further aid the interpretation of the clinical outcomes from the Phase III studies in relation to the decision problem set out by NICE, the top line results for the outcomes assessed in the Phase III clinical trials of tofacitinib as second-line therapy are presented in Table 10 and Table 11. Tofacitinib demonstrated significant improvements compared with placebo across the majority of outcomes outlined in the decision problem. In addition to clinical measures of efficacy (e.g. remission and low disease activity), tofacitinib can provide improvements in patient-reported outcomes measuring physical functioning, pain and fatigue, which have been shown to be important outcomes from the patient's perspective. Although less relevant to the decision problem, the ACR response rates reported in the trials show that tofacitinib is effective at reducing the signs and symptoms of RA. Finally, assessment of EULAR response rates demonstrate that a substantial proportion of patients achieve a good or moderate response at Month 6. Therefore, these patients meet the EULAR criteria for maintenance of treatment.

Table 10: Overview of the outcomes assessed in the Phase III clinical trials of tofacitinib in patients who were predominantly second line

Relevant to decision problem?	Clinical impact		Outcome assessed	Used in CEA?	Time points (months)	Top line results (significant vs MTX+placebo)			
						cDMARD experienced and MTX-IR		DMARD-IR (cDMARD including MTX or bDMARD)	
						Standard	Scan	Sync	Solo (mt)
Yes	Disease activity		Proportion achieving low disease activity (DAS28-4(ESR) ≤3.2)	Yes†	0.5	NR	NR	NR	NR
					1	NS	NS	NR	NR
					3	Sig.	Sig.	Sig.	Sig.
					6‡	Sig.	Sig.	Sig.	NPC
			Proportion achieving disease remission (DAS28-4(ESR) <2.6)	Yes†	0.5	NR	NR	NR	NR
					1	NS	Sig.	NR	NR
					3	Sig.	Sig.	Sig.	**NS**
					6	**Sig.**	**n.sig.§**	**Sig.**	NPC
	Treatment response		EULAR criteria	Yes	6‡	Sig.	Sig.	Sig.	NPC
	Physical function		Change from baseline in HAQ-DI	Yes	0.5	NR	NR	Sig.	Sig.
					1	Sig.	Sig.	Sig.	Sig.
					3	**Sig.**	**Sig.**	**Sig.**	**Sig.**
					6‡	Sig.	n.sig§	Sig.	NPC
	Radiographic progression		Change from baseline in mTSS	Yes	6‡	NR	NS††	NR	NR
					12	NR	NS††	NR	NR
	QoL	HRQoL	Change from baseline in EQ-5D	Yes	1	Sig.	NR	NR	NR
					3	Sig.	Sig.	Sig.	Sig.
					6‡	Sig.	Sig.	Sig.	NPC
		Fatigue	Change from baseline in FACIT-F	Yes	1	Sig.	Sig.	Sig.	NR
					3	Sig.	Sig.	Sig.	Sig.
					6‡	Sig.	Sig.	Sig.	NPC
		Pain	Change from	Yes	0.5	NR	NR	Sig.	Sig.

Relevant to decision problem?	Clinical impact	Outcome assessed	Used in CEA?	Time points (months)	Top line results (significant vs MTX+placebo)			
					cDMARD experienced and MTX-IR		DMARD-IR (cDMARD including MTX or bDMARD)	
					Standard	Scan	Sync	Solo (mt)
		baseline in pain (VAS)		1	Sig.	Sig.	Sig.	Sig.
				3	Sig.	Sig.	Sig.	Sig.
				6‡	Sig.	Sig.	Sig.	NPC
	Mortality	None	Yes	N/A	NR	NR	NR	NR
	EAMs	None	No	N/A	NR	NR	NR	NR
No	Signs and symptoms of RA	ACR20	No	0.5	NR	NR	Sig.	Sig.
				1	Sig.	Sig.	Sig.	Sig.
				3	Sig.	Sig.	Sig.	**Sig.**
				6‡	**Sig.**	**Sig.**	**Sig.**	NPC
		ACR50	No	0.5	NR	NR	Sig.	NS
				1	Sig.	Sig.	Sig.	Sig.
				3	Sig.	Sig.	Sig.	Sig.
				6‡	Sig.	Sig.	Sig.	NPC
		ACR70	No	0.5	NR	NR	NS	Sig.
				1	NS	Sig.	Sig.	NS
				3	Sig.	Sig.	Sig.	Sig.
				6‡	Sig.	Sig.	Sig.	NPC

Abbreviations: ACR, American College of Rheumatology; CEA, cost-effectiveness analysis; DAS28, Disease Activity Score in 28 joints; DMARD, disease-modifying anti-rheumatic drug; EAMs, extra-articular manifestations; EQ-5D, EuroQol five dimension questionnaire; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-disability index; HRQoL, Health-related quality of life; IR, inadequate response; MT, monotherapy; MTX, methotrexate; NPC, not placebo controlled; NR, not reported; NS, not significant; n.Sig, nominally significant; QoL, quality of life; RA, rheumatoid arthritis; mTSS, van der Heijde modified total sharp score; Sig, significant.
†DAS28 is the basis of the EULAR response criteria. ‡Month 6 is subject to placebo crossover to tofacitinib rule (see Section 4.5.1). §Endpoint not formally significant due to stepdown approach applied to statistical analysis.

Table 11: Overview of the outcomes assessed in the Phase III clinical trial of tofacitinib in patients who were predominantly third line (TNFi-IR, ORAL Step)

Relevant to decision problem?	Clinical impact		Outcome assessed	Used in CEA?	Time points (months)	Top line results (significant vs placebo)
Yes	Disease activity		Proportion achieving low disease activity (DAS28-4(ESR) ≤3.2)	Yes†	3	Sig.
			Proportion achieving disease remission (DAS28-4(ESR) <2.6)	Yes†	3	**Sig.**
	Treatment response		EULAR criteria	Yes	6	NPC
	Physical function		Change from baseline in HAQ-DI	Yes	0.5	NS
					1	NS
					3	**Sig.**
	Radiographic progression		None	Yes	NR‡	NR‡
	QoL	HRQoL	Change from baseline in EQ-5D	Yes	1	Sig.
					3	Sig.
		Fatigue	Change from baseline in FACIT-F	Yes	3	Sig.
		Pain	Change from baseline in pain (VAS)	Yes	0.5	Sig.
					1	Sig.
					3	Sig.
	Mortality		None	Yes	NR	NR
	EAMs		None	No	NR	NR
No	Signs and symptoms of RA		ACR20	No	0.5	Sig.
					1	Sig.
					3	**Sig.**
			ACR50	No	0.5	Sig.
					1	Sig.
					3	Sig.
			ACR70	No	0.5	NS
					1	Sig.
					3	Sig.

Abbreviations: ACR, American College of Rheumatology; CEA, cost-effectiveness analysis; DAS28, Disease Activity Score in 28 joints; DMARD, disease-modifying anti-rheumatic drug; EAMs, extra-articular manifestations; EQ-5D, EuroQol five dimension questionnaire; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-disability index; HRQoL, Health-related quality of life; IR, inadequate response; MT, monotherapy; MTX, methotrexate; NPC, not placebo controlled; NR, not reported; NS, not significant; n.Sig, nominally significant; QoL, quality of life; RA, rheumatoid arthritis; mTSS, van der Heijde modified total sharp score; Sig, significant.
†DAS28 is the basis of the EULAR response criteria.

4.1 *Identification and selection of relevant studies*

4.1.1 *Search strategy*

Pfizer conducted a systematic review to identify all relevant clinical data from the published literature regarding the clinical effectiveness of treatments in RA; this is described in 4.10.

4.1.2 *Study selection*

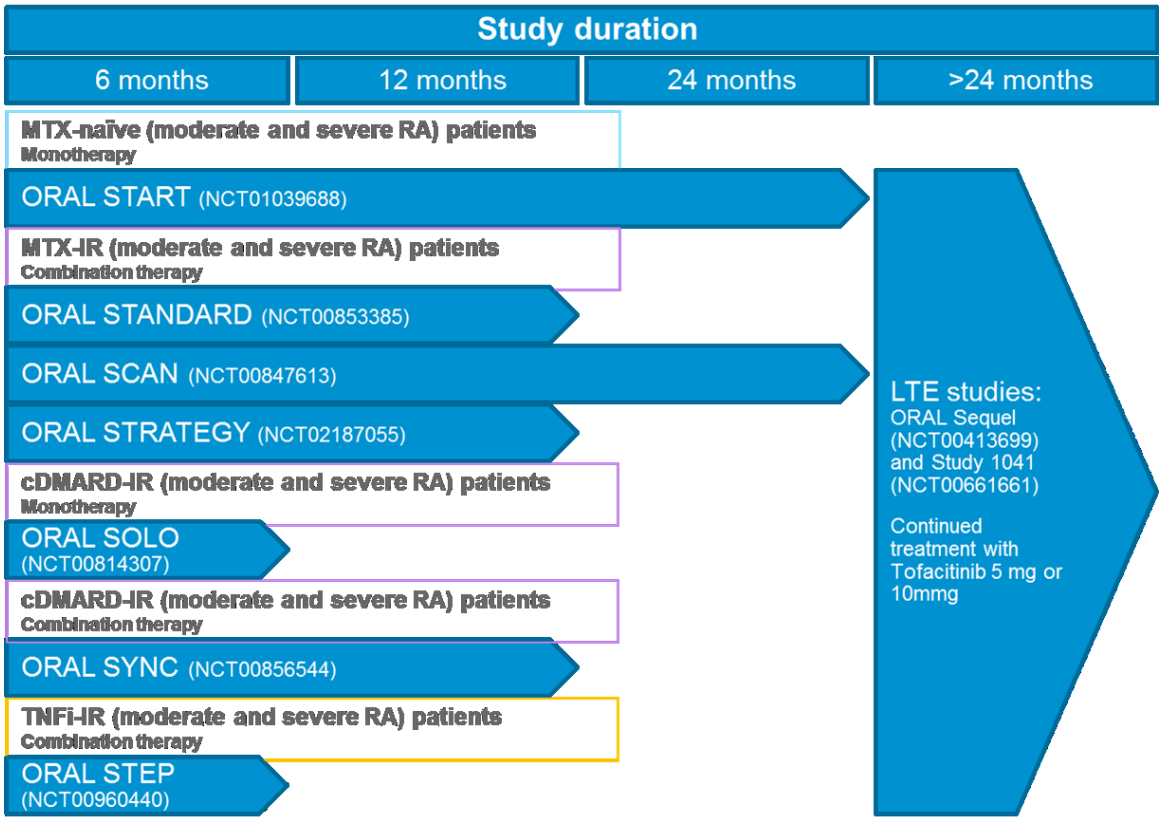
The methods described in Section 4.10 for study selection were further refined to studies which included the licenced formulation of tofacitinib (5 mg, BD).

4.2 *List of relevant randomised controlled trials*

The systematic review of clinical evidence identified four randomised controlled trials (RCT) of tofacitinib in the populations relevant to the decision problem, out of a total of six phase III RCTs performed on tofacitinib (Table 12). MTX plus placebo was the comparator in three studies, while placebo without MTX was the comparator in ORAL Solo; an active comparator treatment (ADA) was also included in one study (ORAL Standard). Both ORAL Standard and ORAL Scan considered adult patients with active moderate-to-severe RA who are cDMARD experienced and MTX-IR, while ORAL Sync and Solo assessed adult patients with active moderate-to-severe RA who are DMARD-IR (cDMARD including MTX or bDMARD). In addition, two studies (ORAL Step and ORAL Start) were included as supporting studies. ORAL Step assessed tofacitinib in patients with moderate-to-severe RA who were TNFi-IR. While this population is within the tofacitinib licence, the study is considered less relevant to submission given the proposed main second-line positioning of tofacitinib within the clinical pathway (Section 3.3.3). ORAL Start assessed tofacitinib as monotherapy in patients who were MTX naïve (approximately 39% of patients had received treatment with non-MTX cDMARDs). While the majority of this population is not within the licence of tofacitinib, this study provides evidence that tofacitinib can significantly impact radiographic progression in a favourable manner (see Section 4.13 for further discussion on radiographic progression).

Tofacitinib (both in combination with MTX and as monotherapy) has been well-studied and characterised throughout an extensive clinical trial programme (Figure 3). In addition to the Phase III studies (see Section 4.7 for clinical evidence from the six Phase III trials), which assessed tofacitinib 5 mg in the populations most relevant to the decision problem, up to 8.5 years of follow-up data have been collected in the long-term extension studies (efficacy is covered in Section 4.11 and safety is covered in Section 4.12.2), providing evidence of long-term efficacy and safety. At the time of this submission, over 6,000 patients have been treated with tofacitinib within the clinical trial programme, of which over 2,000 have received the 5 mg dose, twice daily.

Figure 3: Overview of the tofacitinib clinical trial programme (Phase III to LTE studies)



Abbreviations: LTE, long-term extension studies.

Throughout Section 4, the publications were used as the primary source where possible. Where additional detail was required the Clinical Summary Report (CSR) has been used.

Table 12: List of relevant RCTs

Trial no. (acronym)	Population	Intervention	Comparator	Primary study ref(s)
NCT00853385 (ORAL Standard)	Adult patients with active moderate-to-severe RA who are cDMARD experienced and MTX-IR	MTX and: • TOF 5 mg (N=204) • TOF 10 mg (N=201)	MTX and: • ADA: N=204 • Placebo to TOF 5 mg†: N=56 • Placebo to TOF 10 mg†: N=52	Vollenhoven et al, 2012 (including supplements) (121) and the clinical study report (122)
NCT00847613 (ORAL Scan)	Adult patients with active moderate-to-severe RA who are cDMARD experienced and MTX-IR	MTX and: • TOF 5 mg (N=321) • TOF 10 mg (N=316)	MTX and: • Placebo to TOF 5 mg†: N=81 • Placebo to TOF 10 mg†: N=79	van der Heijde et al, 2013 (including supplements) (9) and the clinical study report (123)
NCT00856544 (ORAL Sync)	Adult patients with active moderate-to-severe RA who are DMARD-IR (cDMARD including MTX or bDMARD)	≥1 cDMARD and: • TOF 5 mg (N=315) • TOF 10 mg (N=318)	≥1 cDMARD and: • Placebo to TOF 5 mg†: N=79 • Placebo to TOF 10 mg†: N=80	Kremer et al, 2013 (including supplements) (66) and the clinical study report (124)
NCT00814307 (ORAL Solo)	Adult patients with active moderate-to-severe RA who are DMARD-IR (cDMARD including MTX or bDMARD)	• TOF 5 mg (N=243) • TOF 10 mg (N=245)	• Placebo to TOF 5 mg‡: N=61 • Placebo to TOF 10 mg‡: N=61	Fleischmann et al, 2012 (including supplements) (125) and the clinical study report (126)
NCT01039688 (ORAL Start)	Adult patients with active moderate-to-severe RA who are naïve to MTX	• TOF 5 mg (N=373) • TOF 10 mg (N=397)	• MTX: N=186	Lee et al, 2014 (including supplements) (7) and the clinical study report (127)
NCT00960440 (ORAL Step)	Adult patients with active moderate-to-severe RA who are TNFi-IR	MTX and: • TOF 5 mg (N=133) • TOF 10 mg (N=134)	MTX and: • Placebo to TOF 5 mg‡: N=66 • Placebo to TOF 10 mg‡: N=66	Burmester et al, 2013 (including supplements) (128) and the clinical study report (129)

Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug; IR, inadequate response; MTX, methotrexate; ORAL, Oral Rheumatoid Arthritis Phase 3 Trials; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor; TOF, tofacitinib.
†Patients receiving placebo advanced to a predetermined dose of TOF (5 mg or 10 mg) at Month 3 if trial response criteria were not met (defined as 20% reduction in number of tender and swollen joints) or Month 6 regardless of response. ‡All patients receiving placebo advanced to a predetermined dose of TOF (5 mg or 10 mg) at Month 3.

4.3 *Summary of methodology of the relevant randomised controlled trials*

4.3.1 *Comparative summary of RCT methodology*

The methodology for the pivotal Phase III RCTs are summarised in Table 13.

Table 13: Comparative summary of methodology of the RCTs

Trial no. (acronym)	NCT00853385 (ORAL Standard)	NCT00847613 (ORAL Scan)	NCT00856544 (ORAL Sync)	NCT00814307 (ORAL Solo)
Study objective	To examine the clinical efficacy and safety of TOF+MTX compared with placebo+MTX.		To evaluate the efficacy and safety of TOF+≥1cDMARD compared with placebo+≥1cDMARD.	To evaluate the efficacy and safety of TOF monotherapy compared with placebo.
Trial design	Phase III, randomised, double-blind, placebo-controlled, parallel group study			
Duration of study	12 months†	24 months (12-month interim analysis)†	12 months†	6 months†
Method of randomisation	Patients were randomised using an IVR system in a 4:4:4:1:1 ratio to receive MTX and: • TOF 5 mg • TOF 10 mg • ADA 40 mg • Placebo to TOF 5 mg‡ • Placebo to TOF 10 mg‡	Patients were randomised using an IVR system in a 4:4:1:1 ratio to receive MTX and: • TOF 5 mg • TOF 10 mg • Placebo to TOF 5 mg‡ • Placebo to TOF 10 mg‡	Patients were randomised using an IVR system in a 4:4:1:1 ratio to receive ≥1 cDMARD and: • TOF 5 mg • TOF 10 mg • Placebo to TOF 5 mg‡ • Placebo to TOF 10 mg‡	Patients were randomised using Impala (automated Web-based or telephone-based system) in a 4:4:1:1 ratio to receive: • TOF 5 mg • TOF 10 mg • Placebo to TOF 5 mg§ • Placebo to TOF 10 mg§

Trial no. (acronym)	NCT00853385 (ORAL Standard)	NCT00847613 (ORAL Scan)	NCT00856544 (ORAL Sync)	NCT00814307 (ORAL Solo)
Method of blinding	Patients and investigators remained blinded to treatment assignment during the study. All patients receiving placebo at the start of the study were advanced in a blinded fashion to a predetermined dose of TOF. **ORAL Scan only:** Radiographs for each patient were scored by two independent readers who were blinded to patient randomisation sequence and visit.			
Eligibility criteria for participants	Adult patients aged ≥18 years with active moderate-to-severe RA who are MTX-IR. Details of inclusion and exclusion criteria are provided in section 4.3.2.		Adult patients aged ≥18 years with active moderate-to-severe RA who are DMARD-IR¶. Details of inclusion and exclusion criteria are provided in section 4.3.2.	
Settings and locations where the data were collected	This study was conducted at 115 study centres across 21 countries (Australia, Bosnia and Herzegovina, Bulgaria, Canada, Chile, Costa Rica, Croatia, Czech Republic, Denmark, Dominican Republic, Finland, Germany, Korea, Mexico, Philippines, Poland, Slovakia, Spain, Thailand, UK, USA). Patients were included from three centres in the UK.	This study was conducted at 111 study centres across 15 countries (Australia, Brazil, Bulgaria, Canada, Colombia, Czech Republic, Greece, India, Japan, Korea, Mexico, Poland, Taiwan, Ukraine, USA). No UK centres were included.	The study was conducted at 114 centres across 20 countries (Australia, Chile, China, Columbia, Croatia, Denmark, Finland, Germany, Greece, Malaysia, Mexico, Poland, Russian Federation, Slovakia, Spain, Sweden, Thailand, UK, USA, Venezuela††). Patients were included from three centres in the UK.	This study was conducted at 94 study centres across 15 countries (Brazil, Bulgaria, Chile, Colombia, Czech Republic, Dominican Republic, Germany, India, Malaysia, Mexico, Philippines, Poland, Russian Federation, Ukraine, USA). No UK centres were included.

Trial no. (acronym)	NCT00853385 (ORAL Standard)	NCT00847613 (ORAL Scan)	NCT00856544 (ORAL Sync)	NCT00814307 (ORAL Solo)
Trial drugs	• TOF 5 mg BD (N=204) • TOF 10 mg BD (N=201) • ADA 40 mg BIW (N=204) • Placebo to TOF 5 mg BD (N=56)‡ • Placebo to TOF 10 mg BD (N=52)‡ All patients self-administered injections of either ADA or placebo once every 2 weeks and took a TOF or placebo pill twice daily.	• TOF 5 mg BD (N=321) • TOF 10 mg BD (N=316) • Placebo to TOF 5 mg BD (N=81)‡ • Placebo to TOF 10 mg BD (N=79)‡	• TOF 5 mg BD (N=315) • TOF 10 mg BD (N=318) • Placebo to TOF 5 mg BD (N=79)‡ • Placebo to TOF 10 mg BD (N=80)‡	• TOF 5 mg BD (N=243) • TOF 10 mg BD (N=245) • Placebo to TOF 5 mg BD (N=61)§ • Placebo to TOF 10 mg BD (N=61)§
Permitted and disallowed concomitant medications	Patients continued on their stable background arthritis therapy, which was required to include MTX supplemented with folic acid and could also include NSAIDs, selective COX-2 inhibitors, opioids, acetaminophen (<2.6 g per day), and/or low dose OCS (≤10 mg prednisone or equivalent per day) at a stable dose throughout the trial. Prohibited medications during the study included: • Administration of vaccines with live components (prohibited until 6 weeks after last dose of study medication) • IV or IM corticosteroids, bDMARDs, and DMARDs other than MTX		Patients continued on their stable background arthritis therapy, which may include a cDMARD and could also include NSAIDs, selective COX-2 inhibitors, opioids, acetaminophen (<2.6 g per day), and/or low dose OCS (≤10 mg prednisone or equivalent per day) at a stable dose Prohibited medications during the study included: • Administration of vaccines with live components (prohibited until 6 weeks after last dose of study medication) • IV or IM corticosteroids and bDMARDs	Patients were required to remain on NSAIDs, selective COX-2 inhibitors, opioids, acetaminophen (<2.6 g per day), and/or low dose OCS (≤10 mg prednisone or equivalent per day) at a stable dose Patients were allowed to remain on antimalarial medication at stable doses during the study. Prohibited medications during the study included: • Administration of vaccines with live components (prohibited until 6 weeks after last dose of study medication) • IV or IM corticosteroids,

Trial no. (acronym)	NCT00853385 (ORAL Standard)	NCT00847613 (ORAL Scan)	NCT00856544 (ORAL Sync)	NCT00814307 (ORAL Solo)
				bDMARDs and cDMARDs
Primary outcomes	**Primary analysis of primary outcomes** The efficacy of TOF vs placebo was compared across three co-primary efficacy endpoints: • Proportion of patients who met ACR20 criteria at Month 6 • Mean change from baseline in HAQ-DI at Month 3 • Proportion of patients with DAS28-4(ESR) <2.6 at Month 6 **Secondary analysis of primary outcomes** Analysis of ACR20 and DAS28-4(ESR) endpoints was also performed without advancement penalty‡‡ to allow any new response to active treatment after Month 3 to be observed (see Section 4.4.2).	**Primary analysis of primary outcomes** The efficacy of TOF vs placebo was compared across three co-primary efficacy endpoints: • Proportion of patients who met ACR20 criteria at Month 6 • Mean change from baseline in mTSS score at Month 6 • Mean change from baseline in HAQ-DI at Month 3 • Proportion of patients with DAS28-4(ESR) <2.6 at Month 6 **Secondary analysis of primary outcomes** Analysis of ACR20 and DAS28-4(ESR) endpoints was also performed without advancement penalty‡‡ to allow any new response to active treatment after Month 3 to be observed (see Section 4.4.2).	**Primary analysis of primary outcomes** The efficacy of TOF vs placebo was compared across three co-primary efficacy endpoints: • Proportion of patients who met ACR20 criteria at Month 6 • Mean change from baseline in HAQ-DI at Month 3 • Proportion of patients with DAS28-4(ESR) <2.6 at Month 6 **Secondary analysis of primary outcomes** Analysis of ACR20 and DAS28-4(ESR) endpoints was also performed without advancement penalty‡‡ to allow any new response to active treatment after Month 3 to be observed (see Section 4.4.2).	**Primary analysis of primary outcomes** The efficacy of TOF vs placebo was compared across three co-primary efficacy endpoints: • Proportion of patients who met ACR20 criteria at Month 3 • Mean change from baseline in HAQ-DI at Month 3 • Proportion of patients with DAS28-4(ESR) <2.6 at Month 3

Trial no. (acronym)	NCT00853385 (ORAL Standard)	NCT00847613 (ORAL Scan)	NCT00856544 (ORAL Sync)	NCT00814307 (ORAL Solo)
Secondary/tertiary outcomes (including scoring methods and timings of assessments)	**Key secondary outcomes** • Proportion of patients achieving ACR20, ACR50 and ACR70 per visit • Change from baseline in HAQ-DI and FACIT-F per visit • Assessment of DAS28-4(ESR) per visit • Change from baseline in the EQ-5D, SF-36, WLQ, MOS-SS **Exploratory outcomes** To estimate the efficacy of ADA vs TOF (5 mg and 10 mg) with regards to ACR20, ACR50, ACR70 and DAS28-4(ESR)	**Key secondary outcomes** • Proportion of patients achieving ACR20, ACR50 and ACR70 per visit • Change from baseline in ACR core set of disease activity measures at Month 6 • Change from baseline in HAQ-DI and FACIT-F per visit • Assessment of DAS28-4(ESR) per visit • Change from baseline in the EQ-5D, SF-36, WLQ, MOS-SS **Key secondary endpoints for structural preservation** • Rates of non-progression (≤0.5 change from baseline in total mTSS or erosion score) at Months 6, 12, 24 • Change from baseline in total mTSS at Months 12 and 24 • Change from baseline in erosion and JSN scores at Months 6, 12, 24	**Key secondary outcomes** • Proportion of patients achieving ACR20, ACR50 and ACR70 per visit • Change from baseline in HAQ-DI and FACIT-F per visit • Assessment of DAS28-4(ESR) per visit • Change from baseline in the EQ-5D, SF-36, WLQ, MOS-SS	
Pre-planned subgroups	[redacted]	Post-hoc subgroup analyses for structure preservation endpoints were performed using population subsets thought to be at higher risk for	Post-hoc subgroup analyses by background DMARD therapy and geographic region were conducted.	Post hoc subgroup analyses were performed to assess ACR20 response rates in subgroups of interest, including those defined according to age,

Trial no. (acronym)	NCT00853385 (ORAL Standard)	NCT00847613 (ORAL Scan)	NCT00856544 (ORAL Sync)	NCT00814307 (ORAL Solo)
		progression of disease. [redacted]		sex, geographic location, seropositivity status (presence or absence of rheumatoid factor or anti–CCP peptide antibodies), and inadequate response to prior treatment with biologic disease-modifying drugs.

Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; BD, twice-daily; bDMARD, biologic disease-modifying anti-rheumatic drug; BIW, twice-weekly; CCP, cyclic citrullinated peptide; cDMARD, conventional disease-modifying anti-rheumatic drug; COX-2, cyclooxygenase-2; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; EQ-5D, EuroQol five-dimension questionnaire; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-disability index; IR, inadequate response; MOS-SS, Medical Outcomes Study – Sleep Scale; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; ORAL, Oral Rheumatoid Arthritis Phase 3 Trials; PAAP-VAS, patient's assessment of arthritis pain – visual analogue scale; IVR, Interactive voice response; RA, rheumatoid arthritis; SF-36, Short Form (36); mTSS, van der Heijde modified total sharp score; TOF, tofacitinib; WLQ, Work Limitations Questionnaire.

[redacted] ‡Patients receiving placebo advanced to a predetermined dose of TOF (5 mg or 10 mg) at Month 3 if trial response criteria were not met (defined as 20% reduction in number of tender and swollen joints) or Month 6. §All patients receiving placebo advanced to a predetermined dose of TOF (5 mg or 10 mg) at Month 3. ¶Patients who had an IR to ≥1 cDMARD or bDMARD.

[redacted] ‡‡Patients who did not achieve a 'response' (defined as 20% reduction in number of tender and swollen joints) at Month 3 were considered non-responders for the remainder of the trial (non-responder imputation with advancement penalty).

4.3.2 *Eligibility criteria*

Key eligibility criteria for the pivotal Phase III RCTs are summarised in Table 14.

Table 14: Eligibility criteria for RCTs

Trial no. (acronym)	NCT00853385 (ORAL Standard)	NCT00847613 (ORAL Scan)	NCT00856544 (ORAL Sync)	NCT00814307 (ORAL Solo)
Inclusion criteria	• Adults aged ≥18 years with a diagnosis of active RA†, consistent with the ACR 1987 Revised Criteria (130) • Ongoing treatment with MTX for ≥4 months with stable dosing (7.5–25 mg/week) ≥6 weeks before receiving the study drug; doses <15 mg were allowed in the case of intolerance or toxicity from higher doses • An inadequate response to MTX (defined as sufficient residual disease activity to meet entry criteria) **ORAL Scan only** • Evidence of ≥3 distinct joint erosions on posteroanterior hand and wrist radiographs or anteroposterior foot radiographs as determined by the investigator, or, if radiographic evidence of joint erosions was unavailable, IgM RF+ or antibodies to CCP		• Adults aged ≥18 years with a diagnosis of active RA‡, consistent with the ACR 1987 Revised Criteria (130) • Ongoing treatment with ≥1 cDMARD therapy – patients receiving MTX required ≥4 months of treatment, with stable dosing (≤25 mg/week) ≥6 weeks before receiving the study drug • An inadequate response to ≥1 cDMARD or bDMARD [redacted]	• Adults aged ≥18 years and had received a diagnosis of active RA†, consistent with the ACR 1987 Revised Criteria (130) • Discontinued all DMARDs except stable doses of anti-malarial agents • An inadequate response to ≥1 cDMARD or bDMARD (lack of efficacy or occurrence of toxicity)
Exclusion criteria	• Haemoglobin <9.0 gm/dL • Haematocrit <30% • White blood cell count <3.0x10^9/L • Absolute neutrophil count <1.2x10^9/L • Platelet count <100x10^9/L • eGFR rate ≤40 ml/min • AST or ALT levels >1.5 x Upper limit of normal • A history of another autoimmune rheumatic disease except Sjögren's syndrome			

Trial no. (acronym)	NCT00853385 (ORAL Standard)	NCT00847613 (ORAL Scan)	NCT00856544 (ORAL Sync)	NCT00814307 (ORAL Solo)
	• Infection that required hospitalisation or parenteral antimicrobial therapy within 6 months of randomisation • Infection requiring antimicrobial therapy within 2 weeks of randomisation • Recurrent or disseminated herpes zoster infection • Recent, current, or chronic infection, including HBV, HCV or HIV • Current infection or evidence of active or inadequately treated infection with Mycobacterium tuberculosis • History of lymphoproliferative disorder or malignancy except for adequately treated non-metastatic basal/squamous cell cancer of the skin or cervical carcinoma in situ • Prior treatment with lymphocyte-depleting therapies or alkylating agents **ORAL Standard only** • Prior treatment with ADA • Lack of response to prior anti-TNF biologic treatment • Current treatment with other anti-rheumatic agents, including biologic agents			

Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; ALT, alanine aminotransferase; AST, aspartate aminotransferase; bDMARD, biologic disease-modifying anti-rheumatic drug; CCP, cyclic citrullinated peptide; cDMARD, conventional disease-modifying anti-rheumatic drug; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MTX, methotrexate; ORAL, Oral Rheumatoid Arthritis Phase 3 Trials; RA, rheumatoid arthritis; RF, rheumatoid factor; TNF, tumour necrosis factor.
[†]Active disease was defined as the presence of ≥6 tender or painful joints (of 68 joints examined) and ≥6 swollen joints (of 66 joints examined) and either an ESR ≥28 mm/hr (Westergren method) or a CRP level >7 mg/L. [‡]Active disease was defined as the presence of ≥4 tender or painful joints (68 joints examined) and ≥4 swollen joints (of 66 joints examined) and either an ESR ≥28 mm/hr or a CRP level >66.7 nmol/L.

4.4 *Statistical analysis and definition of study groups in the relevant randomised controlled trials*

4.4.1 *Analysis sets*

The main analysis sets in the ORAL RCTs are defined below.

Full Analysis Set (FAS): The FAS included all patients who were randomised to the study and received ≥1 dose of the study drug or placebo. This was the primary analysis population for the ORAL studies. Patients must have had ≥1 post-baseline measurement in order to appear in any of the analyses of the FAS datasets.

Per Protocol Analysis Set (PPAS): FAS patients who had a protocol deviation thought to affect the efficacy analysis were excluded from the per protocol efficacy analysis.

Safety Analysis Set (SAS): The safety analysis set was defined as those patients who received ≥1 dose of the study drug or placebo.

4.4.2 *Statistical information*

A summary of the statistical methods used in the ORAL RCTs are presented in Table 15.

Table 15: Summary of statistical analyses in RCTs

Trial no. (acronym)	NCT00853385 (ORAL Standard)	NCT00847613 (ORAL Scan)	NCT00856544 (ORAL Sync)	NCT00814307 (ORAL Solo)
Hypothesis objective	To test the superiority of TOF (5 mg and 10 mg) compared with placebo with respect to ACR20 response rates and the proportion of patients achieving disease remission (DAS28-4[ESR] <2.6).			
Multiple comparisons and multiplicity	To preserve the type I error rate, the three primary efficacy endpoints were assessed sequentially using a step-down approach (shown in Figure 4) as follows: 1.Proportion of patients who met ACR20 criteria 2.The mean change from baseline in the HAQ-DI score 3.The proportion of patients with a DAS28-4(ESR) <2.6 The type I error rate was preserved for the primary endpoints when statistical significance was determined. At a given endpoint, TOF 5 mg could achieve significance only if both TOF 10 mg at the same endpoint and TOF 5 mg at the prior endpoint were significant. No preservation of the type I error rate was applied for the secondary endpoints.	To preserve the type I error rate, the co-primary efficacy endpoints were assessed sequentially using a step-down approach (shown in Figure 5) as follows: 1.Proportion of patients who met ACR20 criteria 2.The mean change in total mTSS 3.The mean change from baseline in the HAQ-DI score 4.The proportion of patients with a DAS28-4(ESR) <2.6 The type I error rate was preserved for the primary endpoints when statistical significance was determined. At a given endpoint, TOF 5 mg could achieve significance only if both TOF 10 mg at the same endpoint and TOF 5 mg at the prior endpoint were significant. No preservation of the type I error rate was applied for the secondary endpoints.	To preserve the type I error rate, the three primary efficacy endpoints were assessed sequentially using a step-down approach (shown in Figure 4) as follows: 1.Proportion of patients who met ACR20 criteria 2.The mean change from baseline in the HAQ-DI score 3.The proportion of patients with a DAS28-4(ESR) <2.6 The type I error rate was preserved for the primary endpoints when statistical significance was determined. At a given endpoint, TOF 5 mg could achieve significance only if both TOF 10 mg at the same endpoint and TOF 5 mg at the prior endpoint were significant. No preservation of the type I error rate was applied for the secondary endpoints.	
	For each endpoint, and for each dose group, the comparison with placebo was conducted using a significance level (alpha) set at 0.05 (2-sided) or equivalently 0.025 (1-sided).			

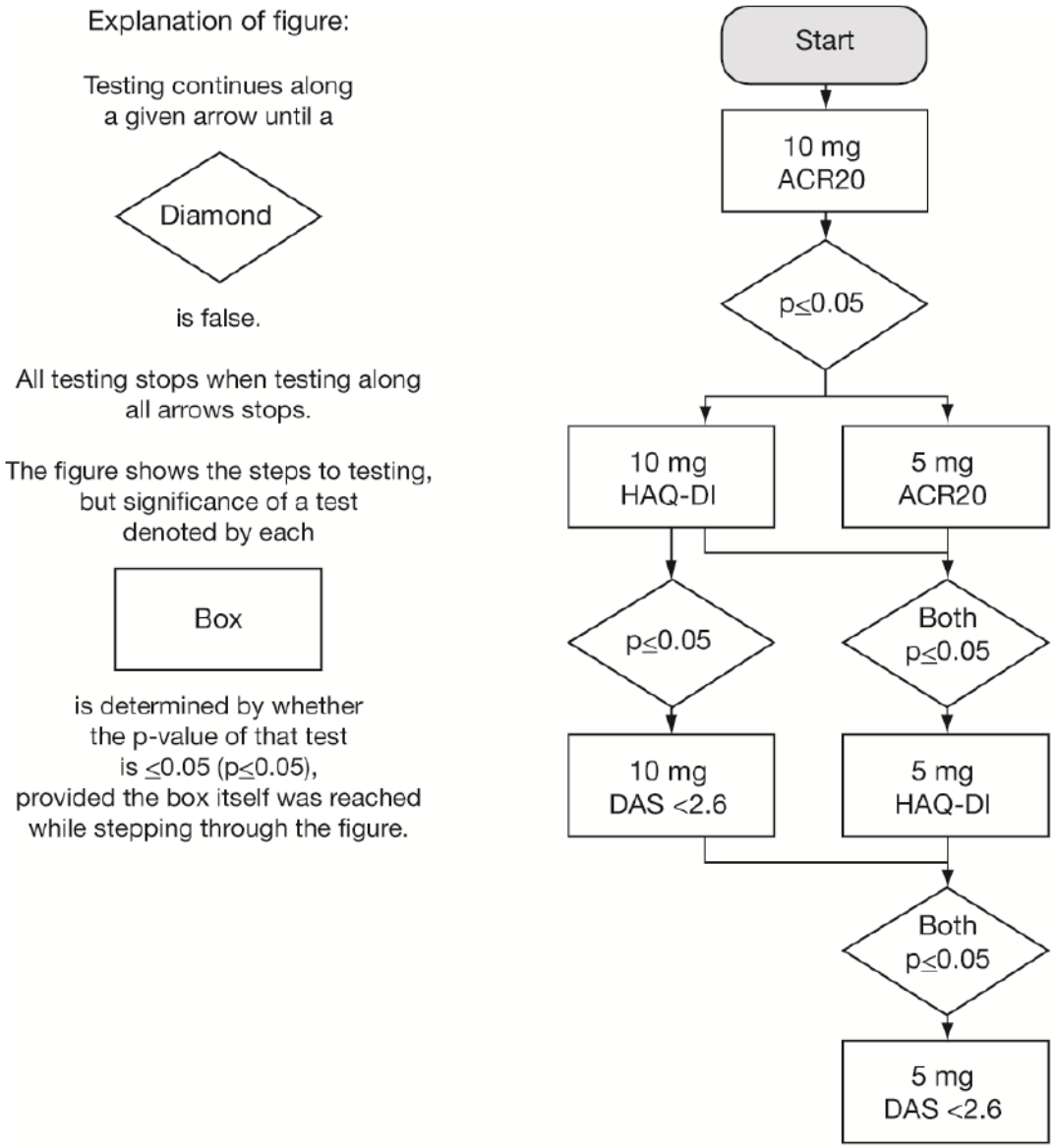
Trial no. (acronym)	NCT00853385 (ORAL Standard)	NCT00847613 (ORAL Scan)	NCT00856544 (ORAL Sync)	NCT00814307 (ORAL Solo)
Statistical analysis of primary endpoint	For ACR20 and DAS28-4(ESR) <2.6 at Month 6, the normal approximation for the difference in binomial proportions was used to test the superiority of TOF (5 mg and 10 mg) compared with placebo. For the change from baseline in the HAQ-DI at Month 3, a mixed-effect model with repeated measures was used.	For ACR20 and DAS28-4(ESR) <2.6 at Month 6, the normal approximation for the difference in binomial proportions was used to test the superiority of TOF (5 mg and 10 mg) compared with placebo. For total mTSS, the primary analysis was an analysis of variance model for change from baseline to month 6, and included baseline total mTSS as a covariate. Associated binary variables were analysed using normal approximation to the binomial. For the change from baseline in the HAQ-DI at Month 3, a mixed-effect model with repeated measures was used.	For ACR20 and DAS28-4(ESR) <2.6 at Month 6, the normal approximation for the difference in binomial proportions was used to test the superiority of TOF (5 mg and 10 mg) compared with placebo. For the change from baseline in the HAQ-DI at Month 3, a mixed-effect model with repeated measures was used.	For ACR20 and DAS28-4(ESR) <2.6 at Month 3, the normal approximation for the difference in binomial proportions was used to test the superiority of TOF (5 mg and 10 mg) compared with placebo. For the change from baseline in the HAQ-DI at Month 3, a mixed-effect model with repeated measures was used.
Statistical analysis of secondary efficacy endpoints	Secondary endpoints that were binary variables were analysed by NRI and continuous endpoints were analysed in the same way as the changes in HAQ-DI scores.			
Data management, patient withdrawals and the advancement of patients from placebo to active treatment	In the primary analysis of binary trial endpoints, NRI was applied: • To patients who discontinued the study drug for any reason (including patients lost to follow up before Month 6) • To patients who did not achieve a 'response' (defined as 20% reduction in number of tender and swollen joints) at Month 3, regardless of treatment assignment (NRI analysis applied to non-responders in any treatment arm referred to as NRI with advancement penalty [NRIWAP], with the advancement penalty specifically referring to the application of NRI at 3 months in the tofacitinib arm)[†]:			NRI was applied: • To patients who discontinued the study drug for any reason Comparisons with placebo a Month 3 were performed using the combined data from the two placebo groups. For continuous measures (e.g. change from baseline), missing

Trial no. (acronym)	NCT00853385 (ORAL Standard)	NCT00847613 (ORAL Scan)	NCT00856544 (ORAL Sync)	NCT00814307 (ORAL Solo)
	○ Patients in the active-treatment groups continued with the same treatment ○ Patients who were receiving placebo were advanced to a predetermined dose of TOF Advancing non-responders from placebo to TOF was important to minimise the exposure to ineffective treatment. For these analyses, the placebo group comprised patients still receiving placebo at Month 6 and those who advanced to TOF treatment at Month 3 (non-responders). Secondary analyses were also performed where the advancement penalty was removed to allow any new response to active treatment after Month 3 to be observed (NRI no advancement penalty [NRINAP]). The NRINAP response could not be calculated for the placebo group as non-responders were advanced to TOF treatment. The ACR20, ACR50 and ACR70 variables are based on several component variables; however, it is possible to calculate the values even if the component variables had some missing values. In the case of missing values for component variables, a LOCF mixed components method was used and the values for ACR20, ACR50 and ACR70 were determined from a mix of actual and carried-forward values. For continuous measures (e.g. change from baseline), missing data were handled using the mixed-effects model. **ORAL Scan only** For all mTSS-related variables: • A patient must have had ≥1 post-baseline radiograph to be included in the linearly extrapolated analysis • Patients who advanced before Month 6 (non-responders) had their Month 6 measurements imputed using a linear extrapolation from Month 3 radiographs even when Month 6 radiographs were available, regardless of treatment assignment • As all placebo-treated patients advanced at ≤Month 6, Month-12 placebo data were imputed using linear extrapolation from Month 3 or Month 6 radiographic scores, whichever was the last month at which placebo was dosed before advancement to TOF The approach of using Month 3 radiographs for linear extrapolation for all treatment groups for advanced patients is similar to applying NRIWAP to all treatment groups, and is used to prevent bias in favour of TOF.			data were handled using the mixed-effect model. The ACR20, ACR50 and ACR70 variables are based on several component variables; however, it is possible to calculate the values even if the component variables had some missing values. In the case of missing values for component variables, a LOCF mixed components method was used and the values for ACR20, ACR50 and ACR70 were determined from a mix of actual and carried-forward values.

Trial no. (acronym)	NCT00853385 (ORAL Standard)	NCT00847613 (ORAL Scan)	NCT00856544 (ORAL Sync)	NCT00814307 (ORAL Solo)
Sample size, power calculation	For the ACR20 analysis, this sample size was planned to yield >90% power, assuming a difference in response rates of ≥20% (with the placebo response at 30%). For the analysis of the HAQ-DI, this sample size resulted in >90% power for differences of 0.3 or greater, assuming a SD of 0.75. For the analysis of DAS28-4(ESR) <2.6, this sample size resulted in 93.8% power for differences in response rates of ≥15% (with placebo response at 10%).	[redacted]	[redacted]For the ACR20 analysis, the sample size was planned to yield >90% power, assuming a difference in response rates of ≥20% (with the placebo response at 30%). For the analysis of the HAQ-DI, the sample size resulted in 97% power for differences of 0.3 or greater, assuming a SD of 0.75. For the analysis of DAS28-4(ESR) <2.6, the sample size resulted in approximately 99% power for differences in response rates of ≥15% (with placebo response at 10%).	[redacted]

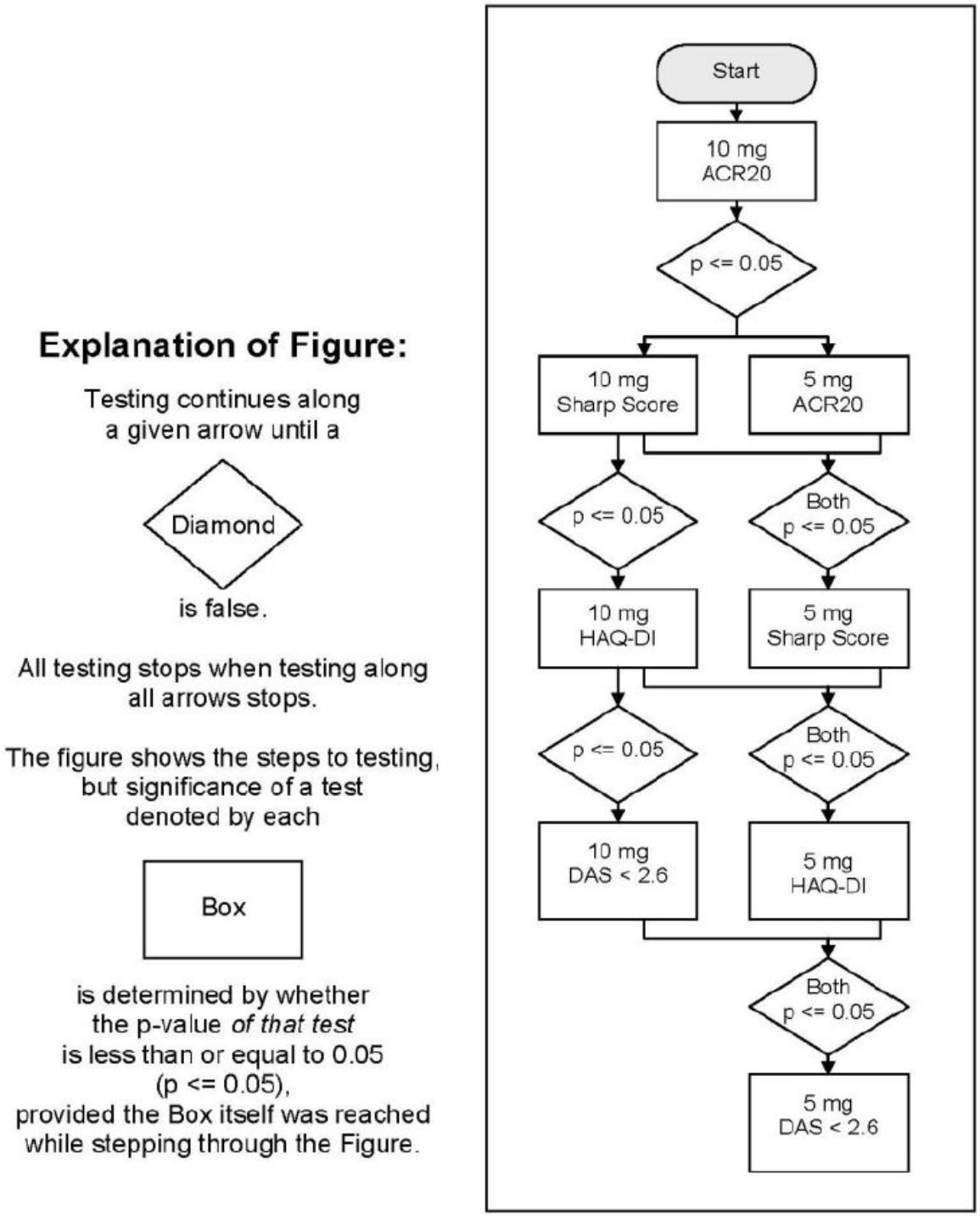
Abbreviations: ACR, American College of Rheumatology; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-disability index; LOCF, last observation carried forward; NRI, non-responder imputation; NRINAP, non-responder imputation no advancement penalty; NRIWAP, non-responder imputation with advancement penalty; ORAL, Oral Rheumatoid Arthritis Phase 3 Trials; mTSS, van der Heijde modified total sharp score; TOF, tofacitinib.
[†]This assumes that patients who did not achieve a response (defined as 20% reduction in number of tender and swollen joints) by Month 3 will not have a response during the remainder of the trial, even if they subsequently meet the criteria for an ACR20 response (defined as 20% reduction in number of tender and swollen joints, and improvement in ≥3 of the other five ACR components) (131).

Figure 4: The step-down approach to assigning statistical significance for the primary endpoints in ORAL Standard, ORAL Sync and ORAL Solo



Abbreviations: ACR, American College of Rheumatology; DAS28, Disease Activity Score in 28 joints; HAQ-DI, Health Assessment Questionnaire-disability index; ORAL, Oral Rheumatoid Arthritis Phase 3 Trials.

Figure 5: The step-down approach to assigning statistical significance for the primary endpoints in ORAL Scan



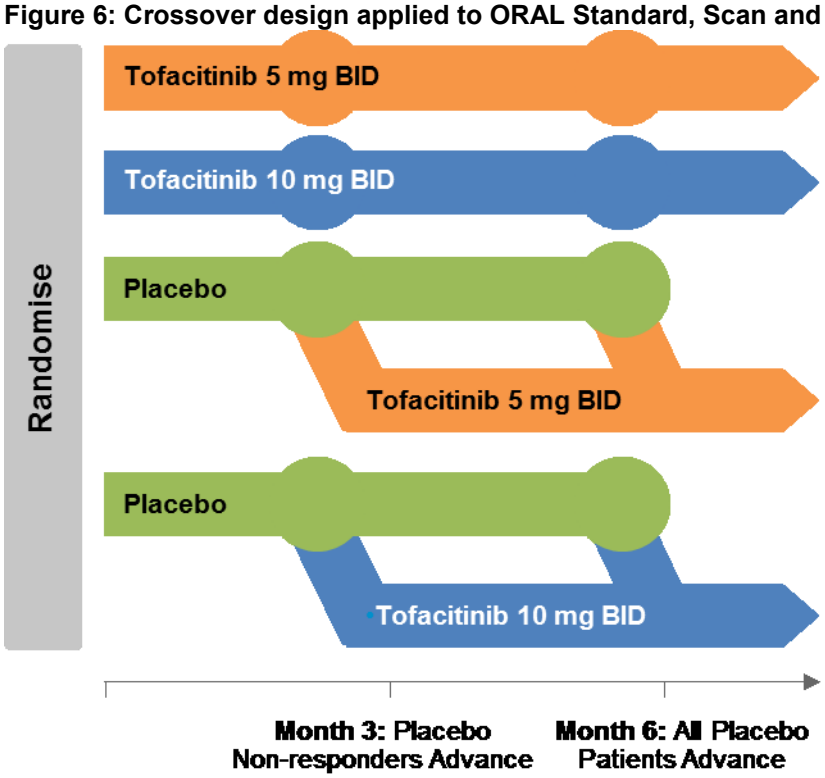
Abbreviations: ACR, American College of Rheumatology; DAS28, Disease Activity Score in 28 joints; HAQ-DI, Health Assessment Questionnaire-disability index; ORAL, Oral Rheumatoid Arthritis Phase 3 Trials.

4.5 *Participant flow in the relevant randomised controlled trials*

4.5.1 *Patient disposition*

In order to minimise the time patients spent on ineffective treatment, a crossover design was applied to the placebo-controlled studies (see Section 4.13.2.2 for detailed discussion). For the ≥12-month studies, ORAL Standard, Scan and Solo, patients who did not meet the trial response criteria at Month 3 (defined as a 20% reduction in number of tender and swollen joints) were advanced to their pre-designated dose of tofacitinib (Figure 6). As this would confound the result of the placebo group at Month 6 (i.e. the group randomised to placebo now contains contain a number of patients who received tofacitinib between Month 3 and 6), an approach was taken where patients who did not meet the response criteria at Month 3 were considered non-responders for the remainder of the trial (see Section 4.4.2 for detailed information on the statistical approach of non-responder imputation). This was applied to the categorical endpoints (such as DAS28-4[ESR] <2.6 and ACR20 response) assessed in both the placebo group and the tofacitinib group (primary analysis), where it is referred to as an advancement penalty. Consequently, the use of such an advancement penalty in the tofacitinib group may underestimate the absolute efficacy of tofacitinib, as it does not allow for non-responders at Month 3 to achieve a response in the trial. After Month 6, all placebo patients were advanced to active treatment, signifying the end of the placebo-controlled period. For the 6-month study ORAL Solo, all placebo patients were advanced to active treatment after Month 3. As the primary endpoint was also at Month 3, the crossover does not confound the result.

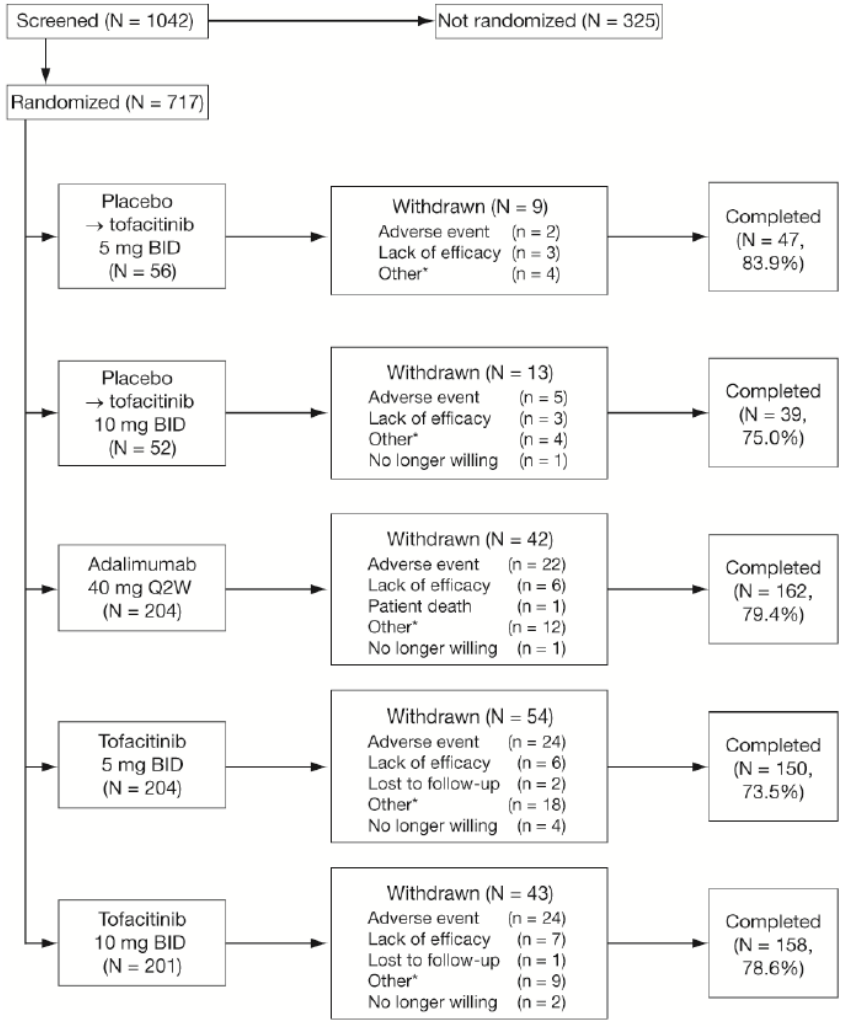
Figure 6: Crossover design applied to ORAL Standard, Scan and Sync



4.5.1.1 ORAL Standard (cDMARD experienced and MTX-IR)

For simplicity, the relevant treatment groups are hereafter referred to by the relevant comparator (i.e. MTX is included in all treatment groups and is therefore not mentioned). A total of 717 patients were randomly assigned to tofacitinib 5 mg (N=204), tofacitinib 10 mg (N=201), ADA (N=204), placebo to tofacitinib 5 mg (N=56) or placebo to tofacitinib 10 mg (N=52) and received treatment. Of the patients receiving placebo, 28 and 21 had not met the trial response criteria at Month 3 (defined as 20% reduction in number of tender and swollen joints) and advanced to tofacitinib 5 mg and tofacitinib 10 mg, respectively. Three patients (two in the tofacitinib 5 mg group and one in the tofacitinib 10 mg group) were lost to follow-up during the study: one at Month 2.5 and two at Month 6. A total of 556 patients (77.5%) completed the 12-month study. A Consolidated Standards of Reporting Trials (CONSORT) diagram for ORAL Standard is shown in Figure 7.

Figure 7: CONSORT diagram for ORAL Standard



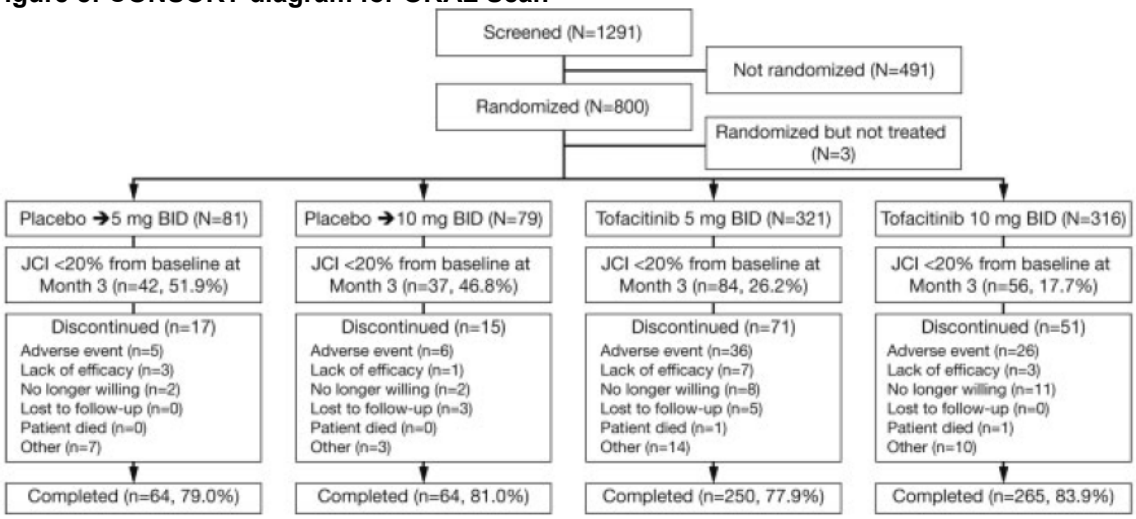
Abbreviations: BID, twice-daily; Q2W, every two weeks.
*patients withdrawn for reasons included in 'Other' consisted primarily of patients in breach of the protocol as they missed their study medication for >10 consecutive days.

4.5.1.2 ORAL Scan (cDMARD experienced and MTX-IR)

For simplicity, the relevant treatment groups are hereafter referred to by the relevant comparator (i.e. MTX is included in all treatment groups and is therefore not mentioned).

A total of 797 patients were randomly assigned to tofacitinib 5 mg (N=321), tofacitinib 10 mg (N=316), placebo to tofacitinib 5 mg (N=81) or placebo to tofacitinib 10 mg (N=79) and received treatment. Of the patients receiving placebo, 42 and 37 had not met the trial response criteria at Month 3 (defined as 20% reduction in number of tender and swollen joints) and had advanced to tofacitinib 5 mg and tofacitinib 10 mg, respectively. Eight patients (three in the placebo to tofacitinib 10 mg group and five in the tofacitinib 5 mg group) were lost to follow-up during the study. At the time of the 12-month interim analysis, a total of 643 patients (80.7%) were still receiving treatment. A CONSORT diagram for ORAL Scan is shown in Figure 8.

Figure 8: CONSORT diagram for ORAL Scan

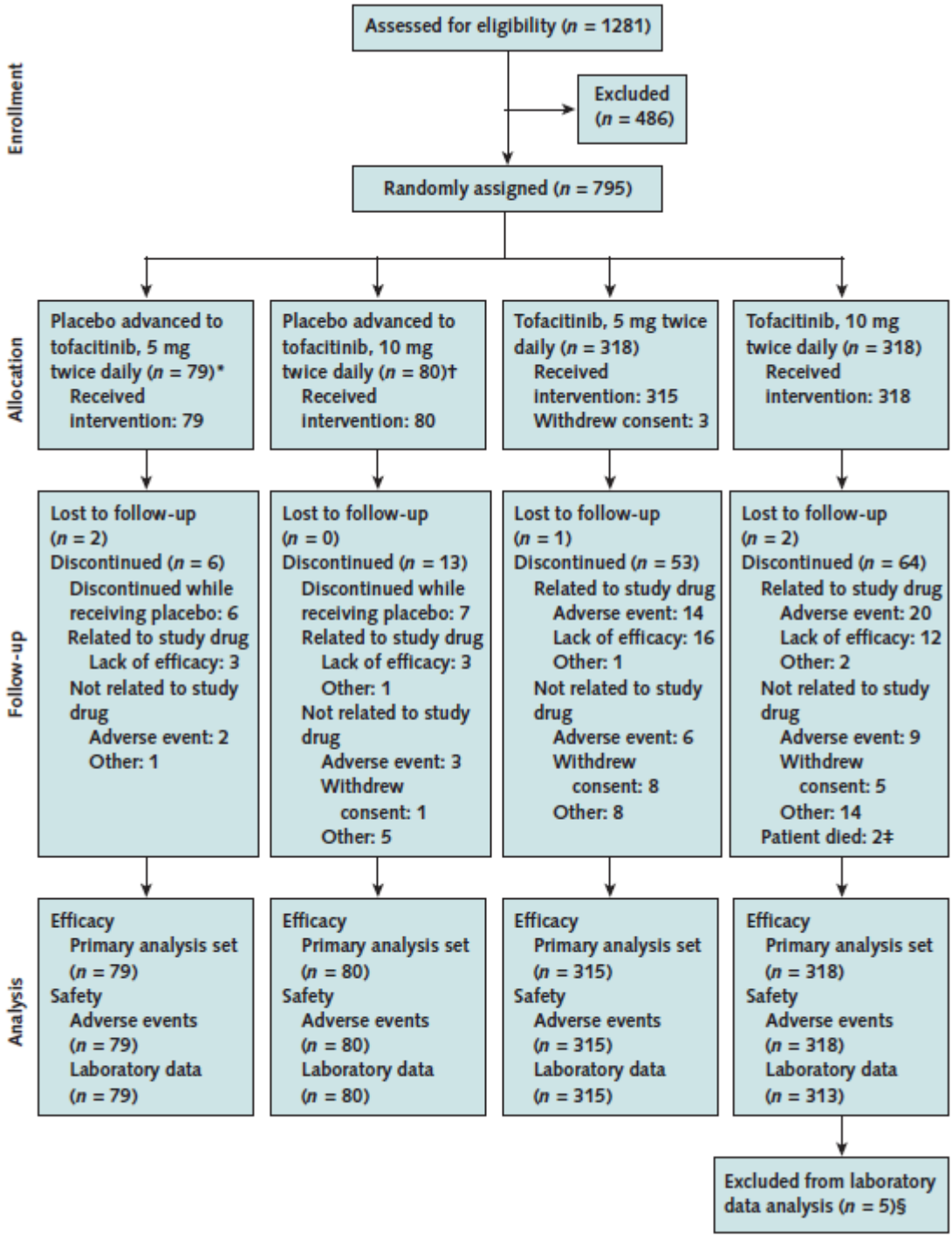


Abbreviations: BID, twice-daily; JCI, (swollen and tender) joint count improvement.

4.5.1.3 ORAL Sync (DMARD-IR: cDMARD including MTX or bDMARD)

For simplicity, the relevant treatment groups are hereafter referred to by the relevant comparator (i.e. ≥1 cDMARD are included in all treatment groups and is therefore not mentioned). A total of 792 patients were randomly assigned to tofacitinib 5 mg (N=315), tofacitinib 10 mg (N=318), placebo to tofacitinib 5 mg (N=79) or placebo to tofacitinib 10 mg (N=80) and received treatment. Of the patients receiving placebo, 38 and 40 had not met the trial response criteria at Month 3 (defined as 20% reduction in number of tender and swollen joints) and had advanced to tofacitinib 5 mg and tofacitinib 10 mg, respectively. Five patients (two in the placebo to tofacitinib 5 mg group, one in the tofacitinib 5 mg group and one in the tofacitinib 10 mg group) were lost to follow-up during the study. A total of 651 patients (82.2%) completed the 12-month study. A CONSORT diagram for ORAL Sync is shown in Figure 9.

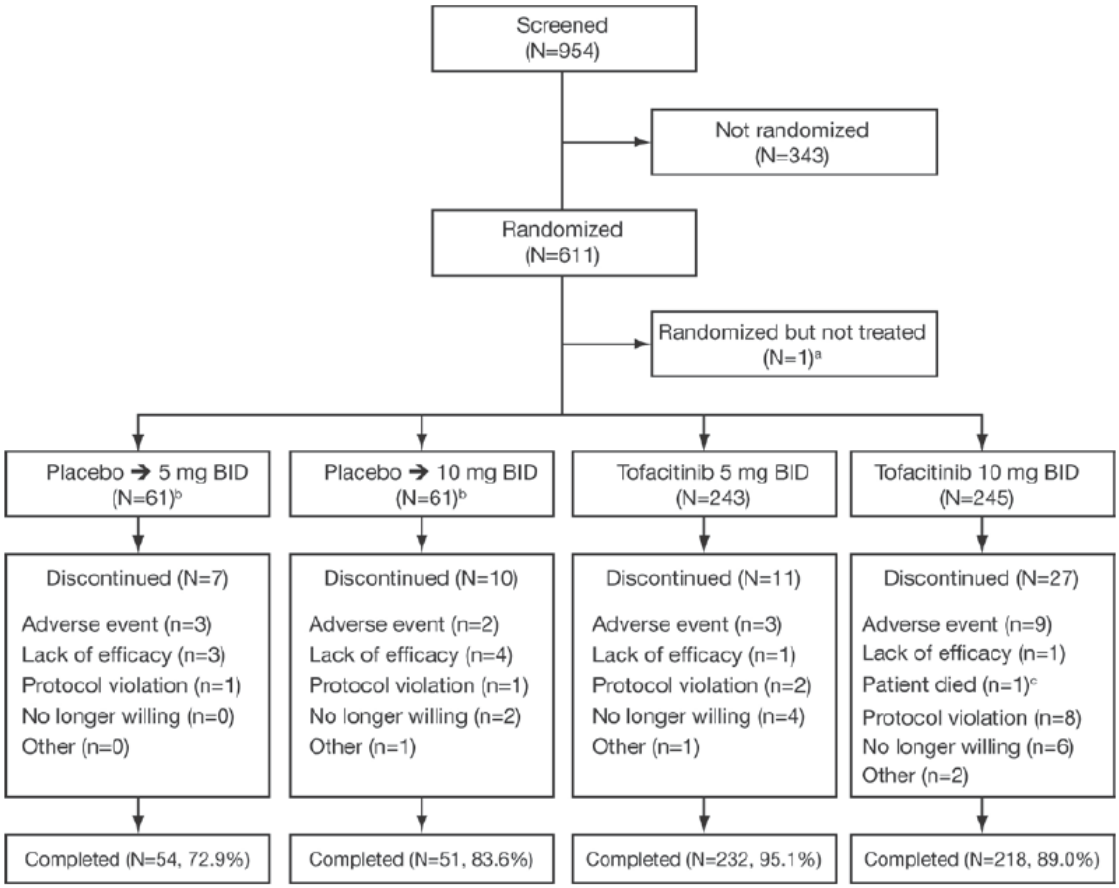
Figure 9: CONSORT diagram for ORAL Sync



4.5.1.4 ORAL Solo (DMARD-IR: cDMARD including MTX or bDMARD)

A total of 610 patients were randomly assigned to tofacitinib 5 mg (N=243), tofacitinib 10 mg (N=245), placebo to tofacitinib 5 mg (N=61) or placebo to tofacitinib 10 mg (N=61) and received treatment. A total of 555 patients (91.0%) completed the 6-month study. A CONSORT diagram for ORAL Solo is shown in Figure 10.

Figure 10: CONSORT diagram for ORAL Solo



Abbreviations: BID, twice-daily.

4.5.2 *Baseline characteristics and demographics*

4.5.2.1 ORAL Standard (cDMARD experienced and MTX-IR)

In ORAL Standard, no significant differences between the treatment groups were observed at baseline. The majority of the 717 patients in the FAS were women (75.0 to 85.3%) and white (67.3 to 74.0%) and the mean duration of RA ranged from 6.9 to 9.0 years.

[redacted] Patient characteristics at baseline are summarised in Table 16.

Table 16: Characteristics of participants in ORAL Standard

Characteristic	TOF 5 mg (N=204)	TOF 10 mg (N=201)	ADA (N=204)	Placebo to TOF 5 mg (N=56)	Placebo to TOF 10 mg (N=52)
Female, n (%)	174 (85.3)	168 (83.6)	162 (79.4)	43 (76.8)	39 (75.0)
Race, n (%)					
White	151 (74.0)	143 (71.1)	148 (72.5)	40 (71.4)	35 (67.3)
[redacted]					
Region of origin, %					
Europe	53.9	55.7	53.9	51.8	44.2
North America	24.5	24.9	25.5	28.6	28.8
Latin America	3.9	1.5	2.9	3.6	5.8
Rest of the world	17.6	17.9	17.6	16.1	21.1
Age, yrs (SD)	53.0 (11.9)	52.9 (11.8)	52.5 (11.7)	55.5 (13.7)	51.9 (13.7)
Mean duration of RA, yrs (range)	7.6	7.4	8.1	6.9	9.0
Rheumatoid factor					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Positive, n (%)	[redacted](66.8)	[redacted] (66.2)	[redacted] (68.2)	[redacted](71.4)	[redacted] (60.8)
Anti-CCP					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Positive, n (%)	[redacted] (71.3)	[redacted] (64.0)	[redacted] (74.8)	[redacted](76.4)	[redacted] (62.0)
Tender and swollen joints					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tender joints, mean (SD)	28.5 [redacted]	26.1 [redacted]	26.7 [redacted]	26.6 [redacted]	28.1 [redacted]
Swollen joints, mean (SD)	16.7 ([redacted]	15.8 [redacted]	16.4 [redacted]	16.9 [redacted]	16.4 [redacted]
DAS28-4(ESR)					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESR, mm/hr					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	48.6 ([redacted])	49.9 ([redacted])	48.5 ([redacted])	52.7 ([redacted])	42.9 ([redacted])

Characteristic	TOF 5 mg (N=204)	TOF 10 mg (N=201)	ADA (N=204)	Placebo to TOF 5 mg (N=56)	Placebo to TOF 10 mg (N=52)
DAS28-3(CRP)					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRP, mg/L					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	14.9 ([redacted])	17.3 ([redacted])	17.5 ([redacted])	20.3 ([redacted])	11.6 ([redacted])
HAQ-DI score					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior therapy, n (%)					
TNF inhibitor	12 (5.9)	14 (7.0)	16 (7.8)	4 (7.1)	5 (9.6)
Non-TNF inhibitor bDMARD	2 (1.0)	4 (2.0)	3 (1.5)	4 (7.1)	2 (3.8)
Non-MTX cDMARD	109 (53.4)	115 (57.2)	114 (55.9)	30 (53.6)	29 (55.8)
Concomitant therapy, n (%)					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lipid-lowering medication	8 (3.9)	10 (5.0)	10 (4.9)	1 (1.8)	3 (5.8)

Abbreviations: ADA, adalimumab; bDMARD, biologic disease-modifying anti-rheumatic drug; CCS, corticosteroid; CCP, cyclic citrullinated peptide; cDMARD, conventional disease-modifying anti-rheumatic drug; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-disability index; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; ORAL, Oral Rheumatoid Arthritis Phase 3 Trials; RA, rheumatoid arthritis; SD, standard deviation; TNF, tumour necrosis factor; TOF, tofacitinib.
[†]In the ORAL trial programme Asian refers to Japanese and Korean patients.

4.5.2.2 ORAL Scan (cDMARD experienced and MTX-IR)

In ORAL Scan, the baseline characteristics were similar across the treatment groups. The majority of the 797 patients in the FAS were women (80.2 to 91.1%) and the mean duration of RA ranged from 8.8 to 9.5 years. In addition, 53.8% of the patients were non-white and the mean total mTSS ranged from 30.1 to 37.3.

[redacted] Patient characteristics at baseline are summarised in Table 17.

Table 17: Characteristics of participants in ORAL Scan

Characteristic	TOF 5 mg (N=321)	TOF 10 mg (N=316)	Placebo to TOF 5 mg (N=81)	Placebo to TOF 10 mg (N=79)
Female, n (%)	269 (83.8)	273 (86.4)	65 (80.2)	72 (91.1)
Race, n (%)				
White	152 (47.4)	144 (45.6)	36 (44.4)	36 (45.6)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, yrs (SD)	53.7 (11.6)	52.0 (11.4)	53.2 (11.5)	52.1 (11.8)
Mean duration of RA, yrs (range)	8.9 (0.3–43.0)	9.0 (0.3–42.0)	8.8 (0.6–30.8)	9.5 (0.4–43.5)
Rheumatoid factor				
n	[redacted]	[redacted]	[redacted]	[redacted]
Positive, n (%)	[redacted] (75.2)	[redacted] (77.6)	[redacted] (79.7)	[redacted] (75.3)
Anti-CCP				
n	[redacted]	[redacted]	[redacted]	[redacted]
Positive, n (%)	[redacted] (85.9)	[redacted] (84.4)	[redacted] (84.0)	[redacted] (82.3)
Tender and swollen joints				
n	[redacted]	[redacted]	[redacted]	[redacted]
Tender joints, mean (SD)	24.1 ([redacted])	23.0 ([redacted])	23.3 ([redacted])	22.6 ([redacted])
Swollen joints, mean (SD)	14.1 ([redacted])	14.4 ([redacted])	14.0 ([redacted])	14.5 ([redacted])
Total mTSS				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	31.1 [redacted]	37.3 [redacted]	35.0 [redacted]	30.1 [redacted]
DAS28-4(ESR)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	6.34 [redacted]	6.25 [redacted]	6.25 [redacted]	6.29 [redacted]
ESR, mm/hr				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	50.1 [redacted]	50.5 [redacted]	47.8 [redacted]	54.4 [redacted]
DAS28-3(CRP)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	5.22 [redacted]	5.20 [redacted]	5.14 [redacted]	5.18 [redacted]
CRP, mg/L				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	15.5 [redacted]	17.0 [redacted]	12.2 [redacted]	15.3 [redacted]

Characteristic	TOF 5 mg (N=321)	TOF 10 mg (N=316)	Placebo to TOF 5 mg (N=81)	Placebo to TOF 10 mg (N=79)
HAQ-DI score				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	1.41 [redacted]	1.39 [redacted]	1.40 [redacted]	1.23 [redacted]
Prior therapy, n (%)				
TNF inhibitor	[redacted](19.3)	[redacted](15.8)	[redacted](9.9)	[redacted](8.9)
Non-TNF inhibitor bDMARD	[redacted](5.3)	[redacted] (4.7)	[redacted] (3.7)	[redacted] (2.5)
Non-MTX cDMARD	[redacted] (60.1)	[redacted] (60.8)	[redacted](76.5)	[redacted] (58.2)
Concomitant therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; CCP, cyclic citrullinated peptide; CCS, corticosteroid; cDMARD, conventional disease-modifying anti-rheumatic drug; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-disability index; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; ORAL, Oral Rheumatoid Arthritis Phase 3 Trials; RA, rheumatoid arthritis; SD, standard deviation; mTSS, van der Heijde modified total sharp score; TNF, tumour necrosis factor; TOF, tofacitinib.
[†]In the ORAL trial programme Asian refers to Japanese and Korean patients.

4.5.2.3 ORAL Sync (DMARD-IR: cDMARD including MTX or bDMARD)

In ORAL Sync, the baseline characteristics were similar across the treatment groups. The majority of the 792 patients in the FAS were women (75.0 to 83.8%) and white (54.7 to 60.8%) and the mean duration of RA ranged from 8.1 to 10.2 years.

[redacted] Patient characteristics at baseline are summarised in Table 18.

Table 18: Characteristics of participants in ORAL Sync

Characteristic	TOF 5 mg (N=315)	TOF 10 mg (N=318)	Placebo to TOF 5 mg (N=79)	Placebo to TOF 10 mg (N=80)
Female, n (%)	[redacted] (83.8)	[redacted] (81.1)	[redacted] (79.7)	[redacted] (75.0)
Race, n (%)				
White	[redacted] (54.9)	[redacted] (54.7)	[redacted] (60.8)	[redacted] (55.0)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region of origin, %				
Europe	28.9	25.5	31.7	28.8
North America	16	17	22.8	18.8
Latin America	14.2	13.2	13.9	13.8
Rest of world	40.9	44.3	31.7	38.8
Age, yrs (SD)	52.7 (11.7)	51.9 (11.8)	50.8 (11.2)	53.3 (10.8)
Mean duration of RA				
Years	8.1	9.2	9.5	10.2
range	0.2–39.9	0.2–41.0	0.3–39.3	0.3–49.0
Rheumatoid factor				
n	[redacted]	[redacted]	[redacted]	[redacted]
Positive, n (%)	[redacted] (73.9)	[redacted] (72.8)	[redacted] (73.1)	[redacted] (72.2)
Anti-CCP				
n	[redacted]	[redacted]	[redacted]	[redacted]
Positive, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Tender and swollen joints				
n	[redacted]	[redacted]	[redacted]	[redacted]
Tender joints, mean (SD)	25.0 (15.3)	26.6 (16.1)	27.2 (16.8)	21.9 (13.0)
Swollen joints, mean (SD)	14.5 (10.3)	14.4 (9.7)	14.6 (9.7)	13.9 (8.6)
DAS28-4(ESR)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	6.27 [redacted]	6.36 [redacted]	6.44 [redacted]	6.14 [redacted]
ESR, mm/hr				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	50.5 (28.7)	51.9 (28.5)	51.0 (23.7)	49.3 (27.7)
DAS28-3(CRP)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	TOF 5 mg (N=315)	TOF 10 mg (N=318)	Placebo to TOF 5 mg (N=79)	Placebo to TOF 10 mg (N=80)
CRP, mg/L				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI score				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	1.44 (0.69)	1.43 (0.68)	1.45 (0.64)	1.24 (0.66)
Prior therapy				
TNF inhibitor, n (%)	[redacted] (7.3)	[redacted] (6.0)	[redacted] (6.3)	[redacted] (6.3)
Non-TNF inhibitor bDMARD, n (%)	[redacted] (2.2)	[redacted] (3.1)	[redacted] (7.6)	0
MTX, n (%)	[redacted] (86.7)	[redacted] (82.7)	[redacted] (83.5)	[redacted] (82.5)
Non-MTX cDMARD, %	232 (73.7)	242 (76.1)	55 (69.6)	62 (77.5)
Failed DMARDs, mean	1.4	1.4	1.3	1.4
Concomitant therapy, n (%)				
MTX	250 (79.4)	251 (78.9)	61(77.2)	64 (80.0)
1 cDMARD	[redacted] (66.7)	[redacted] (64.8)	[redacted] (73.4)	[redacted] (62.5)
≥2 cDMARDs	[redacted] (33.3)	[redacted] (34.9)	[redacted] (25.3)	[redacted] (37.5)
NSAIDs	[redacted] (75.9)	[redacted] (74.2)	[redacted] (72.2)	[redacted] (63.8)
Systemic CCS	[redacted] (61.9)	[redacted] (57.2)	[redacted] (59.5)	[redacted] (58.8)
Lipid-lowering medication	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; CCP, cyclic citrullinated peptide; CCS, corticosteroid; cDMARD, conventional disease-modifying anti-rheumatic drug; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-disability index; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; ORAL, Oral Rheumatoid Arthritis Phase 3 Trials; RA, rheumatoid arthritis; SD, standard deviation; TNF, tumour necrosis factor; TOF, tofacitinib.
[†]In the ORAL trial programme Asian refers to Japanese and Korean patients.

4.5.2.4 ORAL Solo (DMARD-IR: cDMARD including MTX or bDMARD)

In ORAL Solo, the baseline characteristics were similar across the treatment groups. The majority of the 610 patients in the FAS were women (83.6 to 88.5%) and white (63.0 to 75.4%) and the mean duration of RA ranged from 7.3 to 8.6 years.

[redacted]

[redacted] Patient characteristics at baseline are summarised in Table 19.

Table 19: Characteristics of participants in ORAL Solo

Characteristic	TOF 5 mg (N=243)	TOF 10 mg (N=245)	Placebo to TOF 5 mg (N=61)	Placebo to TOF 10 mg (N=61)
Female, n (%)	207 (85.2)	216 (88.2)	[redacted]	[redacted]
Race, n (%)				
White	153 (63.0)	168 (68.6)	46 (75.4)	42 (68.9)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, yrs (SD)	52.2 (11.5)	52.4 (11.7)	50.7 (12.8)	48.8 (11.9)
Mean duration of RA, yrs (range)	8.0 (0.2–42.3)	8.6 (0.2–49.0)	7.3 (0.3–28.0)	8.1 (0.1–28.0)
Rheumatoid factor				
n	[redacted]	[redacted]	[redacted]	[redacted]
Positive, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CCP				
n	[redacted]	[redacted]	[redacted]	[redacted]
Positive, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Tender and swollen joints				
n	[redacted]	[redacted]	[redacted]	[redacted]
Tender joints, mean (SD)	29.4 ([redacted])	29.1 ([redacted])	[redacted]	[redacted]
Swollen joints, mean (SD)	16.3 ([redacted])	17.0 ([redacted])	[redacted]	[redacted]
DAS28-4(ESR)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	6.71 ([redacted])	6.70 ([redacted])	[redacted]	[redacted]
ESR, mm/hr				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted])	52.1 [redacted]	[redacted]	[redacted]
DAS28-3(CRP)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	5.68 ([redacted])	5.60 ([redacted])	[redacted]	[redacted]

Characteristic	TOF 5 mg (N=243)	TOF 10 mg (N=245)	Placebo to TOF 5 mg (N=61)	Placebo to TOF 10 mg (N=61)
			[redacted]	[redacted]
CRP, mg/L				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI score				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	1.53 ([redacted])	1.50 ([redacted])	[redacted]	[redacted]
Prior therapy, n (%)				
TNF inhibitor	[redacted] (14.0)	[redacted] (16.7)	[redacted]	[redacted]
Non-TNF inhibitor bDMARD	[redacted] (4.9)	[redacted] (7.8)	[redacted]	[redacted]
MTX	[redacted] (86.0)	[redacted] (84.5)	[redacted]	[redacted]
Non-MTX cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
Failed DMARDs, mean	1.70	1.71	[redacted]	[redacted]
Concomitant therapy, n (%)				
NSAIDs	[redacted]	[redacted]	[redacted]	[redacted]
Systemic CCS	[redacted]	148 [redacted]	[redacted]	[redacted]
Lipid-lowering medication	[redacted] (11.5)	[redacted] (14.7)	[redacted]	[redacted]
Anti-malarial	[redacted] (18.5)	[redacted] (16.7)	[redacted]	[redacted]

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; CCP, cyclic citrullinated peptide; CCS, corticosteroid; cDMARD, conventional disease-modifying anti-rheumatic drug; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-disability index; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; ORAL, Oral Rheumatoid Arthritis Phase 3 Trials; RA, rheumatoid arthritis; SD, standard deviation; TNF, tumour necrosis factor; TOF, tofacitinib.

[†]In the ORAL trial programme Asian refers to Japanese and Korean patients.

4.6 *Quality assessment of the relevant randomised controlled trials*

A complete quality assessment for each RCT is provided in Table 20.

Table 20: Quality assessment results for parallel group RCTs

Study Question	ORAL Standard	ORAL Scan	ORAL Sync	ORAL Solo
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Intention-to-treat analysis was considered unsuitable for the Month 6 assessment in clinical trials due to the advancement of patients receiving placebo to active treatment at Month 3 (see Section 4.13.2.2 for full discussion). However, for clinical trials, where the primary endpoint was at Month 3, were not impacted by this issue.			

4.7 *Clinical effectiveness results of the relevant randomised controlled trials*

4.7.1 *ORAL Standard (cDMARD experienced and MTX-IR)*

- Tofacitinib 5 mg significantly improved the rate of disease remission (DAS28-4[ESR] <2.6) at Month 6 compared with placebo; a significant difference was observed as early as Month 3.
- Tofacitinib 5 mg significantly improved the physical functioning (reduction in HAQ-DI from baseline) of patients with RA at Month 3 and Month 6 compared with placebo; a significant difference was observed as early as Month 1.
- Tofacitinib 5 mg significantly reduced the signs and symptoms (ACR20) of RA at Month 6 compared with placebo; a significant difference was observed as early as Month 1.
- Tofacitinib 5 mg significantly reduced patients' levels of pain and fatigue, and improved overall quality of life at Month 6 compared with placebo.
    - Scores for pain (VAS), fatigue (FACIT-F) and quality of life (EQ-5D) were all significantly improved in the tofacitinib 5 mg group compared with placebo by Month 6.
- The efficacy of tofacitinib treatment achieved at Month 6 is maintained up to Month 12.
- A comparison with adalimumab also revealed no evidence of a difference in efficacy with tofacitinib 5 mg. However, as the study was not powered to assess the efficacy of tofacitinib with adalimumab, no formal conclusions can be made.

4.7.1.1 Primary efficacy outcomes

The primary efficacy results for ORAL Standard are summarised in Table 21. For these analyses, tofacitinib groups were compared with a combined placebo group (placebo to tofacitinib 5 mg and placebo to tofacitinib 10 mg). Due to the crossover design of the study (see Section 4.5.1), an approach was taken where patients who did not meet the response criteria at Month 3 were considered to be non-responders for the remainder of the trial. This was applied to the categorical endpoints assessed in each treatment group at Month 6, including tofacitinib.

Signs and symptoms of RA – Proportion of patients achieving ACR20 at Month 6

A significantly greater percentage of patients in the tofacitinib 5 mg (51.5%) group achieved an ACR20 response at Month 6 compared with patients in the combined placebo group (28.3%; p<0.001; Figure 11); the difference from placebo was [redacted]

Physical functioning – Mean change from baseline in HAQ-DI score at Month 3

The mean change from baseline in HAQ-DI score at Month 3 was significantly greater in the tofacitinib 5 mg (–0.55) compared with the combined placebo group (–0.24; p<0.001; Figure 12); the difference from placebo was [redacted]

Disease activity – Proportion of patients achieving disease remission (DAS28-4[ESR] <2.6) at Month 6

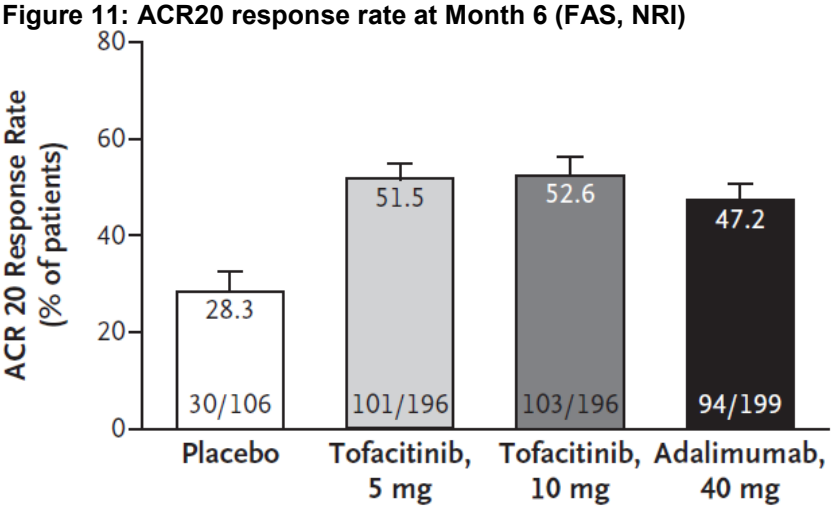
A significantly greater percentage of patients in the tofacitinib 5 mg (6.2%) group achieved disease remission (DAS28-4[ESR] <2.6) at Month 6 compared with patients in the combined placebo group (1.1%; p=0.0151; Figure 13); the difference from placebo was [redacted]

Table 21: Summary of primary efficacy results for ORAL Standard (FAS)

Outcome	TOF 5 mg	TOF 10 mg	ADA	Placebo
ACR20 response rate at Month 6 (NRI)				
N	196	196	199	106
Response rate, n (%)	101 (51.5)	103 (52.6)	94 (47.2)	30 (28.3)
Difference from placebo, %	[redacted]	[redacted]	[redacted]	-
95% CI for difference	[redacted]	[redacted]	[redacted]	-
p-value†	<0.001	<0.001	<0.001	-
HAQ-DI score at Month 3				
N	188	185	190	98
LS mean change from baseline	–0.55	–0.61	–0.49	–0.24
LS mean difference from placebo	[redacted]	[redacted]	[redacted]	-
95% CI for difference	[redacted]	[redacted]	[redacted]	-
p-value†	<0.001	<0.001	<0.001	-
DAS28-4(ESR) <2.6 at Month 6 (NRI)				
N	177	176	178	92
Response rate, n (%)	11 (6.2)	22 (12.5)	12 (6.7)	1 (1.1)
Difference from placebo, %	[redacted]	[redacted]	[redacted]	-
95% CI for difference	[redacted]	[redacted]	[redacted]	-
p-value†	[redacted]	<0.001	[redacted]	-

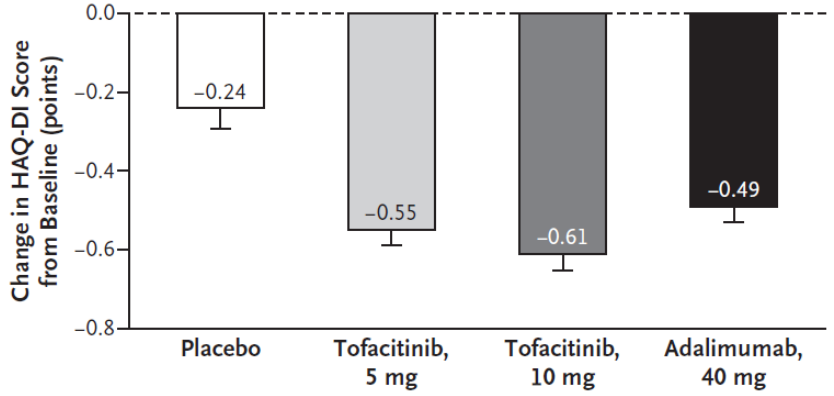
Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-disability index; LS, least squares; NRI, non-responder imputation; TOF, tofacitinib.
†p-value is subject to the step-down approach.

Figure 11: ACR20 response rate at Month 6 (FAS, NRI)



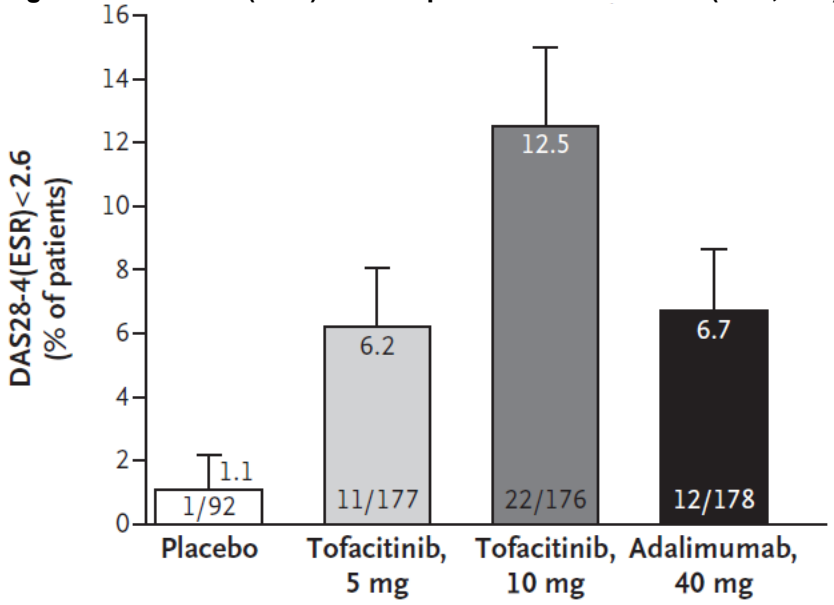
Abbreviations: ACR, American College of Rheumatology FAS, full analysis set; NRI, non-responder imputation.

Figure 12: Mean change from baseline in HAQ-DI score at Month 3 (FAS)



Abbreviations: FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-disability index.

Figure 13: DAS28-4(ESR) <2.6 response rate at Month 6 (FAS, NRI)



Abbreviations: DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; FAS, full analysis set; NRI, non-responder imputation.

4.7.1.2 Secondary analysis of primary outcomes

As an advancement penalty was applied to non-responders at Month 3, secondary analyses were also performed for the ACR20 and DAS28-4(ESR) <2.6 outcomes where the advancement penalty was removed to allow any new response to active treatment after Month 3 to be observed (non-responder imputation no advancement penalty [NRINAP]). The advancement penalty was not applied to the placebo group, as non-responders did not continue with placebo treatment in order to minimise the time spent on ineffective treatment; therefore, no placebo group is available for comparison. The results of these secondary analyses for ORAL Standard are summarised in Table 22.

Table 22: NRINAP ACR20 and DAS28-4(ESR) <2.6 response rates for ORAL Standard (FAS)

Outcome	TOF 5 mg	TOF 10 mg	ADA
ACR20 response rate at Month 6 (NRINAP)			
N	196	196	199
Response rate, n (%)	119 (60.7)	123 (62.8)	116 (58.3)
95% CI	[redacted]	[redacted]	[redacted]
DAS28-4(ESR) <2.6 at Month 6 (NRINAP)			
N	177	176	178
Response rate, n (%)	11 (6.2)	23 (13.1)	13 (7.3)
95% CI	[redacted]	[redacted]	[redacted]

Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; FAS, full analysis set; NRINAP, non-responder imputation no advancement penalty; TOF, tofacitinib.

4.7.1.3 Secondary efficacy outcomes

The secondary efficacy results for ORAL Standard are summarised below. The exploratory comparison between tofacitinib and ADA with regards to ACR response rates and DAS28-4(ESR) assessments are presented in the relevant sections.

Signs and symptoms of RA – Proportion of patients achieving ACR20, ACR50 and ACR70 per visit

A rapid response to tofacitinib 5 mg was observed; after 1 month, ACR20 and ACR50 response rates in the tofacitinib 5 mg group were significantly improved compared with the placebo group (p≤0.001 for all comparisons).

[redacted] The 1-month, 3-month, and 6-month ACR20, ACR50 and ACR70 response rates for ORAL Standard are summarised in Table 23.

Table 23: ACR response rates for ORAL Standard (FAS)

Outcome	TOF 5 mg	TOF 10 mg	ADA	Placebo
ACR20 response rate (NRI), n/N (%)				
Month 1	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	101/196 (51.5)†	103/196 (52.6)†	94/199 (47.2)†	30/106 (28.3)
ACR50 response rate (NRI), n/N (%)				
Month 1	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
ACR70 response rate (NRI), n/N (%)				
Month 1	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; FAS, full analysis set; NRI, non-responder imputation; TOF, tofacitinib.
†p-value <0.001 for comparison with placebo. ‡p-value ≤0.05 for comparison with placebo. §Nominal p-value ≤0.05 for comparison with adalimumab.

Physical functioning – Change from baseline in HAQ-DI scores per visit

Significantly greater changes in HAQ-DI scores from baseline were observed in the tofacitinib 5 mg group from Month 1 through Month 6 compared with the placebo group [redacted] The change from baseline in least squares (LS) mean HAQ-DI scores for ORAL Standard are summarised in Table 24.

Table 24: Change from baseline in LS mean HAQ-DI scores per visit (FAS)

Outcome	TOF 5 mg	TOF 10 mg	ADA	Placebo
Change from baseline in HAQ-DI score, LS mean (SE) [n]				
Month 1	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-disability index; LS, least squares; SD, standard deviation; SE, standard error; TOF, tofacitinib.
†p-value <0.001 for comparison with placebo. ‡p-value ≤0.05 for comparison with placebo.

Disease activity – Assessment of disease activity (DAS28-4[ESR]) per visit

At Month 1, 3 and 6, significantly greater changes in DAS28-4(ESR) scores from baseline were observed in the tofacitinib 5 mg group compared with the placebo group [redacted] No statistical difference was observed between the tofacitinib 5 mg group and the ADA group regarding the proportion of patients achieving disease remission (DAS28-4[ESR] <2.6) at Month 6.

[redacted]. The change from baseline in DAS28-4(ESR) scores and the proportion of patients achieving DAS28-4(ESR) <2.6 or ≤3.2 at Month 1, Month 3 and Month 6 for ORAL Standard are summarised in Table 25.

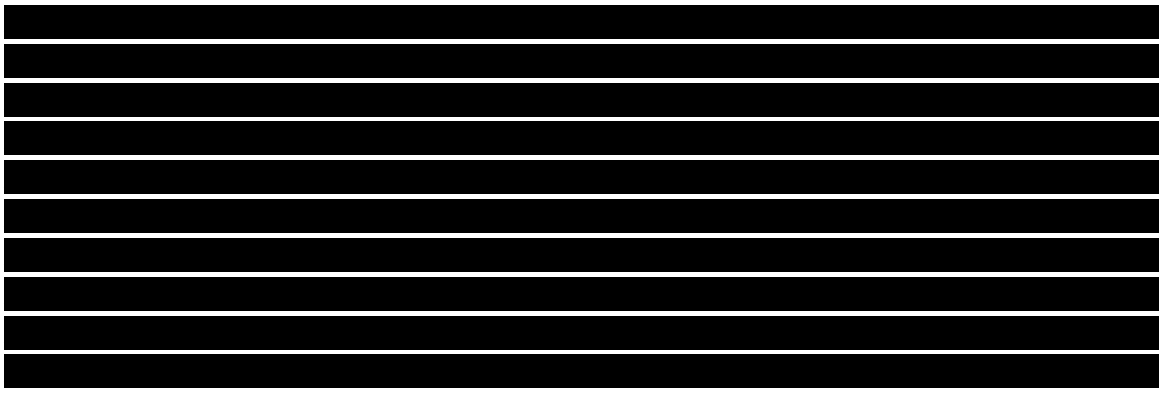
Assessment of EULAR response (improvement in DAS28 from baseline; see Table 7) at Month 6 demonstrated that [redacted]

Table 25: Assessment of DAS28-4(ESR) per visit (FAS)

Outcome	TOF 5 mg	TOF 10 mg	ADA	Placebo
Change from baseline in DAS28-4(ESR), LS mean (SE) [n]				
Month 1				
Month 3				
Month 6				
DAS28-4(ESR) <2.6 (NRI), n/N (%)				
Month 1				
Month 3				
Month 6	11/177 (6.21)‡	22/176 (12.5)†	12/178 (6.74)‡	1/92 (1.09)
DAS28-4(ESR) ≤3.2 (NRI), n/N (%)				
Month 1				
Month 3				
Month 6				
Good or moderate EULAR response, n/N (%)				
Month 6				

Abbreviations: ADA, adalimumab; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; FAS, full analysis set; LS, least squares; NRI, non-responder imputation; SD, standard deviation; SE, standard error; TOF, tofacitinib.
†p-value <0.001 for comparison with placebo. ‡p-value ≤0.05 for comparison with placebo.

Quality of life – Assessment of patient-reported outcomes per visit



[redacted] Changes from baseline in the SF-36 (mental and physical components), EQ-5D, FACIT-F, pain (VAS), Work Limitations Questionnaire (WLQ; Work Loss Index) and MOS-Sleep Scale (overall sleep problem) for ORAL Standard are summarised in Table 26.

Table 26: Assessment of patient-reported outcomes per visit (FAS)

Outcome	TOF 5 mg	TOF 10 mg	ADA	Placebo
Change from baseline in EQ-5D score, LS mean (SE) [n]				
Month 1	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in SF-36 MC score, LS mean (SE) [n]				
Month 1	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in SF-36 PC score, LS mean (SE) [n]				
Month 1	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in FACIT-F score, LS mean (SE) [n]				
Month 1	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]

Outcome	TOF 5 mg	TOF 10 mg	ADA	Placebo
Change from baseline in pain (VAS) score, LS mean (SE) [n]				
Month 1	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in MOS-SS overall sleep problem score, LS mean (SE) [n]				
Month 1	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in WLQ WLI score, LS mean (SE) [n]				
Month 3	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; EQ-5D, EuroQol five-dimension questionnaire; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; FAS, full analysis set; LS, least squares; MC, mental component; MOS-SS, Medical Outcomes Study – Sleep Scale; PC, physical component; SD, standard deviation; SE, standard error; SF-36, Short Form (36); TOF, tofacitinib; Work Limitation Questionnaire Work Loss Index.
†p-value <0.001 for comparison with placebo. ‡p-value ≤0.05 for comparison with placebo.

Maintenance of tofacitinib efficacy

The efficacy of tofacitinib, with regards to disease remission (DAS28-4[ESR] <2.6), physical functioning (HAQ-DI) and the signs and symptoms of RA (ACR20), was assessed beyond the placebo-controlled period up to Month 12 (end of trial). This analysis demonstrated that the magnitude of response achieved at Month 6 was sustained to Month 12. Similarly, the improvement in general HRQoL (EQ-5D), fatigue (FACIT-F) and pain (pain [VAS]) were also sustained until the end of the trial.

4.7.2 *ORAL Scan (cDMARD experienced and MTX-IR)*

- Tofacitinib 5 mg significantly reduced the signs and symptoms (ACR20) of RA at Month 6 compared with placebo; a significant difference was observed as early as Month 1.
- Tofacitinib inhibited radiographic progression in patients with RA compared with placebo at Month 6; while the mean change from baseline in mTSS score was numerically lower in the tofacitinib 5 mg group compared with placebo, the difference was not statistically significant (p=0.0792) (see Section 4.13 for further discussion on radiographic progression).
    - In the pre-specified secondary analysis, tofacitinib 5 mg was superior to placebo in the proportion of patients with no radiographic progression. (<0.5 change from baseline mTSS): 88.8% in the tofacitinib group and 77.7% in the placebo group (p≤0.05).
- Due to the stepwise analysis of the primary endpoints, improvement in physical functioning (HAQ-DI) at Month 3 and the disease remission response rate (DAS28-4[ESR] <2.6) at Month 6 could not be declared statistically significant for the tofacitinib 5 mg group compared with placebo. However, the differences were nominally significant and improvements in HAQ-DI and disease remission (DAS28-4[ESR] <2.6) were observed as early as Month 1.
- Tofacitinib 5 mg significantly reduced patients' levels of pain and fatigue, and improved overall quality of life at Month 6.
    - Scores for pain (VAS), fatigue (FACIT-F) and quality of life (EQ-5D) were all significantly improved in the tofacitinib 5 mg group compared with placebo by Month 6.
- The efficacy of tofacitinib treatment achieved at Month 6 is maintained up to Month 12.

4.7.2.1 Primary efficacy outcomes

The primary efficacy results for ORAL Scan are summarised in

Table 27. These data are from the 12-month interim analysis of the 24-month study; all primary endpoints are at ≤6 months. For these analyses, tofacitinib groups were compared with a combined placebo group (placebo to tofacitinib 5 mg and placebo to tofacitinib 10 mg). Due to the crossover design of the study (see Section 4.5.1), an approach was taken where patients who did not meet the response criteria at Month 3 were considered to be non-responders for the remainder of the trial. This was applied to the categorical endpoints assessed in each treatment group at Month 6, including tofacitinib.

Signs and symptoms of RA – Proportion of patients achieving ACR20 at Month 6

A significantly greater percentage of patients in the tofacitinib 5 mg (51.5%) group achieved an ACR20 response at Month 6 compared with patients in the combined placebo group (25.3%; p<0.001; Figure 14); the difference from placebo was [redacted]

Radiographic progression – Mean change from baseline in mTSS score at Month 6

The mean change from baseline in mTSS score at Month 6 was not significantly different between the tofacitinib 5 mg group (0.12) and the combined placebo group (0.47; 0.0792; Figure 15; see Section 4.13 for further discussion on radiographic progression); the difference from placebo was [redacted] Due to the step-down procedure applied to primary efficacy outcomes, significance was not declared for the HAQ-DI score or DAS28-4(ESR) <2.6 for tofacitinib 5 mg.

Physical functioning – Mean change from baseline in HAQ-DI score at Month 3

The mean change from baseline in HAQ-DI score at Month 3 was numerically greater in the tofacitinib 5 mg (–0.40) compared with the combined placebo group (–0.15; significance not declared; Figure 16); the difference from placebo was [redacted] with a nominal p-value [redacted].

Disease activity – Proportion of patients achieving disease remission (DAS28-4[ESR] <2.6) at Month 6

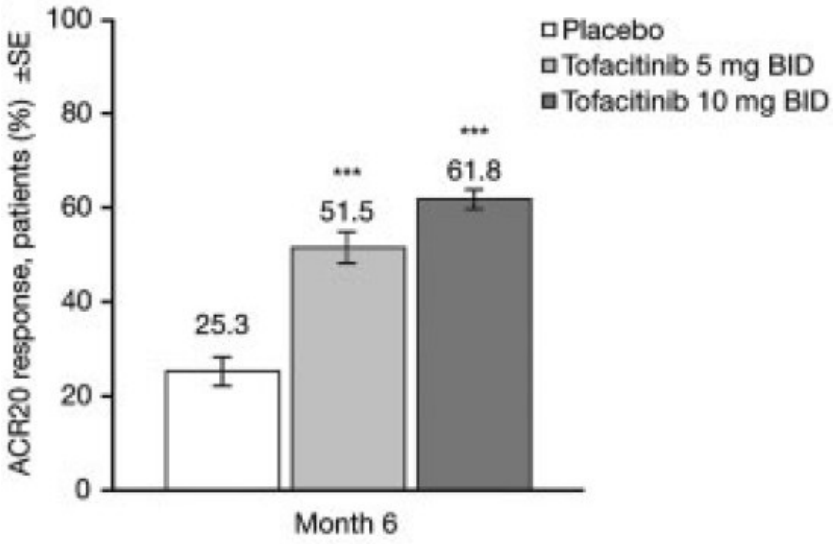
A numerically higher percentage of patients in the tofacitinib 5 mg (7.2%) group achieved disease remission (DAS28-4[ESR] <2.6) at Month 6 compared with patients in the combined placebo group (1.6%; significance not declared; Figure 17); the difference from placebo was [redacted] with a nominal p-value of 0.0034.

Table 27: Summary of primary efficacy results for ORAL Scan (FAS)

Outcome	TOF 5 mg	TOF 10 mg	Placebo
ACR20 response rate at Month 6 (NRI)			
N	[redacted]	[redacted]	[redacted]
Response rate, n (%)	[redacted] (51.5)	[redacted] (61.8)	[redacted] (25.3)
Difference from placebo, %	[redacted]	[redacted]	-
95% CI for difference	[redacted]	[redacted]	-
p-value†	<0.001	<0.001	-
mTSS score at Month 6 (LE)			
N	[redacted]	[redacted]	[redacted]
LS mean change from baseline	0.12	0.06	0.47
LS mean difference from placebo	[redacted]	[redacted]	-
95% CI for difference	[redacted]	[redacted]	-
p-value†	0.0792	[redacted]	-
HAQ-DI score at Month 3			
N	[redacted]	[redacted]	[redacted]
LS mean change from baseline	–0.40	–0.54	–0.15
LS mean difference from placebo	[redacted]	[redacted]	-
95% CI for difference	[redacted]	[redacted]	-
p-value†	Not declared‡	<0.001	-
DAS28-4(ESR) <2.6 at Month 6 (NRI)			
N	[redacted]	[redacted]	[redacted]
Response rate, n (%)	[redacted] (7.2)	[redacted] (16.0)	[redacted] (1.6)
Difference from placebo, %	[redacted]	[redacted]	-
95% CI for difference	[redacted]	[redacted]	-
p-value†	Not declared‡	<0.001	-

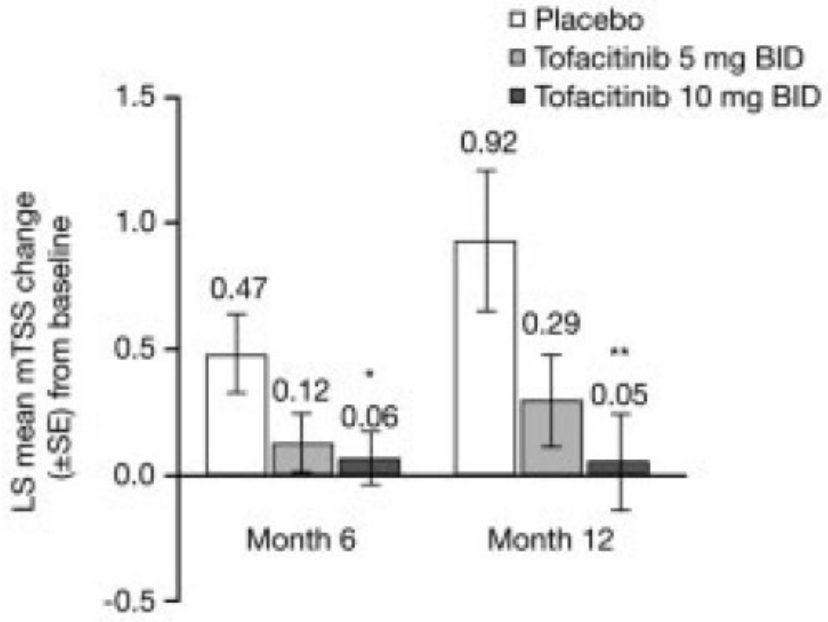
Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; DAS28, Disease Activity Score in 28 joints; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-disability index; LE, linear extrapolation; LS, least squares; NRI, non-responder imputation; mTSS, van der Heijde modified total sharp score; TOF, tofacitinib.
†p-value is subject to the step-down approach. ‡Due to the step-down procedure applied to primary efficacy outcomes, significance was not declared for the HAQ-DI score or DAS28-4(ESR) <2.6 for TOF 5 mg. Nominal p-values (TOF 5 mg vs placebo) for these outcomes were <0.001 and 0.0034, respectively.

Figure 14: ACR20 response rate at Month 6 (FAS, NRI)



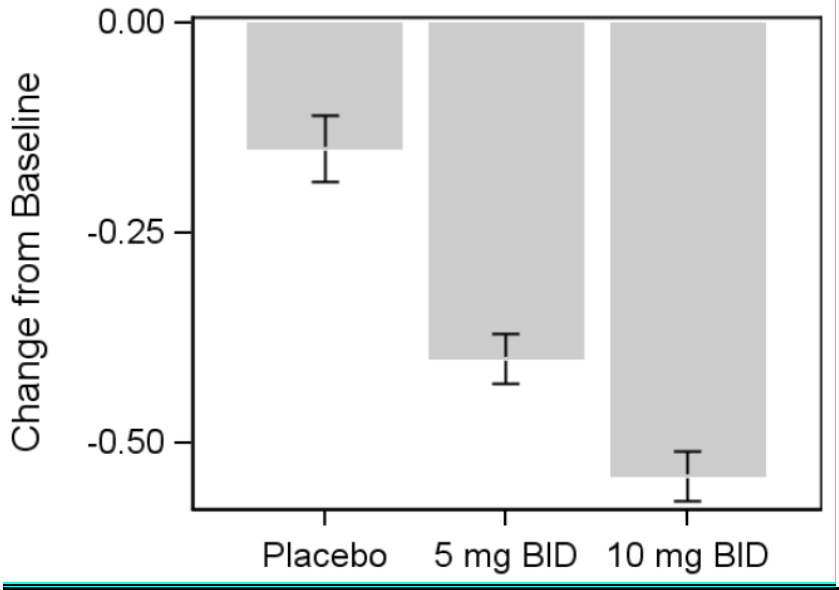
Abbreviations: ACR, American College of Rheumatology; FAS, full analysis set; NRI, non-responder imputation.

Figure 15: Mean change from baseline in mTSS score at Month 6 and Month 12 (FAS, LE)



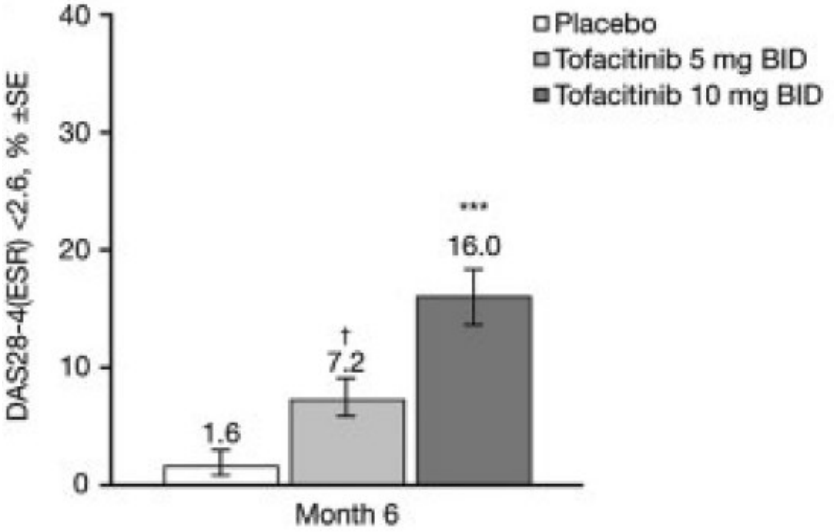
Abbreviations: FAS, full analysis set; LE, linear extrapolation; mTSS, van der Heijde modified total sharp score.

Figure 16: [redacted]



[redacted]

Figure 17: DAS28-4(ESR) <2.6 response rate at Month 6 (FAS, NRI)



Abbreviations: DAS28, Disease Activity Score in 28 joints; FAS, full analysis set; NRI, non-responder imputation.
Note: p-values were not declared due to step down procedure.

4.7.2.2 Secondary analysis of primary outcome

As an advancement penalty was applied to non-responders at Month 3, secondary analyses were also performed for the ACR20 and DAS28-4(ESR) <2.6 outcomes where the advancement penalty was removed to allow any new response to active treatment after Month 3 to be observed (NRINAP). The advancement penalty was not applied to the placebo group, as non-responders did not continue with placebo treatment in order to minimise the time spent on ineffective treatment; therefore, no placebo group is available for comparison. The results of these secondary analyses for ORAL Scan are summarised in Table 28.

Table 28: NRINAP ACR20 and DAS28-4(ESR) <2.6 response rates for ORAL Scan (FAS)

Outcome	TOF 5 mg	TOF 10 mg
ACR20 response rate at Month 6 (NRINAP)		
N	[redacted]	[redacted]
Response rate, n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
DAS28-4(ESR) <2.6 at Month 6 (NRINAP)		
N	[redacted]	[redacted]
Response rate, n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; DAS28, Disease Activity Score in 28 joints; FAS, full analysis set; NRINAP, non-responder imputation no advancement penalty; TOF, tofacitinib.

4.7.2.3 Secondary efficacy outcomes

Signs and symptoms of RA – Proportion of patients achieving ACR20, ACR50 and ACR70 per visit

Statistically significant improvements in ACR20, ACR50 and ACR70 responses were observed in the tofacitinib 5 mg group compared with the placebo group at Month 1, 3 and 6 ($p<0.001$ for all comparisons). The 1-month, 3-month, and 6-month ACR20, ACR50 and ACR70 response rates for ORAL Scan are summarised in Table 29.

Table 29: ACR response rates for ORAL Scan (FAS)

Outcome	TOF 5 mg	TOF 10 mg	Placebo
ACR20 response rate (NRI), n/N (%)			
Month 1	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted] (51.5)†	[redacted] (61.8)†	[redacted] (25.3)
ACR50 response rate (NRI), n/N (%)			
Month 1	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted] (32.4%)†	[redacted] (43.7)†	[redacted] (8.4%)
ACR70 response rate (NRI), n/N (%)			
Month 1	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted] (14.6%)†	[redacted] (22.3)†	[redacted] (1.3%)

Abbreviations: ACR, American College of Rheumatology; FAS, full analysis set; NRI, non-responder imputation; TOF, tofacitinib.
†p-value <0.001 for comparison with placebo.

Physical functioning – Change from baseline in HAQ-DI scores per visit

Statistically significantly decreased (improved) HAQ-DI scores were observed in the tofacitinib 5 mg group compared with placebo at Month 1, 3, and 6 ($p<0.001$ for all comparisons). The change from baseline in LS mean HAQ-DI scores for ORAL Scan are summarised in Table 30.

Table 30: Change from baseline in LS mean HAQ-DI scores per visit (FAS)

Outcome	TOF 5 mg	TOF 10 mg	Placebo
Change from baseline in HAQ-DI score, LS mean (SE) [n]			
Month 1	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-disability index; LS, least squares; SD, standard deviation; SE, standard error; TOF, tofacitinib.
[†]p-value <0.001 for comparison with placebo.

Disease activity – Assessment of disease activity (DAS28-4[ESR]) per visit

At Month 1, 3 and 6, significantly greater changes in DAS28-4(ESR) scores from baseline were observed in the tofacitinib 5 mg group compared with the placebo group ($p<0.001$ for all comparisons).

[redacted] The change from baseline in DAS28-4(ESR) scores and the proportion of patients achieving disease remission (DAS28-4[ESR] <2.6) or low disease activity (DAS28-4[ESR] ≤3.2) at Month 1, Month 3 and Month 6 for ORAL Scan are summarised in Table 31.

Assessment of EULAR response (improvement in DAS28 from baseline; see Table 7) at Month 6 demonstrated that [redacted]

Table 31: Assessment of DAS28-4(ESR) per visit (FAS)

Outcome	TOF 5 mg	TOF 10 mg	Placebo
Change from baseline in DAS28-4(ESR), LS mean (SE) [n]			
Month 1			
Month 3			
Month 6			
DAS28-4(ESR) <2.6 (NRI), n/N (%)			
Month 1			
Month 3			
Month 6			
DAS28-4(ESR) ≤3.2 (NRI), n/N (%)			
Month 1			
Month 3			
Month 6			
Good or moderate EULAR response, n/N (%)			
Month 6			

Abbreviations: DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; FAS, full analysis set; LS, least squares; NRI, non-responder imputation; SD, standard deviation; SE, standard error; TOF, tofacitinib.
†p-value <0.001 for comparison with placebo. ‡p-value ≤0.05 for comparison with placebo.

Key secondary endpoints for structural preservation

For Month 12 results, placebo data were imputed using linear extrapolation from Month 3 or Month 6 radiographic scores (whichever was the last month at which placebo was dosed before advancement to tofacitinib); tofacitinib 5 mg data were imputed using linear extrapolation from Month 3. At baseline, radiographs were available for 98.7% of patients across the treatment groups. At Month 12, the change from baseline in total mTSS score was not significantly different (p=0.0558) between the tofacitinib 5 mg and placebo groups (See Section 4.13 for further discussion on radiographic progression). The change from baseline in erosion score was also not significantly different between the tofacitinib 5 mg and placebo groups at Month 6 and 12. However, the change from baseline in joint-space narrowing (JSN) score at Month 12 (but not at Month 6) was significantly decreased (improved) in the tofacitinib 5 mg group compared with the placebo group (p<0.001). The proportion of patients with no radiographic progression (≤0.5-unit increase from baseline) at Month 6 and 12 was significantly greater in the tofacitinib 5 mg group compared with placebo (p≤0.05 for all comparisons). The proportion of patients with no progression in erosion score at Month 12 (but not at Month 6) was also significantly greater in the tofacitinib 5 mg group compared with placebo

(p≤0.05). The key secondary endpoints for structural preservation are summarised in Table 32.

Table 32: Key secondary outcomes for structural preservation (FAS)

Outcome	TOF 5 mg	TOF 10 mg	Placebo
Change from baseline in total mTSS score (LE)			
Change from baseline in total mTSS score, LS mean (SE) [n]			
Month 12	0.29 ([redacted]]	0.05 ([redacted]	0.92 [redacted]
Change from baseline in erosion and JSN scores (LE)			
Change from baseline in erosion score, LS mean (SE) [n]			
Month 6	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]
Change from baseline in JSN score, LS mean (SE) [n]			
Month 6	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]
Rates of non-progression (LE)			
≤0.5 change from baseline in total mTSS response rate, n/N (%)			
Month 6	[redacted] (88.8)†	[redacted] (86.9)†	[redacted] (77.7)
Month 12	[redacted] (86.0)†	[redacted] (86.4)†	[redacted] (74.1)
≤0.5 change from baseline in erosion score response rate, n/N (%)			
Month 6	[redacted] (93.9)	[redacted] (93.5)	[redacted] (87.8)
Month 12	[redacted] (92.0)†	[redacted] (93.2)†	[redacted] (83.5)

Abbreviations: FAS, full analysis set; JSN, joint space narrowing; LE, linear extrapolation; LS, least squares; SD, standard deviation; SE, standard error; mTSS, van der Heijde modified total sharp score; TOF, tofacitinib.
†p-value ≤0.05 for comparison with placebo.

Quality of life – Assessment of patient-reported outcomes per visit

[redacted]

[redacted] Change from baseline in the SF-36 (mental and physical components), EQ-5D, FACIT-F, pain (VAS), WLQ (Work Loss Index) and MOS-Sleep Scale (overall sleep problem) for ORAL Scan are summarised in Table 33.

Table 33: Assessment of patient-reported outcomes per visit (FAS)

Outcome	TOF 5 mg	TOF 10 mg	Placebo
Change from baseline in EQ-5D score, LS mean (SE) [n]			
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]
Change from baseline in SF-36 MC score, LS mean (SE) [n]			
Month 1	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]
Change from baseline in SF-36 PC score, LS mean (SE) [n]			
Month 1	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]
Change from baseline in FACIT-F score, LS mean (SE) [n]			
Month 1	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]
Change from baseline in pain (VAS) score, LS mean (SE) [n]			
Month 1	[redacted]	[redacted]	[redacted]

Outcome	TOF 5 mg	TOF 10 mg	Placebo
Month 3	[redacted]	[redacted]	[redacted]
Month 6	-26.36 (1.42) [202]†	-29.70 (1.35) [233]†	-15.70 (2.44) [62]
Change from baseline in MOS-SS overall sleep problem score, LS mean (SE) [n]			
Month 1	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]
Change from baseline in WLQ WLI score, LS mean (SE) [n]			
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; EQ-5D, EuroQol five dimension questionnaire; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; FAS, full analysis set; LS, least squares; MC, mental component; MOS-SS, Medical Outcomes Study – Sleep Scale; PC, physical component; SD, standard deviation; SE, standard error; SF-36, Short Form (36); TOF, tofacitinib; WLQ WLI, Work Limitation Questionnaire Work Loss Index.
†p-value <0.001 for comparison with placebo. ‡p-value ≤0.05 for comparison with placebo.

Maintenance of tofacitinib efficacy

The efficacy of tofacitinib was assessed beyond the placebo-controlled period up to Month 24. Efficacy was maintained up to Month 24 as measured by ACR response, DAS28-4(ESR) <2.6, HAQ-DI and mTSS, suggesting that patients maintain their response to tofacitinib for at least two years.

[redacted]

4.7.3 *ORAL Sync (DMARD-IR: cDMARD including MTX or bDMARD)*

- Tofacitinib 5 mg significantly improved the rate of disease remission (DAS28-4[ESR] <2.6) at Month 6 compared with placebo; a significant difference was observed as early as Month 3.
- Tofacitinib 5 mg significantly improved the physical functioning (reduction in HAQ-DI from baseline) of patients with RA at Month 3 compared with placebo; a significant difference was observed as early as Week 2.
- Tofacitinib 5 mg significantly reduced the signs and symptoms (ACR20) of RA at Month 6 compared with placebo; a significant difference was observed as early as Week 2.
- Tofacitinib 5 mg significantly reduced patients' levels of pain and fatigue, and improved overall quality of life at Month 6.
    - Scores for pain (VAS), fatigue (FACIT-F) and quality of life (EQ-5D) were all significantly improved in the tofacitinib 5 mg group compared with placebo by Month 6.
- The efficacy of tofacitinib treatment achieved at Month 6 is maintained up to Month 12.

4.7.3.1 Primary efficacy outcomes

The primary efficacy results for ORAL Standard are summarised in Table 34. For these analyses, tofacitinib groups were compared with a combined placebo group (placebo to tofacitinib 5 mg and placebo to tofacitinib 10 mg). Due to the crossover design of the study (see Section 4.5.1), an approach was taken where patients who did not meet the response criteria at Month 3 were considered to be non-responders for the remainder of the trial. This was applied to the categorical endpoints assessed in each treatment group at Month 6, including tofacitinib.

Signs and symptoms of RA – Proportion of patients achieving ACR20 at Month 6

A significantly greater percentage of patients in the tofacitinib 5 mg (52.7%) group achieved an ACR20 response at Month 6 compared with patients in the combined placebo group (31.2%; p<0.001; Figure 18); the difference from placebo was 21.5% (95% CI: 12.4, 30.7).

Physical functioning – Mean change from baseline in HAQ-DI score at Month 3

The mean change from baseline in HAQ-DI score at Month 3 was significantly greater in the tofacitinib 5 mg group (–0.46) compared with the combined placebo group (–0.21; p<0.001; Figure 19); the difference from placebo was –0.26 (95% CI: –0.35, –0.16).

Disease activity – Proportion of patients achieving disease remission (DAS28-4[ESR] <2.6) at Month 6

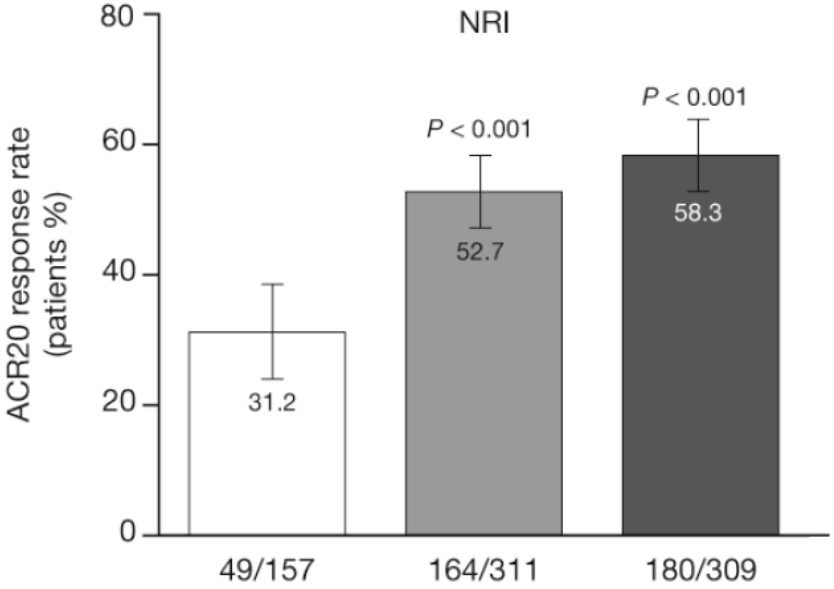
A significantly greater percentage of patients in the tofacitinib 5 mg (9.1%) group achieved disease remission (DAS28-4[ESR] <2.6) at Month 6 compared with patients in the combined placebo group (2.7%; p=0.0038; Figure 20); the difference from placebo was 6.4% (95% CI: 2.1, 10.8).

Table 34: Summary of primary efficacy results for ORAL Sync (FAS)

Outcome	TOF 5 mg	TOF 10 mg	Placebo
ACR20 response rate at Month 6 (NRI)			
n	311	309	157
Response rate, n (%)	164 (52.7)	180 (58.3)	49 (31.2)
Difference from placebo, %	21.5	27.0	-
95% CI for difference	12.4, 30.7	17.9, 36.1	-
p-value†	<0.001	<0.001	-
HAQ-DI score at Month 3			
n	292	292	147
LS mean change from baseline	–0.46	–0.56	–0.21
LS mean difference from placebo	–0.26	–0.35	-
95% CI for difference	–0.35, –0.16	–0.44, –0.26	-
p-value†	<0.001	<0.001	-
DAS28-4(ESR) <2.6 at Month 6 (NRI)			
n‡	263	270	148
Response rate, n (%)	24 (9.1)	36 (13.3)	4 (2.7)
Difference from placebo, %	6.4	10.6	-
95% CI for difference	2.1, 10.8	5.8, 15.5	-
p-value†	0.0038	<0.001	-

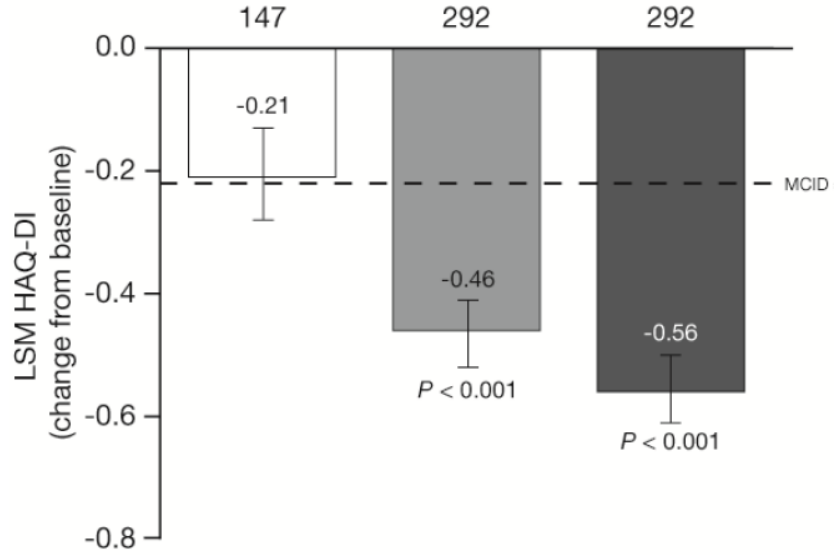
Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; DAS28, Disease Activity Score in 28 joints; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-disability index; LS, least squares; NRI, non-responder imputation; TOF, tofacitinib.
†p-value is subject to the step-down approach. ‡The numbers are different for DAS28-4(ESR) <2.6 because ESR was measured locally and some study sites were not able to collect these data.

Figure 18: ACR20 response rate at Month 6 (FAS, NRI)



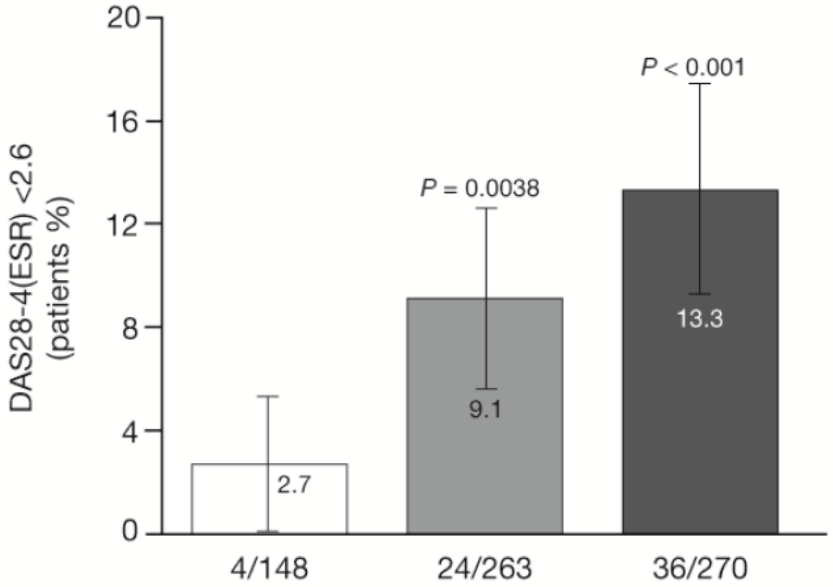
Abbreviations: ACR, American College of Rheumatology; FAS, full analysis set; NRI, non-responder imputation.

Figure 19: Mean change from baseline in HAQ-DI score at Month 3 (FAS)



Abbreviations: FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-disability index.

Figure 20: DAS28-4(ESR) <2.6 response rate at Month 6 (FAS, NRI)



Abbreviations: DAS28, Disease Activity Score in 28 joints; FAS, full analysis set; NRI, non-responder imputation.

4.7.3.2 Secondary analysis of primary outcome

As an advancement penalty was applied to non-responders at Month 3, secondary analyses were also performed for the ACR20 and DAS28-4(ESR) <2.6 outcomes where the advancement penalty was removed to allow any new response to active treatment after Month 3 to be observed (NRINAP). The advancement penalty was not applied to the placebo group, as non-responders did not continue with placebo treatment in order to minimise the time spent on ineffective treatment; therefore, no placebo group is available for comparison. The results of these secondary analyses for ORAL Scan are summarised in Table 35.

Table 35: NRINAP ACR20 and DAS28-4(ESR) <2.6 response rates for ORAL Sync (FAS)

Outcome	TOF 5 mg	TOF 10 mg
ACR20 response rate at Month 6 (NRINAP)		
n	[redacted]	[redacted]
Response rate, n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
DAS28-4(ESR) <2.6 at Month 6 (NRINAP)		
n	[redacted]	[redacted]
Response rate, n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; DAS28, Disease Activity Score in 28 joints; FAS, full analysis set; NRINAP, non-responder imputation no advancement penalty; TOF, tofacitinib.

4.7.3.3 Secondary efficacy outcome

Signs and symptoms of RA – Proportion of patients achieving ACR20, ACR50 and ACR70 per visit

At Month 0.5, significant improvements in ACR20 and ACR50 responses were seen in the tofacitinib 5 mg group compared with the placebo group [redacted] (p<0.001 for all comparisons). The 0.5-month, 1-month, 3-month, and 6-month ACR20, ACR50 and ACR70 response rates for ORAL Sync are summarised in Table 36.

Table 36: ACR response rates for ORAL Sync (FAS)

Outcome	TOF 5 mg	TOF 10 mg	Placebo
ACR20 response rate (NRI), n/N (%)			
Month 0.5	[redacted]	[redacted]	[redacted]
Month 1	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]
Month 6	164/311 (52.7)†	180/309 (58.3)†	49/157 (31.2)
ACR50 response rate (NRI), n/N (%)			
Month 0.5	[redacted]	[redacted]	[redacted]
Month 1	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]
ACR70 response rate (NRI), n/N (%)			
Month 0.5	[redacted]	[redacted]	[redacted]
Month 1	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]

Abbreviations: ACR, American College of Rheumatology; FAS, full analysis set; NRI, non-responder imputation; TOF, tofacitinib.
†p-value <0.001 for comparison with placebo. ‡p-value ≤0.05 for comparison with placebo.

Physical functioning – Change from baseline in HAQ-DI scores per visit

Statistically significantly decreased (improved) HAQ-DI scores were observed in the tofacitinib 5 mg group compared with placebo at Month 0.5, 1, 3 and 6 ([redacted]. The change from baseline in LS mean HAQ-DI scores for ORAL Sync are summarised in Table 37.

Table 37: Change from baseline in LS mean HAQ-DI scores per visit (FAS)

Outcome	TOF 5 mg	TOF 10 mg	Placebo
Change from baseline in HAQ-DI score, LS mean (SE) [n]			
Month 0.5	[redacted]	[redacted]	[redacted]
Month 1	[redacted]	[redacted]	[redacted]
Month 3	–0.46 (0.03) [292]†	–0.56 (0.03) [292]†	–0.21 (0.04) [147]
Month 6	[redacted]	[redacted]	[redacted]

Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-disability index; LS, least squares; SD, standard deviation; SE, standard error; TOF, tofacitinib.
†p-value <0.001 for comparison with placebo. ‡p-value ≤0.05 for comparison with placebo.

Disease activity – Assessment of disease activity (DAS28-4[ESR]) per visit

At Month 3 and 6, significantly greater changes in DAS28-4(ESR) scores from baseline were observed in the tofacitinib 5 mg group compared with the placebo group ([redacted]). At Month 3 and Month 6, the response rates for patients achieving disease remission (DAS28-4[ESR] <2.6) were significantly higher in the tofacitinib 5 mg group compared with placebo ([redacted]). The change from baseline in DAS28-4(ESR) scores and the proportion of patients achieving disease remission (DAS28-4[ESR] <2.6) or low disease activity (DAS28-4[ESR] ≤3.2) at Month 3 and Month 6 for ORAL Sync are summarised in Table 38.

Assessment of EULAR response (improvement in DAS28 from baseline; see Table 7) at Month 6 demonstrated that [redacted]

Table 38: Assessment of DAS28-4(ESR) per visit (FAS)

Outcome	TOF 5 mg	TOF 10 mg	Placebo
Change from baseline in DAS28-4(ESR), LS mean (SE) [n]			
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]
DAS28-4(ESR) <2.6 (NRI), n/N (%)			
Month 3	[redacted]	[redacted]	[redacted]
Month 6	24/263 (9.13)‡	36/270 (13.3)†	4/148 (2.70)
DAS28-4(ESR) ≤3.2 (NRI), n/N (%)			
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]
Good or moderate EULAR response, n/N (%)			
Month 6	[redacted]	[redacted]	[redacted]

Abbreviations: DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; FAS, full analysis set; LS, least squares; NRI, non-responder imputation; SD, standard deviation; SE, standard error; TOF, tofacitinib.
†p-value <0.001 for comparison with placebo. ‡p-value ≤0.05 for comparison with placebo.

Quality of life – Assessment of patient-reported outcomes per visit

[redacted]. Change from baseline in the SF-36 (mental and physical components), EQ-5D, FACIT-F, pain (VAS), WLQ (Work Loss Index) and MOS-Sleep Scale (overall sleep problem) for ORAL Sync are summarised in Table 39.

Table 39: Assessment of patient-reported outcomes per visit (FAS)

Outcome	TOF 5 mg	TOF 10 mg	Placebo
Change from baseline in EQ-5D score, LS mean (SE) [n]			
Month 3			
Month 6			
Change from baseline in SF-36 MC score, LS mean (SE) [n]			
Month 1			
Month 3			
Month 6			
Change from baseline in SF-36 PC score, LS mean (SE) [n]			
Month 1			
Month 3			
Month 6			
Change from baseline in FACIT-F score, LS mean (SE) [n]			
Month 1			
Month 3			
Month 6			
Change from baseline in pain (VAS) score, LS mean (SE) [n]			
Month 0.5			
Month 1			
Month 3			
Month 6			
Change from baseline in MOS-SS overall sleep problem score, LS mean (SE) [n]			

Outcome	TOF 5 mg	TOF 10 mg	Placebo
Month 1	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]
Change from baseline in WLQ WLI score, LS mean (SE) [n]			
Month 3	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; EQ-5D, EuroQol five dimension questionnaire; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; FAS, full analysis set; LS, least squares; MC, mental component; MOS-SS, Medical Outcomes Study – Sleep Scale; PC, physical component; SD, standard deviation; SE, standard error; SF-36, Short Form (36); TOF, tofacitinib; WLQ WLI, Work Limitation Questionnaire Work Loss Index.
†p-value <0.001 for comparison with placebo. ‡p-value ≤0.05 for comparison with placebo.

Maintenance of tofacitinib efficacy

The efficacy of tofacitinib, with regards to disease remission (DAS28-4[ESR] <2.6), physical functioning (HAQ-DI) and the signs and symptoms of RA (ACR20), was assessed beyond the placebo-controlled period up to Month 12 (interim analysis).

[redacted]

4.7.4 *ORAL Solo (DMARD-IR: cDMARD including MTX or bDMARD)*

- Tofacitinib 5 mg improved the rate of disease remission (DAS28-4[ESR] <2.6) at Month 3 compared with placebo; however, no significant difference was observed.
- Tofacitinib 5 mg significantly improved the physical functioning (reduction in HAQ-DI from baseline) of patients with RA at Month 3 compared with placebo; a significant difference was observed as early as Week 2.
- Tofacitinib 5 mg significantly reduced the signs and symptoms (ACR20) of RA at Month 3 compared with placebo; a significant difference was observed as early as Week 2.
- Tofacitinib 5 mg significantly reduced patients' levels of pain and fatigue, and improved overall quality of life at Month 3.
  - Scores for pain (VAS), fatigue (FACIT-F) and quality of life (EQ-5D) were all significantly improved in the tofacitinib 5 mg group compared with placebo by Month 6.
- The efficacy of tofacitinib treatment achieved at Month 3 is maintained up to Month

6 (end of trial).

4.7.4.1 Primary efficacy outcomes

The primary efficacy results for ORAL Solo are summarised in Table 34. For these analyses, tofacitinib groups were compared with a combined placebo group (placebo to tofacitinib 5 mg and placebo to tofacitinib 10 mg), which comprised patients receiving placebo at Month 3.

Signs and symptoms of RA – Proportion of patients achieving ACR20 at Month 3

A significantly greater percentage of patients in the tofacitinib 5 mg (59.8%) group achieved an ACR20 response at Month 3 compared with patients in the combined placebo group (26.7%; p<0.001; Figure 21); the difference from placebo was [redacted]Physical functioning – Mean change from baseline in HAQ-DI score at Month 3

The mean change from baseline in HAQ-DI score at Month 3 was significantly greater in the tofacitinib 5 mg (–0.50) compared with the combined placebo group (–0.19; p<0.001; Figure 22); the difference from placebo was [redacted]

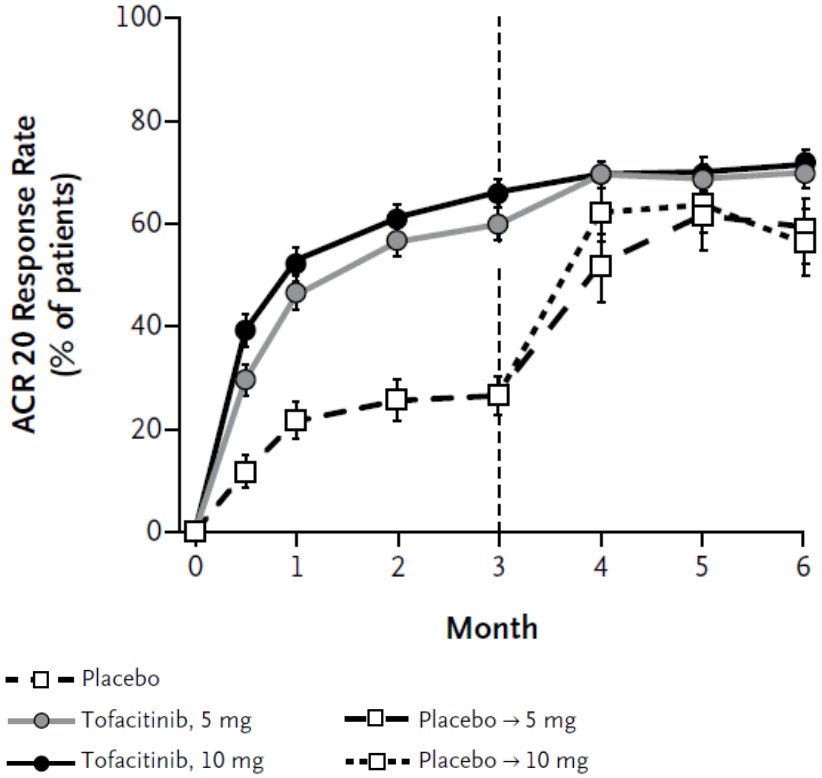
Disease activity – Proportion of patients achieving disease remission (DAS28-4[ESR] <2.6) at Month 3

A similar percentage of patients in the tofacitinib 5 mg (5.6%) group achieved disease remission (DAS28-4[ESR] <2.6) at Month 6 compared with patients in the combined placebo group (4.4%; p=0.62; Figure 23); the difference from placebo was [redacted] Table 40: Summary of primary efficacy results for ORAL Solo (FAS)

Outcome	TOF 5 mg	TOF 10 mg	Placebo
ACR20 response rate at Month 3 (NRI)			
n	[redacted]	[redacted]	[redacted]
Response rate, n (%)	[redacted] (59.8)	[redacted] (65.7)	[redacted] (26.7)
Difference from placebo, %	[redacted]	[redacted]	-
95% CI for difference	[redacted]	[redacted]	-
p-value†	<0.001	<0.001	-
HAQ-DI score at Month 3			
n	[redacted]	[redacted]	[redacted]
LS mean change from baseline	–0.50	–0.57	–0.19
LS mean difference from placebo	[redacted]	[redacted]	-
95% CI for difference	[redacted]	[redacted]	-
p-value†	<0.001	<0.001	-
DAS28-4(ESR) <2.6 at Month 3 (NRI)			
n	232	229	114
Response rate, n (%)	[redacted] (5.6)	[redacted] (8.7)	[redacted] (4.4)
Difference from placebo, %	[redacted]	[redacted]	-
95% CI for difference	[redacted]	[redacted]	-
p-value†	0.62	0.10	-

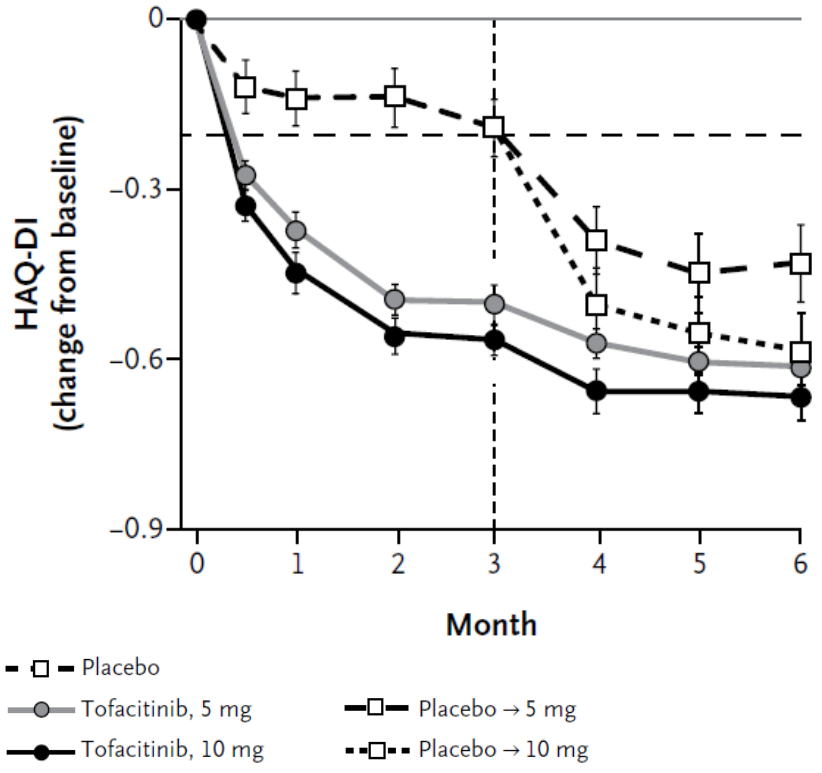
Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; DAS28, Disease Activity Score in 28 joints; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-disability index; LS, least squares; NRI, non-responder imputation; TOF, tofacitinib.
†p-value is subject to the step-down approach.

Figure 21: ACR20 response rate (FAS, NRI)



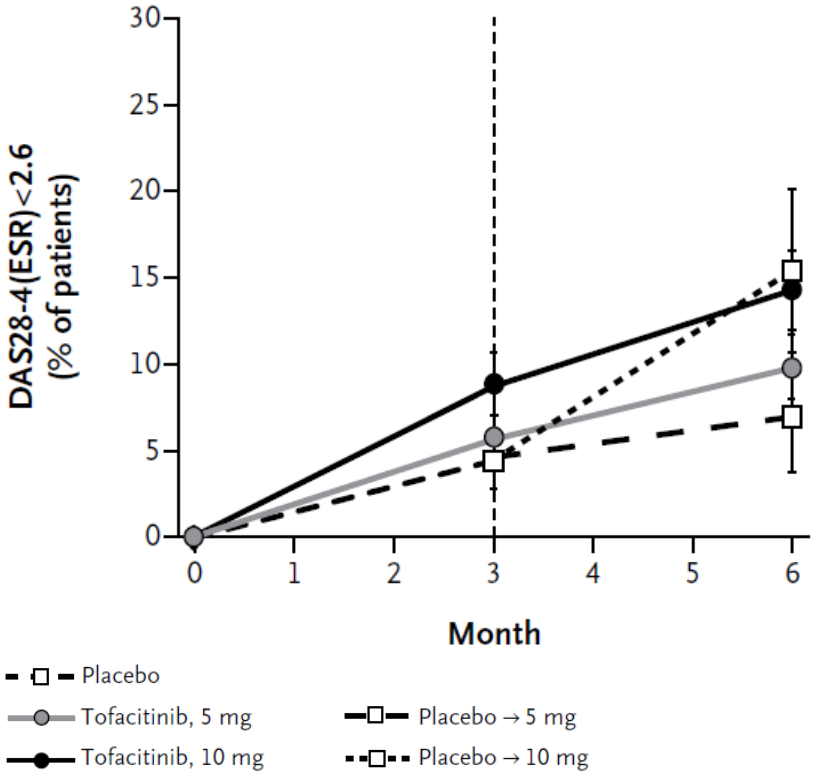
Abbreviations: ACR, American College of Rheumatology; FAS, full analysis set; NRI, non-responder imputation.

Figure 22: Mean change from baseline in HAQ-DI score (FAS)



Abbreviations: FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-disability index.

Figure 23: DAS28-4(ESR) <2.6 response rate (FAS, NRI)



Abbreviations: DAS28, Disease Activity Score in 28 joints; FAS, full analysis set; NRI, non-responder imputation.

4.7.4.2 Secondary efficacy outcomes

Signs and symptoms of RA – Proportion of patients achieving ACR20, ACR50 and ACR70 per visit

[redacted]

[redacted] Statistically significant improvements in ACR20, ACR50 and ACR70 responses were also observed in the tofacitinib 5 mg group compared with the placebo group at Month 3 ($p \leq 0.05$ for all comparisons). The 2-week, 1-month and 3-month ACR20, ACR50 and ACR70 response rates for ORAL Solo are summarised in Table 41.

Table 41: ACR response rates for ORAL Solo (FAS)

Outcome	TOF 5 mg	TOF 10 mg	Placebo
ACR20 response rate (NRI), n/N (%)			
Month 0.5	[redacted]	[redacted]	[redacted]
Month 1	[redacted]	[redacted]	[redacted]
Month 3	[redacted] (59.8)†	[redacted] (65.7)†	[redacted] (26.7)
ACR50 response rate (NRI), n/N (%)			
Month 0.5	[redacted]	[redacted]	[redacted]
Month 1	[redacted]	[redacted]	[redacted]
Month 3	[redacted] (31.1)†	[redacted] (36.8)†	[redacted] (12.5)
ACR70 response rate (NRI), n/N (%)			
Month 0.5	[redacted]	[redacted]	[redacted]
Month 1	[redacted]	[redacted]	[redacted]
Month 3	[redacted] (15.4)‡	[redacted] (20.3)†	[redacted] (5.8)

Abbreviations: ACR, American College of Rheumatology; FAS, full analysis set; NRI, non-responder imputation; TOF, tofacitinib.
†p-value <0.001 for comparison with placebo. ‡p-value ≤0.05 for comparison with placebo.

Physical functioning – Change from baseline in HAQ-DI scores per visit

Statistically significantly decreased (improved) HAQ-DI scores were observed in the tofacitinib 5 mg group compared with placebo at Month 0.5, 1 and 6 (p≤0.05 for all comparisons). The changes from baseline in LS mean HAQ-DI scores for ORAL Solo are summarised in Table 42.

Table 42: Change from baseline in LS mean HAQ-DI scores per visit (FAS)

Outcome	TOF 5 mg	TOF 10 mg	Placebo
Change from baseline in HAQ-DI score, LS mean (SE) [n]			
Month 0.5	[redacted]	[redacted]	[redacted]
Month 1	[redacted]	[redacted]	[redacted]
Month 3	–0.50 ([redacted]	–0.57 ([redacted]	–0.19 ([redacted]

Abbreviations: FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-disability index; LS, least squares; SD, standard deviation; SE, standard error; TOF, tofacitinib.
†p-value <0.001 for comparison with placebo. ‡p-value ≤0.05 for comparison with placebo.

Disease activity – Assessment of disease activity (DAS28-4[ESR]) per visit

At Month 3, a significantly greater change in DAS28-4(ESR) score from baseline was observed in the tofacitinib 5 mg group compared with the placebo group (p<0.001). However, the response rate for patients achieving disease remission (DAS28-4[ESR] <2.6) at Month 3 was not significantly different between tofacitinib 5 mg and placebo.

However, the response rates for patients achieving low disease activity (DAS28-4[ESR] ≤3.2) were significantly higher in the tofacitinib 5 mg group compared with placebo at Month 3 (p≤0.05). The change from baseline in DAS28-4(ESR) scores and the proportion of patients achieving disease remission (DAS28-4[ESR] <2.6) or low disease activity (DAS28-4[ESR] ≤3.2) at Month 3 for ORAL Solo are summarised in Table 43.

Assessment of EULAR response (improvement in DAS28 from baseline; see Table 7) at Month 3 demonstrated that

[redacted]

Table 43: Assessment of DAS28-4(ESR) per visit (FAS)

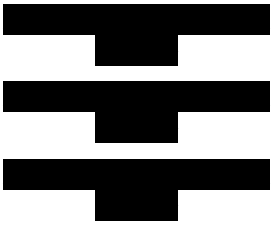
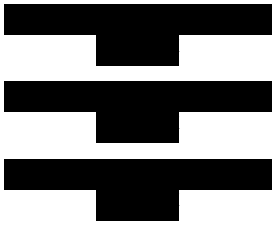
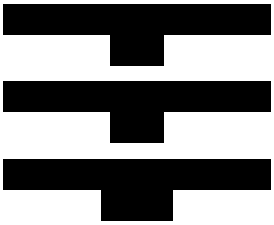
Outcome	TOF 5 mg	TOF 10 mg	Placebo
Change from baseline in DAS28-4(ESR), LS mean (SE) [n]			
Month 3	[redacted](0.09) [226]†	[redacted](0.09) [214]†	[redacted](0.13) [103]
DAS28-4(ESR) <2.6 (NRI), n/N (%)			
Month 3	[redacted]/232 (5.6)	[redacted]/229 (8.7)	[redacted]/114 (4.4)
DAS28-4(ESR) ≤3.2 (NRI), n/N (%)			
Month 3	[redacted]12.5)‡	[redacted]17.0)†	[redacted](5.3)
Good or moderate EULAR response, n/N (%)			
Month 3	[redacted]	[redacted]	[redacted]

Abbreviations: DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; FAS, full analysis set; LS, least squares; NRI, non-responder imputation; SD, standard deviation; SE, standard error; TOF, tofacitinib.
†p-value <0.001 for comparison with placebo.

Quality of life – Assessment of patient-reported outcomes per visit

[redacted] Change from baseline in the SF-36 (mental and physical components), EQ-5D, FACIT-F, pain (VAS), WLQ (Work Loss Index) and MOS-Sleep Scale (overall sleep problem) for ORAL Solo are summarised in Table 44.

Table 44: Assessment of patient-reported outcomes per visit (FAS)

Outcome	TOF 5 mg	TOF 10 mg	Placebo
Change from baseline in EQ-5D score, LS mean (SE) [n] Month 3			
Change from baseline in SF-36 MC score, LS mean (SE) [n] Month 3			
Change from baseline in SF-36 PC score, LS mean (SE) [n] Month 3			
Change from baseline in FACIT-F score, LS mean (SE) [n] Month 3			
Change from baseline in pain (VAS) score, LS mean (SE) [n] Month 0.5 Month 1 Month 3			
Change from baseline in MOS-SS overall sleep problem score, LS mean (SE) [n] Month 3			
Change from baseline in WLQ WLI score, LS mean (SE) [n] Month 3			

Abbreviations: ADA, adalimumab; EQ-5D, EuroQol five-dimension questionnaire; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; FAS, full analysis set; LS, least squares; MC, mental component; MOS-SS, Medical Outcomes Study – Sleep Scale; PC, physical component; SD, standard deviation; SE, standard error; SF-36, Short Form (36); TOF, tofacitinib; WLQ WLI, Work Limitation Questionnaire Work Loss Index.
†p-value <0.001 for comparison with placebo. ‡p-value ≤0.05 for comparison with placebo.

Maintenance of tofacitinib efficacy

The efficacy of tofacitinib, with regards to disease remission (DAS28-4[ESR] <2.6), physical functioning (HAQ-DI) and the signs and symptoms of RA (ACR20), was assessed beyond the placebo-controlled period up to Month 6 (end of trial). This analysis demonstrated that the magnitude of response achieved at Month 3 was sustained to Month 6.

[redacted]

4.7.5 *Supporting studies*

Data are available from the Phase III studies ORAL Start and ORAL Step (summarised below) to support the clinical effectiveness of tofacitinib. ORAL Step assessed tofacitinib in patients with moderate-to-severe RA who were TNFi-IR. While this population is within the tofacitinib licence, the study is considered less relevant to submission given the proposed second-line positioning of tofacitinib within the clinical pathway (Section 3.3.3). ORAL Start assessed tofacitinib as monotherapy in patients who were MTX naïve. While this population is not within the licence of tofacitinib, this study provides evidence that tofacitinib can significantly impact radiographic progression in a favourable manner (see Section 4.13 for further discussion on radiographic progression).

4.7.5.1 Methodology

Table 45: Comparative summary of methodology of the supporting studies

Trial no. (acronym)	NCT01039688 (ORAL Start)	NCT00960440 (ORAL Step)
Study objective	To evaluate the efficacy and safety of TOF monotherapy compared with MTX.	To evaluate the efficacy and safety of TOF+MTX compared with placebo+MTX.
Trial design	Phase III, randomised, double-blind, parallel group study	Phase III, randomised, placebo-controlled, double-blind, parallel group study
Method of randomisation and blinding	Patients were randomised using Impala (automated Web-based or telephone-based system) in a 2:2:1 ratio to receive: • TOF 5 mg • TOF 10 mg • MTX (starting dose of 10 mg) Patients and investigators remained blinded to treatment assignment during the study.	Patients were randomised using Impala (automated Web-based or telephone-based system) in a 4:4:1:1 ratio to receive: • TOF 5 mg • TOF 10 mg • Placebo to TOF 5 mg • Placebo to TOF 10 mg Patients and investigators remained blinded to treatment assignment during the study.
Key inclusion criteria	• Adults aged ≥18 years with a diagnosis of active RA†, consistent with ACR 1987 Revised Criteria (130) • ≥3 distinct joint erosions detected on hand/wrist or foot radiographs or IgM RF+ or antibodies to CCP	• Adults aged ≥18 years with a diagnosis of active RA†, consistent with ACR 1987 Revised Criteria (130) • Previous inadequate response or intolerance to one or more approved TNFi

Trial no. (acronym)	NCT01039688 (ORAL Start)	NCT00960440 (ORAL Step)
		• Ongoing treatment with MTX for ≥4 months with stable dosing (7.5–25 [20 mg in Republic of Ireland] mg/week) ≥6 weeks before receiving the study drug
Key exclusion criteria	• Haemoglobin <9.0 gm/dL • Haematocrit <30% • White blood cell count <3.0x10^9/L • Absolute neutrophil count <1.2x10^9/L • Platelet count <100x10^9/L • eGFR rate ≤40 ml/min • AST or ALT levels >1.5 x Upper limit of normal • [redacted] Evidence of active, latent or inadequately treated Mycobacterium tuberculosis infection • [redacted] History of malignancy except adequately treated non-metastatic basal/squamous cell cancer of the skin or cervical carcinoma in situ • [redacted]	
Settings and locations	151 centres worldwide	82 centres in 13 countries
Duration of study	24 months	6 months

Trial drugs	• TOF 5 mg BD (N=373)
	• TOF 10 mg BD (N=397)
	• MTX (N=186)
	  ○ Starting dose 10 mg/week
	  ○ 20 mg at week 8 (through 5 mg/week increase every four weeks)
		• TOF 5 mg BD (N=133)
		• TOF 10 mg BD (N=134)
		• Placebo to TOF 5 mg BD (N=66)
		• Placebo to TOF 10 mg BD (N=66)

Prior and concomitant medications	[redacted]	Patients had to remain on stable background MTX therapy and were allowed to remain on antimalarial therapy, which had to be stable for ≥8 weeks before first study dose. No concomitant cDMARDs or bDMARDs were permitted and were discontinued (if used) before first study dose. Non-steroidal anti-inflammatory drugs, selective COX-2 inhibitors, or glucocorticoids (≤10 mg per day prednisone or equivalent) were allowed but had to be stably dosed for ≥4 weeks or more before the first study dose and remain stable through Month 3.

Trial no. (acronym)	NCT01039688 (ORAL Start)	NCT00960440 (ORAL Step)
Primary outcomes	• Mean change from baseline in mTSS score at Month 6 • Proportion of patients who met ACR70 criteria at Month 6	• Proportion of patients who met ACR20 criteria at Month 3 • Mean change from baseline in HAQ-DI scores at Month 3 • Proportion of patients with DAS28-4(ESR) <2.6 at Month 3
Key secondary outcomes	• Mean change from baseline in mTSS score at Month 12 and 24 • Mean change from baseline in erosion and JSN scores at Month 6, 12, 24 • Rates of non-progression (≤0.5 change from baseline in total mTSS or erosion score) at Months 6, 12, 24 • Proportion of patients who met ACR20, ACR50 and ACR70 criteria per visit • Mean change from baseline in HAQ-DI per visit • Assessment of DAS28-4(ESR) per visit • Mean change from baseline in the SF-36, EQ-5D, FACIT-F scores, MOS-SS and WLQ	• Proportion of patients who met ACR20, ACR50 and ACR70 criteria per visit • Mean change from baseline in HAQ-DI per visit • Assessment of DAS28-4(ESR) per visit • Mean change from baseline in the SF-36, EQ-5D, FACIT-F scores, MOS-SS and WLQ
Pre-planned subgroups	[redacted]	[redacted]
Populations analysed	Analyses of co-primary endpoints at month 6 were based on the pre-specified interim (year 1) data set; all other analyses were based on the final (year 2) data set. • [redacted]	• FAS: The FAS included all patients who were randomised to the study and received ≥1 dose of the study drug or placebo. Patients must have had ≥1 post-baseline measurement in order to appear in any of the analyses of the FAS datasets. • [redacted]

Trial no. (acronym)	NCT01039688 (ORAL Start)	NCT00960440 (ORAL Step)
	[redacted]	[redacted]
Statistical information	**Sample size and power** The mTSS score was used to determine the sample size, which was planned to provide the study with 90% power, assuming a mean (±SD) difference in the mTSS score of at least 0.9±2.8 units. For the ACR70 response, the sample size was planned to yield more than 90% power, assuming a difference in response rates of 15 percentage points or higher (with a MTX response of approximately 20%).	**Sample size and power** A sample size of 396 patients yielded more than 90% power for each of the three primary endpoints.
	Multiple comparisons To control the type I error rate in the primary analyses, co-primary efficacy endpoints were assessed sequentially using a step-down approach where statistical significance could be claimed: 1. For TOF 10 mg vs MTX in progression in mTSS, if p≤0.05. 2. For TOF 5 mg vs MTX in progression in mTSS, if p≤0.05 and TOF 10 mg vs MTX in progression in mTSS also had p≤0.05. 3. For TOF 10 mg vs MTX in rates of ACR70 response, if p≤0.05 and TOF 10 mg vs MTX in progression in mTSS also had p≤0.05. 4. For TOF 5 mg vs MTX in rates of ACR70 response, if p≤0.05 and TOF 10 mg vs MTX in rates of ACR70 also had p≤0.05, and TOF 5 mg vs MTX in progression in mTSS also had p≤0.05. No adjustment for multiple comparisons was applied to	**Multiple comparisons** To control for type I error, each of the three co-primary endpoints was assessed using a step-down approach in the following order: ACR20 response rates, then mean change from baseline in HAQ-DI, then DAS28<2.6 rates. [redacted] No adjustment for multiple comparisons was applied to secondary endpoints and p≤0.05 was considered to indicate statistical significance.

Trial no. (acronym)	NCT01039688 (ORAL Start)	NCT00960440 (ORAL Step)
	secondary endpoints and p≤0.05 was considered to indicate statistical significance.	
	Analysis of primary and secondary endpoints Analysis of covariance was used to assess mTSS score at month 6 and missing values were extrapolated linearly. For the Month 6 analysis of ACR70 response and other binary end points, the normal approximation for the difference in binomial proportions was used to test the superiority of each dose of TOF over MTX. Changes from baseline in HAQ-DI scores and other continuous endpoints were expressed as LS mean changes and analysed with the use of a mixed-effect longitudinal model. Non-responder imputation was used for missing values due to withdrawal and applied to binary secondary endpoints that were not based on joint structure.	**Analysis of primary and secondary endpoints** The normal approximation for the difference in binomial proportions was used to test the superiority of TOF to placebo for ACR20 and DAS28-4(ESR) <2.6 endpoints. Changes from baseline in HAQ-DI scores and other continuous endpoints were analysed using a mixed-effect longitudinal model.

Abbreviations: ACR, American College of Rheumatology; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BD, twice-daily; CCP, cyclic citrullinated peptide; DAS28, Disease Activity Score in 28 joints; DMARD, disease-modifying anti-rheumatic drug; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; EQ-5D, EuroQol five-dimension questionnaire; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-disability index; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; JSN, joint space narrowing; LS, least squares; MOS-SS, Medical Outcomes Study – Sleep Scale; MTX, methotrexate; ORAL, Oral Rheumatoid Arthritis Phase 3 Trials; PPAS, per-protocol analysis set; RA, rheumatoid arthritis; RF, rheumatoid factor; SAS, safety analysis set; SD, standard deviation; SF-36, Short Form (36); mTSS, van der Heijde modified total sharp score; TOF, tofacitinib; WLQ, Work Limitations Questionnaire.

[†]Active disease was defined as the presence of ≥6 tender or painful joints (of 68 joints examined) and ≥6 swollen joints (of 66 joints examined) and either an ESR ≥28 mm/hr (Westergren method) or a CRP level >7 mg/L.

4.7.5.2 ORAL Start (MTX-naïve)

Patient disposition and baseline characteristics

Patient disposition in ORAL Start and baseline characteristics are presented in Figure 24 and Table 46, respectively.

Figure 24: CONSORT diagram for ORAL Start

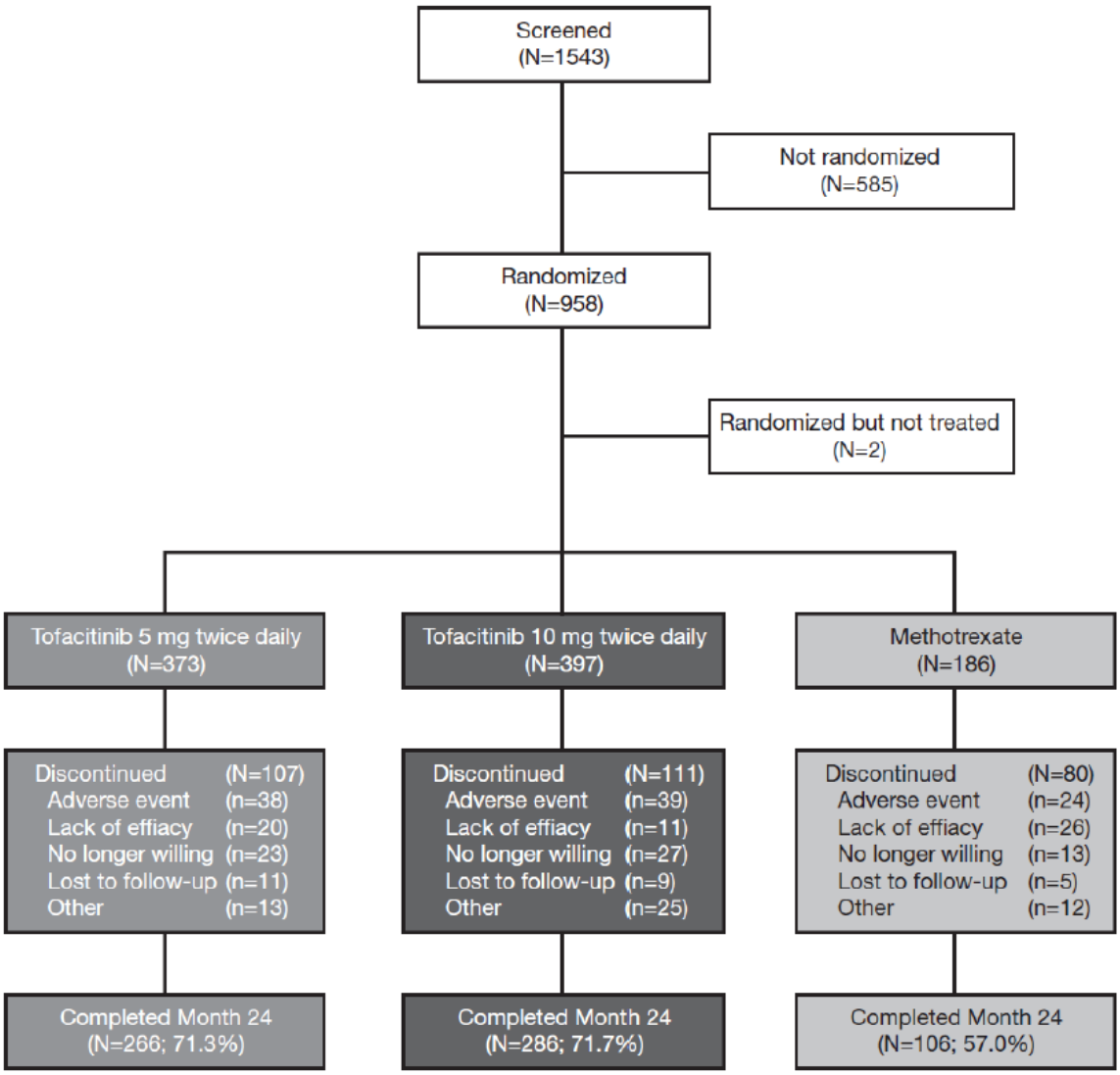


Table 46: Characteristics of participants in ORAL Start

Characteristics	TOF 5 mg (N=373)	TOF 10 mg (N=397)	MTX (N=186)
Female, n (%)	286 (76.7)	327 (82.4)	145 (78.0)
White, n (%)	239 (64.1)	266 (67.0)	127 (68.3)
Mean age, yrs (SD)	50.3 [redacted]	49.3 [redacted]	48.8 ([redacted]
Mean duration of RA, yrs (range)	2.9 (0.0–44.0)	3.4 (0.0–34.0)	2.7 (0.0–30.0)
Tender joints, mean, (SD)	25.7 [redacted]	25.1 [redacted]	25.4 [redacted]
Swollen joints, mean, (SD)	16.3 [redacted]	15.6 [redacted]	16.8 [redacted]
HAQ-DI score, mean, (SD)	1.54 [redacted]	1.50 [redacted]	1.52 [redacted]
mTSS score, mean	19.1	17.9	16.1
Erosion score, mean	9.1	9.1	8.4
JSN score, mean	10.0	8.8	7.7
DAS28-4(ESR) score, mean (SD)	6.61 [redacted]	6.54 [redacted]	6.60 [redacted]
DAS28-4(ESR) >5.1, %	94.4	93.7	93.0
ESR, mm/hr, mean (SD)	55.6 [redacted]	53.4 [redacted]	56.0 [redacted]
CRP, mm/L, mean (SD)	22.7 [redacted]	20.3 [redacted]	25.9 [redacted])
RF positive, n (%)	306 [redacted]	322 [redacted]	157 [redacted]
Anti-CCP positive, n (%)	315 [redacted]	320 [redacted]	161 [redacted]

Abbreviations: CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-disability index; JSN, joint space narrowing; MTX, methotrexate; ORAL, Oral Rheumatoid Arthritis Phase 3 Trials; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; mTSS, van der Heijde modified total sharp score; TOF, tofacitinib.

Primary efficacy outcomes

The outcomes for the primary efficacy endpoints are summarised in Table 47.

The mean change in mTSS score from baseline to Month 6 were significantly improved in the tofacitinib 5 mg group (0.2) compared with the MTX group (0.8; p<0.001). The proportion of patients who met ACR70 criteria at Month 6 was also significantly greater in the tofacitinib 5 mg group (25.5%) compared with the MTX group (12.0%; p<0.001).

Table 47: Summary of primary efficacy results for ORAL Start (FAS)

Outcome	TOF 5 mg	TOF 10 mg	MTX
ACR70 response rate at Month 6 (NRI)			
N	369	393	184
Response rate, n (%)	94 (25.5)	148 (37.7)	22 (12.0)
p-value†	<0.001	<0.001	-
mTSS score at Month 6			
N	346	369	166
LS mean change from baseline (SE)	0.2 (0.1)	<0.1 (0.1)	0.8 (0.2)
p-value†	<0.001	<0.001	-

Abbreviations: ACR, American College of Rheumatology; FAS, full analysis set; LS, least squares; non-responder imputation; SE, standard error; mTSS, van der Heijde modified total sharp score; TOF, tofacitinib.
†p-value is subject to the step-down approach.

Secondary efficacy outcomes

- Mean changes from baseline in mTSS scores at Month 12 and 24 were significantly smaller in the tofacitinib 5 mg group (0.4 and 0.6) compared with the MTX group (1.2 and 2.1; p<0.001 for both comparisons).
- Patients in the tofacitinib 5 mg group had significantly less radiographic progression compared with patients in the MTX group at Month 6, 12 and 24 (p≤0.05 for all comparisons) as indicated by change from baseline in erosion score (Month 6, 0.1 vs 0.4; Month 12, 0.1 vs 0.6; Month 24, 0.2 vs 1.0) and JSN scores (Month 6, 0.1 vs 0.3; Month 12, 0.2 vs 0.6; Month 24, 0.4 vs 1.1).
- The proportions of patients with no radiographic progression or erosion at Month 6, 12 and 24 was significantly larger in the tofacitinib 5 mg group (87.1%, 82.4% and 79.9%, respectively) compared with the MTX group (73.7%, 69.0% and 64.9%, respectively; p≤0.05 for all comparisons).
- Patients in the tofacitinib 5 mg group had significant improvements over time in ACR20, ACR50, and ACR70 response compared with patients in the MTX group (p<0.001 for all comparisons):
    - Month 6: ACR20, 71.3% vs 50.5%; ACR50, 46.6% vs 26.6%; ACR70, 25.5% vs 12.0%.
    - Month 12: ACR20, 67.8% vs 51.1%; ACR50, 49.9% vs 33.7%; ACR70, 28.7% vs 15.2%.
    - Month 24: ACR20, 64.2% vs 42.4%; ACR50, 49.3% vs 28.3%; ACR70, 34.4% vs 15.2%.
- Rates of disease remission (DAS28-4[ESR] <2.6) were significantly higher at Month 6, 12, and 24 in the tofacitinib 5 mg group (14.6%, 18.7% and 20.8%) compared with the MTX group (7.6%, 11.7% and 9.9%; p≤0.05 for all comparisons).

- Mean changes from baseline in DAS28-4(ESR) were significantly improved at Month 6, 12, and 24 in the tofacitinib 5 mg group (–2.5, –2.8 and –3.0) compared with the MTX group (–0.6, –0.7 and –0.7; p<0.001 for all comparisons).
- Mean changes from baseline in HAQ-DI scores at Month 6, 12 and 24 were significantly improved in the tofacitinib 5 mg group (–0.8, –0.9 and –0.9) compared with the MTX group (–0.6, –0.7 and –0.7; p<0.001 for all comparisons).
- For patient-reported outcomes:
  - [redacted]The mean change from baseline in the FACIT-fatigue score was significantly improved in the tofacitinib 5 mg group (8.7) compared with the MTX group (6.3) at Month 6 (p=0.003).

[redacted]

Conclusion

In patients who had not previously received MTX or therapeutic doses of MTX, tofacitinib 5 mg monotherapy was superior to MTX in reducing signs and symptoms of RA and inhibiting the progression of structural joint damage. Treatment with tofacitinib 5 mg also resulted in statistically significant improvements from baseline in HAQ-DI and FACIT-F scores compared with placebo.

4.7.5.3 ORAL Step (TNFi-IR)

Patient disposition and baseline characteristics

The patient disposition in ORAL Step and baseline characteristics are presented in Figure 25 and Table 48.

Figure 25: CONSORT diagram for ORAL Step

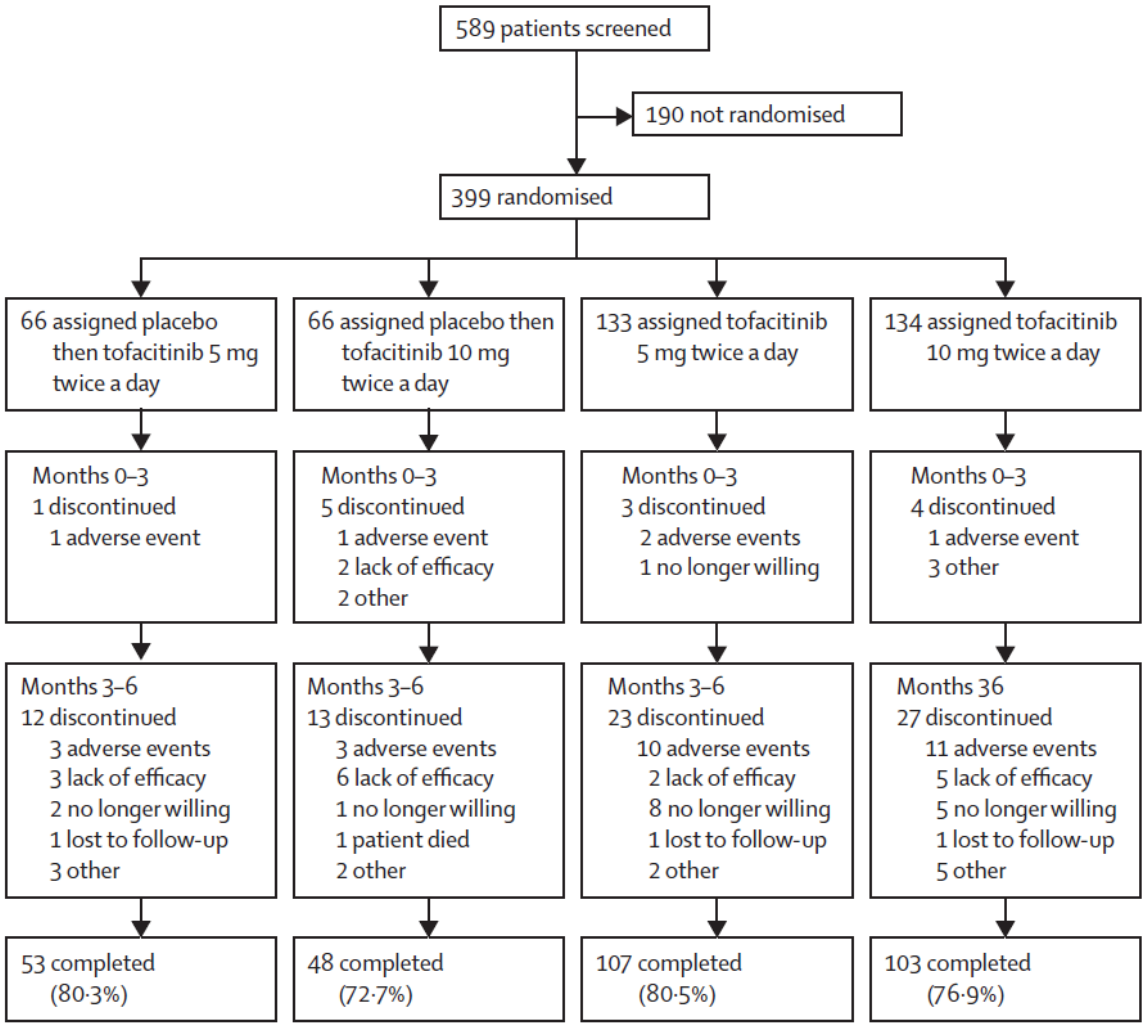


Table 48: Characteristics of participants in ORAL Step

Characteristics	TOF 5 mg (N=133)	TOF 10 mg (N=134)	Placebo (N=132)
Female, n (%)	113 (85.0%)	116 (86.6%)	106 (80.3%)
White, n (%)	108 (81.2%)	112 (83.6%)	112 (84.8%)
Mean age, yrs (SD)	55.4 (11.5)	55.1 (11.3)	54.4 (11.3)
Mean duration of RA, yrs (range)	13.0 (1.2–55.0)	12.6 (0.7–42.0)	11.3 (0.4–47.0)
Tender joints, mean (SD)	28.4 (18.3)	27.6 (15.7)	28.2 (16.7)
Swollen joints, mean (SD)	16.2 (10.1)	16.6 (9.9)	17.2 (10.7)
HAQ-DI score, mean (SD)	1.6 (0.7)	1.5 (0.6)	1.6 (0.7)
DAS28-4(ESR) score, mean (SD)	6.5 (1.1)	6.4 (0.9)	6.4 (1.1)
ESR, mm/hr (SD)	47.8 (26.1)	45.2 (22.9)	46.7 (24.6)
DAS28-3(CRP) score, mean (SD)	5.4 (1.0)	5.3 (0.9)	5.4 (1.0)
CRP, nmol/L (SD)	183.8 (261.9)	149.5 (205.6)	159.1 (186.7)
RF positive, n (%)	80 (60.6%)†	83 (61.9%)	86 (65.6%)†
Anti-CCP positive, n (%)	89 (68.5%)‡	90 (69.8%)‡	97 (75.8%)‡

Abbreviations: CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-disability index; ORAL, Oral Rheumatoid Arthritis Phase 3 Trials; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; TOF, tofacitinib.
†Placebo, n=131 and TOF 5 mg, n=132. ‡Placebo, n=128; TOF 5 mg, n=130; TOF 10 mg, n=129.

Primary efficacy outcomes

The outcomes for the primary efficacy endpoints are summarised in Table 49.

The proportion of patients who met ACR20 criteria at Month 3 was significantly greater in the tofacitinib 5 mg group (41.7%) compared with the placebo group (24.4%; p=0.0024). The mean change in HAQ-DI score from baseline to Month 3 was significantly improved in the tofacitinib 5 mg group (–0.43) compared with the placebo group (0.8; p<0.001). The proportion of patients who achieved disease remission (DAS28-4[ESR] <2.6) at Month 3 was significantly greater in the tofacitinib 5 mg group (6.7%) compared with the placebo group (1.7%; p<0.001).

Table 49: Summary of primary efficacy results for ORAL Step (FAS)

Outcome	TOF 5 mg	TOF 10 mg	Placebo
ACR20 response rate at Month 3 (NRI)			
N	132	133	131
Response rate, n (%)	55 (41.7)	64 (48.1)	32 (24.4)
Difference from placebo, %	[redacted]	[redacted]	-
95% CI for difference	6.06, 28.41	12.45, 34.92	-
p-value†	0.0024	<0.001	-
HAQ-DI score at Month 3			
N	117	125	118
LS mean change from baseline	–0.43	–0.46	–0.18
LS mean difference from placebo	[redacted]	[redacted]	-
95% CI for difference	−0.36, −0.15	−0.38, −0.17	-
p-value†	<0.001	<0.001	-
DAS28-4(ESR) <2.6 at Month 3 (NRI)			
N	119	125	120
Response rate, n (%)	8 (6.7)	11 (8.8)	2 (1.7)
Difference from placebo, %	[redacted]	[redacted]	-
95% CI for difference	0.0, 10.1	1.66, 12.6	-
p-value†	0.0496	0.0105	-

Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; DAS28, Disease Activity Score in 28 joints; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-disability index; LS, least squares; NRI, non-responder imputation; TOF, tofacitinib.
†p-value is subject to the step-down approach.

Secondary efficacy outcomes

- Patients in the tofacitinib 5 mg group had improvements over time in ACR20, ACR50, and ACR70 response compared with patients in the placebo group:
    - Time to onset of a significant ACR20 response was Month 0.5 for tofacitinib 5 mg vs placebo.
    - ACR50 response rates at Month 3 were significantly greater in the tofacitinib 5 mg group (26.5%) compared with placebo (8.4%; p<0.001); significant improvements were observed as early as Month 0.5.
    - ACR70 response rates at Month 3 were significantly greater in the tofacitinib 5 mg group (13.6%) compared with placebo (1.5%; p<0.001); significant improvements were observed as early as Month 1.
- Mean changes from baseline in HAQ-DI scores in the tofacitinib 5 mg group were significant compared with placebo at Month 3 and were maintained through to Month 6.

- The proportion of patients achieving low disease activity (DAS28-4[ESR] ≤3.2) was significantly higher in at Month 3 in the tofacitinib 5 mg group (14.3%) compared with the placebo group (5.0%; p≤0.05).
- Mean change from baseline in DAS28-4(ESR) was significantly improved at Month 3 in the tofacitinib 5 mg group (–1.8) compared with the placebo group (–0.7; p<0.001).
- Assessment of EULAR response (improvement in DAS28 from baseline; see Table 7) at Month 3 demonstrated that [redacted]
- For patient-reported outcomes:
  - [redacted] Mean change from baseline in the FACIT–fatigue score was significantly greater in the tofacitinib 5 mg group (6.3) compared with the placebo group (1.1) at Month 3 (p<0.001).
- [redacted] The efficacy of tofacitinib, with regards to disease remission (DAS28-4[ESR] <2.6), physical functioning (HAQ-DI) and the signs and symptoms of RA (ACR20), was assessed beyond the placebo-controlled period up to Month 6 (end of trial). This analysis demonstrated that the magnitude of response achieved at Month 3 was sustained to Month 6. [redacted]

Conclusion

In patients who had an inadequate response to TNFi, tofacitinib 5 mg with MTX had rapid and clinically meaningful improvements in signs and symptoms of RA and physical function over 6 months.

4.8 *Subgroup analysis*

4.8.1 *Patient level data analyses to inform the appraisal.*

4.8.1.1 Background

Pfizer performed patient-level data analyses using the datasets from the ORAL trials to provide data of relevance to the decision problem, with respect to:

1. Deriving EULAR response where these data are not already available from the trials
2. Analysing outcomes of sub-populations from the trials with respect to prior treatment
3. Exploring uncertainty in the tofacitinib evidence base for 6-month outcomes stemming from the use of an early escape study design that permitted either all the placebo-treated patients or the non-responders to crossover and receive tofacitinib at Month 3

Further details on the rationale for the second and third points are given below.

Rationale for selection of sub-populations by prior treatment

The decision problem for this appraisal covers two clinically distinct groups of patients with RA, whose disease has responded inadequately to, or who are intolerant of ≥1 cDMARDS (second-line patients) or bDMARDS (third-line patients).

As the treatment and costs associated with these groups differ, they are treated separately in the economic analysis. However, the ORAL trials included a mixture of prior treatments, as outlined in section 4.5.1. Table 50 presents an overview of the prior treatments across the pivotal trials within the NICE decision problem.

Table 50: Overview of the prior treatments across the pivotal trials

Study name	ORAL Standard	ORAL Scan	ORAL Sync	ORAL Solo	ORAL Step
Section	**4.5.2.1**	**4.5.2.2**	**4.5.2.3**	**4.5.2.4**	**4.7.5.3**
Study duration	1 year	2 years	1 year	6 months	6 months
Total number of subjects	717	797	792	610	399
Background therapy	MTX	MTX	cDMARD	None	MTX
Prior treatments, %					
MTX	100	99.9	84.3	84.9	99.5
LEF	16.7	17.1	29.9	22.6	17.5
SSZ	28.7	28.6	20.8	24.3	10.5
TNFi	7.1	15.9	6.6	16.2	99.2
Other non-TNFi biologic	2.1	4.6	2.9	6.7	11.5

Abbreviations: LEF, leflunomide; MTX, methotrexate; SSZ, sulfasalazine; TNFi, tumour necrosis factor inhibitor.

Based on this assessment, the trials vary in the prior treatments received by patients. The combination trials, ORAL Standard, Scan and Sync are in predominantly

second-line populations, but include between 9.2 to 20.5% of patients with prior biologic use. Similarly, the ORAL Solo trial is predominantly in a second-line population, but includes 9.5% of patients with a prior biologic who would therefore be considered third-line patients. The ORAL Step trial is performed in a third-line population, as all patients previously received biologic treatment. On the basis of this heterogeneity in the ORAL Standard, Scan, Sync, and Solo trials, it was deemed necessary to provide post-hoc subgroup analyses to ensure the results of these trials corresponded more precisely with the decision problem.

Rationale for exploring uncertainty in outcomes due to the early escape study design

Placebo controlled trials within chronic diseases raise ethical issues as even short-term placebo exposure may lead to a period of poor disease control adversely impacting on patients' health (132). To limit the exposure of patients to ineffective treatments, trials within RA frequently include designs which utilise an early escape. This permits patients to receive alternative treatments if no response to background DMARD is detected early in the trial. In cases where patients are not receiving background DMARDS, the use of early escape is used to limit exposure of patients to treatment without active therapy.

Importantly, in studies such as the ORAL trials and many others, patients crossover to alternative treatments after early escape and prior to the time point of interest in the appraisal (20–30 weeks), which confounds the results. In the ORAL Standard, Scan, and Sync trials, it was the placebo-treated patients deemed as non-responders at Month 3 who then crossed over to receive tofacitinib. The extent of confounding in the placebo arms of the Standard, Scan, and Sync studies can be seen in Table 51, which summarises the Month-3 non-responders across the trials from the publications where available. This shows that at Month 3, there were typically around a quarter of tofacitinib-treated patients who were non-responders, while around half of the placebo patients were non-responders and would have crossed over to receive tofacitinib prior to the 6-month endpoint, therefore confounding any ITT analysis.

Table 51 Summary of month 3 non-responders by treatment sequence in ORAL Scan, Standard and Sync

Treatment sequence	Month 3 non-responders n/N (%)		
	ORAL Scan	ORAL Sync	ORAL Standard
Tofacitinib 5 mg BD	84/321 (26.2%)	80/318 (25.2%)	[redacted]
Tofacitinib 10 mg BD	56/316 (17.7%)	58/318 (18.2%)	[redacted]
Placebo -> Tofacitinib 5 mg BD	42/81 (51.9%)	38/79 (48.1%)	[redacted]
Placebo -> Tofacitinib 10 mg BD	37/79 (46.8%)	40/80 (50%)	[redacted]
Adalimumab	-	-	[redacted]

Abbreviations: BD, twice daily.

In the case of the ORAL Solo and Step trials, a study design was used that allowed for 3 months of treatment in the placebo arm before advancing all placebo patients to tofacitinib. In the context of the decision problem (which requires an analysis of clinical benefit at Month 6), an ITT analysis performed at Month 6 by initially randomised treatment would be significantly biased. By Month 6, all patients in the placebo arm had been exposed to 3 months of tofacitinib, and would result in a substantial underestimation of treatment effect.

Methods for addressing crossover have been developed for trials using time to event outcomes commonly seen in oncology (see TSD16 (133)). However, RA trials do not typically capture time-to-event as part of the clinical evidence base. In the case of the ORAL Solo and Step trials, there are no patients remaining on placebo after 3 months to inform the counterfactual. Therefore, approaches commonly used in RA trials to address confounding from crossover due to early escape include the application of non-responder imputation or last observation carried forward (LOCF).

In the absence of established techniques readily available to address crossover in non-time-to-event outcomes, Pfizer have applied various imputation approaches to the calculation of the EULAR responses. These offer a range of estimates of efficacy that explore uncertainty due to crossover from placebo to tofacitinib. In the case of ORAL Standard, Scan, and Sync, Pfizer have utilised the statistical analysis approaches pre-specified in the ORAL trial protocols for the primary endpoints. In the case of the Solo and Step trials, where all patients in the control arm crossed over to receive tofacitinib at Month 3, the Month 6 data were only analysed in these trials by comparing the sequences of treatment. Therefore, for these trials, Pfizer provide analyses based on various applications of LOCF to the Month 3 data to impute estimate of relative effect at Month 6.

4.8.1.2 Methods

The following approaches were incorporated into a single analysis to provide 6-month EULAR data for trial participants corresponding to the second and third-line populations in the decision problem. This explores the heterogeneity associated with outcomes associated with the use of early escape in the ORAL studies.

Methods for deriving EULAR outcomes

EULAR response data at each time point were derived from DAS28 as shown in Table 52.

Table 52: EULAR response by change in DAS28

DAS28 at time point	Improvement in DAS28 from baseline		
	>1.2	≤1.2 and >0.6	≤0.6
≤3.2	Good	Moderate	No response
≤5.1 and >3.2	Moderate	Moderate	No response
>5.1	Moderate	No response	No response

Abbreviations: DAS28, disease activity score in 28 joints.

Methods for reducing heterogeneity in prior treatment

Subgroups of second-line patients were identified in the ORAL Standard, Scan, Sync, and Solo trials by retaining only patients who had previously been treated using cDMARDs and excluding any patients who had previously been treated with bDMARDs.

Methods for exploring heterogeneity due to early escape/crossover

Three datasets were developed for analysis:

- the second line combination therapy trials (pooled across ORAL Standard, Scan, and Sync)
- the second line monotherapy trial (ORAL Solo)
- the third line combination therapy trial (ORAL Step)

For each dataset, two analyses were performed to provide two estimates of the relative efficacy for tofacitinib, and therefore explore the uncertainty associated with crossover of the placebo non-responders. The application of these approaches in the submission are summarised in Table 53, with details and rationale for selection base case provided in the following sections for the three datasets.

Analysis approaches for ORAL Standard, Scan and Sync

In ORAL Standard, Scan and Sync, if a patient did not show a 20% improvement in both tender/painful swollen joint counts at Month 3, they were considered a non-responder and were blindly advanced into the 'double-blind active extension period'. Therefore, any placebo patients who were classed as non-responder at Month 3 crossed over onto active treatment with tofacitinib, while placebo patients who were responders at Month 3 continued with placebo treatment up to Month 6. Any tofacitinib treated patients who were non-responders at Month 3 remained on tofacitinib until Month 6.

In these trials, the investigators applied a number of non-responder imputation (NRI) approaches, which included:

1. the application of NRI to Month 3 non-responders from the placebo arm (termed NRI without advancement penalty) and,
2. the application of NRI to Month 3 placebo non-responders as well as the Month 3 tofacitinib non-responders regardless of whether they subsequently responded to tofacitinib between Month 3 and 6 (termed NRI with advancement penalty).

The application of these approaches to generate two estimates of treatment effect are summarised in Table 53, with details and rationale for the selection of base case provided in the text below.

Table 53: Summary of analyses presented to explore uncertainty in treatment effect due to early escape in the tofacitinib trial analysis of EULAR outcomes

Trials (name, line and combi or mono)	Estimate 1 of treatment effect	Estimate 2 of treatment effect
Scan, Sync, Standard (predominantly second line, combination therapy)	• Non-responder imputation without advancement penalty. • Control: NRI applied to patients who advance at 3 months. 6-month data used for patients who do not advance • Tofacitinib: 6-month data used	• Non-responder imputation with advancement penalty. • Control: NRI applied to patients who advance at 3 months. 6-month data used for patients who do not advance • Tofacitinib: NRI applied to patients who did not have a 20% improvement in swollen and tender joint counts at month 3. 6-month data used for patients who did have 20% improvement in swollen and tender joint counts at Month 3.
Solo (predominantly second line, monotherapy) Step (third line, combination therapy)	• Control: 3 months for all patients • Tofacitinib: 6-month data for all patients	• Control: 3 months for all patients • Tofacitinib: 3 months for all patients

Estimate 1 of clinical benefit is produced by applying the non-responder imputation only to those patients who received alternative treatments after early escape. Specifically, this includes only those patients from the placebo arm who did not demonstrate a 20% improvement in both tender and swollen joint accounts by Month 3 – this constitutes the non-responder imputation without advancement penalty. This approach has the advantage that it maximises the use of information relevant to the trial decision problem and allows tofacitinib randomised patients to produce a response to treatment at Month 6 as per clinical practice, as well as the Month 3 placebo responders. The disadvantage is that it only applies NRI to the placebo non-responders; therefore, the use of unequal exposure to treatment between the arms assumes that those placebo patients who are non-responders at Month 3 would not go on to subsequently develop a response between Month 3 and 6.

Estimate 2 of treatment benefit of tofacitinib uses the statistical approach used for the primary analysis endpoints in the ORAL Standard, Scan, and Sync in which non-responder imputation was applied to Month 3 non-responders in the placebo group and an advancement penalty was then also applied to the Month 3 non-responders in the tofacitinib arm (i.e. non-responder imputation with advancement penalty). This approach excludes data relevant to the decision problem in the form of tofacitinib-treated patients who develop a response to treatment between Month 3 and Month 6. Therefore, this approach makes the assumption that neither the tofacitinib-treated patients or the placebo-treated patients who were non-responders at Month 3 would subsequently develop a response at Month 6.

While it is not possible to directly test the assumptions made, regarding the Month 3 placebo non-responders, by examining the data for tofacitinib-treated patients from the

trials, it is possible to directly test whether the assumption is correct that Month 3 tofacitinib non-responders would not subsequently develop a response at Month 6. An analysis was performed that pooled patients treated with tofacitinib in ORAL Standard, Scan, and Sync and examined the Month 6 EULAR responses for those who were non-responders at Month 3. Overall, [redacted] of non-responders at Month 3 subsequently developed a response to treatment at Month 6; [redacted] achieved a moderate response and [redacted] achieved a good response (Table 54).

Table 54: Month 6 EULAR responses for Month 3 non-responders treated with tofacitinib

Trial	Total number of non-responders at Month 3	Response at Month 6			Percentage achieving subsequent response (moderate or good)
		No response	Moderate response	Good response	
ORAL Scan – No response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORAL Sync – No response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORAL Standard – No response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORAL trials combined – No response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EULAR, European League Against Rheumatism.

In the absence of ORAL trial data on the 3- to 6-month period of placebo treatment for non-responders, clinical opinion was sought to determine the clinical feasibility of subsequent response in the Month 3 placebo non-responders.

Clinical opinion indicated that the nature of prior exposure of patients to MTX should be taken as a guide to indicate the likely level of response after Month 3 in non-responders. It would be expected that less than 10% of the placebo-treated non-responders at Month 3 would develop a subsequent response at Month 6 in a situation where patients had received a steady dose of MTX (in the maximum tolerable range) for 3 months prior to the 3-Month assessment. In situations where patients may have not achieved a maximum tolerable dose for up to 3 months prior to the Month-3 assessment, clinical opinion suggested that a maximum of 20% of the Month 3 placebo non-responders may subsequently develop a response by Month 6.

The protocol for the ORAL Standard, Scan, and Sync trials indicate that by the assessment at Month 3, patients would have received MTX for ≥7 months in total; the 6 weeks prior to randomisation patients were on a stable dose between 15 mg and 25 mg according to local standard-of-care practices for the administration of MTX (stable weekly doses less than 15 mg were allowed only in the presence of intolerance to or toxicity from higher doses or where higher doses would violate the local label). Given the duration of exposure to MTX prior to the Month 3 assessment, and the fact that dosing was in line with local clinical practice and considered stable, on balance it would be

expected that less than 10% of the Month-3 placebo-treated non-responders would have subsequently developed a EULAR response by Month 6.

Given the likelihood that approximately twice as many non-responders in the tofacitinib arm would subsequently develop a response compared with the placebo treated arm, Pfizer deemed it reasonable to utilise Estimate 1 as a base case in the NMA. This also has the added benefit of minimising the number of patients which have a response imputed for Month 6.

Analyses using the alternative estimate of efficacy are also presented for the NMA and the economic model, although based on this assessment, Pfizer would expect these analyses to underestimate the actual treatment benefit of tofacitinib.

Analysis approaches for ORAL Solo and ORAL Step

Both the ORAL Solo and Step trials mandated the crossover of all placebo treated patients at Month 3, regardless of response. Due to the similar trial designs, the same analytical approaches were used for both Solo and Step trials to impute the Month 6 EULAR response and explore the associated uncertainty due to crossover.

Pfizer present two estimates of treatment effect for each of the Solo and Step trials. Estimate 1 of treatment effect is based on an analysis that utilises placebo-treated patient data from Month 3, immediately prior to patients commencing treatment with tofacitinib. This is then compared to the 6-month data for the patients randomised to tofacitinib. Similar to the analysis performed for the ORAL Standard, Scan and Sync trials, this approach maximises the use of available information relevant to the trial decision problem, and allows tofacitinib-randomised patients at Month 6 to produce a response to treatment as per clinical practice. However, it assumes that the Month-3 EULAR responses of the placebo-treated patients are representative of a Month-6 response.

Estimate 2 of treatment effect is calculated by carrying forward the Month-3 responses for both the control and tofacitinib arms to the Month-6 time point. Similar to Estimate 2 in the ORAL Standard, Scan and Sync trials this approach uses equal treatment durations in the trial arms, but assumes that the 3-month data are representative of the 6-month data in both trial arms.

Similar to the situation for the ORAL Standard, Scan and Sync, it is possible to examine the trial data to determine how well the Month 3 data correspond with the Month 6 data for the tofacitinib treated patients (see Table 55). This analysis indicates that for ORAL Solo, the Month-6 data indicate an [redacted]. There is also [redacted], but as this is combined with [redacted]

[redacted]

Table 55: Comparison of EULAR response rates with tofacitinib in ORAL Solo and ORAL Step for Months 3 and 6

Trial	EULAR response	Month-3 response: n (%)	Month-6 response: n (%)
ORAL Solo	No response	[redacted]	[redacted]
	Moderate response	[redacted]	[redacted]
	Good response	[redacted]	[redacted]
	Total	241	241
ORAL Step	No response	[redacted]	[redacted]
	Moderate response	[redacted]	[redacted]
	Good response	[redacted]	[redacted]
	Total	133	133

Abbreviations: EULAR, European League Against Rheumatism.

It is important to recognise that the control arm of ORAL Solo did not include any DMARD treatment other than antimalarial medications where required. In fact, the lack of any effective treatment in the placebo arm of the trial provides the rationale for restricting the placebo-controlled period of the trial to only three months. Patients were allowed concurrent non-steroidal anti-inflammatory drugs (NSAIDs)/cyclooxygenase 2 (COX-2) inhibitors and corticosteroids, but given that patients had already been receiving at a stable dose for a total of 4 months before the Month-3 assessment in the trial (i.e. a stable dose for 4 weeks or more prior to first study dose), it is reasonable to assume that in the absence of any form of active DMARD treatment, few patients would go on to develop any subsequent response to treatment beyond that already seen in Month 3.

On the basis of this assessment, it was felt that the actual relative benefit of tofacitinib at Month 6 in the ORAL Solo trial would be closer to Estimate 1; therefore, Estimate 1 was used as the base case in the NMA. Estimates of treatment effect based on Estimate 2 are also presented as a scenario analysis.

In the case of ORAL Step, the data for tofacitinib treated patients between Month 3 and Month 6 show that there was [redacted] (Table 55). However, this was combined with a [redacted] and [redacted]. Overall, this suggests a situation in which [redacted]. With respect to these results, there are differences in the EULAR responses between Month 3 and 6 for the tofacitinib-treated patients.

Similar to the ORAL Standard, Sync and Scan trials, the patients in ORAL Step had to have been taking MTX for ≥4 months prior to receiving the first dose of study medication, and had to be on a stable dose of MTX for ≥6 weeks prior to first dose of study medication. The study dose of MTX used was according to local standard of care ranging from between 15 mg to 25 mg per week (20 mg per week in Ireland). Stable weekly doses less than 15 mg were allowed only in the presence of intolerance to or toxicity from higher doses or where higher doses would violate the local label.

Therefore, the patients in the placebo arm would have been exposed to a significant period of MTX treatment (7 months) at levels consistent with local standard of care for ≥4.5 months prior to crossover. In light of this, it is reasonable to assume that there would be a minimal change in the responses of placebo-treated patients between Month 3 and 6. Based on this assessment, Pfizer believe that Estimate 1 is more likely to reflect the relative treatment effect of tofacitinib; therefore, Estimate 1 was used as the base case in the NMA and economic model, although scenario analyses are also presented for Estimate 2.

Accounting for missing data in the calculation of treatment effect

Missing data for reasons other than crossover were treated in accordance with the trial protocols for ORAL studies. In line with the ACR analysis outlined in section 4.4.2, the following corrections have been applied:

- LOCF was applied to account for missing observations.
- Patients who had no baseline DAS score were assumed to be a non-responder.
- Patients who dropped out of the trial prior to Month 6 were imputed as a non-responder.

4.8.1.3 Results

ORAL Scan, Sync and Standard

The results of the analysis of EULAR response rates for ORAL Scan, Sync and Standard are presented in Table 56 and Table 57.

Table 56: Estimate 1 for second-line combination therapy trials

	No response	Moderate	Good	Moderate & Good	Total
ORAL Scan					
Tofacitinib 5 mg BD					
Placebo to tofacitinib 5 mg BD					
ORAL Sync					
Tofacitinib 5 mg BD					
Placebo to tofacitinib 5 mg BD					
ORAL Standard					
Tofacitinib 5 mg BD					
Placebo to tofacitinib 5 mg BD					
Adalimumab 40 mg					
Pooled Analysis					
Tofacitinib 5 mg BD					
Placebo to tofacitinib 5 mg BD					
Adalimumab 40 mg					

Abbreviations: BD, twice daily.

Table 57: Estimate 2 for second-line combination therapy trials

	No response	Moderate	Good	Moderate & Good	Total
ORAL Scan					
Tofacitinib 5 mg BD					
Placebo to tofacitinib 5 mg BD					
ORAL Sync					
Tofacitinib 5 mg BD					
Placebo to tofacitinib 5 mg BD					
ORAL Standard					
Tofacitinib 5 mg BD					
Placebo to tofacitinib 5 mg BD					
Adalimumab 40 mg					
Pooled Analysis					
Tofacitinib 5 mg BD					
Placebo to tofacitinib 5 mg BD					
Adalimumab 40 mg					

Abbreviations: BD, twice daily.

ORAL Solo and Step

Results of the analysis of EULAR response for ORAL Solo and Step are presented in Table 58 and Table 59.

Table 58: Estimate 1 for ORAL Step and Solo

	No response	Moderate	Good	Moderate & Good	Total
ORAL Step					
Tofacitinib 5 mg BD					
Placebo to tofacitinib 5 mg BD					
ORAL Solo					
Tofacitinib 5 mg BD					
Placebo to tofacitinib 5 mg BD					

Abbreviations: BD, twice daily.

Table 59: Estimate 2 for ORAL Step and Solo

	No response	Moderate	Good	Moderate & Good	Total
ORAL Step					
Tofacitinib 5 mg BD					
Placebo to tofacitinib 5 mg BD					
ORAL Solo					
Tofacitinib 5 mg BD					
Placebo to tofacitinib 5 mg BD					

Abbreviations: BD, twice daily.

4.8.2 *Post-hoc analyses performed in ORAL Scan, ORAL Sync and ORAL Solo*

The methodology of the post-hoc analyses performed in ORAL Scan, ORAL Sync and ORAL Solo are described in Section 4.4.2.

4.8.2.1 ORAL Scan

In order further examine radiographic progression (see Section 4.13.24.13 for full discussion on radiographic progression), a post hoc analysis of mTSS scores was performed in subsets of patients with prognostic factors predictive of greater progression of joint damage (anti-CCP positivity, DAS28-4[ESR] >5.1, anti-CCP positivity and/or rheumatoid factor positivity with erosion score ≥3, and baseline total mTSS greater than baseline median total mTSS). This analysis revealed more pronounced effects for tofacitinib 5 mg with greater differences from placebo in these patients

[redacted]

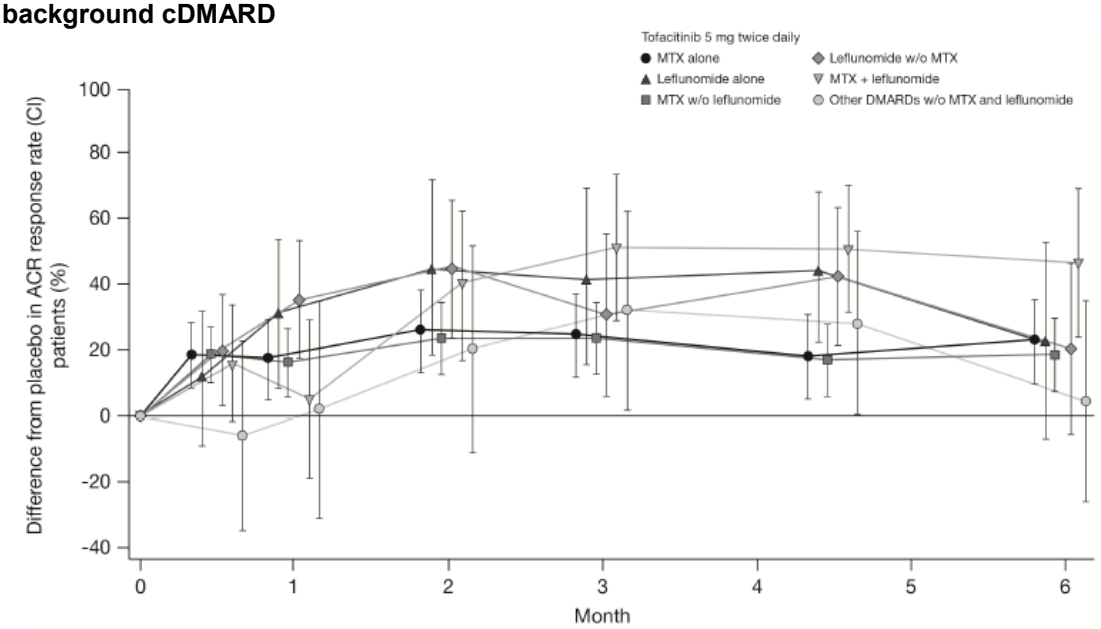
EMPTY

Abbreviations: CCP, cyclic citrullinated peptide; CI, confidence interval; DAS28, Disease Activity Score in 28 joints; DMARD, disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; FAS, full analysis set.

4.8.2.2 ORAL Sync

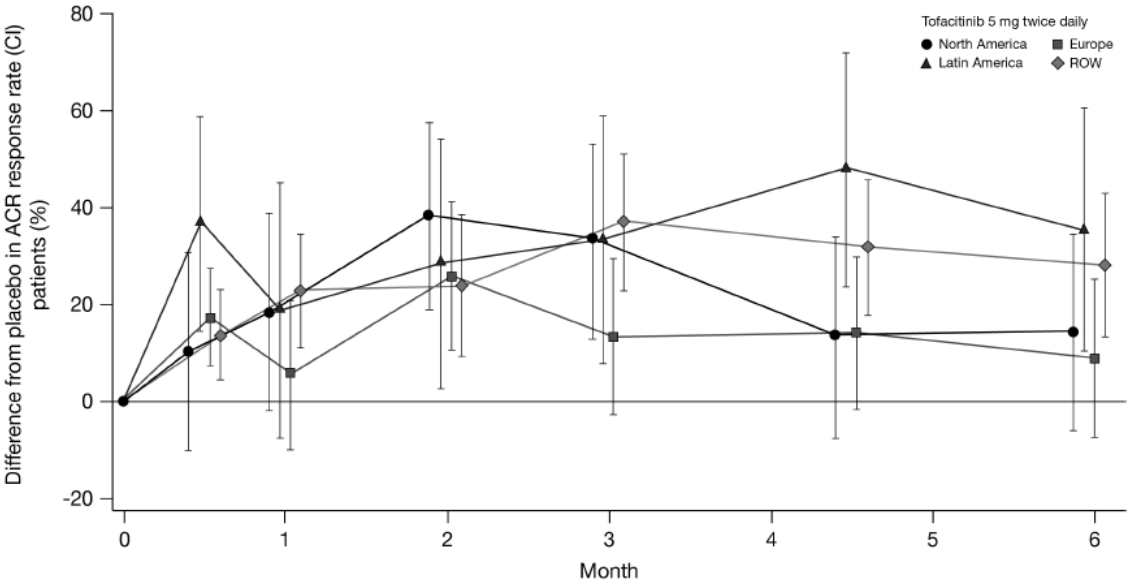
In general, ACR20 responses were consistent across background DMARD therapies, taking into consideration that some of these subgroups contained small numbers of patients (Figure 27). Regional variation in the differences between the proportion of patients achieving ACR20 response for tofacitinib 5 mg and placebo were noted (Figure 28).

Figure 27: Difference from placebo in mean ACR20 response over time categorised by background cDMARD



Abbreviations: ACR, American College of Rheumatology; CI, confidence intervals; DMARD, disease-modifying anti-rheumatic drug; MTX, methotrexate; w/o, without.
'Alone' indicates a single DMARD therapy.

Figure 28: Difference from placebo in mean ACR20 response over time categorised by geographic region



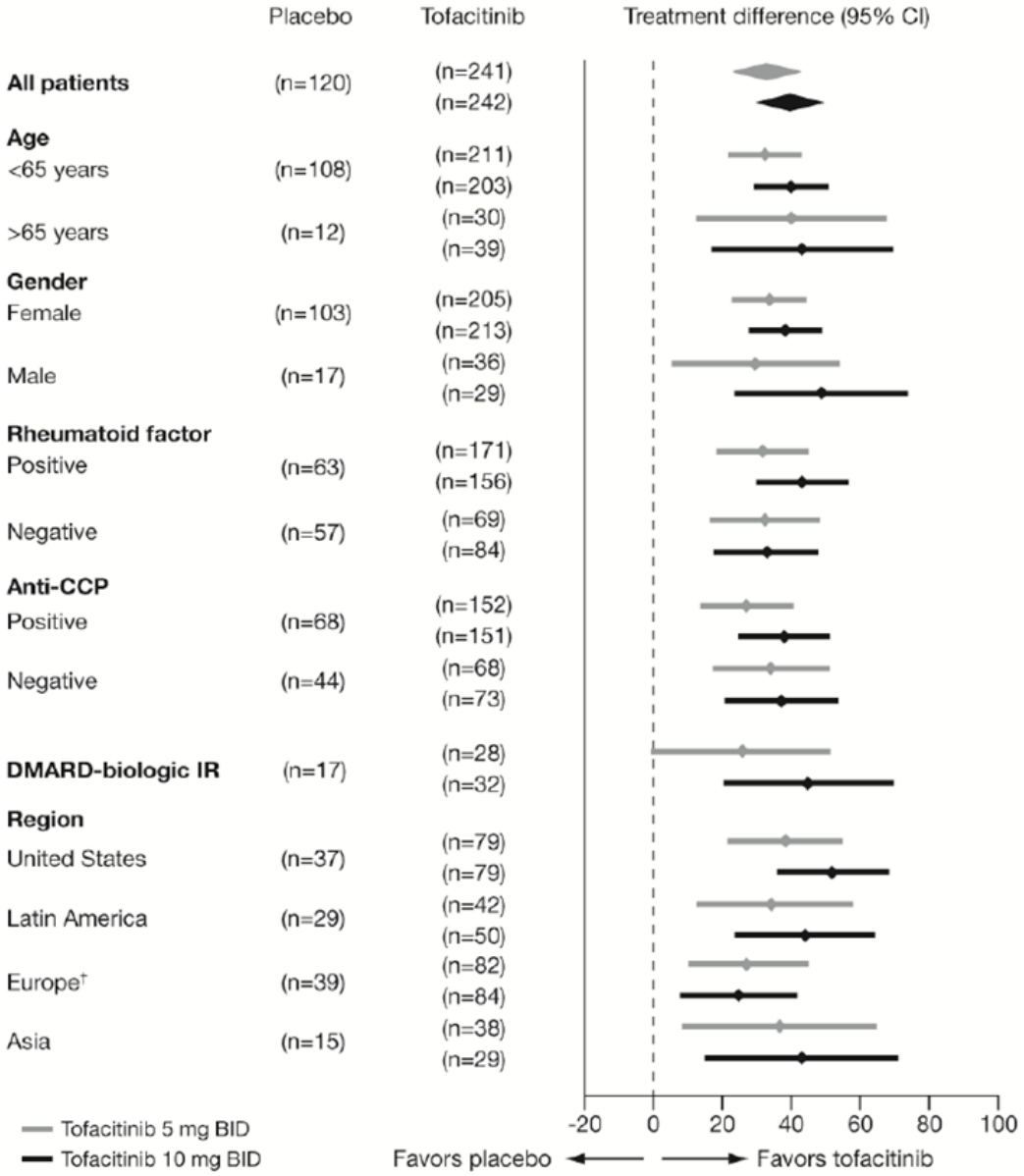
Abbreviations: ACR, American College of Rheumatology; CI, confidence intervals; ROW, rest of world.

4.8.2.3 ORAL Solo

Age, sex, and seropositivity status were not associated with meaningful differences in the ACR20 results, compared with the primary analysis (Figure 29). Among patients who had previously had an inadequate response to TNFi or other biologic agents, 42.9% in the tofacitinib 5 mg group achieved ACR20 at Month 3, compared with 17.7% in the combined placebo group (P=0.06). Significant effects on the rate of ACR20 response with tofacitinib 5 mg were seen in all geographic regions at Month 3 compared with

placebo (United States: p<0.001; Latin America: p=0.002; Europe: p=0.002; rest of world, p=0.01).

Figure 29: Forest plot of treatment differences in ACR20 response at Month 3 (FAS, NRI)



Abbreviations: ACR, American College of Rheumatology; CCP, cyclic citrullinated peptide; CI, confidence intervals; DMARD, disease modifying anti-rheumatic drug; FAS, full analysis set; IR, inadequate response; NRI, non-responder imputation.
†15.0% from Central Europe

4.9 *Meta-analysis*

No meta-analysis was performed as a network meta-analysis was performed to inform Section 4.10.

4.10 *Indirect and mixed treatment comparisons*

A network-meta analysis (NMA) was performed to inform the economic model for the assessment of the cost-effectiveness of tofacitinib relative to other treatments for RA. Studies for this were identified from a systematic review (SR) using criteria from both TA375 (22) and the scope set out by NICE for the appraisal of tofacitinib. It should be noted that the focus of this SR was broader than that of the NICE scope (e.g. additional comparators and outcomes were included) as it was designed to inform Pfizer's ongoing work in the overall RA population. Further exclusion criteria were therefore applied to the results of the SR to produce the final set of studies for the NMA (Section 4.10.2).

4.10.1 *Search strategy*

Systematic reviews (SRs) were conducted in cDMARD-IR and bDMARD-IR patients (for exclusion and inclusion criteria see Table 60). The objectives of these SRs were to identify relevant clinical data from the published literature regarding the clinical effectiveness of tofacitinib and other treatments for RA based on the clinical outcomes outlined in the NICE scope. The original review was performed in June 2010, with subsequent updates in April 2011, September 2012, November 2014, June 2016 and December 2016. Note that while the SR considered safety outcomes, safety data frequently focus on the most commonly reported AEs and data for specific AEs tend not to be reported consistently across studies. An NMA for safety was therefore not performed.

Studies identified by the systematic review were independently assessed by a reviewer in order to ascertain whether they met the pre-defined inclusion and exclusion criteria for the review based on population, interventions, comparators, and outcomes set out in the scope of the appraisal (Table 60). These criteria were selected based on the scope set out by NICE, and, consistent with the decision problem, interventions were included either as monotherapy or in combination with concomitant cDMARDs (including MTX) (Section 1.1). It should be noted that the SR included a broader set of comparators compared with the decision problem for this submission as it was conducted as part of Pfizer's ongoing work in RA; exclusion criteria relating to treatments which are not in the decision were therefore performed when creating the final NMA networks (Section 4.10.2). Any uncertainties were resolved by discussion with a second reviewer and data were extracted from eligible publications into a predefined table by a reviewer.

Only doses licensed for use in the UK were included in the SR. With respect to cDMARD doses, particularly MTX, it should be noted that trials may vary in the dosing used, particularly in trials with Asian populations. To avoid excluding relevant data on bDMARDS the dose of cDMARDS was therefore not restricted. In the base case, the different MTX doses were grouped together assuming that there would have been no differences in outcomes (beyond sampling error) between the different treatments within the group if the same population would have been treated.

Full details of the search strategies and information sources are presented in Appendix 3.

Table 60: Inclusion criteria used in systematic review search strategy

Clinical effectiveness	Inclusion/exclusion criteria	
	cDMARD-IR	**bDMARD-IR**
Population	Adult patients (≥18 years of age) meeting ACR classification criteria for RA who have had an inadequate response to at least one cDMARD or MTX	Adult patients (≥18 years) with RA (as defined by the ACR criteria) who have had an IR to at least one bDMARD
Interventions/comparators†	Only licensed doses of each treatment were included • TNF-α-inhibitors: ○ Adalimumab ○ Etanercept ○ Infliximab ○ Golimumab ○ Certolizumab • JAK-inhibitors: ○ Tofacitinib ○ Baricitinib • Anti-B-cell therapy: ○ Rituximab ○ Co-stimulatory inhibitor molecules ○ Abatacept • Anti-IL-6 therapy: ○ Tocilizumab ○ Sarukinumab ○ Sirulimumab • Anti-IL-1 therapy: ○ Anakinra Biosimilars	
Outcomes	**Efficacy:** • EULAR response • Patient assessment of functional ability (Health Assessment Questionnaire [HAQ], Arthritis Impact Measurement Scales [AIMS], McMaster Toronto Arthritis [MACTAR]) • Radiographic progression (as measured by a valid scoring system e.g. Larsen/Sharp/modified Sharp score). • ACR 20/50/70 response rate to treatment (defined as a 20%/50%/70% improvement in tender and swollen joint counts and the same level of improvement in three of the five following variables: patient and physician global assessments, pain Health Assessment Questionnaire, and acute phase reactants). • C-reactive protein (CRP) levels • Changes in either DAS or DAS28 score. • Achieving 'low disease activity' (defined as DAS28 <3.2) or 'remission' (defined as DAS28 < 2.6). • Patient's assessment of pain (VAS or Likert scale).	

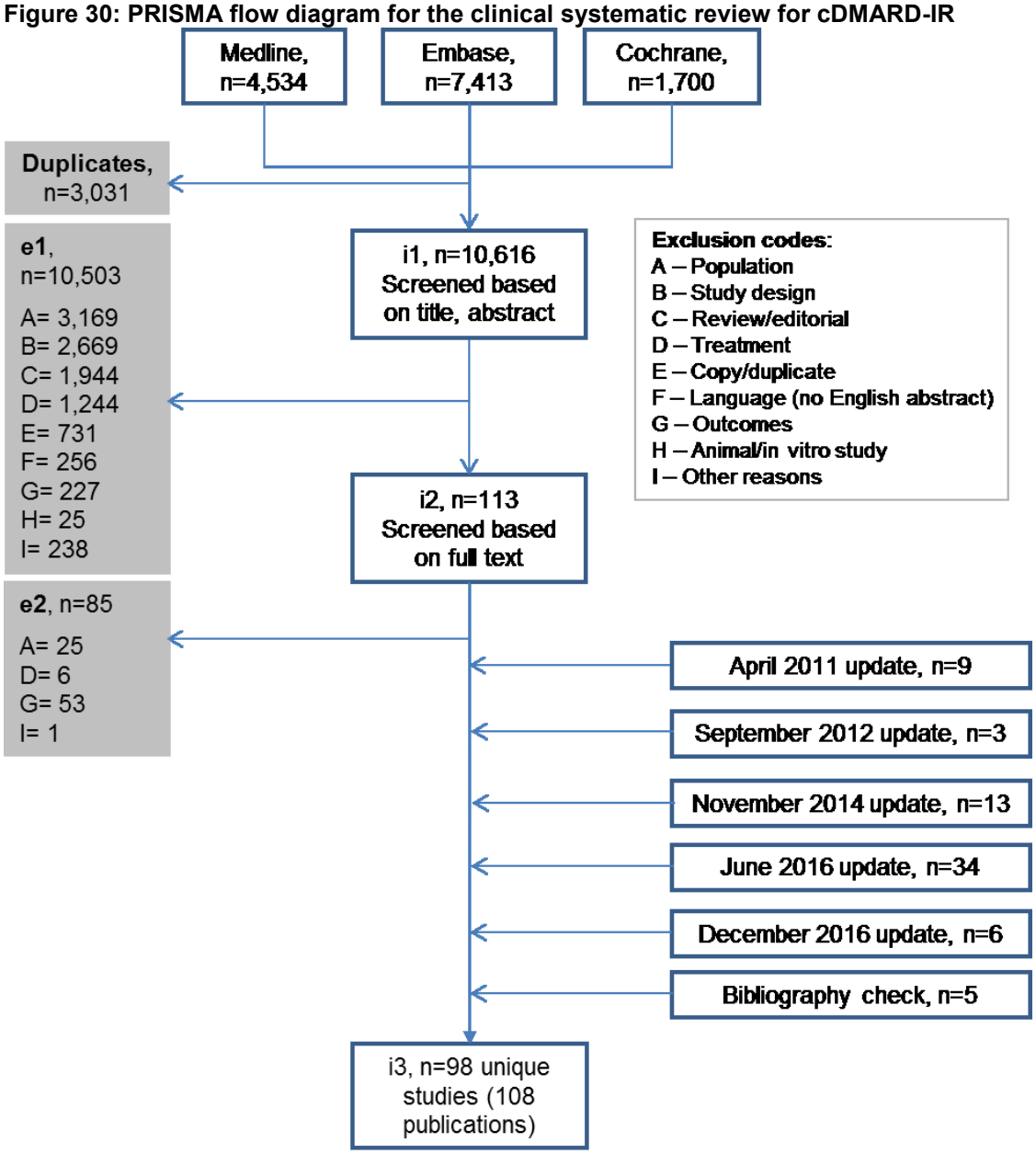
Clinical effectiveness	Inclusion/exclusion criteria	
	cDMARD-IR	bDMARD-IR
	• Patient/physician assessment of disease activity (VAS or Likert scale) • Morning stiffness, number of flares **Safety:** • Incidence of adverse events, including allergic reactions, and infections • Incidence of serious adverse events • Treatment withdrawal (and reason for withdrawal, e.g. lack of efficacy, adverse events, serious adverse events) **Health-related quality of life:** As measured by EQ-5D or other instruments	
Trial design	RCTs, no restriction on phase	
Language restrictions	No restriction. English abstracts of foreign language papers were considered	
Date of publication	Original review: no restriction April 2011 update: post-June 2010 September 2012 update: post-April 2011 November 2014 update: post-September 2012 June 2016 update: post-November 2014 December 2016 update: post-June 2016	No restriction

Abbreviations: Abbreviations: ACR, American College of Rheumatology; DAS, disease activity score; c/bDMARD, conventional/biological disease modifying anti-rheumatic drug; EULAR, European League Against Rheumatism; HAQ, health assessment questionnaire – disability index; IL, interleukin; JAK, Janus kinase; MTX, methotrexate; NICE, National Institute for Health and Care Excellence; QoL, quality of life; RA, rheumatoid arthritis; RCT, randomised controlled trial; SF-36, short-form 36; SJC, swollen joint count; SR, systematic review; TJC, tender joint count; TNF-α, tumour necrosis factor-alpha; VAS, visual analogue scale.
[†]Interventions were considered alone or in combination with other conventional/biological DMARDs. There were no restrictions with regard to drug dose or formulation, mode of delivery, or duration of treatment. However, studies with at least one treatment arm with a licensed dose are of primary interest.

4.10.1.1 Trials included in the systematic review: cDMARD-IR

Overall, a total of 98 unique studies were eligible for inclusion across the original review and five subsequent updates for cDMARD-IR patients. A PRISMA diagram showing the overall flow of studies across the original review and the five updates is shown in Figure 30. Inclusion/exclusion criteria for the NMA are provided in Section 4.10.2, with a list of excluded studies and reasons for exclusion in Section 4.10.2.2. Individual PRISMA flow diagrams showing the separate flow of studies through the original review and subsequent updates are provided in Appendix 3.

Figure 30: PRISMA flow diagram for the clinical systematic review for cDMARD-IR

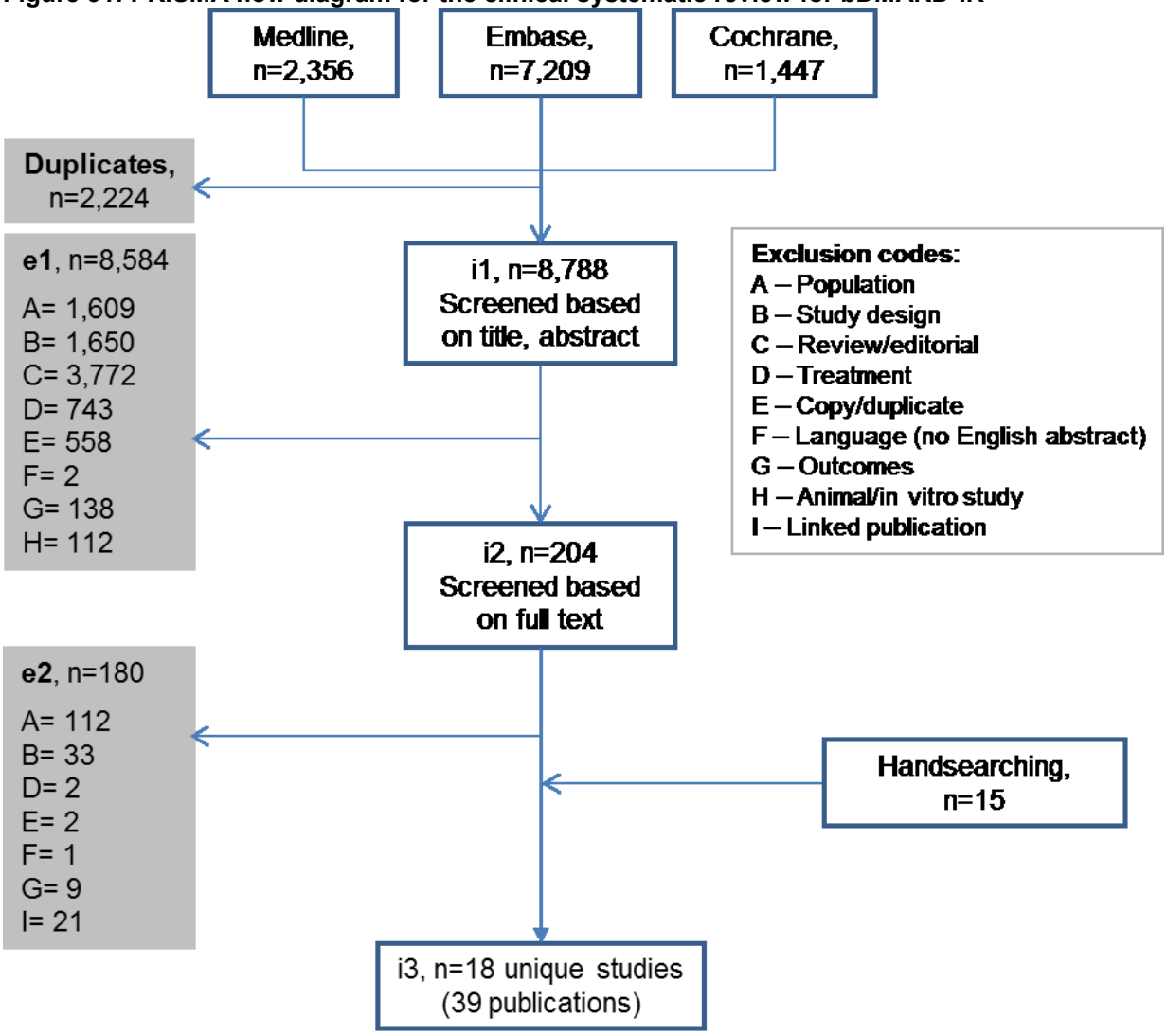


e = exclusion; i = inclusion.

4.10.1.2 *Trials included in the systematic review: bDMARD-IR*

In total, 39 publications representing 18 unique RCTs were identified by the SR, as presented in the PRISMA diagram in Figure 31. Inclusion/exclusion criteria for the NMA are provided in Section 4.10.2, with a list of excluded studies and reasons for exclusion in Section 4.10.2.2.

Figure 31: PRISMA flow diagram for the clinical systematic review for bDMARD-IR



e = exclusion; i = inclusion.

4.10.2 *Study selection for the NMA*

To further refine the results of the SRs to more closely meet the requirements of the decision problem and produce relevant networks, the following exclusion criteria were applied to the studies in each SR:

- Outcomes were restricted to EULAR (moderate, good, or at least a moderate response) and change in HAQ-DI from baseline
- Study follow-up restricted to 20–30 weeks

- Disease duration >3 years
- Currently licensed treatments only at licensed doses (baricitinib, sirukimab, and sarilumab excluded as currently unlicensed or not yet assessed by NICE)

Trials including patients with disease duration <3 years were excluded as previous research has shown that disease duration is a potentially important covariate in NMAs. To limit this aspect of clinical heterogeneity in the network, it was decided to limit the disease duration to between 3 and 10 years, which corresponds to established disease. This is similar to other recent reviews which have defined established RA as being a mean/median disease duration of 2 to 10 years (134). This does mean that some trials (specifically SWEFOT [see Section 4.10.2.1]) previously included in the TA375 NMA are excluded from the base case.

Exposure to treatment was identified as an important potential treatment effect modifier in Thorlund et al (135). This was controlled in the NMA by restricting the time window of analyses included in the NMA to those between 20–30 weeks. This 10-week window is similar (although marginally wider) than the 8-week timeframe used by Thorlund et al (135) and Stevenson et al (136). The 10-week window was selected over an 8-week window to allow incorporation of infliximab (IFX) biosimilars into the NMA, rather than performing further scenario analyses for their inclusion, and therefore represented a pragmatic solution to addressing the decision problem.

For the cDMARD-IR subgroup the NMA exclusion criteria resulted in a total of 37 studies included in the final networks from 98 studies identified by the SR (including SWEFOT for a scenario analysis), with 61 studies excluded from further analysis.

For the bDMARD-IR group application of the NMA exclusion criteria resulted in a total of 8 studies in the final networks from the 18 studies in the SR, with 10 studies excluded.

Note that the trials included and excluded in each NMA were cross-checked with relevant recent NMAs and guidance on conducting NMAs in RA to ensure that the methodology was robust and transparent (Section 4.10.2.2).

A summary of the studies included in the evidence network for each outcome in each patient population (including sensitivity analyses for cDMARD-IR) is presented in Table 61.

Table 61: Summary of studies included in each analysis in the NMA

Trial	Primary analyses				Sensitivity analyses										
	EULAR			HAQ-DI	Exclude Asian			Exclude prior bDMARD			Exclude milder disease			Include SWEFOT	Probit
	Moderate	Good	At least moderate		Moderate	Good	At least moderate	Moderate	Good	At least moderate	Moderate	Good	At least moderate	Good	Probit model
cDMARD															
ACT-RAY Dougados 2013 (137); Dougados 2014 (138)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ADACTA Gabay 2013 (139)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ARMADA Weinblatt 2003 (140)	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
ATTEST Schiff 2008 (141)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
AUGUST II Van Vollenhoven 2011 (142)	No	No	Yes	No	No	No	Yes	No	No	Yes	No	No	Yes	No	Yes
CERTAIN Smolen 2015 (143)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
CHANGE Miyasaka 2008 (144)	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
Choe 2015 (145)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
DE019 Keystone 2004 (146)	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
Emery 2015 (147)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Fleischmann 2012a (148)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
GO-FORTH Tanaka 2012 (149)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
GO-FORWARD Keystone 2009 (150)	No	No	Yes	No	No	No	Yes	No	No	Yes	No	No	Yes	No	Yes
GO-FURTHER Bingham 2014 (151)	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
HERA Bae 2016 (152)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
JESMR Kameda 2010 (153)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
J-RAPID Yamamoto 2014 (154)	No	No	Yes	Yes	No	No	No	No	No	No	No	No	Yes	Yes	Yes
Kim 2007 (155)	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
Kremer 2012 (156)	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No

Trial	Primary analyses				Sensitivity analyses										
	EULAR			HAQ-DI	Exclude Asian			Exclude prior bDMARD			Exclude milder disease			Include SWEFOT	Probit
	Moderate	Good	At least moderate		Moderate	Good	At least moderate	Moderate	Good	At least moderate	Moderate	Good	At least moderate	Good	Probit model
LARA Machado 2014 (157)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Li 2015 (158)	No	No	Yes	Yes	No	No	No	No	No	Yes	No	No	Yes	No	Yes
LITHE Kremer 2011 (159); Fleischmann 2013 (160)	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
OPTION Smolen 2008 (161)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes
ORAL-Scan Van der Heijde 2013 (9)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ORAL-Solo Fleischmann 2012b (125)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ORAL-Standard Strand 2016 (162)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ORAL-Sync Kremer 2013 (66)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
PLANETRA Yoo 2013 (163)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
RAPID 1 Keystone 2008 (164); Strand 2009 (165)	No	No	Yes	Yes	No	No	Yes	No	No	No	No	No	Yes	Yes	Yes
RAPID 2 Smolen 2009 (166)	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
SATORI Nishimoto 2009 (167)	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
START Westhovens 2006 (168)	No	No	Yes	No	No	No	Yes	No	No	Yes	No	No	Yes	No	Yes
SURPRISE Kaneko 2016 (169)	No	No	Yes	Yes	No	No	No	No	No	Yes	No	No	No	No	Yes
Takeuchi 2015 (170)	No	No	Yes	No	No	No	No	No	No	Yes	No	No	Yes	No	Yes
TOWARD Genovese 2008 (171)	No	No	Yes	No	No	No	Yes	No	No	Yes	No	No	Yes	No	Yes
Van de Putte 2004 (172)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
cDMARD-IR scenario analyses only															
SWEFOT van Vollenhoven, 2009 (173)	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No

Trial	Primary analyses				Sensitivity analyses										
	EULAR			HAQ-DI	Exclude Asian			Exclude prior bDMARD			Exclude milder disease			Include SWEFOT	Probit
	Moderate	Good	At least moderate		Moderate	Good	At least moderate	Moderate	Good	At least moderate	Moderate	Good	At least moderate	Good	Probit model
bDMARD															
ATTAIN Genovese 2005 (174)	Yes	Yes	Yes	No	NA										
GO-AFTER Smolen 2009 (175)	No	No	Yes	Yes											
ORAL-Step Burmester 2013 (128)	Yes	Yes	Yes	Yes											
RADIATE Emery 2008 (176)	No	No	Yes	No											
REFLEX Cohen 2006 (177)	Yes	Yes	Yes	Yes											
ROC Gottenberg 2016 (178)	Yes	Yes	Yes	Yes											
Combe 2012† (179)	Yes	Yes	Yes	No											
Manders 2015 NTR1605 (180)	Yes	Yes	Yes	Yes											

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire-disability index.

4.10.2.1 Evidence networks

In line with the scope set out by NICE, two subgroups are included in this submission, cDMARD-IR and bDMARD-IR. Evidence networks for each outcome for these populations are presented in the following sections.

Incorporating ETN into the cDMARD-IR networks was not initially possible as the ETN trials do not share a common comparator with the rest of the network. To meet the decision problem and link in ETN, there were two choices:

- Use the LARA trial to link ETN to the central node, and assume that the intensified DMARD arm is equivalent to the central DMARD node.
- Change the inclusion criteria for trials in the NMA to allow inclusion of the SWEFOT trial (and any other trials meeting the criteria) to generate a separate intensified DMARD link to ETN.

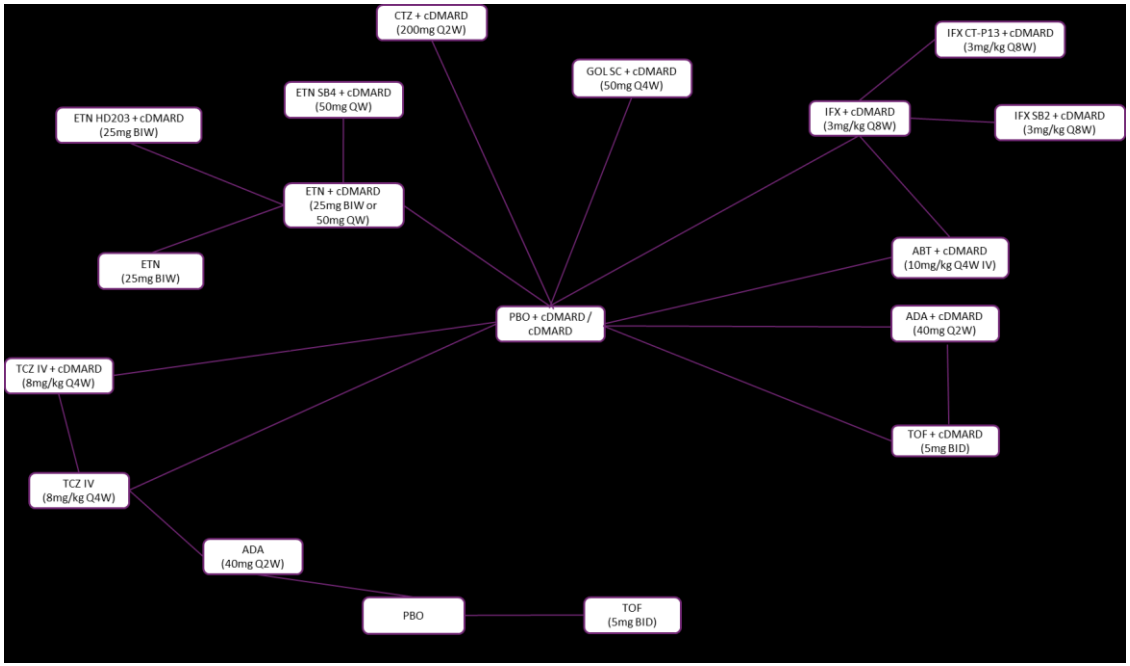
It was judged that the assumptions involved in incorporating LARA to the central node were less of a risk to bias in the network than changing the inclusion criteria for the NMA to include the SWEFOT trial in the base case analysis. The SWEFOT trial was included in the previous NMA produced by the assessment group (AG) in TA375; to provide an analysis using a network structure consistent with that presented in TA375 and explore the impact of omitting SWEFOT in the base case, Pfizer have therefore presented a scenario analysis where the inclusion criteria for the NMA have been modified to allow SWEFOT to be included in the network and provide a link to ETN via intensified cDMARDs.

Consistent with the analysis in TA375 and Thorlund et al, mono and combination therapy studies were treated as separate nodes in the same network.

cDMARD-IR: Primary analyses

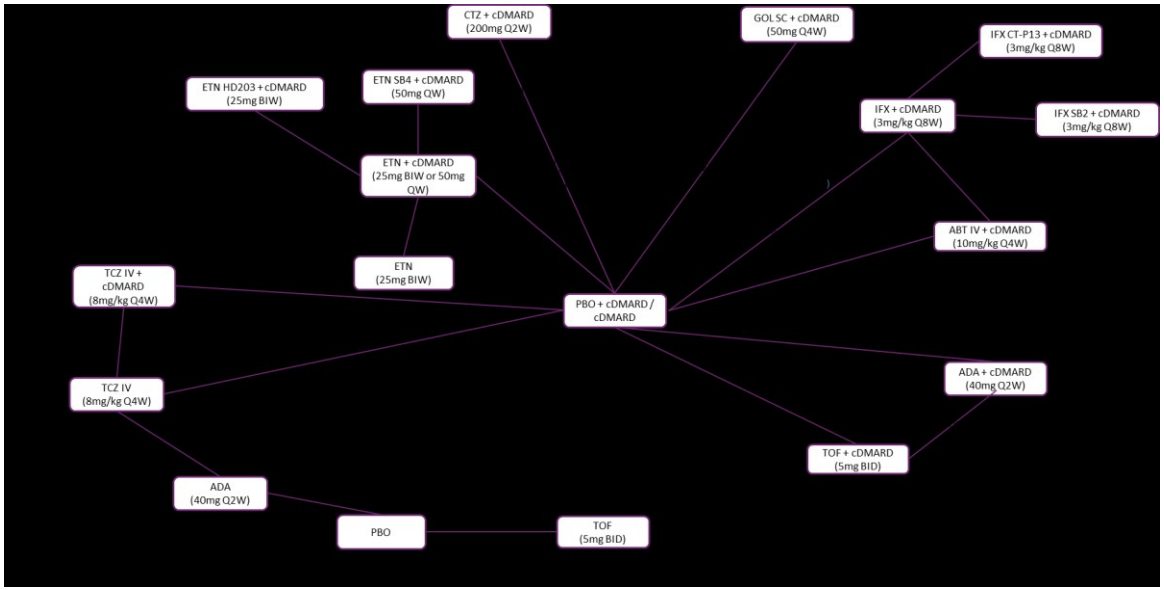
The evidence networks for EULAR moderate response, good response, and at least a moderate response are presented in Figure 32 and Figure 33, with the evidence network for change from baseline in HAQ-DI in Figure 34.

Figure 32: Evidence network for both EULAR moderate response and EULAR good response (as separate analyses)



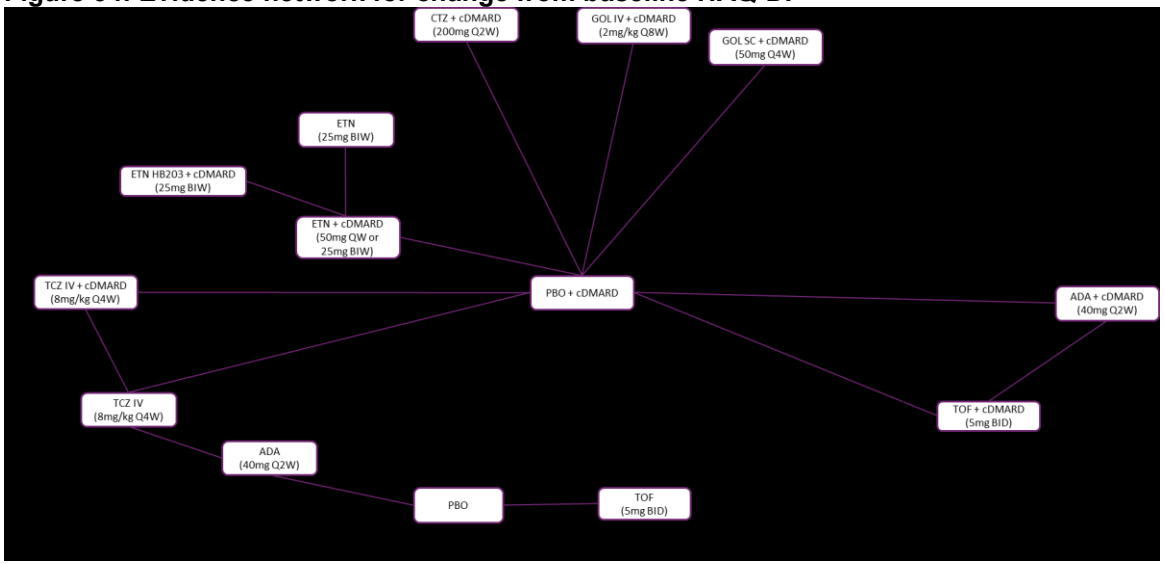
Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; LEF, leflunomide; MTX, methotrexate; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; SFZ, sulfasalazine; TCZ, tocilizumab; TOF, tofacitinib.

Figure 33: Evidence network for at least a moderate EULAR response



Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; LEF, leflunomide; MTX, methotrexate; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; SFZ, sulfasalazine; TCZ, tocilizumab; TOF, tofacitinib.

Figure 34: Evidence network for change from baseline HAQ-DI

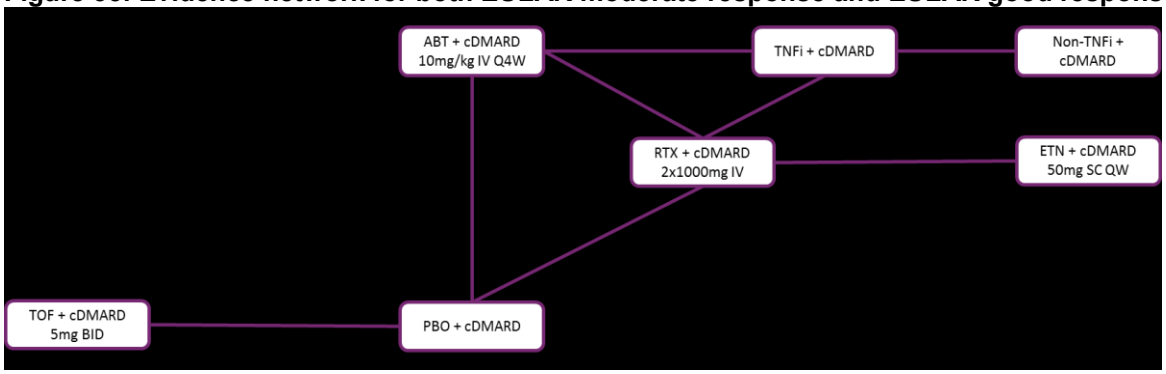


Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; LEF, leflunomide; MTX, methotrexate; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; SFZ, sulfasalazine; TCZ, tocilizumab; TOF, tofacitinib.

bDMARD-IR

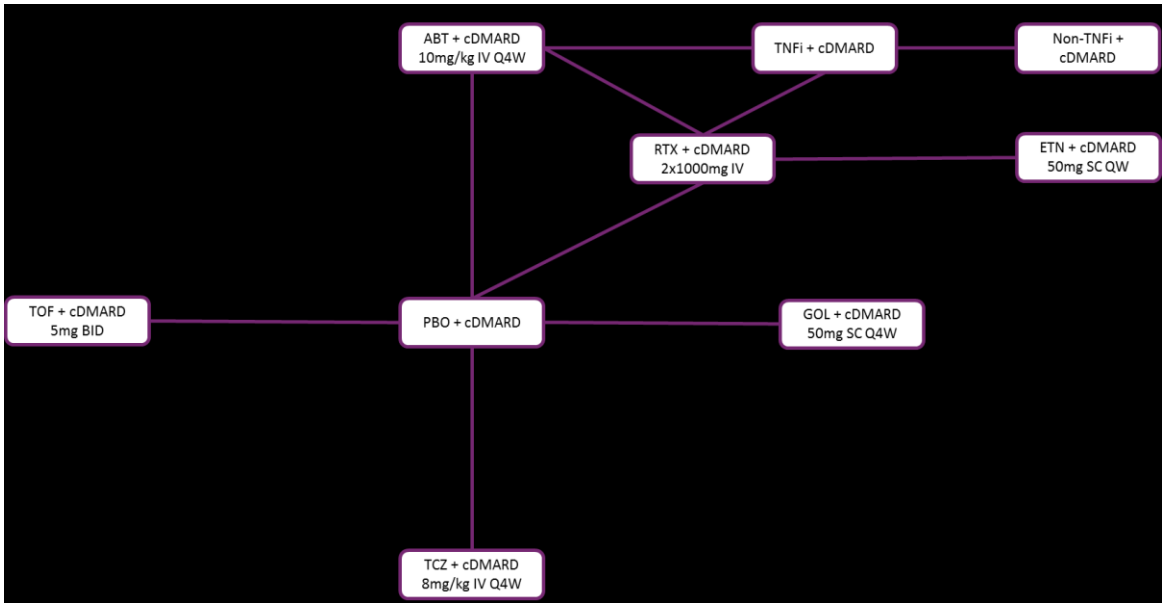
The evidence networks for EULAR moderate response, good response, and at least a moderate response are presented in Figure 35 and Figure 36, with the evidence network for change from baseline in HAQ-DI in Figure 37.

Figure 35: Evidence network for both EULAR moderate response and EULAR good response (as separate analyses)



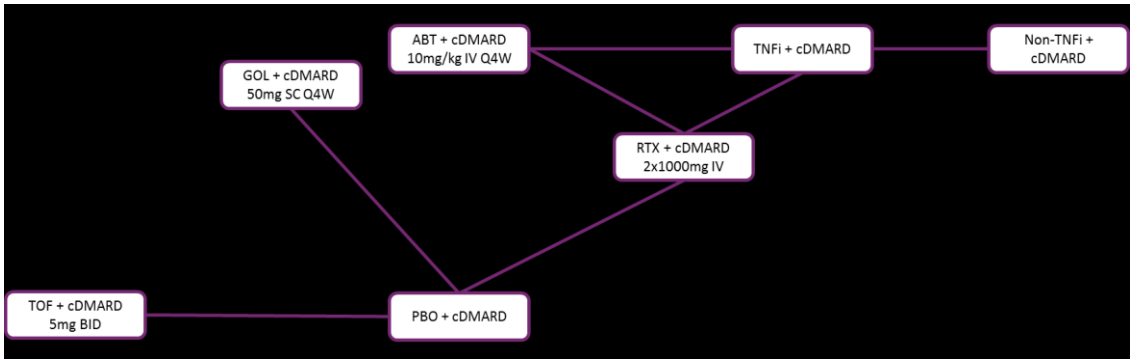
Abbreviations: ABT, abatacept; BID, twice daily; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; IV, intravenous; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; TOF, tofacitinib.

Figure 36: Evidence network for at least a moderate EULAR response



Abbreviations: ABT, abatacept; BID, twice daily; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; IV, intravenous; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; TOF, tofacitinib.

Figure 37: Evidence network for change from baseline HAQ-DI



Abbreviations: ABT, abatacept; BID, twice daily; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; IV, intravenous; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; TOF, tofacitinib.

4.10.2.2 Studies excluded from the analysis

A list of studies which were included in the SR but were excluded from the NMA for the cDMARD-IR population (N=61) and the bDMARD-IR (N=10) population are presented in Table 62 and Table 63, along with rationale for exclusion. For a list of the applied exclusion criteria for each NMA please see Section 4.10.2.

There are more NMAs in RA than in any other field; the conclusions of these NMAs vary, which is predominantly down to the studies included (135). Thorlund et al therefore recommend comparing the final included study list with the list they provide (135). To ensure that the current NMA is as robust and transparent as possible, Pfizer have performed this exercise, and have also compared the list of excluded studies with the lists of included studies in TA375 (22) and the recent Cochrane reviews by Singh et al and Hazlewood et al (134, 181, 182). The results of this comparison and the reasons for exclusion from the current NMA of studies included in these NMAs are provided in Appendix 5.

Based on these additional checking steps, Pfizer have taken all possible measures to ensure the relevant trials were included in the NMA and to provide a rationale for decision makers where the included list of trials differs from recent relevant NMA publications in RA.

Table 62: List of studies included in the SR but excluded from the base case NMA for the cDMARD-IR population (n=61)

Study	Reason for exclusion
14V-MC-JADA Keystone 2015 (183)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported at 20 to 30 weeks
Abe 2006 (184)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
ACQUIRE Genovese 2011 (185)	Study not connected in the HAQ-DI network and data for EULAR responses not reported
ADORE Van Riel 2006 (186); Van Riel 2008 (187)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported at 20 to 30 weeks
AIM Kremer 2006 (188); Russell 2007 (189)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
ALTARA Kennedy 2014 (190)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported at 20 to 30 weeks
AMPLE Weinblatt 2013 (191)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
APPEAL Kim 2012 (192)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported at 20 to 30 weeks
ASSET Conaghan 2013 (193)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
ATTRACT Maini 1999 (194); Lipsky 2000 (195)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported

Study	Reason for exclusion
BREVACTA Kivitz 2014 (196)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
CHARISMA Maini 2006 (197)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
Chen 2009 (198)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
Chen 2016 (199)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
Choy 2012 (200)	Variance data not reported for HAQ-DI
Cohen 2004 (201)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
Combe 2006 (202)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
Durez 2004 (203)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
ENCOURAGE Yamanaka 2016 (204)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
EXXELERATE Smolen 2016 (205)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
FAST4WARD Fleischmann 2009 (206)	Variance data not reported for HAQ-DI
Genovese 2004 (207)	Study evaluated combination of bDMARDs (ETN + ANA) which was not of interest
Gerlag 2010 (208)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
Hobbs 2015 (209)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported at 20 to 30 weeks
Huang 2009 (210)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
Iwahashi 2014 (211)	Study not connected in the HAQ-DI network and data for EULAR responses not reported
Jani 2015 (212)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported at 20 to 30 weeks
Johnsen 2006§ (213)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
Kang 2012 (214)	Variance data not reported for HAQ-DI
Kay 2008 (215)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported at 20 to 30 weeks
Kay 2014 (216)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
Kay 2016 (217)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
Kim 2013 (218)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported

Study	Reason for exclusion
Kremer 2003 (219)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
Lan 2004 (220)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported at 20 to 30 weeks
Li 2013 (221)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported at 20 to 30 weeks
Lim 2012 (222)	Conference abstract only with imited information
MacIsaac 2014 (223)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
Matsumoto 2015 (224)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
MOBILITY-Part A Huizinga 2014 (225)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported at 20 to 30 weeks
MOBILITY-Part B Genovese 2015 (226)	Unlicensed intervention
MONARCH Burmester 2016 (227)	Unlicensed intervention
Moreland 1999 (228); Mathias 2000 (229)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
MUSASHI Ogata 2014 (230)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
MUSICA Kaeley 2016 (231)	Treatment comparison is not of interest
RA-BEAM Taylor 2015 (232)	Variance data not reported for HAQ-DI
RA-BUILD Dougados 2015 (233); Emery 2015 (234)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
Shi 2013 (235)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
SIRROUND-D Bingham 2016 (236)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
SIRROUND-H Taylor 2016 (237)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
Smolen 2014 (238)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported at 20 to 30 weeks
STREAM Nishimoto 2004 (239)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported at 20 to 30 weeks
SUMMACTA Burmester 2014 (240)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
SWEFOT van Vollenhoven, 2009 (173)	Disease duration at study entry was under 3 years (approximately 6 months)

Study	Reason for exclusion
Takeuchi 2013 (241)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported at 20 to 30 weeks
Tanaka 2011 (242)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported at 20 to 30 weeks
Tanaka 2015 (243)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported at 20 to 30 weeks
Tanaka 2016 (244)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported at 20 to 30 weeks
Weinblatt 1999 (245)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
Weinblatt 2015 (246)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
Weinblatt 2015 (247)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
Zhang 2006 (248)	Variance data not reported for HAQ-DI

Abbreviations: EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire-disability index.

Table 63: List of studies included in the SR but excluded from the NMA for the bDMARD-IR population (n=10)

Study	Reason for exclusion
ACT-STAR Weinblatt 2013 (249)	Monotherapy (comparator) treatment arm not randomised
ASCERTAIN Emery 2015 (250)	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported
BIORA Eremeeva 2016 (251)	Treatment comparison is not of interest
EXXELERATE Smolen 2016 (252)	Does not connect to the base case networks
RA-BEACON Genovese 2016 (253)	Treatment comparison is not of interest
REFLECTIONS Williams 2016 (254)	Treatment comparison is not of interest
SIRROUND-T Aletha 2016 (255)	Treatment comparison is not of interest
TARGET Fleischmann 2017 (256)	Treatment comparison is not of interest
NCT01242488 Genovese 2014 (257)	Treatment comparison is not of interest
NCT01147341 Schiff 2014 (258)	Insufficient treatment duration (12 week follow up only)

Abbreviations: EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire-disability index.

4.10.3 *Methods and outcomes of included studies*

4.10.3.1 Rationale for choice of outcome measure and scale

The outcomes included in the indirect comparison are among those which are most commonly used in clinical trials in RA, are directly relevant to patients, and were set out in the scope provided by NICE (Section 1.1):

- EULAR response. Consistent with TA375, where DAS was reported based on both CRP and ESR, the score based on ESR was used, as it is believed that these are interchangeable and DAS is most commonly reported and widely available based on ESR.
- Change from baseline in HAQ-DI. For continuous measures such as HAQ, change from baseline is commonly used to provide data for analyses.

As safety data frequently focus on the most commonly reported AEs, data for specific AEs tend not to be reported consistently across studies, therefore an NMA on safety was not considered to be robust enough for submission.

4.10.3.2 Participants included

The subpopulations included in the indirect comparison were those set out in the NICE scope, i.e. adults with moderate-to-severe, active RA whose disease has responded inadequately to, or who are intolerant of ≥1 DMARD, including cDMARDs or bDMARDs. As the cDMARD-IR and bDMARD-IR populations are considered to be clinically distinct groups of patients, they were analysed in separate networks.

RA is a heterogeneous disease, with the clinical characteristics of patients varying within the UK population; there are consequently a number of possible treatment effect modifiers in patients with RA which could impact the results of the NMA. Furthermore, differences in study design can also act as a source of heterogeneity. An a priori assessment of potential treatment effect modifiers was therefore conducted on the basis of clinical advice and previous work on NMAs in RA (134-136, 181, 182). Table 64 lists the study factors and patient characteristics identified and how these were addressed in the analysis.

Table 64: Potential a priori treatment effect modifiers and how these were handled in the analysis

Potential treatment effect modifier	Rationale	How this was addressed in the analysis
Prior exposure to bDMARDs	Patients with prior exposure to bDMARDS would typically be considered 3rd line, and expected to be clinically distinct from those with no prior exposure to bDMARDS (2nd line).	Separate analyses performed for cDMARD-IR and bDMARD-IR patient populations. Some trials in the cDMARD-IR network allowed for prior use of bDMARDS (OPTION, J-RAPID and RAPID-1). These trials were excluded in a sensitivity analysis. The ORAL Sync, Standard and Scan trials also allowed a proportion of patients to be treated with bDMARDS prior to enrolment, which was addressed via patient level data analysis (Section 4.11)
Concomitant therapy use (mono- vs combination-therapy)	In light of current UK clinical practice, patients receiving monotherapy are expected to be intolerant to MTX, and therefore considered a clinically distinct population from those who are not intolerant to MTX.	Combination and monotherapy treatments treated as separate therapies in the same network, as per recommendations of Thorlund et al, 2013 (135). Note that due to the structure of the network, with monotherapies forming their own arm off a central comparator, it was not considered necessary to perform analyses on separate networks for monotherapy and combi therapy as had also been recommended as a scenario analysis by Thorlund et al.
bDMARD dose (low, standard, high)	Identified in review of previous analyses by Thorlund et al, 2013 (135).	Networks restricted to licensed doses only.
Exposure to treatment	Identified in review of previous analyses by Thorlund et al, 2013 (135).	Time window of analyses included in the NMA restricted to between 20-30 weeks. This 10-week window is similar (although marginally wider) to the 8-week timeframe used by Thorlund et al and Stevenson et al (135, 136). The 10-week window was selected over an 8-week window to allow incorporation of IFX biosimilars into the NMA, rather than performing further scenario analyses for their inclusion.
Whether prior bDMARD was an anti-TNF	Identified in review of previous analyses by Thorlund et al, 2013 (135).	Heterogeneity assessed (see Section 4.10.5.6). No significant variation identified.
Proportion of RhF+ patients	Evidence of a dose-dependent link between the level of RF and radiographic progression has been published (259).	Heterogeneity assessed (see Section 4.10.5.6). No outliers identified.
Health Assessment Questionnaire (HAQ) baseline score	Identified in review of previous analyses by Thorlund et al, 2013 (135).	Heterogeneity assessed (see Section 4.10.5.6). All trials have average HAQ between 1 and 2. No outliers identified.
Age	Identified in review of previous analyses by Thorlund et al, 2013 (135).	Heterogeneity assessed (see Section 4.10.5.6). No significant variation identified.

Potential treatment effect modifier	Rationale	How this was addressed in the analysis
Sex	Known difference between sexes in prevalence of RA (260).	Heterogeneity assessed (see Section 4.10.5.6 and Appendix 7). No significant variation identified.
Anti-CCP	Common serological marker for RA, with some evidence for impacting treatment outcome (261)	Heterogeneity assessed (see Section 4.10.5.6 and Appendix 7). No significant variation identified.
Baseline DAS (ESR) and DAS (CRP)	Identified in review of previous analyses by Thorlund et al, 2013 (135).	Heterogeneity assessed (see Section 4.10.5.6 and Appendix 7). No significant variation identified.
Year of publication	Older studies may be less likely to reflect current treatment practice and diagnostic criteria.	Some heterogeneity exists between publications ranging from 2004-2016. The diagnostic criteria for RA were updated in 2010 (64). It may therefore be expected that publications from 2012 onwards represent a more homogenous patient population. However, it was not considered feasible to exclude trials before 2012 without significantly impacting the structure of the network and severely limiting the ability of the analysis to inform the decision problem. No scenario analysis was therefore performed to explore the impact of publication date.
Mean baseline disease duration	Identified in review of previous analyses by Thorlund et al, 2013 (135).	Some heterogeneity identified between studies in these characteristics. Overall, the CERTAIN and SURPRISE studies repeatedly appeared as outliers with lower levels in these characteristics, suggesting they might have been patients with disease that is at the milder end of the spectrum of established RA. On the basis of this overall assessment, a scenario analysis was performed that excluded CERTAIN and SURPRISE.
Baseline ESR	Identified in review of previous analyses by Thorlund et al, 2013 (135).	
Baseline C reactive protein	Identified in review of previous analyses by Thorlund et al, 2013 (135).	
Baseline swollen joint count.	Identified in review of previous analyses by Thorlund et al, 2013 (135).	
Baseline tender joint count.	Identified in review of previous analyses by Thorlund et al, 2013 (135).	
Asian population	Potential for different responses to treatment compared with UK population.	Assessment of the studies performed in Asian populations shows that these studies also use a lower dose of MTX. A scenario analysis is therefore performed that excludes these studies, which will also exclude those studies with lower doses of MTX used in the combination treatments (J-RAPID, JESMR, Li 2015, Takeuchi 2015, SURPRISE, GO-FORTH).
MTX dose	Studies that differ in the dose of MTX used in UK clinical practice in the combination treatment may have restricted generalisability to the UK population.	
Early escape design and crossover	Study designs that limit exposure to treatments of patients who are not deemed to receive benefit can confound efficacy endpoints measured after early escape or if treatment advancement/cross-over is implemented.	A number of studies allowed patients early escape based on interim assessment of response. There was variation in the time at which early escape occurred in relation to 6 months and the analytical approaches used to address any confounding from subsequent crossover. Pfizer have performed patient level data analyses on the tofacitinib trial data to provide multiple estimates of treatment effect for tofacitinib that are

Potential treatment effect modifier	Rationale	How this was addressed in the analysis
		used to explore uncertainty impacting on comparative efficacy in the ORAL studies. See Section 4.8.1 for further details.

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug; HAQ, Health Assessment Questionnaire; MTX, methotrexate; RA, rheumatoid arthritis; RhF, rheumatoid factor; TNF, tumour necrosis factor.

4.10.3.3 Assessment of heterogeneity in trials included in the NMA

For the cDMARD-IR population graphical representations of the baseline characteristics were plotted and used in the assessment of heterogeneity. Graphs for those characteristics that were not considered to display significant heterogeneity can be found in Appendix 7. The graphs for those characteristics that were considered to display heterogeneity can be found in Figure 38–Figure 42. A summary of the baseline characteristics for the bDMARD-IR trials is provided in Table 65 (note that for the ORAL trials these are taken from the PLD rather than trial publications).

cDMARD-IR

Given the complex aetiology and pathology of RA, it is challenging to identify single clinical characteristics that may act as potential treatment effect modifiers by themselves in the NMA. However, in the overview of heterogeneity in the cDMARD-IR NMA a pattern emerged of particular studies that displayed a cluster of characteristics that were towards the lower end of the ranges found in the network. Taken together, this analysis indicates that the CERTAIN and SURPRISE studies tend to have patients who have a shorter disease duration (4.5–4.7 years and 3.6–3.8 years, respectively), lower baseline ESR (31–32 mm/hr and 41–45 mm/hr, respectively) and baseline CRP (6–8 mg/L and 12–18 mg/L, respectively), and fewer tender and swollen joint counts (3 and 8–10, respectively). Based on this analysis, this suggests that the patients included in the CERTAIN and SURPRISE trials may have had, on average, less severe disease than seen in other trials in the network. Consequently, the impact of these trials on the network has been explored in a scenario analysis in which these trials are excluded. Whilst the GO-FORWARD trial also had a mean disease duration and mean baseline CRP that appeared to be towards the lower end of the range seen in the network, it was decided not to exclude the trial as part of the scenario analysis as other baseline characteristics did not appear to signal this trial as a particular outlier overall. The assessment of MTX dose across the studies identified six studies in which lower doses of MTX were used (J-RAPID, JESMR, Li 2015, Takeuchi 2015, SURPRISE and GO-FORTH). A cross assessment of the studies in the NMA performed on Asian populations showed that all of the studies with low MTX doses were included in the set of Asian studies. Therefore, a single scenario analysis was performed to exclude the Asian populations, which also therefore serves to exclude those studies with low doses of MTX.

bDMARD-IR

As this network was much smaller than the cDMARD-IR there was less scope for heterogeneity. Trials were generally well-matched across the majority of baseline

characteristics. Disease duration in NTR1605 was shorter than in other trials, at 5.6–7.6 years compared with 8.7–12.6 years. DAS28 and HAQ-DI were also slightly lower in NTR1605 (4.7–4.9 and 1.4–1.5, respectively) compared with other trials (5.25–6.9 and 1.5–1.9, respectively), although swollen and tender joint counts were similar. In ROC HAQ-DI (5.0–5.5 vs 5.25–6.9) and swollen (4–5 vs 13–23.4) and tender joint counts (6–8 vs 26–33.9) were lower than in other trials. As the bDMARD-IR network is already small and exclusion of these trials would remove the comparisons against TNF inhibitors and non-TNF inhibitors (as groups) it was decided not to perform a scenario analysis excluding these trials.

Figure 38: Baseline mean disease duration in trials in the EULAR cDMARD-IR network

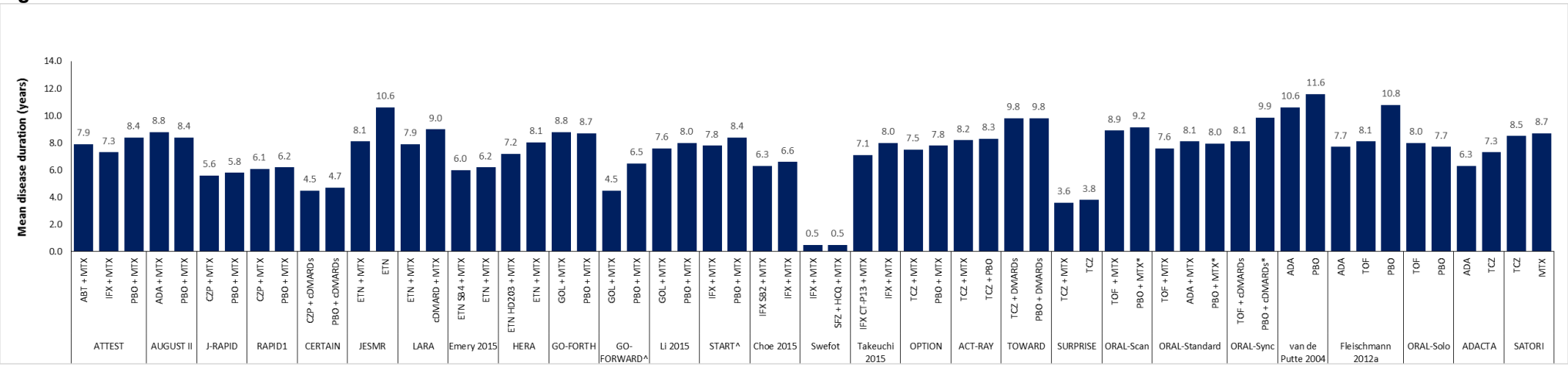


Figure 39: Baseline ESR in trials in the EULAR cDMARD-IR network

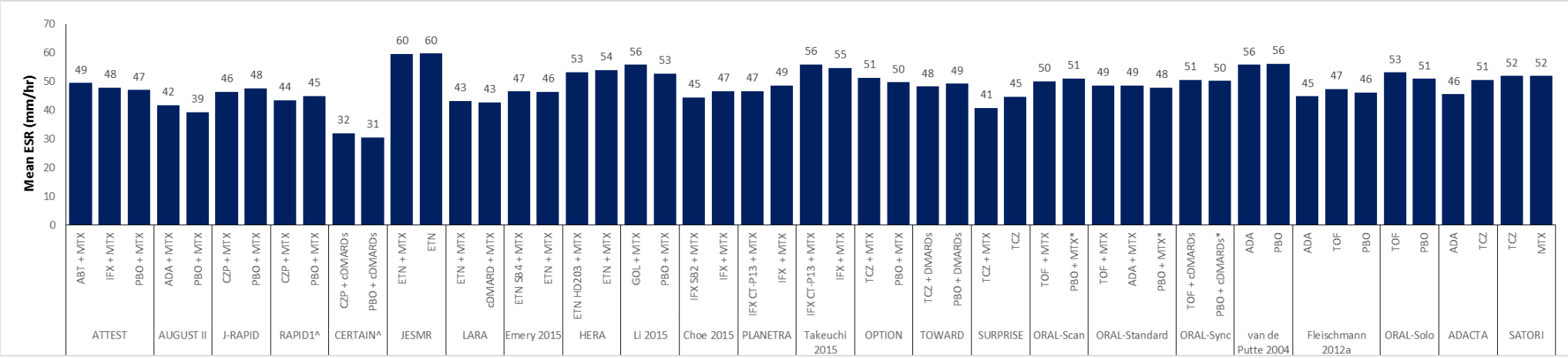


Figure 40: Baseline CRP in trials in the EULAR cDMARD-IR network

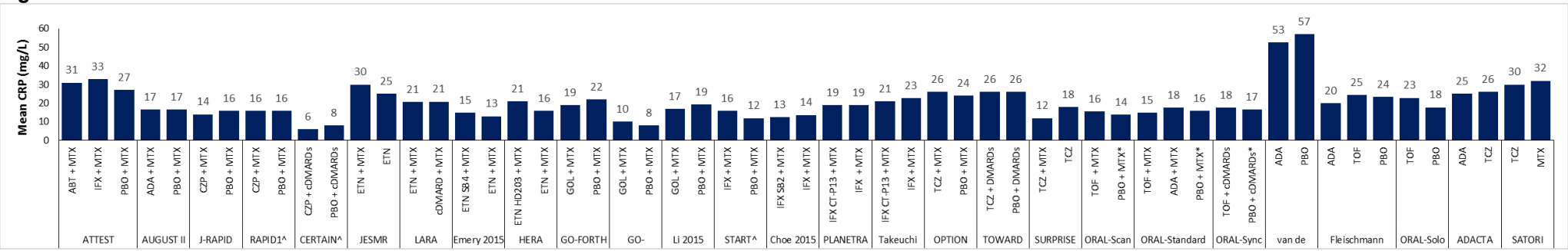


Figure 41: Baseline swollen joint count (SJC) in trials in the EULAR cDMARD-IR network

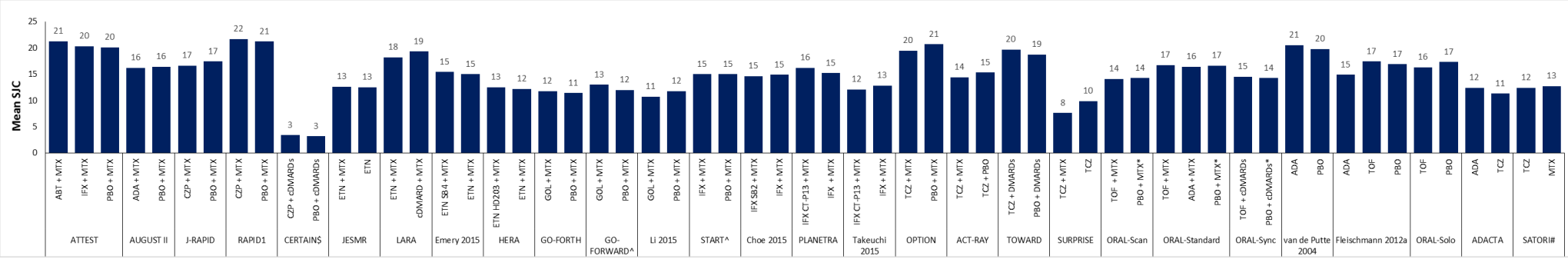


Figure 42: Baseline tender joint count (TJC) in trials in the EULAR cDMARD-IR network

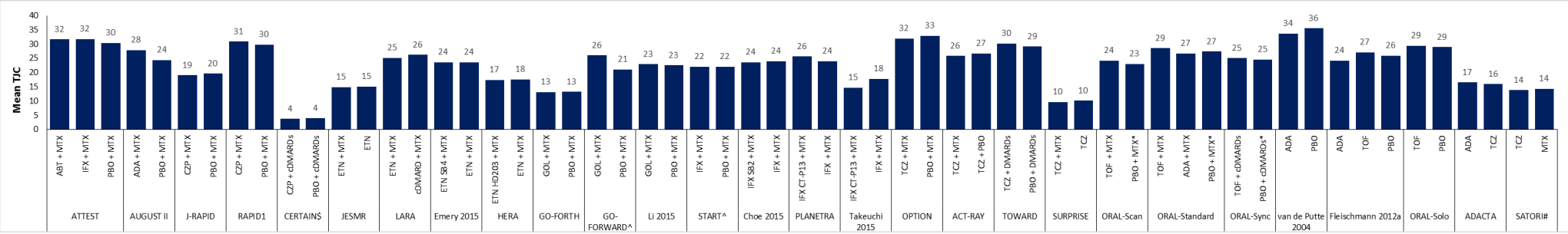


Figure 43: Mean concomitant MTX dose in trials in the EULAR cDMARD-IR network

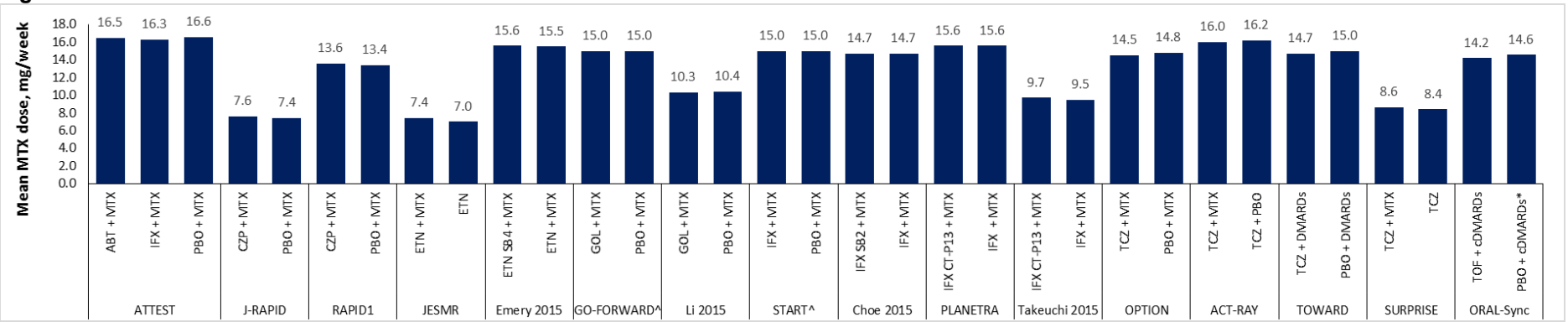


Table 65: Baseline characteristics in trials in the bDMARD-IR NMA for EULAR

Study	Treatment	Disease duration (y)	Mean age (y)	Females (%)	RF+ (%)	Anti-CCP+ (%)	ESR	CRP (mg/dL)	DAS28	HAQ-DI	SJC	TJC	Prior cDMARD (n)	Prior bDMARDs (n)
ATTAIN	ABT	12.2	53.4	77.1	189 (73.3%)	NR	NR	4.6 mg/dlL	6.5 (0.9)	1.8	22.3	31.2	NR	NR
	PBO	11.4	52.7	79.7	97 (72.9%)	NR	NR	4 mg/dL	6.5 (0.8)	1.8	22	32.8	NR	NR
Combe 2012	ETN	NR	NR	NR	NR	NR	NR	NR	5.85 (0.8)	NR	NR	NR	NR	NR
	RTX	NR	NR	NR	NR	NR	NR	NR	5.25 (0.7)	NR	NR	NR	NR	NR
GO-AFTER	PBO	9·8	54	85	NR	112 (72%)	32	10 mg/dL	6.3 (IQR: 5.5–7.1)	1.8	14	26	NR	NR
	GOL 50 mg	9.6	55	74	NR	107 (72%)	27.5	8 mg/dL	6.3 (IQR: 5.6–7.2)	1.6	14	27	NR	NR
	GOL 100 mg	8.7	55	80	NR	107 (73%)	30	8 mg/dL	6.1 (IQR: 5.4–7.1)	1.5	13	26	NR	NR
NTR1605	ABT	6.6	56.2	88.1	56.40%	NR	NR	NR	4.7 (1.5)	1.5 (0.6)	NR	NR	2	NR
	RTX	7.6	57.1	63.6	80.00%	NR	NR	NR	4.9 (1.2)	1.4 (0.7)	NR	NR	3	NR
	Alternative TNF	5.6	55.8	74	62.50%	NR	NR	NR	4.9 (1.1)	1.4 (0.6)	NR	NR	2	NR
ORAL-Step	PBO+MTX	11.3	54.4	80.3	86 (65.6%)	97 (75.8%)	46.7	159.1 nmol/dL	6.4 (1.1)/5.4 (1)	1.6	17.2	28.2	NR	1.5 (0.7)
	TOF 5 mg	13	55.4	85	80 (60.6%)	89 (68.5%)	47.8	183.8 nmol/L	6.5 (1.1)/5.4 (1)	1.6	16.2	28.4	NR	1.5 (0.7)
	TOF 10 mg	12.6	55.1	86.6	83 (61.9%)	90 (69.8%)	45.2	149.5 nmol/L	6.4 (0.9)/5.3 (0.9)	1.5	16.6	27.6	NR	1.4 (0.7)
RADIATE	TOC 8 mg	12.6	53.9	84	79%	NR	49.1	2.8 mg/dL	6.79 (0.93)	1.7	18.9	31.7	1.9	1.9

Study	Treatment	Disease duration (y)	Mean age (y)	Females (%)	RF+ (%)	Anti-CCP+ (%)	ESR	CRP (mg/dL)	DAS28	HAQ-DI	SJC	TJC	Prior cDMARD (n)	Prior bDMARDs (n)
	TOC 4 mg	11	50.9	81	73%	NR	51.3	3.11 mg/dL	6.78 (0.97)	1.7	19.5	31.3	2	2
	PBO	11.4	53.4	79	75%	NR	54.6	3.71 mg/dL	6.8 (1.06)	1.7	18.9	30.4	2.1	2.1
REFLEX	PBO+MTX	11.7	52.8	81	165 (79%)	NR	48.4	3.8 mg/dL	6.8 (1.0)	1.9	22.9	33	2.4	1.5
	RTX+MTX	12.1	52.2	81	242 (79%)	NR	48	3.7 mg/dL	6.9 (1.0)	1.9	23.4	33.9	2.6	1.5
ROC	Non-TNF	10	58.2	82	121 (85%)	115 (83%)	27	7.7 mg/L	5.2 (1.2)/4.8 (1.1)	1.3	5	8	2	NR
	TNF	11	55.9	84	111 (77%)	112 (80%)	22	8.8 mg/L	5.0 (1.1)/4.7 (0.9)	1.3	4	6	2	NR

Abbreviations: bDMARD, biologic disease modifying anti-rheumatic drug; CCP, cyclic citrullinated peptide; cDMARD, conventional disease modifying anti-rheumatic drug; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; SJC, swollen joint count; TJC, tender joint count.

4.10.3.4 Detailed study information

Appendix 4 provides tables of methods, patient baseline characteristics (Table 204 and Table 205), and outcomes and results for each trial in the cDMARD-IR and bDMARD-IR NMA (Table 206–Table 209).

4.10.4 *Risk of bias*

A quality assessment of each trial in the cDMARD-IR and bDMARD-IR NMA was completed according to NICE guidance and is provided in Table 210 and Table 211, respectively (Appendix 4). Overall, the majority of trials in both NMAs did not clearly report how randomisation and allocation were conducted; however, this is likely due to the fact that the majority of studies were assessed based on publications rather than CSRs. It is therefore not possible to determine what impact this may have upon the risk of bias.

For other assessments of quality in the cDMARD-IR base case:

- Baseline characteristics were similar between groups in all trials except one (Van de Putte 2004 (172))
- Three studies were not blinded (SURPRISE (169), LARA (157), and JESMR (153))
- There were unexpected imbalances in dropouts in 5 studies (JESMR (153), ORAL-Solo (125), RAPID 2 (166), SATORI (167), and Van de Putte 2004 (172))
- Outcome measures were used but not reported in 1 trial (AUGUST II (142))
- An ITT analysis was used in all studies with the exception of ARMADA (140), in which the analysis type was unclear

Studies with >1 low quality indicators are therefore Van de Putte 2004 (172), and JESMR (153). JESMR was excluded in the sensitivity analysis which excluded Asian trials (along with other Asian trials). An additional sensitivity analysis removing trials with >1 low quality indicators was not deemed necessary. This is because the removal of Van de Putte 2004 removes placebo and tofacitinib monotherapy as comparators from the networks as ORAL Solo and Fleishmann 2012a trials are connected into the networks via this trial. Furthermore, the removal of these trials does not influence any of the remaining treatment comparisons of the networks. In addition, the removal of the JESMR trial also removes etanercept monotherapy form the network and the removal of this trial does not influence any of the remaining treatment comparisons of the networks.

For other assessments of quality in the bDMARD-IR base case:

- Baseline characteristics were similar between groups in all trials
- Two studies were not blinded (ROC (178) and Combe 2012 (179))
- The reporting of dropouts was unclear in one study (Combe 2012 (179))
- Outcome measures were used but not reported in one study (Manders 2015 (180), although these may have been published separately)

Only one trial therefore has >1 indicator of low quality (Combe 2012 (179)). However, as one of these indicators is due to unclear reporting of dropouts this may not represent a risk of bias.

Summary of sensitivity analyses performed

In addition to the primary analyses for EULAR responses, sensitivity analyses were performed to address some of the potential confounding issues set out in Table 64. Meta-regression was considered however, there were insufficient data in the bDMARD-IR network (<10 trials) and the geometries in the cDMARD-IR network meant that a meta-regression would potentially adjust for factors across the trials which include a placebo + cDMARD arm. Due to the inconsistent reporting of trial baseline characteristics and the relatively few trials which included a placebo + cDMARD arm it was deemed that there would be insufficient statistical power to perform a meta-regression analysis.

1. The exclusion of trials conducted in exclusively Asian populations from the networks (GO-FORTH, HERA, JESMR, J-RAPID, Li 2015, SATORI, and SURPRISE). These trials may not be reflective of the UK population with RA and patients also received a lower dose of MTX than that used in other trials (10-25 mg/week).

2. The exclusion of the OPTION, J-RAPID and RAPID-1 trials from the networks. These trials allowed for prior bDMARD exposure (and a proportion of patients in each trial had prior bDMARD exposure) and therefore this scenario is presented to explore the influence of prior bDMARD exposure on the results of the network.

3. The exclusion of the SUPRISE and CERTAIN trials from the networks. These two trials included populations that demonstrated a number of baseline characteristics that were towards the lower end of the range in the evidence network, which were indicative of less severe disease (see Section 4.10.3.3), and therefore were excluded from the network in a scenario analysis.

4. Inclusion of the SWEFOT trial which was included in TA375 and provided a link to etanercept to the rest of the network via intensified cDMARDs. As outlined in Section 4.10.2.1, a scenario is presented in this submission where SWEFOT has been incorporated into the network to provide a similar link between etanercept and the rest of the network. This analysis was only feasible in the EULAR good response network because the SWEFOT trial reported 6-month good response data only.

5. The exploration of an alternative modelling approach of the EULAR responses using the multinomial probit model. The base case analyses were conducted using a binomial logit approach for the reasons discussed in Section 4.10.5; however, TA375 used a multinomial probit model. A sensitivity analysis using this model was therefore conducted.

6. Alternative estimates for the clinical efficacy of tofacitinib are presented that utilises a different method for response imputation and the generation of relative efficacy from the trials. This alternative analysis is used to explore the potential impact of heterogeneity in the relative effectiveness of tofacitinib vs other treatments stemming

from variation in the evidence base in the time of early escape and imputation methods (see Section 4.11)

Evidence networks for these sensitivity analyses are presented in Appendix 3.

4.10.5 *Methods of analysis and presentation of results*

4.10.5.1 Methodology

Dichotomous outcomes (EULAR responses)

The main efficacy outcome of interest for the current analysis was the proportion of patients achieving EULAR responses ('no response', 'good', 'moderate' and 'at least a moderate response' at 6 months). In the base-case analysis, the dichotomous outcome data were fitted to a binomial likelihood, logit link model to estimate treatment effects for each EULAR response category separately. In a sensitivity analysis an alternative approach was explored to fit all the EULAR response data to a single multinomial probit model. A latent continuous variable z was used to model the cut-off between the EULAR response categories.

Where percentages of patients achieving an outcome were reported, the number of patients were calculated. Similarly, where feasible, the number of patients achieving responses were calculated (i.e. if the number of patients reporting at least a moderate response were reported-then the number of patients with no response could be calculated using the total number of patients analysed).

For this outcome we assume that all patients who report an outcome do so by a specific follow up time and that further follow up would make no difference to the relative treatment effect. The current analysis includes data at 20-30 weeks follow up to be consistent with the decision problem (see Section 4.10.2 for further details). A summary of potential sources of heterogeneity and how they were dealt with in the NMA is provided in Section 4.10.3.2.

Network meta-analysis model: Binomial logit model

The network binomial logit meta-analysis model is constructed as follows: assuming an evidence network with I studies (*i*=1,…..*I*), J interventions (*j*=1,…..*J*) and a_i treatments in each study; the likelihood of the data is:

$$r_{ik} \sim binomial(p_{ik}, n_{ik}) \qquad \textbf{(1)}$$

where r_{ik}, p_{ik} and n_{ik} denote the number of events, probability of the event, and number randomised in arm *k* of study *i*, respectively, and $k \leq a_i$.

A logit link function is used to link the probability of an event in a given arm of a study, $p_{i,k}$, the study specific effect (i.e. the intercept), μ_i and the study level, intervention specific effect size δ_{ijk}:

$$logit(p_{ik}) = \mu_i + \delta_{ijk} \qquad \textbf{(2)}$$

Study level effect sizes are considered exchangeable across comparisons, i.e.:

$$\delta_{ijk} \sim N(d_{jk}, \sigma^2) \quad \textbf{(3)}$$

where d_{jk} is the NMA estimate of the effect size for intervention j relative to intervention k. In the consistency model:

$$d_{jk} = d_{tk} - d_{tj} \quad \textbf{(4)}$$

where t denotes another arbitrary intervention in the model. For multi-arm trials, as there is more than one study level effect size, correlations are incorporated using a multi-arm trial correction and the δ_{ijk} are assumed to come from a multivariate normal distribution with co-variances of $\frac{\sigma^2}{2}$. In the random-effect model, study level effect sizes are considered exchangeable across comparisons and the trial-specific treatment effects come from a common distribution (as per equation 7). The fixed-effect model is a special case of the model described in equation 3, with $\sigma^2 = 0$. This assumes homogeneity of the underlying true treatment effects.

Vague priors are used for the study specific treatment effect μ_i and treatment effect sizes relative to treatment 1 (d_{1k}) in the form of a normal distribution with a mean of 1 and variance of 100^2 as recommended by Dias et al., 2011 (262). Random-effect models will use the vague priors in the form of uniformly distributed prior between 0 and 5 for the between trial SD (σ) as recommended by Dias et al., 2011 (262).

Network meta-analysis model: Multinomial probit model

The network multinomial probit model is constructed as follows: trials report r_{ijk}, the number of patients in arm *k* of trial *i* belonging to different, mutually exclusive categories j=1,2,…J. The responses for each arm of each trial *i* in category *j* will follow a multinomial distribution:

$$r_{ijk} \sim multinomial(p_{ikj}, n_{ik}) \quad \textbf{(5)}$$

$$\text{where} \quad \sum_{j=1}^{J} p_{ikj} = 1$$

The parameters of interest are the probabilities, p_{ikj} that a patient in arm *k* of trial *i* belongs to category *j*. The model is set-up by assuming that there is an underlying continuous variable z_j that corresponds to the different cut-offs at which an individual moves form one category to the next. The probit link function is used to map p_{ikj} onto to the study specific effect μ_i and the study level, intervention specific effect size $\delta_{i,bk}$ as follows:

$$p_{ikj} = \Phi(\mu_{ij} + z_j + \delta_{i,bk} I_{k \neq 1}) \quad \textbf{(6)}$$

In our model we assume that z_j for each of the J-1 categories is fixed across all trials and use a vague uniform prior U(0,5) for z_aux_j along with the constraint $z_j = z_{j-1} + z\_aux_j$.

Continuous outcomes (HAQ-DI)

An additional efficacy outcome of interest included HAQ-DI in terms of change in score from baseline to the 24-week assessment (20-30 weeks). For modelling the change in HAQ-DI from baseline it was assumed that the mean changes in HAQ-DI observed in trials followed a normal distribution and treatment differences were modelled using a hierarchical Bayesian regression model for each outcome. Since changes of a continuous measure are unconstrained on the real line (i.e. they can be positive or negative and theoretically there is no limit on magnitude) the identity link function was used. The normal identify link model was the approach used to model the continuous data.

Continuous outcomes: computing change from baseline scores

Change from baseline scores of continuous outcomes (HAQ-DI) were computed from mean baseline and endpoint scores where necessary. The methods proposed are well established and are outlined in the Cochrane Handbook (263) and NICE Technical Support Documents (TSD) (262). However, in instances where median scores were reported we made the following assumptions to allow for the inclusion of the studies reporting median scores into the network:

- The distribution of scores (mean change from baseline [CFB], or baseline and endpoint scores) are normally distributed and the median of the scores is equivalent to the mean.
- The interquartile range (IQR) of the distributions is assumed to be 1.35 times the standard deviation (263).

Network meta-analysis model: Arm-level data

The most common method for continuous outcomes which are measured at baseline and at a pre-specified follow-up point is to base the analysis on the mean CFB for each patient and a measure of uncertainty.

A normal distribution for the mean CFB in arm k in trial *i*, y_{ik}^{Δ} with change variance V_{ik}^{Δ} is assumed, such that:

$$y_{ik}^{\Delta} \sim N(\theta_{ik}, V_{ik}^{\Delta}) \quad \textbf{(7)}$$

The parameter of interest is the mean θ_{ik} which is unconstrained on the real line. An identity link is used and therefore the linear predictor is such that:

$$\theta_{ik} = \mu_i + \delta_{ijk} \quad \textbf{(8)}$$

where δ_{ijk} is the intervention specific effect size. Study level effect sizes are considered exchangeable across comparisons, i.e.:

$$\delta_{ijk} \sim N(d_{jk}, \sigma^2) \quad \textbf{(9)}$$

where d_{jk} is the NMA estimate of the effect size for intervention j relative to intervention k. In the consistency model:

$$d_{jk} = d_{tk} - d_{tj} \quad \textbf{(10)}$$

Where t denotes another arbitrary intervention in the model. In the random-effect model, study level effect sizes are considered exchangeable across comparisons and the trial-specific treatment effects come from a common distribution (as per equation 3). The fixed-effect (FE) model is a special case of the model described, with $\sigma^2 = 0$. This assumes homogeneity of the underlying true treatment effects.

Vague priors are used for the treatment effect sizes relative to treatment 1 (d_{1k}) in the form of a normal distribution with a mean of 1 and variance of 100^2 as recommended by Dias et al., 2011 (25). Random-effect models (RE) employed the vague priors in the form of a uniformly distributed prior between 0 and 5 for the SD as recommended by Dias et al., 2011 (25).

Measures of model complexity and fit

Model fit was measured by assessment of the posterior residual deviance and between-study heterogeneity (for RE models only). A model with adequate fit would be expected to have a residual deviance roughly equal to the number of unconstrained data points. Model comparisons (FE vs RE, adjusted vs unadjusted) were based on comparing the above, in addition to the model results and the deviance information criterion (DIC) (25). Note that residual deviance is an absolute measure and DIC is a relative measure. In general a model is favoured if it has a lower DIC (3-5 points are considered important), a posterior residual deviance close to the number of data points, and a more preferable leverage plot with fewer outlying observations (25).

4.10.5.2 Choice of model

Fixed- vs random-effects models

In FE meta-analysis, we assume that treatment effects can be estimated directly from the trial data, while in random-effects meta-analysis we assume that the treatment effects are drawn from a common distribution with a variance parameter equal to the between-study variance, or heterogeneity.

A RE model is more complex than a FE model as it requires more parameters, and therefore the added flexibility means it will usually provide a better fit to the data based on the average residual deviance. However, as with all statistical modelling, it is important to find a trade-off between improved fit and added complexity in order to make meaningful inferences. Therefore, a more complex model should only be preferred if it provides an improvement in model fit substantial enough to justify its added complexity. If the RE model is chosen, this may be an indication of the presence of effect modifiers resulting in heterogeneity in the network. Model fit statistics used in the choice of model for the cDMARD-IR and bDMARD-IR NMA are presented in Table 66 and Table 67, respectively.

Table 66: Model fit statistics for the cDMARD-IR NMA (base case, binomial logit)

	Number of data points	DIC	Posterior residual deviance	Average residual deviance	Standard deviation (95% CI)
EULAR moderate					
Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Random effects		[redacted]	[redacted]	[redacted]	[redacted]
EULAR good					
Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Random effects		[redacted]	[redacted]	[redacted]	[redacted]
EULAR at least moderate					
Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Random effects		[redacted]	[redacted]	[redacted]	[redacted]
HAQ					
Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Random effects		[redacted]	[redacted]	[redacted]	[redacted]

In general, a model is favoured if it has a lower DIC (3-5 points are considered important), a posterior residual deviance close to the number of data points, and a more preferable leverage plot with fewer outlying observations. Grey highlighting indicates the model ultimately used in each analysis.
Abbreviations: DIC, deviance information criterion.

Table 67: Model fit statistics for the bDMARD-IR NMA (base case, multinomial probit)

	Number of data points	DIC	Posterior residual deviance	Average residual deviance	Standard deviation (95% CI)
EULAR probit model					
Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Random effects		[redacted]	[redacted]	[redacted]	[redacted]
HAQ					
Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Random effects		[redacted]	[redacted]	[redacted]	[redacted]

In general, a model is favoured if it has a lower DIC (3-5 points are considered important), a posterior residual deviance close to the number of data points, and a more preferable leverage plot with fewer outlying observations. Grey highlighting indicates the model ultimately used in each analysis.
Abbreviations: DIC, deviance information criterion.

In the cDMARD IR population a fixed effects (FE) model was used for EULAR other than for “at least a moderate response” which used the random effects (RE) model. The evidence network was larger for the “at least a moderate response” network compared with the “moderate” and the “good” networks. The RE model was consequently better fitting for this larger network compared with the FE model.

The RE model was also used for HAQ-DI in the cDMARD-IR population. All sensitivity analyses for EULAR in the cDMARD-IR population were performed using the same choice of base-case model (i.e. FE for the good response and the moderate response and the RE model for at least a moderate response).

For EULAR in the bDMARD-IR population an FE model was used for all analyses. While the posterior residual deviance values were large for both the RE and FE model for EULAR, the DIC was lower for the FE model. As a FE model assumes that treatment effects are drawn from a common distribution with a variance parameter equal to zero, using such models may over-estimate the significance of any differences between treatments. While the FE model was a better fit and therefore more appropriate than the RE model in most analyses, the implications of using such a model must be considered when interpreting the results.

Network meta-analysis model: Binomial probit versus the multinomial probit

The EULAR response outcomes are categorical data and therefore both the binomial logit and multinomial probit models are relevant approaches to modelling which were explored. A comparison of the binomial logit and multinomial probit modelling approaches considered in this analysis is provided in Table 68.

Table 68: Top-line comparison of the advantages and disadvantages of the two modelling approaches for the EULAR outcomes

Binomial logit	Multinomial probit
Advantages	
• Fewer assumptions than alternatives. • Easier to fit RE models. • RCTs in RA likely highly heterogeneous so random effects may be justified	• Recommended for ordered categorical outcomes by NICE TSD DSU and already used by TA375. • Accounts for competing risks and natural ordering of EULAR response categories. • Combines data across outcome networks (‘moderate’/’good’ contributes to ‘at least a moderate’.
Disadvantages	
• Ignores correlation between outcomes and their natural ordering. Treatment with high probability of ‘good’ response likely to have lower probability of ‘no response’. • Assumes ‘at least a moderate’ probability is independent of ’moderate‘ and ’good‘ probabilities, so does not use evidence efficiently.	• May need weakly informative prior to attain convergence for RE models • Shared effect across outcomes may not hold

Abbreviations: EULAR, European League Against Rheumatism; RE, random effects.

Summary of choice of network meta-analysis models

The models used for each analysis were:

- cDMARD-IR
    - EULAR – binomial logit (FE for “moderate” and “good” EULAR response and RE for “at least a moderate” EULAR) as it provided better convergence than the multinomial probit approach. Many trials did not report all categorical responses so there was limited evidence to fit the probit model that assumes shared effect across categories.
        - A multinomial probit approach was considered for “moderate” and “good” EULAR response as this was the approach used in TA375; however, such a model may require informative priors which may shape the results. The use of such priors has been criticised in past submissions to NICE and, as the binomial model provided better convergence, a binomial logit approach was deemed more appropriate
    - A scenario analysis using the multinomial probit model was also considered (Appendix 8)
    - HAQ – As this is a continuous outcome a normal likelihood model was used (RE)
- bDMARD-IR
    - EULAR – multinomial probit (FE) as this network had fewer trials than the cDMARD-IR network (8 vs 35) and this model provided better convergence than the binomial logit approach
    - A scenario analysis using the binomial logit model was not considered as there were insufficient data to inform the comparisons and key comparators such as tocilizumab and golimumab could not be connected to the network
    - HAQ – As this is a continuous outcome a normal likelihood model was used (FE)

4.10.5.3 WinBUGS code

WinBUGS code for the NMA is supplied in Appendix 6.

4.10.5.4 Results

Please note that, while mono- and combination-therapy were considered within the same network, comparisons between mono- and combination-therapy are unlikely to be credible due to the evidence network geometry. For example, tofacitinib monotherapy is indirectly linked to its closest combination therapy treatment in the network via 4 trials; the estimates will be therefore be associated with very wide confidence intervals due to the uncertainty from indirect links via a long chain of trials. It should be noted that, while

mono- and combination-therapy were analyses together, the results for each would be the same if analysed separately.

For the monotherapy comparisons, the ORAL Strategy trial (which includes tofacitinib monotherapy) is due to report the final data set soon; Pfizer will therefore be able to provide further comparative analysis at the end of April/early May, which will allow a more reliable direct comparison of both head-to-head trial data and an updated NMA network.

Please note that etanercept is also linked into the cDMARD-IR networks via a long chain of trials and is not in the main monotherapy section of the network. Comparisons against etanercept must therefore be considered with this in mind.

cDMARD-IR: EULAR response (binomial)

A fixed effects model was used for EULAR moderate and EULAR good responses, with a random effects model for at least a moderate EULAR response. A summary of the results is presented for intervention vs placebo (comparator) in Table 69 and for tofacitinib (intervention) vs comparators in Table 70:

Response vs placebo

[redacted]

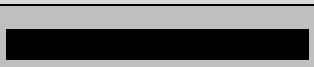
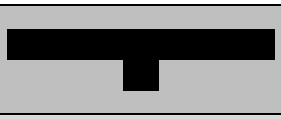
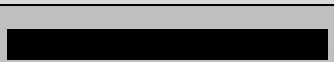
Response vs comparators

- **Moderate EULAR, combination therapy:**
  [redacted]
- **Moderate EULAR, monotherapy:**
  [redacted]
- **Good EULAR, combination therapy:**
  [redacted]

[redacted]

- **Good EULAR, monotherapy:**
  [redacted]
- **At least moderate EULAR, combination therapy:**
  [redacted]**At least moderate EULAR, monotherapy**
  [redacted]

Table 69: Summary of NMA results for all treatments vs placebo or placebo + cDMARD: cDMARD-IR, per EULAR response

Intervention	Comparator: placebo		
	OR (95% CrI) intervention + cDMARD vs comparator		
	Moderate EULAR response	Good EULAR response	At least moderate EULAR response
ABT + cDMARD			
ADA + cDMARD			
CTZ 200mg Q2W SC + cDMARD			
ETN + cDMARD			
ETN HD203 25 mg BIW + cDMARD			
ETN SB4 50mg QW SC + cDMARD			
GOL + cDMARD			
IFX + cDMARD			
IFX CT-P13 3mg/kg Q8W + cDMARD			
IFX SB2 + cDMARD			
TOC + cDMARD			
TOF 5mg BID + cDMARD			
	OR (95% CrI) intervention vs comparator		
ADA			
TOC			
ETN 25mg SC BIW			
TOF 5 mg BID			

An OR >1 indicates that the intervention is favoured over placebo or placebo+cDMARD (comparator), respectively. Cells highlighted in grey indicate a significant result.
Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; LEF, leflunomide; MTX, methotrexate; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; SFZ, sulfasalazine; TOC, tocilizumab; TOF, tofacitinib.

Table 70: Summary of NMA results for tofacitinib and tofacitinib + cDMARD: cDMARD-IR, by EULAR response

Comparator	Intervention: Tofacitinib		
	OR (95% CrI) intervention + cDMARD vs comparator		
	Moderate EULAR response	Good EULAR response	At least moderate EULAR response
ABT + cDMARD	[redacted]	[redacted]	[redacted]
ADA + cDMARD	[redacted]	[redacted]	[redacted]
CTZ 200mg Q2W SC + cDMARD	[redacted]	[redacted]	[redacted]
ETN + cDMARD	[redacted]	[redacted]	[redacted]
ETN HD203 25 mg BIW + cDMARD	[redacted]	[redacted]	[redacted]
ETN SB4 50mg QW SC + cDMARD	[redacted]	[redacted]	[redacted]
GOL + cDMARD	[redacted]	[redacted]	[redacted]
IFX + cDMARD	[redacted]	[redacted]	[redacted]
IFX CT-P13 3mg/kg Q8W + cDMARD	[redacted]	[redacted]	[redacted]
IFX SB2 + cDMARD	[redacted]	[redacted]	[redacted]
TOC + cDMARD	[redacted]	[redacted]	[redacted]
PBO + cDMARD	[redacted]	[redacted]	[redacted]
	OR (95% CrI) intervention vs comparator		
PBO	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]
TOC	[redacted]	[redacted]	[redacted]

Comparator	Intervention: Tofacitinib		
	OR (95% CrI) intervention + cDMARD vs comparator		
	Moderate EULAR response	Good EULAR response	At least moderate EULAR response
ETN 25mg SC BIW	[redacted]	[redacted]	[redacted]

An OR >1 indicates that tofacitinib (intervention) is favoured over the comparator. Cells highlighted in grey indicate a significant result.
Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; LEF, leflunomide; MTX, methotrexate; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; SFZ, sulfasalazine; TOC, tocilizumab; TOF, tofacitinib.

cDMARD-IR: Change from baseline in HAQ-DI (normal likelihood)

The results of the NMA using a random effects model are shown in Table 71 and Table 72, which show that:

[redacted]

Table 71: Summary of NMA results for all treatments vs placebo and placebo + CDMARD: cDMARD-IR, Change from baseline in HAQ-DI

Intervention	Comparator: placebo
	MTD (95% CrI) intervention + cDMARD vs comparator
ADA 40mg Q2W SC + cDMARDs	[redacted]
CTZ 200mg Q2W SC + cDMARDs	[redacted]
ETN 25mg BIW SC	[redacted]
ETN SC (BIW or QW) + cDMARDs	[redacted]
ETN HD203 25mg/BIW + cDMARDs	[redacted]
GOL 2mg/kg Q8W IV + cDMARDs	[redacted]
GOL 50mg Q4W SC + cDMARDs	[redacted]
TOC 8mg/kg Q4W IV + cDMARDs	[redacted]
TOF 5mg BID + cDMARDs	[redacted]
	MTD (95% CrI) intervention vs comparator
ADA 40mg Q2W SC	[redacted]
TOC 8mg/kg Q4W IV	[redacted]
TOF 5mg BID	[redacted]

Grey cells indicate a significant result, shown by CrIs which exclude the null value.
Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; LEF, leflunomide; MTD, mean treatment difference; MTX, methotrexate; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; SFZ, sulfasalazine; TOC, tocilizumab; TOF, tofacitinib.

Table 72: Summary of NMA results for tofacitinib and tofacitinib + cDMARD: cDMARD-IR, Change from baseline in HAQ-DI

Comparator	Intervention: Tofacitinib
	MTD (95% CrI) intervention + cDMARD vs comparator
PBO + cDMARDs	[redacted]
ADA 40mg Q2W SC + cDMARDs	[redacted]
CTZ 200mg Q2W SC + cDMARDs	[redacted]
ETN 25mg BIW SC	[redacted]
ETN SC (BIW or QW) + cDMARDs	[redacted]
ETN HD203 25mg/BIW + cDMARDs	[redacted]
GOL 2mg/kg Q8W IV + cDMARDs	[redacted]
GOL 50mg Q4W SC + cDMARDs	[redacted]
TOC 8mg/kg Q4W IV + cDMARDs	[redacted]
	MTD (95% CrI) intervention vs comparator
PBO	[redacted]
ADA 40mg Q2W SC	[redacted]
TOC 8mg/kg Q4W IV	[redacted]

Grey cells indicate a significant result, shown by CrIs which exclude the null value.
Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; LEF, leflunomide; MTD, mean treatment difference; MTX, methotrexate; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; SFZ, sulfasalazine; TOC, tocilizumab; TOF, tofacitinib.

bDMARD-IR: EULAR (probit)

A fixed effects model was used for all analyses. A summary of the results is presented for intervention vs placebo (comparator) in Table 73 and for tofacitinib (intervention) vs comparators in Table 74:

Response vs placebo

- [redacted])

Response vs comparator

- **Good EULAR response:**
  [redacted]

- **At least moderate EULAR response:**

[redacted]

Table 73: Summary of NMA results for all treatments vs placebo + DMARD for bDMARD-IR for EULAR

Intervention	Comparator: placebo + cDMARD	
	OR (95% CrI) intervention vs comparator	
	Good EULAR response	At least moderate EULAR response
ABT + cDMARD	[redacted]	[redacted]
GOL + cDMARD	[redacted]	[redacted]
Non TNFi+ cDMARD	[redacted]	[redacted]
RTX + cDMARD 2x1000mg IV	[redacted]	[redacted]
TOC + cDMARD 8mg/kg IV Q4W	[redacted]	[redacted]
TNFi + cDMARD	[redacted]	[redacted]
TOF + cDMARD 5mg BID	[redacted]	[redacted]

An OR >1 indicates that the intervention is favoured over placebo+cDMARD (comparator). Cells highlighted in grey indicate a significant result.
Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; LEF, leflunomide; MTX, methotrexate; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; SFZ, sulfasalazine; TOC, tocilizumab; TOF, tofacitinib.

Table 74: Summary of NMA results for tofacitinib + cDMARD vs comparator for bDMARD-IR for EULAR

Comparator	Intervention: Tofacitinib + cDMARD	
	OR (95% CrI) intervention vs comparator	
	Good EULAR response	At least moderate EULAR response
ABT + cDMARD	[redacted]	[redacted]
GOL + cDMARD	[redacted]	[redacted]
Non TNFi+ cDMARD	[redacted]	[redacted]
RTX + cDMARD 2x1000mg IV	[redacted]	[redacted]
TOC + cDMARD 8mg/kg IV Q4W	[redacted]	[redacted]
TNFi + cDMARD	[redacted]	[redacted]
Placebo + cDMARD	[redacted]	[redacted]

An OR >1 indicates that tofacitinib + cDMARD (intervention) is significantly favoured over comparator + cDMARD. Cells highlighted in grey indicate a significant result.
Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; LEF, leflunomide; MTX, methotrexate; PBO, placebo;

Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; SFZ, sulfasalazine; TOC, tocilizumab; TOF, tofacitinib.

bDMARD-IR: Change from baseline in HAQ-DI (normal likelihood)

The results of the NMA using a fixed effects model are shown in Table 75 and Table 76, which show that:

[redacted]

Table 75: Summary of NMA results for all treatments placebo + cDMARD: bDMARD-IR, Change from baseline in HAQ-DI

Intervention	Comparator: placebo + cDMARD
	MTD (95% CrI) intervention vs comparator
ABT 10mg/kg IV Q4W + cDMARD	[redacted]
GOL 50mg SC Q4W + cDMARD	[redacted]
Non-TNFi bDMARD + cDMARD	[redacted]
RTX + cDMARD	[redacted]
TNFi + cDMARD	[redacted]
TOF 5mg BID + cDMARD	[redacted]

Grey cells indicate a significant result, shown by CrIs which exclude the null value.
Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; LEF, leflunomide; MTX, methotrexate; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; SFZ, sulfasalazine; TOC, tocilizumab; TOF, tofacitinib.

Table 76: Summary of NMA results for tofacitinib + cDMARD: bDMARD-IR, Change from baseline in HAQ-DI

Comparator	Intervention: Tofacitinib + cDMARD
	MTD (95% CrI) intervention vs comparator
PBO + cDMARD	[redacted]
ABT 10mg/kg IV Q4W + cDMARD	[redacted]
GOL 50mg SC Q4W + cDMARD	[redacted]
Non-TNFi bDMARD + cDMARD	[redacted]
RTX + cDMARD	[redacted]
TNFi + cDMARD	[redacted]

Grey cells indicate a significant result, shown by CrIs which exclude the null value.
Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; LEF, leflunomide; MTX, methotrexate; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; SFZ, sulfasalazine; TOC, tocilizumab; TOF, tofacitinib.

4.10.5.5 Sensitivity analysis

Results of the sensitivity analyses for exclusion of trials conducted in exclusively Asian populations (which also excluded studies with lower doses of MTX), exclusion of trials with prior bDMARD exposure, exclusion of trials with milder disease, inclusion of the SWEFOT trial (in line with TA375), and using a multinomial probit model are provided in Appendix 8. as well as alternative estimate of efficacy. The results of the probit model were generally consistent with the binomial model. This suggests that the results of the base case model are robust and largely insensitive to changes in the networks.

Interpretation of findings per scenario;

a) Scenario 1 - Exclusion predominantly Asian populations trials/lower dose MTX:

   By removing Asian based studies from the network, which also excluded the studies with lower dosing of MTX, the main impact was observed for certolizumab pegol, golimumab and tocilizumab (Table 213–Table 218). [redacted]. The OR for tofacitinib versus certolizumab pegol, golimumab and tocilizumab numerically improved compared to the basecase NMA structure across all EULAR responses. In addition, the exclusion of the GO-FORTH trial means that comparisons are no longer possible between golimumab and the rest of the network for the moderate EULAR and good EULAR responses. In this respect, this scenario analysis cannot be used to inform the economic model as it excludes a relevant comparator for the decision problem. In the case of the monotherapy trials, the results were consistent with the base case across all networks.

b) Scenario 2 - Exclusion of trials that included patients with prior bDMARD exposure (Table 219–Table 224);

   As expected the exclusion of OPTION, J-RAPID and RAPID-1 would only affect comparative efficacy results versus certolizumab pegol and tocilizumab. The exclusion of J-RAPID and RAPID-1 [redacted]. The moderate EULAR responses and good EULAR responses are unaffected as neither J-RAPID nor RAPID-1 reported these. In line with Table 79 this suggests greater heterogeneity between certolizumab pegol trials.

   The exclusion of OPTION [redacted]

[redacted].

c) Scenarioi 3 - Exclusion of trials with milder disease (Table 225–Table 230)

In general, the exclusion of SURPRISE and CERTAIN mirrors the findings of scenarios 1 and 2, in terms of having affected the comparisons with tocilizumab and certolizumab pegol, [redacted]. In addition, the exclusion of the CERTAIN trial disconnects certolizumab pegol from the network for the moderate EULAR and good EULAR response analyses. In this respect, this scenario analysis cannot be used to inform the economic model as it excludes a relevant comparator for the decision problem [redacted].

d) Scenario 4 - Separating intensified cDMARDs from central node (Table 232 and Table 232):

As discussed in section 4.10.2.1 incorporating etanercept into the cDMARD-IR networks was not initially possible as the etanercept trials do not share a common comparator with the rest of the network. Including SWEFOT in this scenario analysis provides an alternative link between ETN and the rest of the network via an intensified cDMARD node. [redacted]. The role of using SWEFOT to link ETN into the network is limited when using the binomial model as only good EULAR response data are available to form the evidence network, and therefore it is not possible to provide all of the evidence required to inform the economic model. In the case of the monotherapy trials, the results were generally consistent with the base case.

e) Scenario 5 - Alternative modelling approach (probit) for cDMARD-IR (Table 233):

The NMA model outputs from the probit analysis are presented as probabilities for each of the interventions for at least moderate EULAR response and good EULAR response in Figure 44 and Figure 45. The analyses presented used the fixed effect model, plotting the mean and 95% CrI.

[redacted]

EMPTY

[redacted]

EMPTY

[redacted]

[redacted]

These results [redacted].

The results of this analysis are also subject to the same caveats regarding the potential impact of heterogeneity in the TCZ+cDMARD and CTZ+CDMARD trials as has been discussed for the binomial model.

Out of the monotherapies, [redacted]

As outlined in Section 4.10.5.2, it was not possible to form a connected network with all comparators for the bDMARD-IR population using the binomial model, and therefore the probit model was used for the basecase.

[redacted]

f) Alternative estimates tofacitinib (Table 234–Table 239):

To explore uncertainty around the 6 month relative efficacy of tofactinib combination and monotherapy an alternative estimate of clinical efficacy was generated based on patient level data analysis (see Section 4.8.1 for details). Table 77 provides the ORs and 95% CrIs based on estimate 1 and 2 for tofactinib combination therapy compared with comparators in the appraisal for the combination therapies and monotherpaies separately.

[redacted]

Table 77: Comparison of ORs for Estimate 1 and Estimate 2: tofactinib+cDMARD vs comparator and tofactinib monotherapy vs comparator

	Moderate EULAR response		Good EULAR response		At least moderate EULAR response	
Comparator	***Estimate 1***	***Estimate 2***	***Estimate 1***	***Estimate 2***	***Estimate 1***	***Estimate 2***
Tofactinib+cDMARD vs comparator						
PBO + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABT + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTZ 200mg Q2W SC + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN HD203 25 mg BIW + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN SB4 50mg QW SC + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX CT-P13 3mg/kg Q8W + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX SB2 + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofactinib monotherapy vs comparator						
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN 25mg SC BIW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; LEF, leflunomide; MTX, methotrexate; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; SFZ, sulfasalazine; TOC, tocilizumab; TOF, tofacitinib.

Conclusion

Scenario analyses exploring the impact of clinical heterogeneity in patient charactersitics (milder disease, Asian population/lower MTX dose) and prior exposure to bDMARDS [redacted]. Only comparisons between tofactitnib and certolizumab pegol, tocilizumab or golimumab (all combined with MTX) were influenced, [redacted].

Using a network with a separate node for intensified cDMARD via the inclusion of the SWEFOT trial [redacted]

The use of the probit model for the cDMARD population [redacted]

[redacted].

Although the sensitivity analyses consistently highlight the uncertainty surrounding certain key trials within the network, for the base-case a pragmatic approach of including all trials has been pursued. This is likely to provide an advantage for certolizumab pegol, golimumab and tocilizumab in the comparative network compared to other biologics and tofacitinib, and thus influences the economic analysis. However, using all available evidence allowed inclusion of all comparators for the economic analysis in order to meet the decision problem as regression analysis was not possible to adjust for the differences in the network, as outlined in 4.10.4. Therefore caution is advised in interpreting the NMA and economic analysis results for etanercept, certolizumab pegol, golimumab and tocilizumab compared to tofacitinib in particular.

4.10.5.6 Heterogeneity and inconsistency

In NMA, as in standard meta-analysis, it is important to assess heterogeneity and its potential impact on conclusions from statistical modelling. Heterogeneity can be thought of as the unexplained variance between study level treatment effects and could be due to, for example, differences in study population or treatment regimen. If heterogeneity is detected it may indicate the presence of effect modifiers that have not been considered.

Inconsistency

NMA brings together all available evidence from clinical trials to estimate treatment effects. As this involves combining direct and indirect measures of effect, it is important to examine whether or not these two 'sources' of evidence are consistent with one another. Inconsistency can be thought of as incoherence in loops within an evidence network.

Inconsistency was explored by comparing estimates of relative treatment effect from direct evidence with those from the NMA alongside the formal Bucher method as outlined in the NICE TSD4 which is considered the simplest analysis of inconsistency and can be easily interpreted (264). This method of testing inconsistencies within a network can only be applied to loops of evidence that contain independent sources of data and cannot be used on loops that include multi-arm trials as they are considered internally consistent (264). In the current analysis inconsistency checks were performed where necessary in base-case networks.

Assessment of heterogeneity and inconsistency

Differences in direct evidence caused by heterogeneity was assessed by examining the study level ORs (EULAR) or mean treatment differences (HAQ), and assessing the direction of treatment effect and the 95% CIs. Formal tests for heterogeneity have also been performed in instances where multiple trials contribute evidence for pair-wise comparisons within the networks. The I^2 statistic from this test describes the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error. Caution is urged in the interpretation of I^2 as this can be misleading since the test has low power when there are few studies or studies are of low sample size. As a rough

guide I^2 levels ≥50% represent substantial heterogeneity as outlined by the Cochrane handbook (263).

cDMARD population

The evidence networks for the EULAR good response and the EULAR moderate response generally consisted of single trials per direct treatment comparison except for the comparisons of tofacitinib monotherapy with placebo (ORAL-Solo and Fleischman 2012a) and the comparison of tofacitinib combination therapy with placebo combination therapy (ORAL trials). The data for the combination therapy ORAL trials were provided as single input therefore a statistical assessment of heterogeneity is not feasible in this instance. Estimates of statistical heterogeneity in terms of I^2 for the pair-wise treatment comparisons of tofacitinib monotherapy with placebo have been obtained for the EULAR good response and the EULAR moderate responses (Table 78).

[redacted]

Table 78: Estimates of I^2 for the tofacitinib vs placebo comparison within the moderate EULAR response and good EULAR response networks.

Treatment comparison	Trials contributing evidence to comparison	Trial estimate, OR [95% CI]	Statistical heterogeneity, I^2
Moderate EULAR response			
Tofacitinib vs placebo	Fleischmann 2012	[redacted]	[redacted]
	ORAL-SOLO	[redacted]	
Good EULAR response			
Tofacitinib vs placebo	Fleischmann 2012	[redacted]	[redacted]
	ORAL-SOLO	[redacted]	

Abbreviations: CI, confidence interval; EULAR, European League Against Rheumatism; OR, odds ratio.

The evidence network for at least a moderate EULAR response included several direct treatment comparisons for which data were available from more than one trial. The trials contributing to each of these direct treatment comparisons and the estimate of statistical heterogeneity for each is presented in Table 79 (moderate EULAR response).

[redacted]

Table 79. Estimates of I2 for each pair-wise comparison within the at least a moderate EULAR response network.

Treatment comparison	Trials contributing evidence to comparison	Trial estimate, OR [95% CI]	Statistical heterogeneity, I^2
Golimumab + cDMARD vs cDMARD + placebo	GO-FORWARD	[redacted]	[redacted]
	Li 2015	[redacted]	
	GO-FORTH	[redacted]	
Certolizumab pegol + cDMARD vs cDMARD + placebo	CERTAIN	[redacted]	[redacted]
	J-RAPID	[redacted]	
	RAPID-1	[redacted]	
Infliximab + cDMARD vs cDMARD + placebo	ATTEST	[redacted]	[redacted]
	START	[redacted]	
Tocilizumab + cDMARD vs Tocilizumab	ACT-RAY	[redacted]	[redacted]
	SUPRISE	[redacted]	
Tocilizumab + cDMARD vs cDMARD + placebo	TOWARD	[redacted]	[redacted]
	OPTION	[redacted]	
Tofacitinib vs placebo	Fleischmann 2012	[redacted]	[redacted]
	ORAL-SOLO	[redacted]	

Abbreviations: cDMARD, conventional disease-modifying anti-rheumatic drug; CI, confidence interval; EULAR, European League Against Rheumatism; OR, odds ratio.

The evidence network for HAQ also included several direct treatment comparisons for which data were available from more than one trial. Each of the trials contributing to each of these direct treatment comparisons and the estimate of statistical heterogeneity for each is presented in the Table 80.

Table 80. Estimates of I2 for each pair-wise comparison within the HAQ network.

Treatment comparison	Trials contributing evidence to comparison	Trial estimate, mean difference [95% CI]	Statistical heterogeneity, I^2
Golimumab + cDMARD vs cDMARD + placebo	GO-FORTH	[redacted]	[redacted]
	Li 2015	[redacted]	
	GO-FORWARD	[redacted]	
Certolizumab pegol + cDMARD vs cDMARD + placebo	CERTAIN	[redacted]	[redacted]
	J-RAPID	[redacted]	
	RAPID-2	[redacted]	
Tocilizumab + cDMARD vs Tocilizumab	ACT-RAY	[redacted]	[redacted]
	SUPRISE	[redacted]	
Tocilizumab + cDMARD vs cDMARD + placebo	LITHE	[redacted]	[redacted]
	OPTION	[redacted]	
Tofacitinib vs placebo	Fleischmann 2012	[redacted]	[redacted]
	ORAL-SOLO	[redacted]	
Adalimumab vs placebo	Van de Putte 2004	[redacted]	[redacted]
	Myasaka 2008	[redacted]	
Adalimumab + cDMARD vs cDMARD + placebo	ORAL-Standard	[redacted]	[redacted]
	ARMADA	[redacted]	
	DE019	[redacted]	
	Kim 2007	[redacted]	
Tofacitinib + cDMARD vs cDMARD + placebo	ORAL trials	[redacted]	[redacted]
	Kremer 2012	[redacted]	

Abbreviations: cDMARD, conventionl disease-modifying anti-rheumatic drug; CI, confidence interval; HAQ, Health Assessment Questionnaire.

[redacted]

[redacted]

bDMARD population

Single trials contributed to each direct comparison within the bDMARD evidence networks and therefore statistical assessments of heterogeneity are not feasible.

4.11 *Non-randomised and non-controlled evidence*

4.11.1 *List of relevant non-randomised and non-controlled evidence*

The long-term safety and efficacy of tofacitinib was evaluated in two studies. Study A3921024 (ORAL Sequel) and Study A3921041 were Phase II/III, open-label extension studies involving long-term follow-up of patients who had previously participated in randomised Phase I, Phase II, or Phase III tofacitinib trials. ORAL Sequel is ongoing, and Study A3921041, which only assessed Japanese patients, was completed in December 2013 (Table 81**)**.

Table 81: List of relevant non-RCTs

Study number (acronym)	Objective	Population	Intervention	Comparator	Primary study reference	Justification for inclusion
A3921024 (ORAL Sequel; study ongoing)	• To assess the long-term safety and efficacy of TOF	• Patients with moderate-to-severe RA qualifying from Phase I, Phase II, and Phase III TOF RCTs (global population)	• TOF 5 mg BD for patients previously enrolled in Phase II studies of TOF • TOF 10 mg BD for patients previously enrolled in Phase III studies of TOF	• None	• Wollenhaupt et al, 2014 (265) • Supporting information from protocol • Result of pooled analysis: data on file	• Provides long-term data on the safety and efficacy of TOF
A3921041	• To assess the long-term safety and efficacy of TOF in Japan	• Patients with moderate-to-severe RA qualifying from Phase I, Phase II, and Phase III TOF RCTs (Japanese population only)	• TOF 5 mg for all patients	• None	• Wollenhaupt et al, 2014 (265) • Supporting information from protocol • Result of pooled analysis: data on file	• Provides long-term data on the safety and efficacy of TOF

Abbreviations: BD, twice daily; RCT, randomised controlled trial; TOF, tofacitinib.

4.11.2 *List of RCTs excluded from further discussion*

None were excluded from further discussion.

4.11.3 *Summary of methodology of the relevant non-randomised and non-controlled evidence*

Trial no. (acronym)	NCT00413699 (ORAL Sequel)	NCT00661661 (A3921041)
Study objective	To assess the long-term safety and efficacy of TOF	To assess the long-term safety and efficacy of TOF in Japanese patients
Trial design	Open-label, long-term extension study	
Method of randomisation and blinding	These studies were open-label and patients were not randomised to treatment.	
Key inclusion criteria	• Aged ≥18 years • Diagnosed with RA consistent with ACR 1987 Revised Criteria (130) • Previously received TOF in a Phase I, II or III study	• Aged ≥20 years • Diagnosed with RA consistent with ACR 1987 Revised Criteria (130) • Previously received TOF in a Phase I, II or III study
Key exclusion criteria	• Haemoglobin <9 g/dl or haematocrit < 30% • White blood cell count <3.0 x 10^9/L • Absolute neutrophil count <1.2 x 10^9/l • Platelet count <100 x 10^9/L • Estimated glomerular filtration rate <40 ml/min • Total bilirubin, ALT or AST >1.5 x ULN or **>2 x ULN (Japanese study only, A3921041)** • Treatment-related SAE in previous study • Serious chronic or recurrent infections, including active or inadequately treated latent mycobacterium tuberculosis, herpes zoster, or other opportunistic infection • Evidence or history of malignancy, with the exception of adequately treated or excised, non-metastatic basal or squamous cell cancer of the skin or cervical carcinoma in situ • Any lymphoproliferative disorder, history of lymphoma, leukaemia, or signs and symptoms suggestive of current lymphatic disease	
Settings and locations	Global clinical trial population (excluding Japan)	Japan
Duration of study	Ongoing. [redacted]	[redacted]
Trial drugs	• TOF 5 mg BD for patients previously enrolled in Phase II studies of TOF • TOF 10 mg BD for patients previously enrolled in Phase III studies of TOF	TOF 5 mg for all patients
Prior and concomitant	• Patients either received their dose of TOF as monotherapy or in combination with background DMARD.	

Trial no. (acronym)	NCT00413699 (ORAL Sequel)	NCT00661661 (A3921041)
medications	• Permitted concomitant RA medications included MTX, leflunomide, sulfasalazine, antimalarials, auranofin, injectable gold preparations, NSAID and/or glucocorticoids at approved doses	
Primary outcomes	To determine the long-term safety and tolerability of TOF.	
Key secondary outcomes	To determine the long-term efficacy of TOF with regards to: • ACR20, ACR50 and ACR70 • Disease activity as measured by DAS28-4(ESR) • Change from baseline in HAQ-DI	
Pre-planned subgroups	No subgroup analysis was planned.	

Abbreviations: ACR, American College of Rheumatology; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BD, twice daily; DAS28, Disease Activity Score in 28 joints; DMARD, disease-modifying anti-rheumatic drug; HAQ-DI, Health Assessment Questionnaire-disability index; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; SAE, serious adverse event; TOF, tofacitinib; ULN, upper limit of normal.

4.11.4 *Statistical analysis of the non-randomised and non-controlled evidence*

Both studies involved similar patient populations (other than race and its associated characteristics) and thus were deemed appropriate to be pooled. Therefore, the efficacy data reported in Section 4.11.7 are pooled data.

[redacted] Baseline values for efficacy endpoints were the same baseline values used for patients in their previous clinical trial of tofacitinib.

4.11.5 *Quality assessment of the relevant non-randomised and non-controlled evidence*

Study question	ORAL Sequel and Study A3921041
Was randomisation carried out appropriately?	These were non-randomised trials.
Was the concealment of treatment allocation adequate?	The studies were open-label.
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Demographic and baseline clinical characteristics were generally well balanced between the dose groups.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Studies were open-label.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Data were presented using descriptive statistics only.

4.11.6 *Participant flow in the studies*

4.11.6.1 Patient disposition

ORAL sequel is currently ongoing; data presented here are from the pooled analysis.

Overall, 4,102 patients were assigned to study treatment: 1,421 to tofacitinib 5 mg and 2,681 to tofacitinib 10 mg. As of the cut-off date of 19 April 2012, 3,665 (89.3%) patients were ongoing and a total of 852 (20.8%) patients had discontinued. The most frequent reason for discontinuation for all patients was due to AEs (10.7% patients). The data presented in Section 4.11.6.2 and 4.11.7 are from the subset of patients (N=3,146) who enrolled in the long-term extension studies from the six Phase III studies.

4.11.6.2 Baseline characteristics

Table 82: Pooled baseline characteristics of patients (from Phase III studies) in long-term extension studies

Characteristic	TOF 5 mg (N=431)	TOF 10 mg (N=2,715)
Female, n (%)	369 (85.6%)	2,234 (82.2%)
Age, years (SD)	51.9 (11.7)	51.9 (11.6)
Race		
White	135 (31.3%)	1,919 (70.6%)
Black	7 (1.6%)	92 (3.4%)
Asian	267 (62.0%)	426 (15.7%)
Other	22 (5.1%)	281 (10.3%)
Weight, kg		
Mean (SD)	63.8 (16.3%)	72.7 (19.2)
BMI, kg/m^2		
Mean (SD)	24.7 (5.6)	27.3 (6.4)

Abbreviations: BMI, body mass index; SD, standard deviation; TOF, tofacitinib.

4.11.7 *Clinical effectiveness results of the relevant non-randomised and non-controlled evidence*

4.11.7.1 Long-term effect of tofacitinib on disease activity and physical functioning

The results for the change from baseline in DAS28-4(ESR) and HAQ-DI up to Month 75 are shown in Table 83. These results demonstrated that improvements in disease activity and physical functioning achieved by tofacitinib treatment are maintained in the long term. Both doses of tofacitinib produced a similar effect.

Table 83: Change from baseline in DAS28-4(ESR) and HAQ-DI up to Month 75

Time point	Change from baseline							
	DAS28-4(ESR)				HAQ-DI			
	TOF 5 mg		TOF 10 mg		TOF 5 mg		TOF 10 mg	
	n	Mean	n	Mean	n	Mean	n	Mean
12	[redacted]							
24	[redacted]							
36	[redacted]							
48	[redacted]							
60	[redacted]							
72	[redacted]							
75	[redacted]							

Abbreviations: DAS28, disease activity score in 28 joints; HAQ-DI, Health Assessment Questionnaire-disability index; TOF, tofacitinib.

4.12 *Adverse reactions*

4.12.1 *Studies reported in section 4.2*

Safety evidence for tofacitinib in support of this technology appraisal is drawn from a published (Cohen et al, 2016 (12)) pooled analysis of data from patients treated with tofacitinib across the clinical development programme, including the six Phase III clinical trials described in Section 4.2. The analysis provides the most comprehensive long-term safety data available for tofacitinib. For completeness, the adverse event profiles obtained from the six Phase III clinical trials are described in Appendix 2.

4.12.2 *Pooled long-term safety analysis*

Methodology

Safety data from patients treated with tofacitinib in Phase I, II and III clinical trials and long-term extension studies were pooled to provide long-term safety data. Included studies had to be completed (with the exception of NCT00413699) at the time of the data cut (31st March 2015). As this pooled analysis comprises data from the Phase III ORAL clinical trials (see Section 4.2, Table 12 for study details), the results are reported in this section. An overview of the additional studies included in the pooled safety analysis is shown in Table 84.

Table 84: Phase I, Phase II, Phase III and long-term extension studies included in the pooled safety analysis

Trial number	Study details	Patients receiving TOF	TOF dose
Phase I			
NCT01262118 (266)	6-week study of patients with active RA (n=36) and healthy volunteers (n=33)	69	10 mg BD ± MTX
NCT01484561 (267)	6-week, placebo-controlled study of patients with active RA, who were DMARD-IR	97	10 mg BD ± cDMARDs
Phase II			
NCT00147498 (268)	6-week, placebo-controlled study of patients with active RA who has an IR or unacceptable toxicity to MTX, ETN, INF or ADA	199	5, 15 or 30 mg BD as monotherapy
NCT00413660 (156)	24-week, placebo-controlled study of patients with active RA, who were MTX-IR	438	MTX and: • 1, 3, 5, 10 or 15 mg BD • 20 mg OD
NCT00550446 (148)	24-week, placebo- and active-controlled (ADA) study of patients with active RA, who were DMARD-IR	272	1, 3, 5, 10 or 15 mg BD as monotherapy
NCT00603512 (242)	12-week, placebo-controlled study of patients with active RA, who were MTX-IR	108	MTX and 1, 3, 5 or 10 mg BD
NCT00687193 (243)	12-week, placebo-controlled study of	265	1, 3, 5, 10 or 15

Trial number	Study details	Patients receiving TOF	TOF dose
	patients with active RA, who were DMARD-IR		mg BD as monotherapy
NCT01164579 (269)	52-week, active-controlled (MTX) study of patients with early active RA, who were MTX-naïve	72	• 10 mg BD with MTX • 10 mg BD as monotherapy
NCT00976599 (270)	4-week, placebo-controlled study of patients with active RA, who were MTX-IR	15	10 mg BD with MTX
NCT01059864 (271)	12-week study of patients with active RA	111	10 mg BD Half of patients also received concomitant atorvastatin (10 mg OD) for Weeks 6–12
NCT01359150 (272)	9-week, placebo-controlled study of patients with active RA	102	• 10 mg BD with MTX • 10 mg BD as monotherapy
Phase III			
NCT00853385 (ORAL Standard) (122)	12-month study, placebo-controlled study of patients with active moderate-to-severe RA who are cDMARD experienced and MTX-IR	513	MTX and: • TOF 5 mg • TOF 10 mg
NCT00847613 (ORAL Scan) (123)	24-month study (12-month interim), placebo-controlled study of patients with active moderate-to-severe RA who are cDMARD experienced and MTX-IR	797	MTX and: • TOF 5 mg • TOF 10 mg
NCT00856544 (ORAL Sync) (124)	12-month study, placebo-controlled study of patients with active moderate-to-severe RA who are DMARD-IR (cDMARD including MTX or bDMARD)	792	≥1 cDMARD and: • TOF 5 mg • TOF 10 mg
NCT00814307 (ORAL Solo) (126)	6-month study, placebo-controlled study of patients with active moderate-to-severe RA who are DMARD-IR (cDMARD including MTX or bDMARD)	610	• TOF 5 mg • TOF 10 mg
NCT01039688 (ORAL Start) (127)	24-month study, active-controlled (MTX) study of patients with active moderate-to-severe RA who are naïve to MTX	770	• TOF 5 mg • TOF 10 mg
NCT00960440 (ORAL Step) (129)	6-month study, placebo-controlled study of patients with active moderate-to-severe RA who are TNFi-IR	267	MTX and: • TOF 5 mg • TOF 10 mg
Long-term extension			
NCT00413699 (ORAL Sequel) (265)	An ongoing study of patients with active RA who participated in TOF clinical trials	2,308[†]	5 or 10 mg BD ± DMARDs

Trial number	Study details	Patients receiving TOF	TOF dose
NCT00661661 (265)	72-month study of Japanese patients with active RA who participated in NCT00603512, NCT00687193 and NCT00847613 (ORAL Scan)	486	5 or 10 mg BD ± DMARDs

Abbreviations: ADA, adalimumab; BD, twice daily; DMARD, disease-modifying anti-rheumatic drug; ETN, etanercept; INF, infliximab; IR, inadequate response; MTX, methotrexate; OD, once daily; RA, rheumatoid arthritis; TOF, tofacitinib.
[†]At the time of the data cut-off (31st March 2015).

Baseline characteristics and demographics

The baseline characteristics and demographics of patients included in the long-term safety analysis are shown in Table 85.

Table 85: Characteristics of participants in the pooled safety analysis

Characteristic	All TOF doses (N=6,194)	Average[†] TOF 5 mg (N=2,239)	Average[†] TOF 10 mg (N=3,955)	Constant[‡] TOF 5 mg (N=2,342)	Constant[‡] TOF 10 mg (N=2,814)
Female, (%)	82.7	83.2	82.5	82.6	83.0
Race, n (%)					
White	3,895 (62.9)	1,177 (52.6)	2,718 (68.7)	1,418 (60.5)	1,817 (64.6)
Asian	1,486 (24.0)	800 (35.7)	686 (17.3)	626 (26.7)	605 (21.5)
Black	182 (2.9)	55 (2.5)	127 (3.2)	75 (3.2)	88 (3.1)
Other	631 (10.2)	207 (9.2)	424 (10.7)	223 (9.5)	304 (10.8)
Age					
Mean (yrs)	52.9	53.3	52.7	53.3	52.6
Range	18–86	18–86	18–86	18–86	18–86
Duration of RA					
Mean (yrs)	8.0	8.2	7.9	7.9	7.7
Range	0.0–65.0	0.0–50.1	0.0–65.0	0.0–55.0	0.0–49.4
Tender and swollen joints					
N	6,140	2,222	3,918	2,324	2,779
Tender joints, mean (SD)	24.9 (14.7)	23.6 (14.4)	25.6 (14.8)	25.7 (14.9)	24.8 (14.9)
Swollen joints, mean (SD)	15.4 (9.1)	15.3 (9.2)	15.4 (9.1)	15.5 (9.2)	15.2 (9.2)
DAS28-4(ESR)					
N	5,487	1,923	3,564	2,182	2,562
Mean (SD)	6.4 (1.0)	6.3 (1.0)	6.4 (1.0)	6.4 (1.0)	6.3 (1.1)

Characteristic	All TOF doses (N=6,194)	Average† TOF 5 mg (N=2,239)	Average† TOF 10 mg (N=3,955)	Constant‡ TOF 5 mg (N=2,342)	Constant‡ TOF 10 mg (N=2,814)
Concomitant disease, n (%)					
Diabetes mellitus	264 (4.3)	121 (5.4)	143 (3.6)	110 (4.7)	110 (3.9)
COPD	115 (1.9)	36 (1.6)	79 (2.0)	47 (2.0)	60 (2.1)
History of TB, n (%)	34 (0.5)	16 (0.7)	18 (0.5)	15 (0.6)	13 (0.5)
Prior therapy, n (%)					
MTX	4,869 (78.6)	1,877 (83.8)	2,992 (75.7)	1,876 (80.1)	2,041 (72.5)
Non-MTX cDMARD	3,263 (52.7)	1,220 (54.5)	2,043 (51.7)	1,300 (55.5)	1,401 (49.8)
TNF inhibitor	1,026 (16.6)	279 (12.5)	747 (18.9)	428 (18.3)	493 (17.5)
Non-TNF inhibitor bDMARD	273 (4.4)	71 (3.2)	202 (5.1)	114 (4.9)	141 (5.0)
Concomitant therapy, n (%)					
Glucocorticoids	3,468 (56.0)	1,304 (58.2)	2,164 (54.7)	1,359 (58.0)	1,487 (52.8)
Any DMARD	3,456 (55.8)	1,268 (56.6)	2,188 (55.3)	1,394 (59.5)	1,554 (55.2)
MTX	3,161 (51.0)	1,163 (51.9)	1,998 (50.5)	1,260 (53.8)	1,408 (50.0)
HCQ	251 (4.1)	86 (3.8)	165 (4.2)	112 (4.8)	123 (4.4)
Leflunomide	219 (3.5)	96 (4.3)	123 (3.1)	104 (4.4)	112 (4.0)

Abbreviations: ADA, adalimumab; bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug; COPD, chronic obstructive pulmonary disease; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HCQ, hydroxychloroquine; MTX, methotrexate; RA, rheumatoid arthritis; SD, standard deviation; TNF, tumour necrosis factor; TB, tuberculosis; TOF, tofacitinib.
†Average dose was based on average daily dose. Patients receiving <15 mg/day were assigned to the 5 mg BD group; patients receiving ≥15 mg/day were assigned to the 10 mg BD group. ‡Constant dosage without prior exposure to another TOF dose or ADA during the study; patients who switched doses were not included in this group.

Safety overview of the pooled long-term safety analysis

A summary of the pooled analysis is presented in Table 86. As of 31 March 2015, no new risks or safety signals were identified in long-term safety database compared to those previously reported in the randomised controlled trials and long-term extension data from the tofacitinib RA development programme.

Overall, the incidence rates (InR; patient with events/100 patient-years) for any AE or SAE was 136.9 (95% CI: 133.3, 140.5) and 9.4 (95% CI: 9.0, 9.9), respectively. The InR of discontinuation due to AEs was 7.5 (95% CI: 7.1, 7.8), while the InR of mortality within 30 days of last dose of study drug was 0.3 (95% CI: 0.2, 0.3). Incidence rates for AEs, SAEs, discontinuations due to AEs, and deaths were similar for average and constant tofacitinib 5 and 10 mg groups. For patients receiving a constant dose of tofacitinib (N=2,342), the InR was 153.1 (95% CI: 146.1, 160.4) for any AE, 9.2 (95% CI: 8.2, 10.3) for any SAE, 7.2 (95% CI: 6.4, 8.2) for discontinuation due to AEs and 0.3 (95% CI: 0.2, 0.5) for mortality within 30 days of last dose of study drug.

Table 86: Summary of the pooled safety analysis

	All TOF doses (N=6,194)	Average† TOF 5 mg (N=2,239)	Average† TOF 10 mg (N=3,955)	Constant‡ TOF 5 mg (N=2,342)	Constant‡ TOF 10 mg (N=2,814)
Patient-years of exposure					
Total	19,406	6,870	12,536	3,623	6,702
Median	3.4	3.0	3.5	1.0	2.0
Duration of exposure, n (%)					
>1 year	4,794 (77.4)	-	-	-	-
>2 years	4,032 (65.1)	-	-	-	-
>3 years	3,351 (54.1)	-	-	-	-
>4 years	2,489 (40.2)	-	-	-	-
Any AE					
InR (pe/100 py)	136.9	136.1	137.3	153.1	157.9
95% CI	133.3, 140.5	130.2, 142.3	132.8, 141.8	146.1, 160.4	151.7, 164.3
Any SAE					
InR (pe/100 py)	9.4	10.1	9.1	9.2	9.3
95% CI	9.0, 9.9	9.4, 11.0	8.5, 9.7	8.2, 10.3	8.6, 10.1
Discontinuation due to AEs					
InR (pe/100 py)	7.5	8.6	6.8	7.2	7.8
95% CI	7.1, 7.8	7.9, 9.3	6.4, 7.3	6.4, 8.2	7.1, 8.5
Mortality§					
InR (pe/100 py)	0.3	0.4	0.2	0.3	0.2
95% CI	0.2, 0.3	0.3, 0.6	0.1, 0.3	0.2, 0.5	0.1, 0.3

Abbreviations: AE, adverse event; CI, confidence interval; InR, incidence rate; pe/100 py, patients with events/100 patient-years; SAE, serious adverse events; TOF, tofacitinib.
†Average dose was based on average daily dose. Patients receiving <15 mg/day were assigned to the 5 mg BD group; patients receiving ≥15 mg/day were assigned to the 10 mg BD group. ‡Constant dosage without prior exposure to another TOF dose or ADA during the study; patients who switched doses were not included in this group. §Within 30 days of last dose of study drug.

Safety events of special interest

Safety events of special interest included serious infection events (SIE), opportunistic infections (including tuberculosis [TB]), herpes zoster and malignancies. Incidence rates for these special interest events are summarised by group in Table 87.

In total, 527 patients experienced a SIE (InR: 2.7; 95% CI: 2.5, 3.0) and 23 patients died due to an infection (InR: 0.1; 95% CI: 0.08, 0.2). The most common types of SIE were pneumonia, herpes zoster, urinary tract infection and cellulitis. Overall, 703 patients developed non-serious/serious herpes zoster (InR: 3.9; 95%CI: 3.6, 4.2). Most cases of herpes zoster (92%) involved one dermatome; the InR of disseminated/multidermatomal herpes zoster was 0.3 (95% CI: 0.2 to 0.4). Opportunistic infections excluding TB and including TB were reported in 61 patients and 97 patients, respectively, with overall InRs

of 0.3 (95% CI: 0.2, 0.4) and 0.5 (95% CI: 0.4, 0.6). Active TB was reported in 36 patients with an overall InR of 0.2 (95% CI: 0.1, 0.3). The InR of SIEs, deaths due to infections, herpes zoster (non-serious/serious), opportunistic infections (excluding and including TB) and TB were also similar between the average and constant tofacitinib dose groups.

Overall, malignancies (excluding non-melanoma skin cancer [NMSC]) occurred in 173 patients (InR: 0.9; 95% CI: 0.8, 1.0) and NMSC was reported in 118 patients (InR: 0.6; 95% CI: 0.5, 0.7). The InRs of malignancies were similar between the average and constant tofacitinib dose groups. Standardised incidence ratios (SIRs) were calculated as the ratio of observed AEs to those in the US National Cancer Institute Surveillance and Epidemiology and End Results (SEER) database, 1992–2011 (273). Age- and sex-adjusted SIRs (95% CI) compared with SEER were 1.0 (0.8 to 1.1) for all malignancies (excluding NMSC), 2.6 (1.6 to 4.1) for lymphoma, 1.4 (1.0 to 2.0) for lung cancer and 0.5 (0.3 to 0.7) for breast cancer. Twenty-two patients experienced GI perforations at an overall InR of 0.11 (95% CI: 0.07 to 0.17). Perforations occurred in the large bowel, excluding anus and rectum (n=13), gastroduodenal area (n=3), small bowel (n=1), anus and rectum (n=2) and undetermined locations (n=3). The InRs of GI perforations were similar between the average and constant tofacitinib dose groups.

Table 87: Incidence rates of infections and malignancies

InR (pe/100 py)	All TOF doses (N=6,194)	Average† TOF 5 mg (N=2,239)	Average† TOF 10 mg (N=3,955)	Constant‡ TOF 5 mg (N=2,342)	Constant‡ TOF 10 mg (N=2,814)
Infections, InR (95% CI)					
SIE	2.7 (2.5, 3.0)	3.1 (2.7, 3.5)	2.6 (2.3, 2.9)	2.3 (1.8, 2.8)	2.7 (2.3, 3.1)
HZ ns/s	3.9 (3.6, 4.2)	3.8 (3.3, 4.3)	4.0 (3.6, 4.4)	3.5 (2.9, 4.1)	4.1 (3.6, 4.7)
HZ serious	0.3 (0.2, 0.4)	0.3 (0.2, 0.5)	0.2 (0.2, 0.4)	0.3 (0.1, 0.5)	0.2 (0.1, 0.3)
HZ ds/md	0.3 (0.2, 0.4)	-	-	0.1 (0.0, 0.2)	0.2 (0.1, 0.4)
OI ex. TB	0.3 (0.2, 0.4)	0.4 (0.2, 0.6)	0.3 (0.2, 0.4)	0.2 (0.1, 0.5)	0.3 (0.1, 0.4)
OI inc. TB	0.5 (0.4, 0.6)	0.5 (0.4, 0.7)	0.5 (0.4, 0.6)	0.3 (0.2, 0.6)	0.5 (0.4, 0.7)
TB	0.2 (0.1, 0.3)	0.1 (0.07, 0.3)	0.2 (0.1, 0.3)	0.08 (0.02, 0.2)	0.3 (0.2, 0.4)
Mortality due to infections	0.1 (0.08, 0.2)	0.2 (0.1, 0.4)	0.1 (0.0, 0.1)	0.2 (0.1, 0.4)	0.05 (0.01, 0.1)
Malignancies, InR (95% CI)					
Ex. NMSC	0.9 (0.8, 1.0)	1.0 (0.8, 1.3)	0.8 (0.7, 1.0)	0.8 (0.5, 1.2)	0.9 (0.7, 1.2)
NMSC	0.6 (0.5, 0.7)	0.5 (0.4, 0.7)	0.7 (0.5, 0.8)	0.4 (0.3, 0.7)	0.6 (0.5, 0.9)
Lung	0.2 (0.1, 0.2)	0.2 (0.1, 0.3)	0.1 (0.1, 0.2)	0.2 (0.1, 0.4)	0.1 (0.1, 0.2)
Breast	0.2 (0.1, 0.2)	0.2 (0.1, 0.3)	0.1 (0.1, 0.2)	0.2 (0.1, 0.4)	0.2 (0.1, 0.3)
Lymphoma	0.1 (0.1, 0.2)	0.09 (0.0, 0.2)	0.1 (0.1, 0.2)	0.1 (0.0, 0.3)	0.1 (0.1, 0.2)
Malignancies, SIR (95% CI)¶					
Ex. NMSC	1.0 (0.8, 1.1)	-	-	-	-
Lung	1.4 (1.0, 2.0)	-	-	-	-
Breast	0.5 (0.3, 0.7)	-	-	-	-

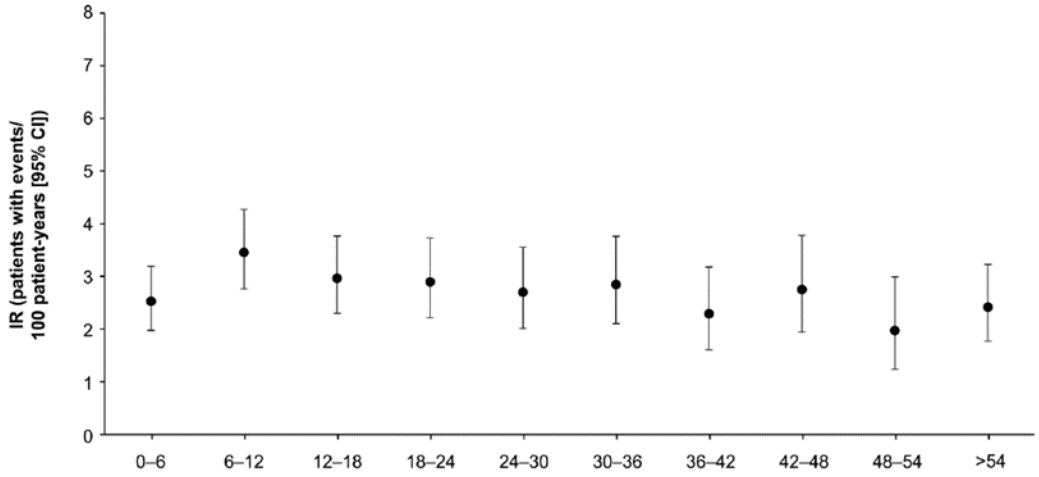
InR (pe/100 py)	All TOF doses (N=6,194)	Average† TOF 5 mg (N=2,239)	Average† TOF 10 mg (N=3,955)	Constant‡ TOF 5 mg (N=2,342)	Constant‡ TOF 10 mg (N=2,814)
Lymphoma	2.6 (1.6, 4.1)	-	-	-	-
GI perforations	0.1 (0.07, 0.2)	0.1 (0.0, 0.2)	0.1 (0.08, 0.2)	0.00 (0.00, 0.1)	0.15 (0.07, 0.3)

Abbreviations: CI, confidence interval; ds/md, disseminated/multidermatomal; HZ, herpes zoster; InR, incidence rate; NMSC, non-melanoma skin cancer; ns/s, non-serious/serious; OI, opportunistic infection; pe/100 py, patients with events/100 patient-years; SEER, Surveillance and Epidemiology and End Results; SIE, serious infection event; SIR, standardised incidence rate; TB, tuberculosis; TOF, tofacitinib. †Average dose was based on average daily dose. Patients receiving <15 mg/day were assigned to the 5 mg BD group; patients receiving ≥15 mg/day were assigned to the 10 mg BD group. ‡Constant dosage without prior exposure to another TOF dose or ADA during the study; patients who switched doses were not included in this group. §Within 30 days of last dose of study drug. ¶SIRs were compared with the SEER database.

Serious infection events by 6-monthly interval and associated risk factors

The InRs for SIEs is presented by six-monthly intervals in Figure 46 and shows that InRs did not increase with longer treatment.

Figure 46: Incidence rates for serious infection events



	0–6	6–12	12–18	18–24	24–30	30–36	36–42	42–48	48–54	>54
Total patient exposure, n	6,194	5,293	4,823	4,420	4,106	3,645	3,372	2,996	2,605	1,979
Patients with SIE, n	71	86	67	61	51	49	36	38	22	46
Total patient-year exposure for event	2,806.9	2,488.3	2,259.8	2,103.0	1,886.2	1,721.9	1,567.8	1,380.4	1,113.6	1,900.9
IR, patients with events/100 patient-years (95% CI)	2.5 (2.0–3.2)	3.5 (2.8–4.3)	3.0 (2.3–3.8)	2.9 (2.2–3.7)	2.7 (2.0–3.6)	2.8 (2.1–3.8)	2.3 (1.6–3.2)	2.8 (1.9–3.8)	2.0 (1.2–3.0)	2.4 (1.8–3.2)

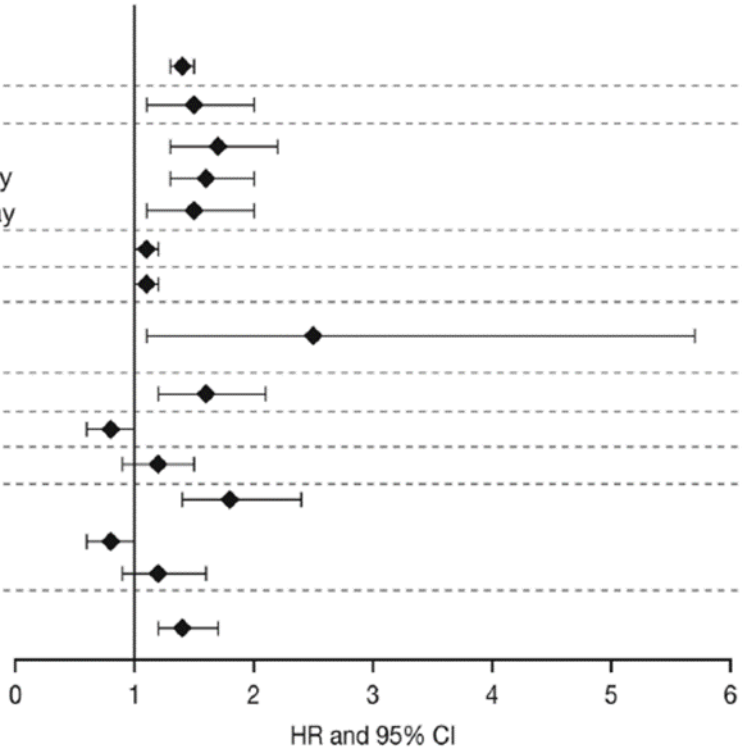
Abbreviations: CI, confidence interval; IR, incidence rate; SIE, serious infection event.

The analysis of risk factors for SIEs is presented in Figure 47. Baseline glucocorticoid doses of >0–<7.5 and ≥7.5 mg/day (selected based on clinical relevancy and sample size) were significantly associated with an increased risk of SIEs compared with no glucocorticoid use ($p<0.001$); HR: 1.6 (95% CI: 1.3, 2.0) and 1.7 (95% CI: 1.3, 2.2), respectively. Other significant (all $p\leq0.05$) baseline risk factors were higher age,

presence of chronic obstructive pulmonary disease (COPD), higher HAQ-DI score, higher body mass index (BMI), prior confirmed post-baseline lymphopenia (<500 cells/mL), diabetes, female gender, line of therapy (3rd vs 2nd line), geographical region (Asia, Europe and Latin America, each vs US/Canada) and time-varying tofacitinib dose (referent to 5 mg twice daily).

Figure 47: Hazard ratios of potential risk factors for serious infection events

Factors	Comparisons	HR	95% CI	Type 3 Wald p-value
Baseline age, years	Unit=10†	1.4	1.3, 1.5	<0.0001
Baseline COPD*	Yes vs No	1.5	1.1, 2.0	0.0145
Baseline glucocorticoid use	≥7.5 mg/day vs 0 mg/day	1.7	1.3, 2.2	0.0001
	0-<7.5 mg/day vs 0 mg/day	1.6	1.3, 2.0	
	Unknown dose vs 0 mg/day	1.5	1.1, 2.0	
Baseline HAQ-DI score	Unit=0.5†	1.1	1.0, 1.2	0.0078
Baseline body mass index	Unit=5†	1.1	1.0, 1.2	0.0320
Prior confirmed post-baseline lymphopenia <500 cells/µL‡	Unit=1†	2.5	1.1, 5.7	0.0249
Baseline diabetes	Yes vs No	1.6	1.2, 2.1	0.0009
Gender	Female vs Male	0.8	0.6, 1.0	0.0299
Line of therapy	3rd line vs 2nd line	1.2	0.9, 1.5	0.0399
Geographic region	Asia vs USA/Canada	1.8	1.4, 2.4	<0.0001
	Europe vs USA/Canada	0.8	0.6, 1.0	
	LA vs USA/Canada	1.2	0.9, 1.6	
Time-varying tofacitinib dose, mg BID	Unit=5†	1.4	1.2, 1.7	0.0003

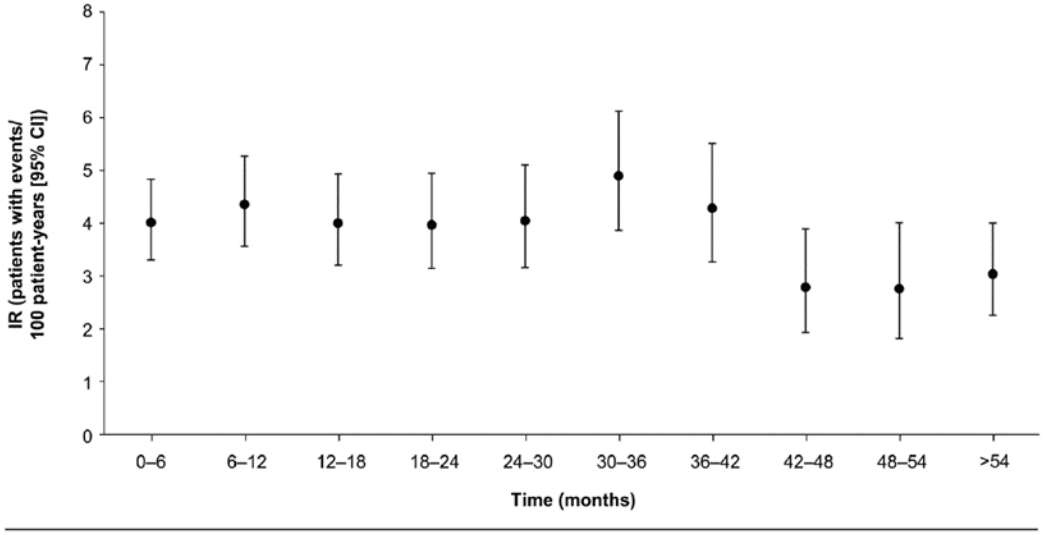


Abbreviations: BID, twice daily; COPD, chronic obstructive pulmonary disease; HAQ-DI, Health Assessment Questionnaire Disability Index; LA, Latin America.
*Medical history and/or complication of COPD. †In Unit=x, 'x' is the change in the continuous variable corresponding to which the change in hazards is observed. ‡Based on exposure period before lymphopenia <500 cells/mL versus exposure period after lymphopenia <500 cells/mL.

Herpes zoster by 6-monthly intervals and associated risk factors

The InRs for herpes zoster is presented by six-monthly intervals in Figure 48 and shows that InRs did not increase with longer treatment.

Figure 48: Incidence rates for herpes zoster



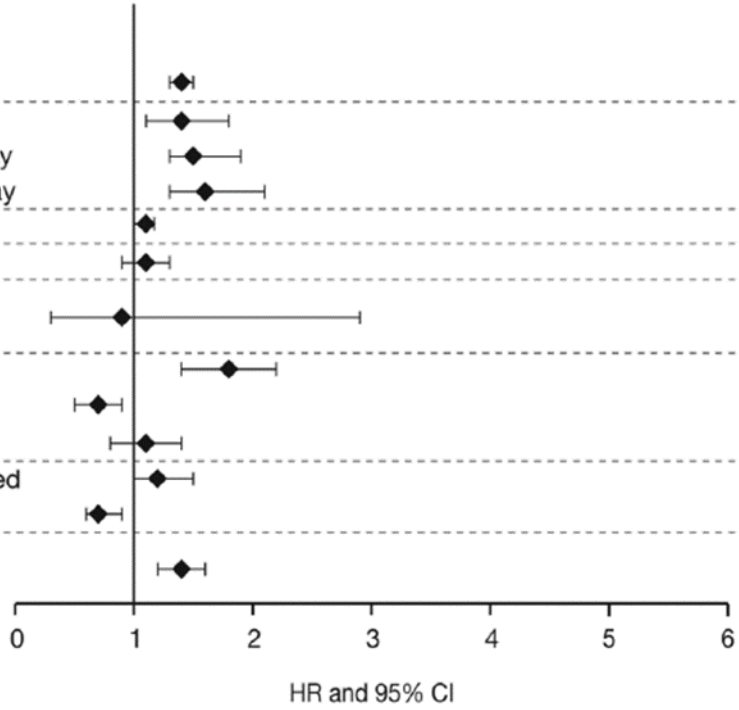
	0–6	6–12	12–18	18–24	24–30	30–36	36–42	42–48	48–54	>54
Total patient exposure, n	6,194	5,222	4,677	4,217	3,858	3,361	3,043	2,656	2,303	1,727
Patients with HZ, n	112	106	87	79	71	77	60	34	27	50
Total patient-year exposure for event	2,790.3	2,433.2	2,174.6	1,989.4	1,754.8	1,571.8	1,401.6	1,220.2	979.1	1,646.2
IR, patients with events/100 patient-years (95% CI)	4.0 (3.3–4.8)	4.4 (3.6–5.3)	4.0 (3.2–4.9)	4.0 (3.1–4.9)	4.0 (3.2–5.1)	4.9 (3.9–6.1)	4.3 (3.3–5.5)	2.8 (1.9–3.9)	2.8 (1.8–4.0)	3.0 (2.3–4.0)

Abbreviations: CI, confidence interval; HZ, herpes zoster; IR, incidence rate.

The analysis of risk factors for herpes zoster is presented in Figure 49. Baseline glucocorticoid doses of >0–<7.5 mg/day and ≥7.5 mg/day were significantly associated with an increased risk of herpes zoster compared with no glucocorticoid use ($p<0.001$); HR: 1.5 (95% CI: 1.3, 1.9) and 1.4 (95% CI: 1.1, 1.8), respectively. Other significant (all $p\leq0.05$) risk factors were baseline age, geographical region, smoking history (ex-smoker and smoker, each vs never smoked) and time-varying tofacitinib dose.

Figure 49: Hazard ratios of potential risk factors for herpes zoster

Factors	Comparisons	HR	95% CI	Type 3 Wald p-value
Baseline age, years	Unit=10†	1.4	1.3, 1.5	<0.0001
Baseline glucocorticoid use	⩾7.5 mg/day vs 0 mg/day	1.4	1.1, 1.8	<0.0001
	0-<7.5 mg/day vs 0 mg/day	1.5	1.3, 1.9	
	Unknown dose vs 0 mg/day	1.6	1.3, 2.1	
Baseline HAQ-DI score	Unit=0.5†	1.1	1.0, 1.1	0.0539
Baseline methotrexate use	Yes vs No	1.1	0.9, 1.3	0.3334
Prior confirmed post-baseline lymphopenia <500 cells/µL‡	Unit=1†	0.9	0.3, 2.9	0.8943
Geographic region	Asia vs USA/Canada	1.8	1.4, 2.2	<0.0001
	Europe vs USA/Canada	0.7	0.5, 0.9	
	LA vs USA/Canada	1.1	0.8, 1.4	
Smoking history	Ex-smoker vs never smoked	1.2	1.0, 1.5	0.0014
	Smoker vs never smoked	0.7	0.6, 0.9	
Time-varying tofacitinib dose, mg BID	Unit=5†	1.4	1.2, 1.6	<0.0001

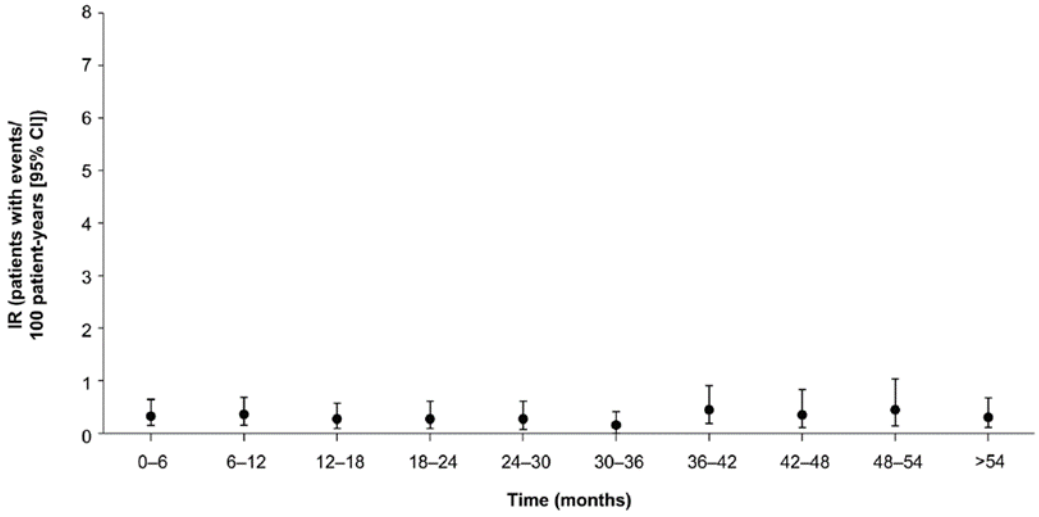


Abbreviations: BID, twice daily; HAQ-DI, Health Assessment Questionnaire Disability Index; LA, Latin America.
†In Unit=x, 'x' is the change in the continuous variable corresponding to which the change in hazards is observed. ‡Based on exposure period before lymphopenia <500 cells/mL versus exposure period after lymphopenia <500 cells/mL.

Opportunistic infections (excluding TB) by 6-monthly intervals and associated risk factors

The InRs for opportunistic infections (excluding TB) is presented by six-monthly intervals in Figure 50 and shows that InRs did not increase with longer treatment.

Figure 50: Incidence rates for opportunistic infections

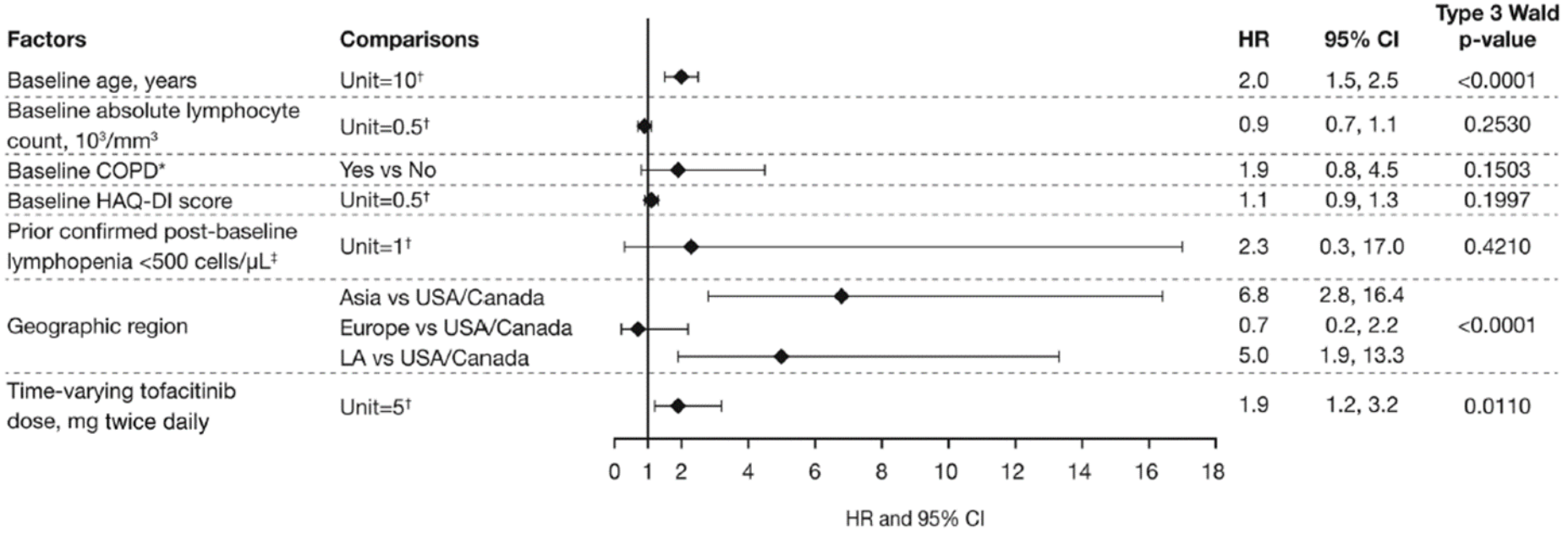


	0–6	6–12	12–18	18–24	24–30	30–36	36–42	42–48	48–54	>54
Total patient exposure, n	6,194	5,305	4,846	4,446	4,137	3,675	3,409	3,024	2,637	1,998
Patients with OI, n	10	9	6	6	5	2	7	5	5	6
Total patient-year exposure for event	2,810.1	2,494.9	2,272.6	2,117.1	1,901.9	1,738.5	1,583.0	1,395.4	1,125.7	1,932.3
IR, patients with events/100 patient-years (95% CI)	0.4 (0.2–0.7)	0.4 (0.2–0.7)	0.3 (0.1–0.6)	0.3 (0.1–0.6)	0.3 (0.1–0.6)	0.1 (0.0–0.4)	0.4 (0.2–0.9)	0.4 (0.1–0.8)	0.4 (0.1–1.0)	0.3 (0.1–0.7)

Abbreviations: CI, confidence interval; HZ, herpes zoster; IR, incidence rate.

The analysis of risk factors for opportunistic infections (excluding TB) is presented in Figure 51. Baseline age, geographical region and time-varying tofacitinib dose were associated with an increased risk of opportunistic infections excluding TB (all $p<0.05$).

Figure 51: Hazard ratios of potential risk factors for opportunistic infections (excluding tuberculosis)

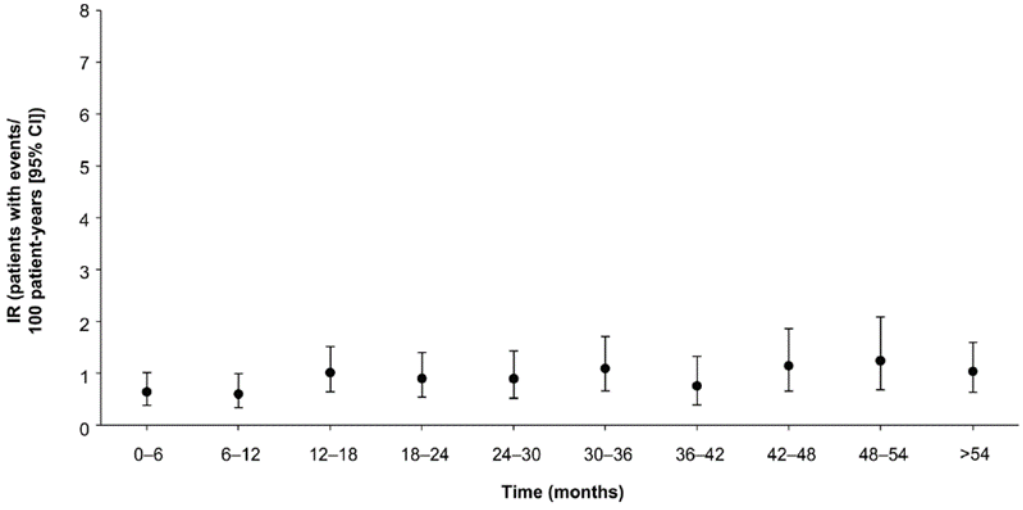


Abbreviations: BID, twice daily; COPD, chronic obstructive pulmonary disease; HAQ-DI, Health Assessment Questionnaire Disability Index; LA, Latin America.
*Medical history and/or complication of COPD. †In Unit=x, 'x' is the change in the continuous variable corresponding to which the change in hazards is observed. ‡Based on exposure period before lymphopenia <500 cells/mL versus exposure period after lymphopenia <500 cells/mL.

Malignancies by 6-monthly intervals

Incidence rates are presented by six-monthly intervals for malignancies (excluding NMSC) in Figure 52 and for NMSC in Figure 53. Overall, these analyses show that InRs did not increase with longer treatment.

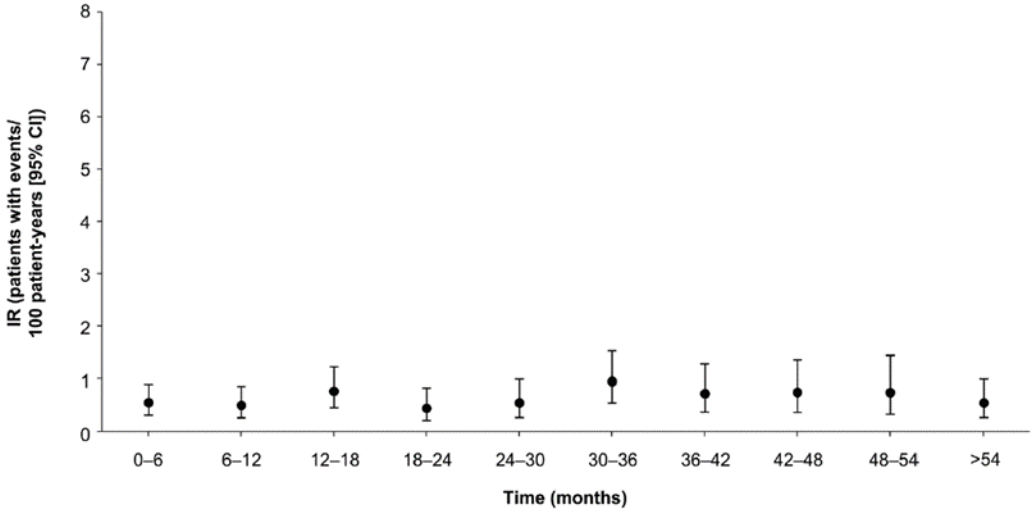
Figure 52: Incidence rates for malignancies excluding non-melanoma skin cancer



	0–6	6–12	12–18	18–24	24–30	30–36	36–42	42–48	48–54	>54
Total patient exposure, n	6,194	5,306	4,852	4,450	4,143	3,681	3,407	3,030	2,640	1,999
Patients with malignancies, n	18	15	23	19	17	19	12	16	14	20
Total patient-year exposure for event	2,810.3	2,497.1	2,275.3	2,118.8	1,903.6	1,738.7	1,584.4	1,397.0	1,126.7	1,933.0
IR, patients with events/100 patient-years (95% CI)	0.6 (0.4–1.0)	0.6 (0.3–1.0)	1.0 (0.6–1.5)	0.9 (0.5–1.4)	0.9 (0.5–1.4)	1.1 (0.7–1.7)	0.8 (0.4–1.3)	1.1 (0.7–1.9)	1.2 (0.7–2.1)	1.0 (0.6–1.6)

Abbreviations: CI, confidence interval; IR, incidence rate.

Figure 53: Incidence rates for non-melanoma skin cancer



	0–6	6–12	12–18	18–24	24–30	30–36	36–42	42–48	48–54	>54
Total patient exposure, n	6,194	5,297	4,831	4,422	4,110	3,639	3,362	2,984	2,596	1,962
Patients with NMSC, n	15	12	17	9	10	16	11	10	8	10
Total patient-year exposure for event	2,807.9	2,490.4	2,263.0	2,104.7	1,885.7	1,716.8	1,561.4	1,375.0	1,106.8	1,885.3
IR, patients with events/100 patient-years (95% CI)	0.5 (0.3–0.9)	0.5 (0.2–0.8)	0.8 (0.4–1.2)	0.4 (0.2–0.8)	0.5 (0.3–1.0)	0.9 (0.5–1.5)	0.7 (0.4–1.3)	0.7 (0.3–1.3)	0.7 (0.3–1.4)	0.5 (0.3–1.0)

Abbreviations: CI, confidence interval; IR, incidence rate; NMSC, non-melanoma skin cancer.

Conclusion

This analysis presents an integrated view of safety data across the tofacitinib RA development programme. As of 31 March 2015, no new risks or safety signals were identified in long-term safety database compared to those previously reported in the randomised controlled trials and long-term extension data from the tofacitinib RA development programme. Types and rates of AEs (including infections and malignancies) were similar to those observed in Phase III trials and were stable over time, with no evidence of directional trends with longer-term tofacitinib exposure through 8.5 years.

4.12.3 *Additional studies*

No additional trials are included.

4.12.4 *Safety overview*

Overall, tofacitinib (both in combination with MTX and as a monotherapy) demonstrated an acceptable safety profile across the Phase III clinical trial programme. The most frequent AEs reported throughout the Phase III trials were upper respiratory tract infections and nasopharyngitis. To provide long-term safety information, data were pooled and analysed from patients treated with tofacitinib in Phase I, II, III and long term extension studies. As of 31 March 2015, no new risks or safety signals were identified in long-term safety database compared to those previously reported in the randomised controlled trials and long-term extension data from the tofacitinib RA development programme. Types and rates of AEs (including infections and malignancies) were similar to those observed in Phase III trials and were stable over time, with no evidence of directional trends with longer-term tofacitinib exposure through 8.5 years. For patients receiving a constant 5 mg dose of tofacitinib (N=2,342), the incidence rates (patient with events/100 patient-years) were 153.1 (95% CI: 146.1, 160.4) for any AE, 9.2 (95% CI: 8.2, 10.3) for any SAE, 7.2 (95% CI: 6.4, 8.2) for discontinuation due to AEs and 0.3 (95% CI: 0.2, 0.5) for mortality within 30 days of last dose of study drug. With the exception of the rates for herpes zoster, the incidence of most AEs were generally comparable with that of biologics of RA (28).

Infections are noted as an AE of interest in the SmPC for tofacitinib. Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in RA patients receiving tofacitinib. The risk of opportunistic infections is higher in Asian geographic regions. Tofacitinib should not be initiated in patients with active infections, including localised infections. The risks and benefits of treatment should be considered prior to initiating tofacitinib in patients:

- with recurrent infections,
- with a history of a serious or an opportunistic infection,
- who have resided or travelled in areas of endemic mycoses,
- who have underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with tofacitinib. Treatment should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with tofacitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection.

4.13 *Interpretation of clinical effectiveness and safety evidence*

4.13.1 *Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology*

Key efficacy data supporting the use of tofacitinib 5 mg for patients with moderate (DAS28 3.2–5.1) to severe (DAS28 >5.1) active RA who are cDMARD experienced and MTX-IR or DMARD-IR (cDMARD including MTX or bDMARD) are summarised in Table 88. Overall, tofacitinib 5 mg was an effective treatment for these patients and resulted in significant improvements in disease activity, physical functioning and signs and symptoms of RA compared with placebo. Significant improvements occurred as early as Week 2 for measures of physical functioning and signs and symptoms of RA, and before Month 6 for the proportion of patients achieving disease remission. A comparison with adalimumab also revealed no evidence of a difference in efficacy with tofacitinib 5 mg in moderate-to-severe RA patients who were cDMARD experienced and MTX-IR. However, as the study was not powered to assess the efficacy of tofacitinib with adalimumab, no formal conclusions can be made. Tofacitinib 5 mg also associated with a reduction in patients' levels of pain and fatigue, and improved overall quality of life in patients. Results from long-term extension studies demonstrated that the efficacy of tofacitinib 5 mg is maintained for up to 78 months with respect to disease activity and physical functioning.

Demonstrating radiographic outcomes has become more difficult in the modern era as early access to treat-to-target strategies have become more common place. The design of a study is also complicated by the ethical necessity to limit patient exposure to placebo. The efficacy of tofacitinib combined with MTX with regard to this outcome was examined in ORAL Scan (cDMARD experienced and MTX-IR). The radiographic progression was numerically more favourable in the tofacitinib 5 mg group but the difference was not significant compared with placebo + MTX (p=0.0792). During the past decade, radiographic progression rates observed in RA clinical trials have gradually decreased, creating a greater disparity between estimated annual radiographic progression at baseline and actual annual progression (120, 274). Consequently, the detection of statistically significant reductions in radiographic progression is increasingly difficult (120). The ORAL Scan study was powered based on the assumption that radiographic progression would be 2.8 units (mTSS) per year based on the published literature available at the time. However, the placebo group progressed at a slower rate than that anticipated (0.47 observed vs 1.4 units predicted at Month 6). Consequently, the ORAL SCAN study was underpowered and unable to reach statistical significance on the 6-month primary structural endpoint for the tofacitinib 5 mg dose.

Similar to the results of ORAL Scan, a Cochrane review by Hazlewood et al, 2016 found that bDMARDs did not significantly improve radiographic progression in cDMARD experienced and MTX-IR patients, in the studies assessed (181). In contrast, bDMARDs were found to provide significant improvements in radiographic progression in MTX-naïve patients (181). Similar to the Cochrane review, a significant difference was not observed in ORAL Scan, but robust evidence that tofacitinib 5 mg can positively and significantly impact radiographic progression was demonstrated in ORAL Start (an MTX-naïve, first-line population). This study demonstrated that treatment with tofacitinib 5 mg

as monotherapy resulted in significant improvements compared with MTX across a range of outcomes measuring radiographic progression (Section 4.7.5.2). While this population is less relevant to the decision problem it does demonstrate that tofacitinib can be considered a DMARD.

When considering the secondary endpoint of non-progression (≤0.5 change from baseline mTSS) in both trial (ORAL Scan and Start) populations, it can be concluded that the majority of patients have no progression in the tofacitinib 5 mg group, which is statistically significant compared with placebo. Month 6 non-progression in the ORAL Scan population was observed in 88.8% of patients receiving in tofacitinib 5 mg and 77.7% of patients receiving placebo (p≤0.05).

Pfizer are currently addressing the relative safety and efficacy of tofacitinib 5 mg in combination with MTX and as monotherapy in a head-to-head trial (ORAL Strategy [NCT02187055]; Section 4.14).

Tofacitinib is an oral therapy that is well tolerated in patients with moderate-to-severe RA and has a safety profile which is broadly consistent with bDMARDs (Section 4.12.4). Results from the NMA confirmed that tofacitinib was similarly efficacious to range of bDMARDs (Section 4.10.5.3).

Table 88: Key efficacy results

Clinical impact	Outcome assessed (Month 6 except for HAQ-DI or where indicated)	Moderate-to-severe, cDMARD experienced and MTX-IR					Moderate-to-severe and DMARD-IR (cDMARD including MTX or bDMARD)			
		ORAL Standard			ORAL Scan		ORAL Sync		ORAL Solo (mt)	
		Section 4.7.1			Section 4.7.2		Section 4.7.3		Section 4.7.4	
		TOF	ADA	Placebo	TOF	Placebo	TOF	Placebo	TOF	Placebo
Disease activity	Remission: DAS28-4(ESR) <2.6, %	6.2‡	6.7‡	1.1	7.2§	1.6	9.1‡	2.7	M3: 5.6	M3: 4.4
	Low disease activity: DAS28-4(ESR) ≤3.2, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	M3: [redacted]	M3: [redacted]
Physical functioning	Mean change from baseline in HAQ-DI (Month 3)	–0.55†	–0.49†	–0.24	–0.40§	–0.15	–0.46†	–0.21	–0.50†	–0.19
Radiographic progression	Mean change from baseline in mTSS	N/A	N/A	N/A	0.12	0.47	N/A	N/A	N/A	N/A
	No progression (≤0.5 change in mTSS from baseline), %	-	-	-	88.8‡	77.7	-	-	-	-
Generic HRQoL	Mean change from baseline in EQ-5D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	M3: [redacted]	M3: [redacted]
Fatigue	Mean change from baseline in FACIT-F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	M3: [redacted]	M3: [redacted]
Pain	Mean change from baseline in pain (VAS)	[redacted]	[redacted]	[redacted]	-26.36†	-15.70	[redacted]	[redacted]	M3: [redacted]	M3: [redacted]
Signs and symptoms	ACR20, %	51.5†	47.2†	28.3	51.5†	25.3	52.7†	31.2	M3: 59.8†	M3: 26.7

Abbreviations: ADA, adalimumab; DAS28, disease activity score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-disability index; IR, inadequate response; LS, least squares; mt; monotherapy; MTX, methotrexate; RA, rheumatoid arthritis; TOF, tofacitinib.

†p-value <0.001 for comparison with placebo. ‡p-value ≤0.05 for comparison with placebo. §Due to the step-down procedure applied to primary efficacy outcomes, significance was not declared for the HAQ-DI score or DAS28-4(ESR) <2.6 for TOF 5 mg. Nominal p-values (TOF 5 mg vs placebo) for these outcomes were <0.001 and 0.0034, respectively.

4.13.2 *Strengths and limitations of the clinical evidence base for the technology*

4.13.2.1 Strengths of the evidence base

The six Phase III clinical trials of tofacitinib were multi-centre, double-blind, randomised, placebo-controlled studies, which represent the gold standard in clinical evidence. These trials were international, but included a number of sites in the UK and are therefore generally representative of the likely efficacy and safety of tofacitinib in the UK population.

The tofacitinib trials addressed the decision problem and included patient populations and clinical outcomes relevant to the final NICE scope. The trials included patients with both moderate (DAS28 3.2–5.1) and severe (DAS28 >5.1) RA, which represents the patients that may receive tofacitinib in clinical practice. Baseline demographics and disease-specific characteristics were generally similar across the trials and were well-balanced between the treatment groups in each trial. More female subjects than male subjects were enrolled in each trial, reflective of the gender imbalance in clinical practice (59). Furthermore, the relevance of the trial population to the UK RA population was apparent in ORAL Sync (DMARD-IR: cDMARD including MTX or bDMARD), where 86% of patients receiving tofacitinib 5 mg had previous exposure to MTX, which is consistent with UK prescribing practice. The dose of MTX provided across the trials was also consistent with dosing in the UK.

The endpoints measured across the Phase III trials were well-recognised, clinically-relevant outcomes and were consistent with clinical practice in the UK (22, 87). These outcomes also covered aspects identified as important in the treat-to-target recommendations of RA, including disease remission (primary target), physical functioning, radiographic progression, and quality of life. All co-primary endpoints were met for the tofacitinib 5 mg group in ORAL Standard, Sync, Start and Step, while two out of three co-primary endpoints were achieved in ORAL Solo. Furthermore, the long-term extension studies demonstrate that the magnitude of response achieved with tofacitinib is maintained for up to 75 months. This includes HAQ-DI data which was used to inform the economic model (Section 5.3.2.3)

The statistical analyses employed across the tofacitinib clinical trials were robust and conservative in nature. Due to the number of co-primary endpoints in each trial, a step-down statistical method was adopted to preserve type I error (false positives), where endpoints were examined sequentially (see Section 4.4.2, Figure 4 and Figure 5). At a given endpoint, tofacitinib 5 mg could only achieve significance if both tofacitinib 10 mg at the same endpoint and tofacitinib 5 mg at the prior endpoint were significant. While all co-primary endpoints were met for the tofacitinib 5 mg group in ORAL Standard, Sync, Start and Step, only one endpoint in ORAL Scan could be formally declared as significantly different from placebo, although the results for HAQ-DI and DAS28 were nominally significant, due to the non-significant difference observed for the mTSS score (see Section 4.13.1 for discussion on radiographic progression).

The data supporting the safety of tofacitinib are comprehensive and includes a pooled safety analysis presenting up to 8.5 years of follow-up data. Overall, tofacitinib is well tolerated with a stable AE profile over time. The potential increased risk of infections has

been well-characterised in the pooled safety analysis, and also shows that the incidence rates of infections is low and stable over time.

4.13.2.2 Potential limitations of the evidence base

Although a comparison with adalimumab was made in ORAL Standard, no other active comparators were included in the clinical trials. However, the results from ORAL Standard suggest that tofacitinib 5 mg can provide equivalent efficacy to adalimumab; however, conclusions cannot be drawn as the study was not sufficiently powered to detect a difference. The results from the NMA also suggest that tofacitinib 5 mg has comparable efficacy compared other bDMARDs (Section 4.10.5.3).

While the clinical trials included both patients with moderate and severe RA, the proportion of patients with moderate RA across the Phase III clinical trials was approximately 8.2% (323 out of 3,954) (275). No formal subgroup analysis was carried out, and it is therefore not possible to assess if the efficacy of tofacitinib differs between moderate and severe RA. ORAL Standard, Scan, Sync and Solo also contained a mixed population of second and third-line patients. Given the difficulties in revealing the treatment benefit as patients progress through lines of therapy (as noted by the CHMP; Section 4.13.1), a trial with a mixture of second and third-line patients may underestimate the average benefit received by second-line patients. This assumption was validated by the patient-level data subgroup analysis (Section 4.8), which demonstrated that a greater proportion of second-line patients achieved a moderate or good response compared with third-line patients.

Trial designs within RA can pose challenges in determining the relative efficacy of therapies at 6 months required for the decision problem of this appraisal. Of particular note is the use of early escape, which can result in crossover and consequent confounding of results. Similarly, the use of restricted periods of placebo control (an extreme case of early escape) can have a similar impact when all participants in the control arm crossover to receive the intervention. In either case, the extent of crossover can be large enough to significantly confound the outcomes measured at Month 6 using ITT.

As outlined previously in Section 4.8.1, the combination therapy trials, ORAL Standard, Sync, and Scan, utilised an early escape design that allowed non-responders treated with placebo to crossover and receive tofacitinib at Month 3. The rationale for this design was based on ethical requirements to limit the exposure of patients to ineffective treatment. For those placebo patients who were deemed to be receiving benefit from their background MTX therapy, treatment was allowed to continue for a further 3 months.

Where the risk of ineffective treatment to the patients' health is deemed greater, trials may limit the exposure to control therapy to 3 months in total, regardless of response. This was the case for the ORAL Solo trial, in which placebo treated patients did not receive background DMARDs and in Step, where patients had previously exhausted effective cDMARD options and were now classed as bDMARD-IR.

There are no established statistical techniques readily available to address confounding from crossover in non-time-to-event outcomes; therefore, Pfizer have utilised various applications of non-responder imputation and LOCF to explore the clinical uncertainty

around relative treatment effect of tofacitinib in the ORAL trials via patient level data analyses (Section 4.8.1).

4.14 *Ongoing studies*

4.14.1 *ORAL Sequel*

ORAL Sequel (see Section 4.11 for data up to Month 75) is currently ongoing. The results from the next data cut off are expected in September 2017.

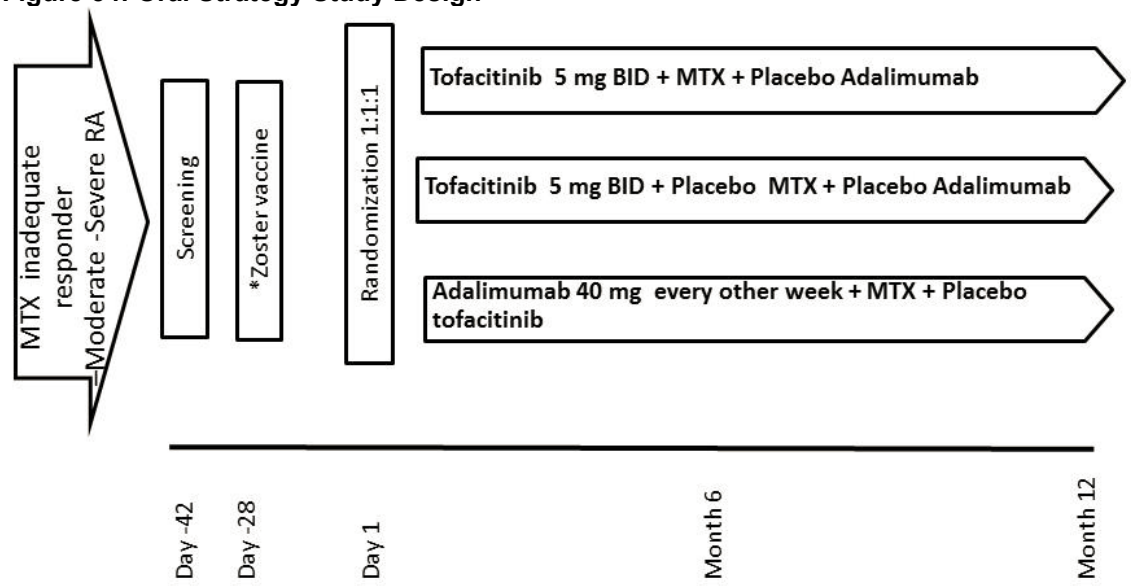
4.14.2 *ORAL Strategy*

ORAL Strategy (NCT02187055) (276) is a one year double-blind, triple-dummy, active comparator-controlled study evaluating tofacitinib 5 mg BD with or without MTX and adalimumab 40 mg subcutaneously every other week with MTX. Patients (N=1080) who have active RA and an inadequate response to MTX were randomised to treatment groups in a 1:1:1 ratio. The primary objectives of the study are to:

- compare the efficacy of tofacitinib 5 mg (with and without background MTX) with adalimumab (with MTX) as measured by ACR50 response rates at Month 6.
- compare the efficacy of tofacitinib 5 mg monotherapy vs tofacitinib 5 mg with MTX as measured by ACR50 response rates at Month 6.

Key secondary objectives are to compare the efficacy among the three arms in terms of ACR20, ACR50, ACR70, change from baseline in simple disease activity index (SDAI), DAS 28-4(ESR), and HAQ-DI over time.

Figure 54: Oral Strategy Study Design



Abbreviations: BID, twice daily; MTX, methotrexate; RA, rheumatoid arthritis.

[redacted]

[redacted]

EMPTY

[redacted]

[redacted]				
[redacted]				
[redacted]				
[redacted]	[redacted]			
[redacted]	[redacted]			

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

5 Cost effectiveness

- A patient-level simulation (PLS) model was used to determine the cost-effectiveness of tofacitinib in accordance with recent NICE Decision Support Unit guidance on PLS and statistical methods (24-27).
- The model utilises a two-step approach: EULAR response criteria are used to assess short-term efficacy (in line with clinical practice and TA375 (22)), while HAQ-DI is used to model long-term outcomes.
- Patient-level data were derived from the tofacitinib ORAL trials (Standard, Scan, Sync, Solo, and Step).
- The following base cases were considered using the PAS price, with the list price considered in scenarios:
  - Severe (DAS≥5.1) cDMARD-IR:
    - Combination therapy or monotherapy using Norton or rapid progression
  - bDMARD-IR:
    - Combination therapy for rituximab non-contraindicated (with tofacitinib as an option alongside rituximab) or rituximab contraindicated patients using Norton progression
    - Monotherapy for MTX intolerant and rituximab contraindicated patients using Norton progression
    - Combination therapy for rituximab non-contraindicated patients using Norton progression with tofacitinib as an option only after rituximab
- A scenario analysis was also considered for patients with moderate RA (3.2>DAS<5.1) who are cDMARD-IR receiving combination therapy or monotherapy with either Norton or rapid progression
  - This scenario used either the model used for severe cDMARD-IR or an adapted 'moderate' version of the model

Severe (DAS≥5.1) cDMARD-IR combination therapy

- The ICER for tofacitinib + MTX vs MTX ranged from £23,676–41,617 with rapid and Norton progression, respectively
- Tofacitinib + MTX dominated or extendedly dominated all other treatments using both progression assumptions with the exception of tocilizumab + MTX and infliximab biosimilar + MTX (rapid progression only
- The ICER for tocilizumab + MTX vs tofacitinib + MTX ranged from £88,129–139,113 with rapid and Norton progression, respectively
- The ICER for tofacitinib + MTX vs infliximab biosimilar + MTX with rapid progression was £34,201
- In scenario analysis:
  - The ICER for tofacitinib + MTX vs MTX ranged from £25,241–48,915.
  - Tofacitinib dominated or extendedly dominated treatments other than MTX in 16 of 21 scenarios, had ICERs ranging from £43,056–53,210 vs infliximab biosimilar + MTX in

three scenarios and was extendedly dominated by infliximab biosimilar + MTX in two scenarios.

- In the scenarios representing the two base cases using the list price instead of the PAS price the ICER for tofacitinib + MTX vs MTX was £25,241 using rapid progression and tofacitinib + MTX was dominated by MTX using Norton progression.

Severe (DAS≥5.1) cDMARD-IR monotherapy

- The ICER for tofacitinib vs MTX ranged from £25,807–56,231 for rapid progression and Norton progression, respectively
- Tofacitinib dominated or extendedly dominated all other treatments for both progression settings with the exception of tocilizumab
- The ICER for tocilizumab vs tofacitinib + MTX was £38,974–57,475 for rapid progression and Norton progression, respectively
- In scenario analysis:
  - The ICER for tofacitinib vs MTX ranged from £27,335–58,597 across the scenarios considered, and tofacitinib was extendedly dominated by MTX in 9 of the 17 scenarios.
  - Tofacitinib dominated or extendedly dominated treatments other than MTX in 6 of 17 scenarios.
  - In the scenarios representing the two base cases using the list price instead of the PAS price the ICER for tofacitinib vs MTX was £27,335 with rapid progression and tofacitinib was extendedly dominated by MTX using Norton progression

bDMARD-IR combination therapy

- For rituximab non-contraindicated:
  - Tofacitinib + MTX was not cost-effective
- For rituximab contraindicated:
  - Tofacitinib + MTX dominated or extendedly dominated all treatments
- In all scenarios, tofacitinib dominated or extendedly dominated all comparators, or the comparator had an ICER >£63,685 vs tofacitinib.

bDMARD-IR monotherapy, MTX and rituximab intolerant

- The ICER for tofacitinib vs tocilizumab was £25,932

bDMARD-IR combination therapy, rituximab non-contraindicated, tofacitinib used after rituximab

- The ICER for tofacitinib + MTX after rituximab vs rituximab + MTX was £28,379
- Tofacitinib + MTX after rituximab dominated or extendedly dominated all other treatments with the exception of abatacept + MTX
- The ICER for abatacept + MTX vs tofacitinib + MTX was £1,544,810

Moderate (3.2>DAS<5.1) cDMARD-IR results

- For combination therapy using the severe model and TA375 sequence the ICER for tofacitinib + MTX vs DMC ranged from £31,397–52,549 depending on price and progression setting
- For combination therapy using the severe model and **alternate** sequence the ICER for tofacitinib + MTX vs DMC ranged from £29,186–46,623 depending on price and progression setting
- For combination therapy using the **moderate** model and alternate sequence the ICER for tofacitinib + MTX vs DMC ranged from £38,389–60,364 depending on price and progression setting
- For **monotherapy** using the moderate model and alternate sequence the ICER for tofacitinib + MTX vs DMC ranged from £38,140–60,041 depending on price and progression setting

Conclusion

- Compared with MTX, tofacitinib (with or without MTX) is a cost-effective treatment in the severe cDMARD-IR population when rapid progression is assumed
- Compared with bDMARDs, tofacitinib (with or without MTX) is a cost-effective treatment for severe RA in both cDMARD-IR and bDMARD-IR patients, with the exception of when tofacitinib is assumed to be used alongside/instead of rituximab in bDMARD-IR patients
- In patients with moderate RA the ICER for tofacitinib + MTX vs DMC ranged from £29,186–60,364.

5.1 *Published cost-effectiveness studies*

5.1.1 *Identification of studies*

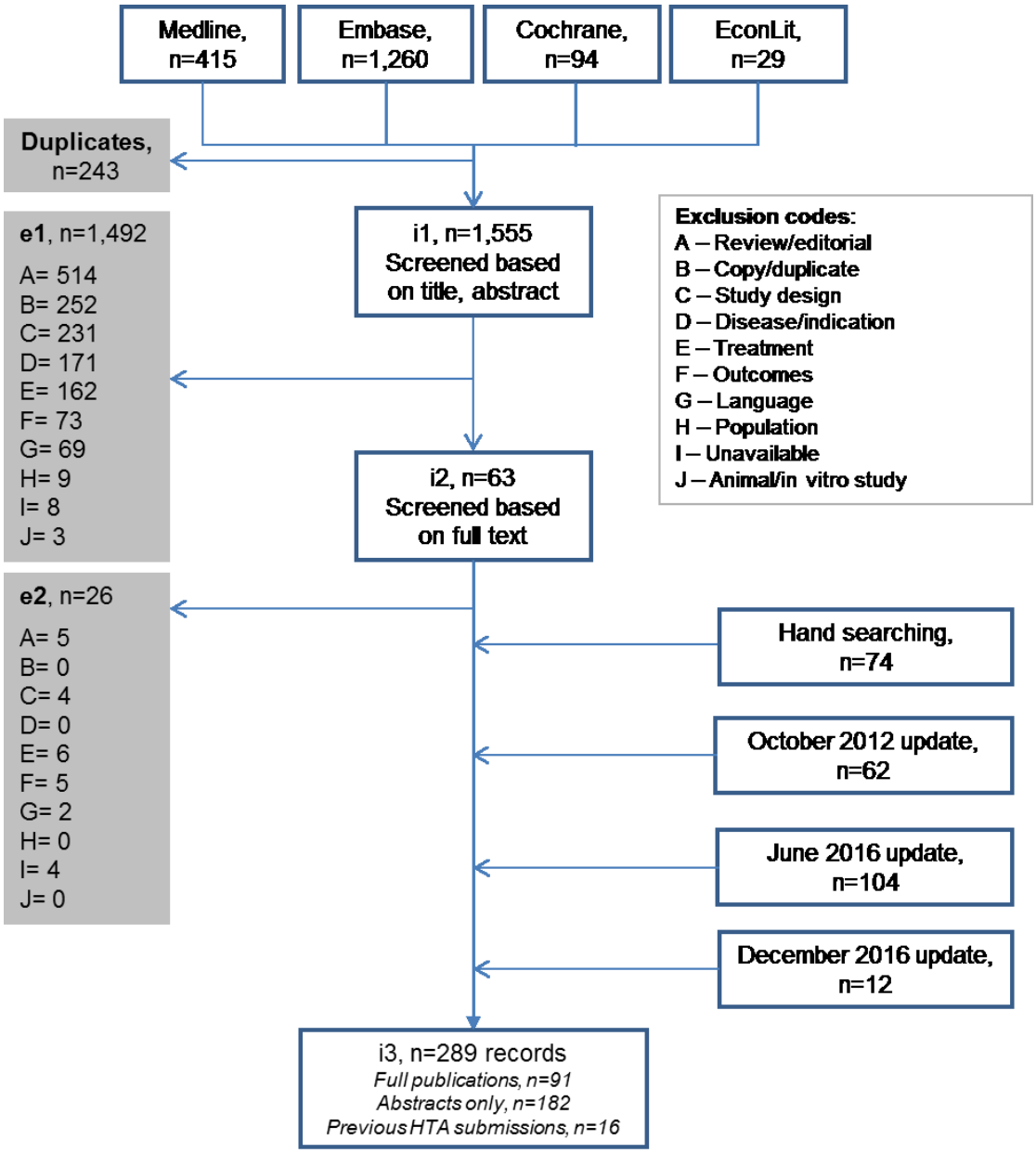
A systematic review was conducted to identify cost-effectiveness studies from the published literature relevant to the decision problem. Full details of the search are provided in Appendix 9.

Overall, a total of 289 publications were eligible for inclusion across the original review and three subsequent updates (full publications, n=91; abstracts, n=182; previous HTA submissions, n=16). This total includes 16 relevant previous HTA submissions (NICE, n=7; CADTH, n=4; PBAC, n=4; SMC, n=1). On completion of the June 2016 update, one abstract included in the original review (277), and five abstracts included in the October 2012 update (278-282) were found to have been superseded by full publications included in the most recent update (283-288). In addition, on completion of the December 2016 update, two abstracts identified by the June 2016 update were superseded by full publications (289, 290). For completeness, these abstracts were not excluded and their details have been retained in the current report. Furthermore, five of the previous HTA submissions identified by the original review and the October 2012 update (NICE TA130, TA186, TA198, TA225, and TA234) were replaced or updated by the guidance in NICE TA375 which was identified by the June 2016 update.

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the overall flow of studies across the original review and the two updates is shown

in Figure 56. Individual PRISMA flow diagrams showing the separate flow of studies through the original review, the October 2012 update, the June 2016 update, and the December 2016 update are shown in Figure 117, Figure 118, Figure 119, and Figure 120 (Appendix 9), respectively.

Figure 56. PRISMA flow diagram for the economic systematic reviews



5.1.2 *Description of identified studies*

5.1.2.1 Full publications

Across the three reviews, a total of 91 relevant full publications were identified (original review, n=44; October 2012 update, n=10; June 2016 update, n=30; December 2016 update, n=7). Overall, 60 were cost-utility analyses, 12 were cost-effectiveness analyses,

two were cost-minimisation analyses, and two were cost-benefit analyses. The remaining 15 studies reported both cost-effectiveness and cost-utility outcomes. Countries in which the economic evaluations were conducted included: the US (n=17), the UK (n=13), Sweden (n=12), the Netherlands (n=8), Italy (n=5), Canada (n=5), Finland (n=5), France (n=4), Germany (n=4), Japan (n=3), Spain (n=3), China (n=2), Iran (n=2), Greece (n=2), South Korea (n=2), Serbia (n=1), Norway (n=1), Colombia (n=1) and the Republic of Ireland (n=1). All included studies considered a population of patients with rheumatoid arthritis. In terms of disease severity, the following populations were considered:

- Patients with moderate-to-severe RA (n=19)
- Patients with early/newly diagnosed RA (n=11)
- Patients with active RA (n=10)
- Patients with severe RA (n=4)
- Patients with refractory RA (n=1)
- Patients with established/long-standing RA (n=1)
- Patients with advanced RA (n=1)
- Patients with stable low-disease activity RA (n=1)
- Patients with RA with no indication of disease severity (n=43)

With regards to prior treatment, the following populations were considered (note: some studies may fall under more than one category):

- Patients with an inadequate response to at least one bDMARD/anti-TNF (n=14)
- Patients with an inadequate response to MTX or who are MTX-resistant (n=13)
- Patients with an inadequate response to at least one cDMARD/traditional DMARD (n=10)
- Patients with an inadequate response to DMARDs in general (n=10)
- Patients who are bDMARD-naïve or who are receiving first-line biologic therapy
- Patients who are cDMARD/MTX naïve (n=3)
- Patients who are DMARD naïve (n=1)
- Patients eligible for anti-TNF therapy (n=1)
- Patients in whom a previous biologic drug has not failed (n=1)

In 11 studies, patients were treated with a bDMARD/anti-TNF agent; however, the line of therapy was not clear. In 28 studies details regarding patients' prior treatment were not reported. Overall, seven publications explicitly considered a population of patients with moderate-to-severe RA and with an inadequate response to DMARDs (cDMARDs, traditional DMARDs, or synthetic DMARDs) and three studies assessed the cost-effectiveness of bDMARDs in the first-line setting for patients with moderate-to-severe RA. The following approaches to modelling were adopted in the included studies:

- Patient simulation model (n=32)

- Markov model (n=33)
- Decision tree model (n=8)
- Trial-based analyses (no model) (n=18)

The analyses were conducted from the following perspectives: payer perspective (n=39) (of these, seven studies specifically considered a UK NHS perspective); societal perspective (n=27); policy maker perspective (n=2); both payer and societal perspectives (n=10); perspective not reported (n=13). The time horizon of the analyses ranged from 6 months to a lifetime. The methodology and results of included full publications are shown in Table 241 and Table 242 of Appendix 9 Section 8.9.4).

5.1.2.2 Abstracts

The 182 abstracts (original review, n=62; October 2012 update, n=51; June 2016 update, n=64; December 2016 update, n=5) included across the three reviews are summarised in Table 243 of Appendix 9 (Section 8.9.5).

5.1.2.3 HTA submissions

All relevant previous HTA submissions (n=16) identified by the reviews are summarised in Table 244 of Appendix 9 (Section 8.9.6). All but one (TA195) of the six previous HTA submissions identified by the original review and October 2012 update were replaced or updated by the guidance in TA375, which was identified by the June 2016 update. The full publication by Stevenson et al, 2016 (136) provided a critique of the manufacturer's submissions for TA375 and was used to obtain information regarding the approaches taken to modelling.

Previous NICE submissions (n=2)

TA195: ADA, ETN, INF, RTX, and ABA for the treatment of RA after failure of a TNF inhibitor

Five manufacturers provided economic analyses to support their submissions. All submissions were based on cost-utility analyses run over a lifetime horizon and from the perspective of the healthcare provider. All but one submission (abatacept [ABA], Bristol-Myers Squibb) used cDMARDs as the base-case comparator. The ABA submission compared ABA with rituximab (RTX) and with a 'basket' of tumour necrosis factors (TNF) inhibitors.

The Assessment Group's independent economic analysis was carried out using the Birmingham Rheumatoid Arthritis Model (BRAM), which has been further updated to allow for a non-linear relationship between the Health Assessment Questionnaire and utility. The model is an individual patient sampling model that simulates a large population. Patients are assumed to follow a sequence of treatments, each of which involves starting a treatment, spending some time on that treatment, stopping the treatment if it is toxic or ineffective, and starting the next treatment. The BRAM compares six treatment sequences.

A summary of the five economic analyses provided by the manufacturers for TA195 is provided in Table 245 of Appendix 9 (Section 8.9.6).

TA375: ADA, ETN, INF, CZP, GOL, TOC, and ABA for RA not previously treated with DMARDs or after cDMARDs only have failed

The Assessment Group received submissions for a total of seven interventions, from six manufacturers (golimumab [GOL] and infliximab [INF] are both manufactured by Merck Sharp and Dohme). The Bristol-Myers Squibb submission evaluated both the intravenous (IV) and subcutaneous (SC) formulations of ABA.

Data from the manufacturer's submissions for TA375 were obtained from Stevenson et al, 2016, as the manufacturer's submissions were not available from the NICE website (Table 246 of Appendix 9 (Section 8.9.6)).

Previous CADTH (n=4), PBAC (n=4) and SMC (n=1) submissions

Four relevant previous CADTH submissions, four PBAC submissions, and one SMC submission were also identified and included in the June 2016 update review. A summary of these is provided in Table 247 of Appendix 9 (Section 8.9.6).

The treatments considered in these submissions included:

- Abatacept (n=1)
- Golimumab (n=1)
- Infliximab (n=1)
- Tocilizumab (n=4)
- Tofacitinib (n=2)

Six of the submissions considered a population of patients with moderate-to-severe RA (all four CADTH submissions, PBAC TOC 2013, and SMC TOC), and three considered only patients with severe active RA (PBAC INF, PBAC TOF, and PBAC TOC 2016). In addition, six submissions specified that patients were required to have failed on or have an inadequate response to previous therapy with DMARDs (CADTH IV GOL, CADTH TOC, CADTH TOF, PBAC TOC 2013, PBAC TOF, and SMC TOC) (see Table 247). All nine submissions used cost-minimisation analyses to demonstrate the cost-effectiveness of their product.

Other previous HTA submissions not included in the review

In addition to the 16 included previous HTA submissions, a number of relevant submissions were identified as part of the June 2016 update for which inadequate information was available regarding the manufacturer's submission, or, in the case of some SMC submissions, had been superseded by a NICE multiple technology appraisal (MTA). Although these were not formally included in the review, they are listed in Table 248 of Appendix 9 (Section 8.9.6) for completeness.

5.1.3 *Quality assessment of identified studies*

Quality assessments are provided in Appendix 10.

5.2 *De novo analysis*

5.2.1 *Patient population*

An economic evaluation was conducted to determine the cost-effectiveness of tofacitinib treatment in people with moderate-to-severe active RA who have had an inadequate response or are intolerant to previous therapy with a DMARD (cDMARD or bDMARD). Severe disease is defined by NICE as a DAS28 >5.1, while a DAS28 between 3.2 and 5.1 indicates moderate disease (1). Current clinical guidelines and product indications within this patient population are not homogenous, and treatment may differ based on disease severity (moderate or severe RA) and the previous use of DMARDs (bDMARDs or cDMARDs). This population is therefore further defined as the following mutually exclusive patient populations:

Base-case analyses

- Individuals with severe RA (DAS28 >5.1) who have had inadequate response or are intolerant to cDMARDs only (Severe-cDMARD-IR)
- Individuals with severe RA (DAS28 >5.1) who have had inadequate response or are intolerant to bDMARDs (Severe-bDMARD-IR)

Scenario analysis

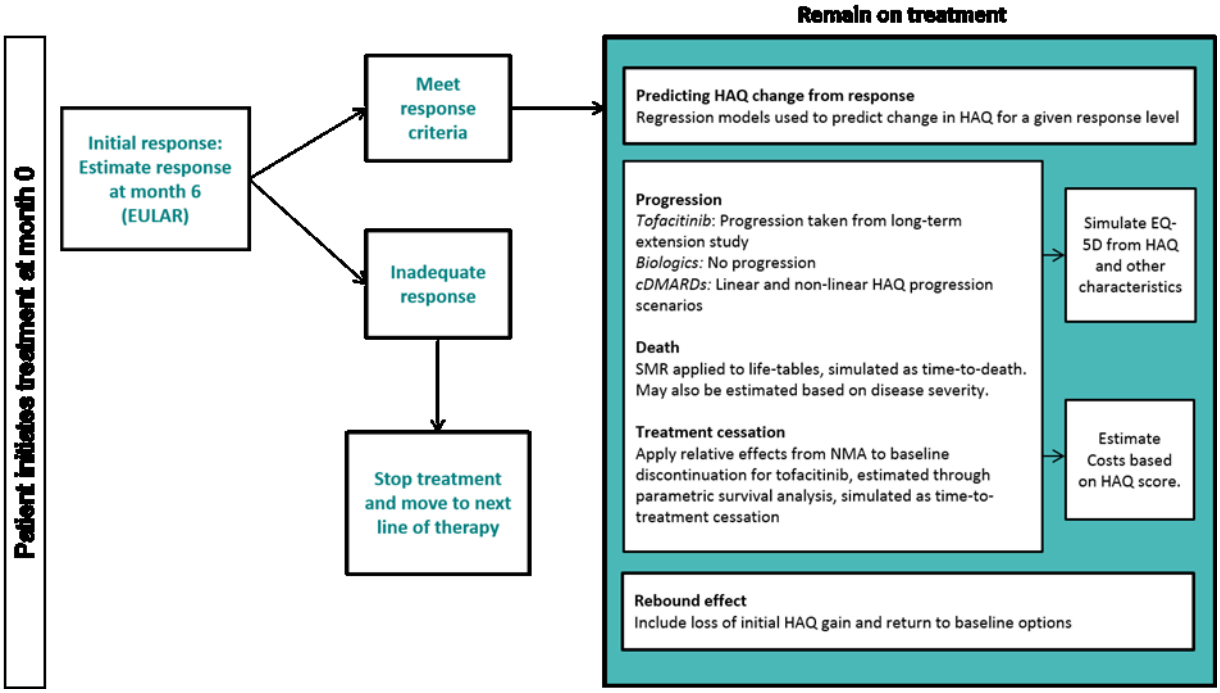
- Individuals with moderate RA (DAS28 3.2–5.1) who have had inadequate response or are intolerant to cDMARDs only (Moderate-cDMARD-IR)

5.2.2 *Model structure*

A patient-level simulation (PLS) model was used and the model has been developed in accordance with recent NICE Decision Support Unit guidance on PLS and statistical methods (24-27).

PLS has been undertaken extensively in RA, as the clinical pathway, treatment duration and sequential use of treatments allow for patient characteristics to be tracked within a simulation model (291-293). Time on treatment and disease progression are time-dependent, while modelling the effects of treatment withdrawal, and any subsequent rebound effect, requires knowledge of patients' disease status prior to treatment. Furthermore, in a previous NICE appraisal a PLS approach was suggested by the Evidence Review Group (ERG) to be the most appropriate model for RA due to the ability to allow more structural changes to the model and more varied sensitivity analyses (294); a PLS approach was also applied by the manufacturers and the assessment group in TA375 (136). A diagram of the model is shown in Figure 57.

Figure 57: Outline of model methods



Abbreviations: cDMARD, conventional disease-modifying anti-rheumatic drug; EQ-5D, European Quality of Life 5 Dimensions; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; NMA, network meta-analysis; SMR, standardised mortality ratio.

PLS requires the generation of a hypothetical patient cohort, with each patient given a set of clinical characteristics at baseline. These include baseline age, gender, weight, HAQ-DI score, DAS28, previous DMARD use (number and type of prior therapies), and disease duration. These characteristics are sampled directly from the baseline characteristics of the Phase III tofacitinib ORAL trials: Standard, Scan, Sync, Solo and Step (122-124, 126, 129). Patient-level data within each of these trials were stratified according to disease severity and treatment history, and the model randomly samples with replacement from trial participants based on the population defined for the base case. The patient population is sampled prior to the model being run and each sequence is run for each patient.

Our approach differs from TA375 which used BSRBR data simulate a patient cohort (1); however, it has the advantage of using tofacitinib-specific data which contains variables not included in the BSRBR data set. By using data from ORAL clinical trials we are able to test the inclusion of variables such as rheumatoid factor, anti-CCP positivity and cholesterol in predictive models of patient's response to treatment. Additionally, using available BSRBR data would involve simulating a population, which makes assumptions about the covariance structure in the population which sampling does not.

NICE DSU guidance from TA375 presents three sets of baseline characteristics from the BSRBR. These are the mean characteristics of the full, UK treated biologics population from the British Society for Rheumatology Biologics Register (BSRBR) that formed the sampling frame for the AG cost effectiveness model. The "severe active" group: the mean characteristics for patients treated with biologics, (Jan 2010 – June 2014), and with a DAS>5.1 from the BSRBR register. The "moderate active" group: the mean characteristics for patients treated with biologics, (Jan 2010 – June 2014), and with a

DAS≤5.1 and >3.2. These characteristics are presented in Table 91. It can be seen that patients in the ORAL clinical trials were [redacted].

Table 91: Comparison of baseline characteristics from the BSRBR and ORAL clinical trials

	BSRBR		Severe		Moderate		ORAL CTs	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age	56.2	12.2	57.3	12.5	58	13.6	[redacted]	[redacted]
Proportion female	0.8	0.4	0.8	0.2	0.7	0.2	[redacted]	[redacted]
Disease duration (years)	13.3	9.6	9.4	9.3	10.2	10.5	[redacted]	[redacted]
DAS28	6.6	1	6.2	0.8	4.4	0.6	[redacted]	[redacted]
Previous DMARDs	3.9	1.6	2.8	1	2.9	1	[redacted]	[redacted]
HAQ	2	0.6	1.6	0.7	1.5	0.8	[redacted]	[redacted]
Weight (kg)	73.1	17.6	78.8	19.6	76.1	19.1	[redacted]	[redacted]

The impact of sampling a patient cohort using mean characteristics from the BSRBR were ecplored in scenarios analyses. Where a variable that was not available was required, the mean was taken from ORAL clinical trial data.

All patient populations considered (moderate and severe; cDMARD-IR and bDMARD-IR) flow through the model in the same way. Patients enter the model on initiation of the first therapy in the treatment sequence and have an initial probability of responding to treatment (EULAR response criteria; see Section 5.3.2.1), based on their clinical characteristics at baseline. Patients who do not respond transition to the next treatment in the sequence, while those who do respond continue on treatment for a period randomly sampled from a log-normal distribution where the hazard rate is determined by their clinical characteristics at baseline. The impact of using alternative distributions to estimate treatment cessation is explored in scenario analysis. This is repeated for each treatment in the sequence until a patient moves to the final phase of the sequence (palliative care therapy). Patients continue in the model until death.

The model utilises a two-step approach: EULAR response criteria are used to assess short-term efficacy (in line with clinical practice and TA375 (22)), while HAQ-DI is used to model long-term outcomes. A previous systematic review concluded that HAQ-DI remains the primary clinical measure for use within economic analyses; it is measured by almost all clinical studies, and correlates closely to health state utilities and costs (295). HAQ-DI is used to measure disease progression while on treatment and is associated with quality of life by mapping to EQ-5D. While DAS28 is the primary instrument now used in clinical practice and could be used to measure disease progression, it has been shown that it does not adequately explain variations in HRQoL (295) and was not used by the ERG in TA375 (22).

On initiation of a therapy, a patient experiences an initial improvement (decrease) in their HAQ-DI score based on their initial EULAR response (see Section 5.3.2.2). Following treatment initiation, patients are exposed to the risk of treatment cessation, HAQ-DI

progression, and death. On cessation of treatment, patients experience a worsening in HAQ-DI equal to their initial gain, an assumption which has been used previously (291).

[redacted]Under current NICE guidance, patients with moderate RA are not eligible to receive treatment with bDMARDs. Consequently, we would suggest that the treatment sequence for patients with moderate RA should only contain cDMARDs after tofacitinib, and not follow the sequence used in TA375, which mirrors the treatment pathway for patients with severe RA.

In addition, patients with moderate RA are at risk of their disease progressing, such that they cross the severe disease threshold, i.e., DAS>5.1, and become eligible for treatment with bDMARDs, which the model used in the base case analysis of this submission is not equipped to do. This is because of the way the base-case model handles treatment sequences. Treatment sequences in the base case are fixed, so that if a patient discontinues they start the next treatment in the sequence, regardless of their disease severity. Using this structure, it is not possible to model sequences that capture the progression of disease from moderate to severe in a sophisticated way.

[redacted]

Table 92: [redacted]

	Coefficient	SE	t	P>t	LCI	UCI
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DAS28, disease activity score in 28 joints; HAQ, Health Assessment Questionnaire; LCI, lower confidence interval; OLS, ordinary least squares; SE, standard error; UCI, upper confidence interval.

5.2.2.1 Key features of the de novo analysis

Table 93: Key features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime	Long enough to reflect all important differences in costs or outcomes between the technologies being compared
Were health effects measured in QALYs; if not, what was used?	Yes	N/A
Discount of 3.5% for utilities and costs	Yes	N/A
Perspective (NHS/PSS)	NHS and PSS	N/A

Abbreviations: NHS, National Health Service; PSS, Personal and Social Services; QALYs, quality-adjusted life years.

5.2.3 *Intervention technology and comparators*

5.2.3.1 Interventions

The intervention considered in the model is tofacitinib. Tofacitinib in combination with MTX is indicated for the treatment of moderate-to-severe active RA in adult patients who have responded inadequately to, or who are intolerant to ≥1 DMARDs.

Tofacitinib can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate. Tofacitinib is orally administered and is dosed at 5 mg twice a day and may be taken with or without food.

5.2.3.2 Comparators

Comparator therapies, current indications and current NICE recommendations are summarised in Table 94. Current treatment guidelines in RA recommend initiating treatment with cDMARDs as soon as a diagnosis of RA is made, with MTX forming part of the first treatment strategy (5). A list of the relevant treatment combinations within the model is provided in Table 95.

Table 94: Current treatments licenced and recommended in rheumatoid arthritis

Treatment	Population				Can be provided as monotherapy (without MTX)	NICE recommendations	
	Moderate-cDMARD-IR	Moderate-bDMARD-IR	Severe-cDMARD-IR	Severe-bDMARD-IR		Moderate	Severe
Tofacitinib	✓	✓	✓	✓	✓	N/A	
Etanercept	✓	✓	✓	✓	✓	Not recommended	Use in cDMARD-IR or restricted bDMARD-IR§ populations (22)
Abatacept	✓	✓	✓	✓	X	Not recommended	Use in cDMARD-IR or restricted bDMARD-IR§ populations (22)
Adalimumab	✓	✓	✓	✓	✓	Not recommended	Use in cDMARD-IR or restricted bDMARD-IR§ populations (22)
Certolizumab pegol	✓	✓	✓	✓	✓	Not recommended	Use in restricted bDMARD-IR§ populations (23)
Golimumab	✓	✓	✓	✓	X	Not recommended	Use in cDMARD-IR or restricted bDMARD-IR§ populations (22)
Infliximab†	✓	✓	✓	✓	X	Not recommended	Use in cDMARD-IR or restricted bDMARD-IR§ populations (22)
Rituximab	x	x	x	✓	X	Not recommended	Use in bDMARD-IR populations (21)
Tocilizumab	✓	✓	✓	✓	✓	Not recommended	Use in cDMARD-IR or restricted bDMARD-IR§ or rituximab-IR populations (100)
Methotrexate	✓	✓	✓	✓	N/A	First-line treatment‡	

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug; IR, inadequate response; MTX, methotrexate; NICE, National Institute of Health and Care Excellence.
†Infliximab is indicated for adult patients with active disease when the response to DMARDs, including MTX, has been inadequate. The licence for infliximab does not specify whether such patients are moderate and/or severe disease DMARD-IR patients (infliximab is also indicated in adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs). ‡In people with newly diagnosed active rheumatoid arthritis, a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) should be offered as first-line treatment as soon as possible, ideally within 3 months of the onset of persistent symptoms. §Can be used in bDMARD-IR patients who cannot receive rituximab therapy because they have a contraindication to rituximab, or when rituximab is withdrawn because of an adverse event.

Table 95: Treatments considered in the economic evaluation

Therapy	Drug class
Tofacitinib + MTX	JAK inhibitor
Adalimumab + MTX	bDMARD
Certolizumab + MTX	
Etanercept + MTX	
Abatacept + MTX	
Golimumab + MTX	
Infliximab + MTX	
Rituximab + MTX	
Tocilizumab + MTX	
Etanercept Biosimilar + MTX	
Infliximab Biosimilar + MTX	
MTX	cDMARD
Ciclosporin	
Leflunomide	
Sulfasalazine	
DMARD combination	
Tofacitinib monotherapy	JAK inhibitor
Adalimumab monotherapy	bDMARD
Certolizumab monotherapy	
Etanercept monotherapy	
Tocilizumab monotherapy	
Etanercept Biosimilar monotherapy	
Palliative care	cDMARD

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug; JAK, Janus kinase; MTX, methotrexate.

This economic evaluation compared treatment sequences following an inadequate response to intensive therapy with a combination of cDMARDs (cDMARD-IR) or failure of treatment with ≥1 bDMARDs (bDMARD-IR). Comparator treatment sequences which follow current NICE recommendations are summarised for:

- Base case 1 – severe cDMARD-IR (Table 96)
- Base case 2 – bDMARD-IR (Table 97)
- Scenario – moderate cDMARD-IR (Table 98)

All treatment sequences finishing with the use of palliative care (other cDMARDs), which was adopted previously in TA375 (136). The sequences contain up to seven therapies, as this reflects the current NICE guidelines (22). For the severe cDMARD-IR population, current

NICE guidance (CG79) recommends offering a combination of DMARDs, which should include MTX (if tolerated) and ≥1 DMARD plus short-term glucocorticoids (87).

The following rationales were made for the treatment sequences used in the economic analyses;

1. Base case 1 – severe cDMARD-IR (Table 96);

The treatment sequences follow the approach taken by the assessment group in TA375. Using these sequences has two advantages; firstly, making full use of the seven therapies avoids patients receiving palliative care early in the lifetime treatment, thus avoiding increased costs in the comparator arm (DMC). Secondly, using these sequences enhances the comparability of the TA375 outputs with the economic analysis presented in this submission. Scenario analyses with different treatment sequences are presented in sections 5.7.6, 8.14 and 8.15.

2. Base case 2 – bDMARD-IR (Table 97)

The treatment sequences are aligned with current NICE treatment pathways and broadly replicate the strategies used in TA415 (23). The same rationales apply as outlined in base case 1. Further scenario analyses with different treatment sequences are presented in section 5.7.6, 8.14 and 8.15.

3. Scenario – moderate cDMARD-IR (Table 98)

[redacted]

Table 96: Treatment sequences considered by the economic evaluation for moderate-to-severe cDMARD-IR

Treatment sequence	Combination therapy											Monotherapy				
	DMC	ABT+ MTX	ADA+ MTX	CZP+ MTX	ETN+ MTX	GOL+ MTX	INF+M TX	TOC+ MTX	TOF+ MTX	ETNb+ MTX	INFb+ MTX	SSZ+ HQC	TOC	TOF	ETN	ADA
1	DMC	ABT+ MTX	ADA+ MTX	CZP+ MTX	ETN+ MTX	GOL+ MTX	INF+ MTX	TOC+ MTX	TOF+ MTX	ETNb+ MTX	INF+ MTX	SSZ+H QC	TOC	TOF	ETN	ADA
2	DMC	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	SSZ+H QC	ETN	ETN	ADA	ETN
3	DMC	TOC+ MTX	TOC+ MTX	TOC+ MTX	TOC+ MTX	TOC+ MTX	TOC+ MTX	ETN+ MTX	TOC+ MTX	TOC+ MTX	TOC+ MTX	SSZ+H QC	SSZ+H QC	SSZ+H QC	SSZ+H QC	SSZ+H QC
4	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	SSZ+H QC	SSZ+H QC	SSZ+H QC	SSZ+H QC	SSZ+H QC
5	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	SSZ+H QC	SSZ+H QC	SSZ+H QC	SSZ+H QC	SSZ+H QC
6	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF
7	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC

Abbreviations: ABA, abatacept; ADA, adalimumab; cDMARD, conventional disease modifying anti-rheumatic drug; CZP, certolizumab pegol; DMC, DMARD combination; ETN, etanercept; GOL, golimumab; INF, infliximab; PaC, palliative care; RTX, rituximab TOC, tocilizumab; TOF, tofacitinib.
‡This will reflect a combination of potential therapies, including monotherapy and combination therapy.

Table 97: Treatment sequences considered by the economic evaluation for bDMARD-IR

Treatment sequence	RTX tolerant (with RTX)				RTX intolerant				RTX tolerant (after) RTX)			
	RTX+MTX	**TOF+MTX**	**ABT+MTX**	**GOL+MTX**	**TOF+MTX**	**ABT+MTX**	**TOC+MTX**	**GOL+MTX**	**RTX+MTX**	**TOF+MTX**	**ABT+MTX**	**GOL+MTX**
1	RTX+MTX	TOF+MTX	ABT+MTX	GOL+MTX	TOF+MTX	ABT+MTX	TOC+MTX	GOL+MTX	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX
2	TOC+MTX	TOC+MTX	TOC+MTX	TOC+MTX	TOC+MTX	TOC+MTX	GOL+MTX	TOC+MTX	TOC+MTX	TOF+MTX	ABT+MTX	GOL+MTX
3	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	TOC+MTX	TOC+MTX	TOC+MTX
4	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC
5	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	DMC	DMC	DMC
6	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	LEF	LEF	LEF
7	-	-	-	-	-	-	-	-	-	PaC	PaC	PaC

Abbreviations: ABA, abatacept; ADA, adalimumab; cDMARD, conventional disease modifying anti-rheumatic drug; DMC, DMARD combination; GOL, golimumab; LEF, leflunomide; PaC, palliative care; RTX, rituximab TOC, tocilizumab; TOF, tofacitinib.
‡This will reflect a combination of potential therapies, including monotherapy and combination therapy.

Table 98: Treatment sequences considered by the economic evaluation for moderate cDMARD-IR

Treatment sequence†	Moderate sequence						Severe sequence
	Combination TA375 sequence		Combination alternate sequence		Monotherapy		
	MTX	TOF+MTX	MTX	TOF+MTX	MTX	TOF	ETN+MTX
1	DMC	TOF+MTX	DMC	TOF+MTX	DMC	TOF	ETN+MTX
2	RTX+MTX	RTX+MTX	DMC	DMC	DMC	DMC	RTX+MTX
3	TOC+MTX	TOC+MTX	DMC	DMC	DMC	DMC	TOC+MTX
4	DMC	DMC	DMC	DMC	DMC	DMC	DMC
5	DMC	DMC	DMC	DMC	DMC	DMC	DMC
6	LEF	LEF	PaC	DMC	LEF	LEF	LEF
7	PaC	PaC		PaC	PaC	PaC	PaC

Abbreviations: cDMARD, conventional disease modifying anti-rheumatic drug; PaC, palliative care; TOF, tofacitinib.
†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. ‡This will reflect a combination of potential therapies, including monotherapy and combination therapy. ¶Combination therapy will still be possible with cDMARD but will not include MTX.

5.3 *Clinical parameters and variables*

5.3.1 *How are clinical data incorporated into the model?*

5.3.1.1 Description of analyses

This section contains a summary of the analyses used to inform the health economic modelling of tofacitinib in RA based on patient-level clinical data from Phase III clinical trials. Patient-level data are used to inform:

- EULAR response at Month 6
- Changes in HAQ-DI from the long-term extension studies
- Treatment discontinuation
- Changes in HAQ-DI score at Month 6 (optional in scenario analysis)

Data were derived from the ORAL trials (Standard, Scan, Sync, and Step) (122-124, 129) and the long-term extension study (pooled results from ORAL Sequel and Study 1041, see Section 4.11). These analyses were performed in accordance with relevant NICE Decision Support Unit (DSU) methodology (296, 297). All analyses were based on the full analysis set (FAS) population. The FAS is the primary efficacy population applied in analyses for all efficacy endpoints and included all patients who were randomised to the study and received ≥1 dose of the study drug.

5.3.2 *Transition probabilities*

5.3.2.1 Baseline probability of initial response – EULAR response

Initial EULAR response ("good", "moderate" and "no response") is based on improvements in DAS28 at Month 6 in line with TA375 (Table 99).

NICE stopping criteria require a patient to have at least a moderate EULAR response at Month 6 to continue treatment, thus a predictive regression model is applied to obtain the probability of each level of response, based on baseline characteristics (Table 101).

Table 99: EULAR response by change in DAS28

DAS28 at Month 6	Improvement in DAS28 from baseline		
	>1.2	≤1.2 and >0.6	≤0.6
≤3.2	Good	Moderate	No response
≤5.1 and >3.2	Moderate	Moderate	No response
>5.1	Moderate	No response	No response

Abbreviations: DAS28, Disease Activity Score in 28 joints; EULAR, EULAR, European League Against Rheumatism.
Source: Fransen et al, 2009 (88).

The baseline probability of response is estimated using patients from the tofacitinib 5 mg arms of the ORAL clinical trials. The analysis is based solely on tofacitinib patients as the relative effects for other drugs are based on the NMA data (Section 4.8.2.3). Patients

that discontinue before Month 6 for any reason are assumed to be non-responders, i.e. patients do not have a good or moderate EULAR response.

As EULAR response is an ordinal variable, the feasibility of an ordered logistic regression was assessed first. An ordered logistic model would be the preferred analysis as it makes the best use of the data by taking into account its ordinal nature. However, it also requires the proportional odds assumption, which states that a relationship between each pair of outcome groups is the same. This is a strong assumption and was tested using the 'omodel logit' command in Stata, which performs a likelihood ratio test with the null hypothesis that the coefficients are equal across categories. The results of this were then confirmed using a Brant test.

These tests were run initially on an ordered logistic model that estimates EULAR response at Month 6 based on age at baseline, gender, HAQ-DI at baseline, DAS28 at baseline and whether a patient is taking tofacitinib monotherapy or combination therapy. As both tests reject the parallel odds assumption, a multinomial logistic regression was applied instead. This model treats EULAR response as a categorical variable. The 'omodel logit' and Brant tests were reapplied using the coefficients of the final model and the parallel odds assumption was again rejected. Parameter selection was performed using Collett's approach.

Multinomial logistic regression avoids the proportional odds assumption, but ignores that the data are ordinal, instead treating data as categorical. To estimate such a model, a base category should be specified and then a model is estimated which explains the risk of being in each of the other categories, relative to the base category. A multinomial logistic regression with three categories will estimate two sets of parameters. If the 'No response' is used as the base category, the vectors of parameters β_2 and β_3 will correspond to outcomes 'Moderate' and 'Good', respectively. The probability of each outcome is then

$$P(response = j) = \frac{\exp(\beta_j X_i)}{\sum_{k=1}^{3} \exp(\beta_k X_i)},$$

where β_1 is a vector of zeros, so that $\exp(\beta_1 X_i) = 1$. The choice of base categories is not important, as the parameters will change but the relative probabilities will not.

In the selection procedure, the significance of parameters was tested using a Wald test, which uses the null hypothesis that the parameters associated with a variable in each equation of the regression model are simultaneously equal to zero. Thus all parameters are significant in the model overall, but may not be significant for the equations for moderate or good response individually. No response has been selected as the base-case outcome for the model, thus the relative risk ratios are relative to no response.

There were a total of 712 observations of EULAR response at Month 6 for patients treated with tofacitinib from the ORAL trials (Standard, Scan, Sync, and Step) (122-124, 129) including imputed values for patients who had left the trial. Table 100 presents the response rates for these patients.

Table 100: EULAR response rates at Month 6

EULAR response	N	Percent
No response	[redacted]	[redacted]
Moderate response	[redacted]	[redacted]
Good response	[redacted]	[redacted]
Total	712	100%

Abbreviations: EULAR, European League Against Rheumatism.

The results of the estimated multinomial logistic regression model are presented in Table 101. The results show that the probability of moderate and good responses decreases as patients get older or if they have previously received treatment with bDMARDs and that response rates are worse among females. Response rates increase among patient who are anti-CCP positive and a higher HAQ or DAS28 at baseline increases the chances of a moderate response but decreases the chance of a good response, while the opposite is true for CDAI.

Table 101: Results of the multinomial logistic model for EULAR response at Month 6

Variable	Moderate response			Good response		
	Coefficient	RRR	SE	Coefficient	RRR	SE
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti CCP positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DAS28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior bDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CDAI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; CCP, cyclic citrullinated peptide; DAS28, Disease Activity Score in 28 joints; HAQ-DI, Health Assessment Questionnaire-disability index; RRR, relative risk ratio; SE, standard error.
[†]Significant at the 10% level. [‡]Significant at the 5% level. [§]Significant at the 1% level.

Table 102 presents the observed and predicted response rates for tofacitinib 5mg in ORAL Scan, Sync and Standard and the pooled trials. This analysis presents results of the sample used to estimate response only. There are differences of up to 3.3% between observed and predicted response rates in the individual trials, but overall the model is a good predictor of response rates.

Table 102: Observed and predicted response rates for ORAL Scan, Sync and Standard

Response	ORAL Scan		ORAL Sync		ORAL Standard		Overall	
	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted
No response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Good response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.3.2.2 Change in HAQ-DI score at Month 6

A patient's initial response to treatment is defined by the EULAR response criteria, which results in a reduction in HAQ-DI at Month 6. Similarly, to TA375, the model base case uses fixed changes in HAQ score for good and moderate responders, which uses data from the BSRBR (136). In addition, change in HAQ-DI at Month 6 from the ORAL Scan, Sync and Standard are explored in scenario analyses (see Table 103).

Table 103: Change in HAQ-DI at Month 6 for each EULAR response type

EULAR response	TA375	Source	ORAL Trials	Source
No response	0.00	Assumption	[redacted]	[redacted]
Moderate response	-0.321	BSRBR	[redacted]	
Good response	-0.678		[redacted]	

For the scenario analysis, a predictive model of change in HAQ-DI score at Month 6, based on the level of EULAR response at Month 6, therapy type and baseline characteristics has been estimated using data from ORAL Scan, Sync and Standard (Table 104). A linear model is estimated, with HAQ-DI scores artificially constrained to be between 0 and 3 in the tofacitinib RA economic model when the regression model predicts a change outside of these bounds. A linear model has the advantage of being simple, with coefficients that are easy to interpret. This model is only applied in the short term and is not related to HAQ-DI progression after Month 6. While HAQ-DI progression in cDMARDs should not be modelled in a linear fashion, it is acceptable to use a linear model for changes at Month 6, as this corresponds to previous assumptions of an average change in HAQ-DI based on the level of response (293). This approach is considered in scenario analysis.

Table 104: Predictive model of change in HAQ score at Month 6

Variable	Coefficient	SE
Moderate response	[redacted]	[redacted]
Good response	[redacted]	[redacted]
JAK/bDMARD	[redacted]	[redacted]
Age	[redacted]	[redacted]
Weight	[redacted]	[redacted]
HAQ-DI	[redacted]	[redacted]
Disease duration (years)	[redacted]	[redacted]
ESR	[redacted]	[redacted]
Total cholesterol	[redacted]	[redacted]
Constant	[redacted]	[redacted]

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-disability index; JAK, Janus kinase; SE, standard error.

The model has a R^2 of 0.3545 and a root mean-squared error of 0.4650. The model includes a benefit in HAQ drop for JAK inhibitors and bDMARD therapies. T-tests were applied to identify differences between treatments for different levels of EULAR response. There was no significant difference in HAQ change at Month 6 between the 5 mg and 10 mg doses of tofacitinib (Table 105), or between the tofacitinib and adalimumab arms of ORAL Standard (Table 106). However, there was a significant difference between the placebo and active treatment arms in the pooled data (Table 107). As the placebo arms for Scan, Sync and Standard include background MTX, they have been assumed to be representative of cDMARDs in this scenario. This analysis does not account for treatment switching in the placebo arms, thus some patients at Month 6 will be receiving active treatment. This approach is assumed to be conservative for tofacitinib and biologics, as HAQ changes in the active treatment arm are larger. Patients in the placebo arms who switch treatments are likely to have larger changes in HAQ than if they had remained on placebo.

Table 105: Comparison of HAQ change at Month 6 for different doses of tofacitinib

	HAQ change at Month 6	
	Moderate response	Good response
Tofacitinib 5 mg	[redacted]	[redacted]
Tofacitinib 10 mg	[redacted]	[redacted]
Difference	[redacted]	[redacted]
p-value for difference	[redacted]	[redacted]

Abbreviations: HAQ, Health Assessment Questionnaire.

Table 106: Comparison of HAQ change at Month 6 for tofacitinib 5 mg and adalimumab 40 mg in ORAL Standard

	HAQ change at Month 6	
	Moderate response	Good response
Tofacitinib 5 mg	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]	[redacted]
Difference	[redacted]	[redacted]
p-value for difference	[redacted]	[redacted]

Abbreviations: HAQ, Health Assessment Questionnaire.

Table 107: Comparison of HAQ change at Month 6 between placebo and active treatment arms

	HAQ change at Month 6	
	Moderate response	Good response
Placebo arms	[redacted]	[redacted]
Active treatment arms	[redacted]	[redacted]
Difference	[redacted]	[redacted]
p-value for difference	[redacted]	[redacted]

Abbreviations: HAQ, Health Assessment Questionnaire.

5.3.2.3 HAQ-DI long-term progression

The model contains five options for on-treatment HAQ progression.

Base case for tofacitinib and bDMARDs – No progression

This option is applied to tofacitinib and bDMARDs and assumes that while patients are on treatment their HAQ-DI score will not get worse. Thus a patient's HAQ-DI score is constant after the initial response at Month 6. This approach was applied by the manufacturers in TA375 and a similar approach was taken by the assessment group (AG) (136). The long-term HAQ-DI data from the tofacitinib long-term extension study showed no HAQ-DI progression over time. This supports the assumption of no HAQ-DI progression in line with current biologics on the market.

Base case for cDMARDs – Norton et al progression

The Norton et al (298) latent class analysis of HAQ-DI progression (as modified and used by the AG in TA375 (136)) is applied to cDMARDs. Norton et al identifies four classes of patients, whose HAQ-DI changes in different ways while receiving treatment with cDMARDs. These classes are low, moderate, high and severe HAQ progression. Norton et al presents the results of an analysis that predicts which class a patient will be in based on their baseline characteristics. As the patient's initial HAQ-DI response at Month 6 (based on the EULAR response) is assessed, the latent class method is not directly used. Instead, the method employed by the AG (applied in TA375 (136)) is used and the HAQ-DI change from the value at Year 1 in each class, weighted by the probability of being in each class, is applied. The value at Year 1 is used instead of the value at Month 6, as it is assumed that all HAQ-DI improvements occur in the initial 6 months of treatment and allows the HAQ-DI scores in the latent classes to plateau. The values used to produce probabilities for membership of each latent class, based on baseline characteristics, are shown in Table 108. These are defined relative to the low progression class; therefore, this does not appear in the table. A patient's age updates throughout the model, thus the probabilities are adjusted depending on the time spent in the model. These probabilities are also applied to the NICE DSU analysis for *rapid progressors* option.

Table 108: Predictors of class membership – Norton et al latent class analysis

Variable	Moderate		High		Severe	
	Parameter	SE	Parameter	SE	Parameter	SE
Constant	-3.50	0.62	-6.69	0.66	-12.06	1.10
Age	0.03	0.01	0.04	0.01	0.08	0.01
Female	0.84	0.20	1.69	0.21	1.98	0.27
DAS28	0.30	0.08	0.57	0.08	0.80	0.09
Disease Duration (years)	0.38	0.02	0.55	0.02	0.50	0.02
Rheumatoid factor positive	0.21	0.24	0.32	0.25	0.30	0.29
1987 ACR criteria	0.28	0.23	0.41	0.24	0.94	0.32
Socio-economic status	0.99	0.37	1.12	0.34	1.43	0.38

Abbreviations: ACR, American College of Rheumatology; DAS28, Disease Activity Score in 28 joints; SE, standard error.
Source: Norton et al, 2014 (298)

Table 109 presents the probabilities of class membership from the original paper (298), TA375 (136) and in the ORAL clinical trial series. The probability of being in the low or moderate classes is lower in the ORAL trial data. This is due to patients in the ORAL trials having a higher average DAS28 score and disease duration. The Early Rheumatoid Arthritis Study (ERAS) cohort used to estimate the Norton model recruited patients prior to a formal diagnosis of RA and all patients in the analysis have a symptom duration less than two years. The ORAL clinical trials recruited patients with established disease so have a higher average DAS28 and disease duration.

Table 109: Probability of class membership

Progression class	ERAS cohort	TA375	ORAL trials
Low	21.3%	13%	[redacted]
Moderate	33.4%	36%	[redacted]
High	29.5%	38%	[redacted]
Severe	15.8%	12%	[redacted]

Abbreviations: ERAS, Early Rheumatoid Arthritis Study; TA, technology appraisal.

Basecase for cDMARDs – NICE DSU analysis for rapid progressors

This option follows the analysis suggested by the NICE DSU (298), which was used by the NICE Appraisal Committee to inform its decision to recommend biologics for the severe RA cDMARD-IR in TA375, and is used to inform the base-case ICER range for this submission. This approach considered a subgroup within the early RA study (ERAS) who experienced rapid HAQ-DI progression utilising the latent class dropout analysis methodology as outlined by the DSU.

The DSU carried out a systematic review of the evidence for long-term HAQ-DI progression for cDMARDs and concluded that the Norton et al publication was the

preferred model. The DSU extended this analysis to examine dropout classes for each of the four progression classes. A model was fitted with three dropout classes for each progression class and a sensitivity analysis was recommended, which is based on utilising the highest HAQ-DI trajectory from the dropout classes within each progression class. This is class 1 for the severe and high classes and class 3 for the moderate class and class 2 for the low class.

This option is included in the model and the analysis uses the same probabilities of class membership as in the original analysis as outlined in the *Norton et al. progression* method outlined above.

ORAL long-term extension data (used in scenario analyses)

Two long-term extension studies, NCT00413699 (ORAL Sequel; Study 1024) and NCT00661661 (Study 1041), were conducted to evaluate the long-term efficacy and safety of tofacitinib. The data from these two studies were pooled and the results are presented in Section 4.11. ORAL Sequel is currently ongoing, whereas Study 1041, conducted in Japan, concluded in December 2013.

Patient-level HAQ-DI data for patients treated with tofacitinib are available up to 96 months. These data were applied directly in order to model the average change in HAQ-DI from Month 6, separated by EULAR response at month 6 in the acute study. The analysis of these data shows essentially no progression (Table 110, Figure 58). At the latter part of data collection, patient numbers become small and large variations in the change in HAQ-DI are observed. To address this, a cut-off point after which HAQ-DI is assumed to be constant is applied at Month 78.

This analysis is not applied in the base case, but is used as a scenario analysis. In this scenario tofacitinib HAQ progression is assumed to follow the curves in Figure 58, while no HAQ progression is assumed for biologics.

This analysis only considers HAQ scores while patients are receiving tofacitinib (5 or 10mg), thus all changes are measured from the time patients start taking tofacitinib. This is done to avoid capturing an additional reduction in HAQ when a patient switches to tofacitinib after previously receiving placebo or adalimumab.

Figure 59 presents HAQ change over time for the 5 mg and 10 mg doses individually. This shows little difference between the two doses[c].

[c] Using 5 mg data alone was considered but the small sample size resulted in fluctuations in the curve over time.

Table 110: Mean change in HAQ-DI from the long-term extension study by level of response at month 6

Month	Moderate response	Good response
0	[redacted]	[redacted]
3	[redacted]	[redacted]
6	[redacted]	[redacted]
9	[redacted]	[redacted]
12	[redacted]	[redacted]
15	[redacted]	[redacted]
18	[redacted]	[redacted]
21	[redacted]	[redacted]
24	[redacted]	[redacted]
27	[redacted]	[redacted]
30	[redacted]	[redacted]
33	[redacted]	[redacted]
36	[redacted]	[redacted]
39	[redacted]	[redacted]
42	[redacted]	[redacted]
45	[redacted]	[redacted]
48	[redacted]	[redacted]
51	[redacted]	[redacted]
54	[redacted]	[redacted]
57	[redacted]	[redacted]
60	[redacted]	[redacted]
63	[redacted]	[redacted]
66	[redacted]	[redacted]
69	[redacted]	[redacted]
72	[redacted]	[redacted]
75	[redacted]	[redacted]
78	[redacted]	[redacted]
81	[redacted]	[redacted]
84	[redacted]	[redacted]
87	[redacted]	[redacted]

Figure 58: [redacted]

EMPTY

[redacted]

EMPTY

NICE DSU analysis for rapid progressors

This option follows the analysis suggested by the NICE DSU (299), which was used by the NICE Appraisal Committee to inform its decision to recommend biologics for the severe RA cDMARD-IR in TA375, and is used to inform the base-case ICER range for this submission. This approach considered a subgroup within the early RA study (ERAS) who experienced rapid HAQ-DI progression utilising the latent class dropout analysis methodology as outlined by the DSU.

The DSU carried out a systematic review of the evidence for long-term HAQ-DI progression for cDMARDs and concluded that the Norton et al publication was the preferred model. The DSU extended this analysis to examine dropout classes for each of the four progression classes. A model was fitted with three dropout classes for each progression class and a sensitivity analysis was recommended, which is based on utilising the highest HAQ-DI trajectory from the dropout classes within each progression class. This is class 1 for the severe and high classes and class 3 for the moderate class and class 2 for the low class.

This option is included in the model and the analysis uses the same probabilities of class membership as in the original analysis as outlined in Option 2.

Linear HAQ-DI progression (used in scenario analyses)

For this option a linear HAQ-DI progression can be applied to treatments. The HAQ-DI scores are assumed to increase at an assigned constant rate at fixed intervals. The option is applied to palliative care at a rate of 0.06 HAQ per year, which translates to 0.125 approximately every 2.1 years and leflunomide at a rate of 0.045 per year, a 0.125 change every 2.7 years.

5.3.2.4 Treatment discontinuation

It is assumed that all patients will remain on therapy for at least 6 months. For patients who achieved a good or moderate EULAR response and remained on therapy after Month 6, treatment discontinuation was modelled using parametric regression.

Time on treatment was assessed using parametric survival analysis based on NICE DSU TSD14 (297). Data from the acute studies (Scan, Solo, Sync, Standard and Step) were pooled with data from the long-term extension studies in order to maximise the observed time on treatment. In order to pool data from the acute and long-term extension studies a patient's total time on treatment was used. The time to discontinuation was assumed to be the time to their first discontinuation; therefore, a patient's long-term extension data was only considered if they had completed the acute study.

[redacted]. Figure 60 presents Kaplan-Meier survival curves during the acute studies, Figure 61 presents the survival curves for the pooled acute and long-term extension studies and Figure 62 presents the survival curves by EULAR response at Month 6. The survival curves are similar to those provided in TA375 (Figure 63).

Figure 60: [redacted]

EMPTY

[redacted]

EMPTY

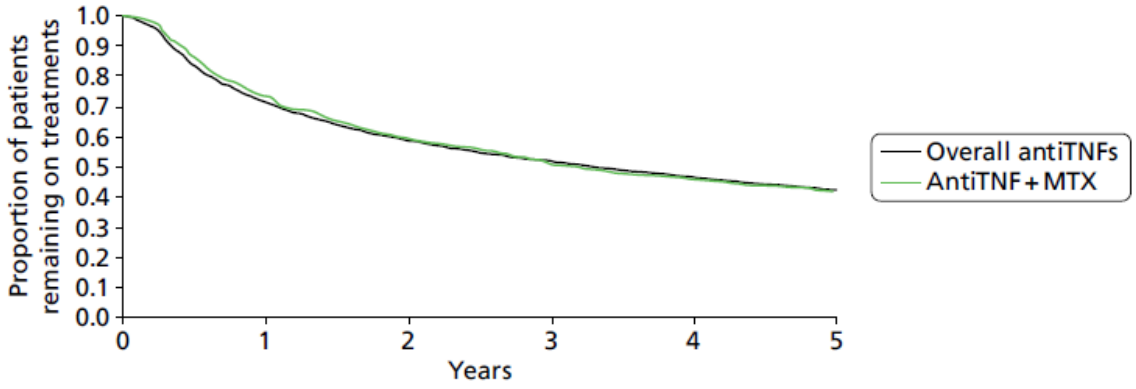
[redacted]

[redacted]

EMPTY

Abbreviations: EULAR, European League Against Rheumatism.

Figure 63: Kaplan–Meier estimates of the observed persistence with all anti-TNFs and with the combination from TA375



Source: Stevenson et al (136)

After controlling for levels of response, no significant differences between treatment arms were identified during the acute studies, or between the 5 mg and 10 mg doses of tofacitinib in the long-term extension studies. Therefore, it was assumed for this analysis that time to treatment discontinuation was independent of treatment allocation. As no treatment effects are being assessed, the effect of treatment switching upon entering the long-term extension study is assumed to be negligible.

A separate analysis has been performed for good and moderate responders, using age, sex, baseline DAS28, disease duration, number of previous DMARDs and HAQ-DI as

covariates, in line with analyses performed as part of TA375 (22). No transformations of variables were considered. No analysis was performed for non-responders as it is assumed that these patients will discontinue treatment after 6 months. Six distributions were considered: exponential; Weibull; Gompertz; log-normal; log-logistic; and generalised gamma (Table 111 and Table 112). The preferred model was selected based on Akaike information criterion (AIC), Bayesian information criterion (BIC) and visual inspection. The log-normal model has been selected for the base-case analysis as it performs best for both AIC and BIC for the good responders and best on BIC for the moderate responders; however, the gamma model was superior to the log-normal model on AIC (Table 113).

Table 111: Predictors of treatment discontinuation: Moderate responders

Variable	Exponential		Lognormal		Gompertz		Weibull		Loglogistic		Generalised Gamma	
	Coefficient	Standard Error	Coefficient	Standard Error	Coefficient	Standard Error	Coefficient	Standard Error	Coefficient	Standard Error	Coefficient	Standard Error
Age	[redacted]											
Female	[redacted]											
DAS28	[redacted]											
Disease Duration (years)	[redacted]											
Number of previous DMARDs	[redacted]											
HAQ-DI	[redacted]											
Constant	[redacted]											
Ancillary parameter (1)	[redacted]											
Ancillary parameter (2)	[redacted]											

Abbreviations: DAS28, Disease Activity Score in 28 joints; DMARDs, disease-modifying anti-rheumatic drug; HAQ-DI, Health Assessment Questionnaire-disability index.
†Ancillary parameter (1) is sigma. ‡Ancillary parameter (2) is kappa.

Table 112: Predictors of treatment discontinuation: Good responders

Variable	Exponential		Lognormal		Gompertz		Weibull		Log logistic		Generalised Gamma	
	Coefficient	Standard Error	Coefficient	Standard Error	Coefficient	Standard Error	Coefficient	Standard Error	Coefficient	Standard Error	Coefficient	Standard Error
Age	[redacted]											
Female	[redacted]											
DAS28	[redacted]											
Disease Duration (years)	[redacted]											
Number of previous DMARDs	[redacted]											
HAQ-DI	[redacted]											
Constant	[redacted]											
Ancillary parameter (1)	[redacted]											
Ancillary parameter (2)	[redacted]											

Abbreviations: DAS28, Disease Activity Score in 28 joints; DMARDs, disease-modifying anti-rheumatic drug; HAQ-DI, Health Assessment Questionnaire-disability index.
†Ancillary parameter (1) is sigma. ‡Ancillary parameter (2) is kappa.

Table 113: Selection of preferred model based on AIC and BIC for moderate and good responders

Distribution	AIC – moderate responders	BIC – moderate responders	AIC – good responders	BIC – good responders
Exponential	3180.809	3226.781	1226.02	1265.467
Weibull	3096.505	3149.043	1202.542	1247.624
Gompertz	3149.823	3202.361	1215.713	1260.796
Log-logistic	3069.907	3122.445	1199.353	1244.435
Log-normal	3043.964	3096.502	1195.594	1240.676
Gamma	3041.838	3100.943	1197.339	1248.057

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

5.3.2.5 Rebound effect

As in a previous decision analytic model developed in RA (22), treatment cessation is assumed to be associated with a 'rebound effect', in which a patient's HAQ-DI is assumed to have worsened prior to the initiation of the next treatment.

In the base-case, the initial gain in HAQ-DI declines over a 6-month period prior to treatment cessation. Upon treatment cessation, HAQ-DI will have returned to baseline levels. This is in line with the approach used in TA375 (22) and is preferred to the alternative option, where HAQ-DI returns to baseline. The return to baseline assumption is counterintuitive as the patient's underlying disease will have progressed over time with advancing age.

5.3.2.6 Mortality

The base-case uses the methodology for mortality applied during TA375 (22). A hazard ratio for mortality, varied depending on a patient's baseline HAQ-DI score, was applied to UK lifetables (Table 114). These ratios increase monotonically with HAQ-DI score.

Table 114: Mortality ratios by baseline HAQ-DI

HAQ-DI band	Standardised mortality rate
0, <0.125	1.0
≥0.125, <0.5	1.4
≥0.5, <1.0	1.5
≥1.0, <1.5	1.8
≥1.5, <2.0	2.7
≥2.0, <2.5	4.0
≥2.5	5.5

Abbreviations: HAQ-DI, Health Assessment Questionnaire-disability index.

The tofacitinib model only considers mortality based on baseline disease severity and does not update based on reductions in severity within the model. It has also been noted in previous submissions that the impact of any treatment for RA on mortality on cost-effectiveness ratios is marginal due to discounting (136). In practice, this means that

mortality can be modelled independently of the therapy received. As such, a patient's age at death is calculated upon the patient being read into the model and is constant between strategies.

5.3.3 *Clinical expert assessment of applicability of clinical parameters*

During an advisory board on the 3rd of February 2017 in London assumptions related to the submission were discussed with an UK expert panel consisting of clinicians, health economists, epidemiologists and representatives of NRAS. Several assumptions used in the economic analysis were confirmed. The experts suggested that the ORAL trial patient level baseline characteristics broadly reflects UK practice, although the disease duration is higher than seen in clinical practice (~9yrs for ORAL trials vs ~4yrs for MTX-IR patients in clinical practice). However, clinicians suggested that it appears that the ORAL trial patients would better reflect the harder to treat patients and the patients who were required to maintain treatment until DAS≥5.1, and eligible for biologic DMARD, thus using the ORAL trial patient level data may underestimate the benefits of tofacitinib. Other key assumptions were discussed and confirmed and are summarised below;

- Model-methodology: the expert panel suggested to follow TA375 modelling pathway in terms of EULAR response at month 6 and subsequent long-term HAQ progression to derive QALYs via EQ5D mapping. However, where possible it was suggested to incorporate tofacitinib ORAL trial data to inform the model further. Therefore, tofacitinib trial data to estimate the probability of EULAR response (Section 5.3.2.1) at month 6 were used in a scenario analysis, instead of the fixed EULAR change at month 6 as used in TA375. This is also the case for the HAQ-DI change at month 6. Clinicians advised to use tofacitinib data (Section 5.3.2.2), which is included as a scenario analysis in the economic results section.

- Comparators and treatment sequences for the relevant decision problem populations in the economic analyses were confirmed by the expert panel. However, clinicians suggested a different treatment pathway of using tofacitinib before biologics in the cDMARD-IR population. Clinicians felt that this would be the most appropriate positioning for tofacitinib. This sequence is not presented in this submission.

- HAQ progression; Clinical experts strongly recommended to use tofacitinib long-term extension HAQ data as it was felt to be an impressive data set to support zero HAQ progression assumption, which is assumed for current biologic DMARDs. Pfizer included it in the submission as a scenario analysis. The expert panel also confirmed that for end of sequence treatment (palliative care) a linear HAQ progression should be assumed, in line with TA375 assumptions. Rapid progression assumptions (NICE DSU analysis, Section 5.3.2.3) in the TA375 and as outlined in this submission were confirmed by the experts as relevant and applicable to the decision problem. Furthermore, clinicians stated that predictors of these patients are double-seropositivity of anti-CCP and Rheumatoid Factor, elevated ESR and CRP levels and erosion are any timepoint. These markers are a simple decision tool in clinical practice, however it was acknowledged that no clear published data on agreed threshold levels is currently available. However,

NRAS confirmed that a study on this is close to conclusion and will be able to provide this data. The expert panel suggested that Pfizer applies the same methodologies as in TA375 for its tofacitinib STA submission.

5.4 *Measurement and valuation of health effects*

5.4.1 *Health-related quality-of-life data from clinical trials*

Quality of life at all time points in the model is assessed in the base case by mapping patient HAQ-DI scores to the EQ-5D scale over the duration of the model. HAQ-DI response is a widely used measure in clinical trials and has been shown to correlate well with EQ-5D (295). While EQ-5D data were collected in the tofacitinib clinical trials, the relationship between quality of life in RA and treatment response is highly complex. As treatment durations are long, there is a need to extrapolate the effects of treatment on quality of life outside the trial periods. Previous studies appraising the cost-effectiveness of treatments for RA have used data on long-term HAQ-DI progression, as this is judged to provide the most robust relationship. Thus, this approach is consistent with previous models and is well validated (22).

5.4.2 *Mapping*

As of December 2016, there are 22 studies published exploring mappings from HAQ-DI to EQ-5D (300). One of the most recent of these is a mixture model produced by Hernández et al (301) in 2013, which was applied in the assessment group model for TA375 and will used in the base-case.

The Hernández model combines bespoke distributions in a mixture model to provide an estimate of EQ-5D based on a patients HAQ-DI, pain on a visual analogue scale (VAS), age and sex (301). HAQ-DI, age and sex are all baseline characteristics that will be included in the model. However, pain presents a greater challenge as it is closely linked to a patient's HAQ-DI score. In TA375 the assessment group assigned patients the expected pain score associated with their HAQ-DI score and their model used this relationship to estimate pain and subsequently predict EQ-5D (293). The tofacitinib model uses the same approach; however, a new relationship between HAQ-DI and VAS pain has been estimated using patient-level data from the Phase III tofacitinib ORAL trials: Standard, Scan, Sync, Solo, Start and Step (122-124, 126, 129). In the tofacitinib model, the benefit of using patient-level data is that it is a better predictor of EQ-5D scores, as shown in Section 5.4.3. The main difference is that no decrease in pain scores are observed for patients with a HAQ score of 3 and that HAQ scores are generally larger. This relationship is presented in Table 115.

The base-case uses the mixture model produced by Hernández et al (301) and applied by the assessment group in TA375 (136). A number of linear models are tested in scenario analyses.

Table 115: The relationship between HAQ-DI and VAS pain used to map to EQ-5D-3L

HAQ-DI	Mean VAS pain	SD	N
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HAQ-DI, Health Assessment Questionnaire-disability index; SD, standard deviations; VAS, visual analogue scale.

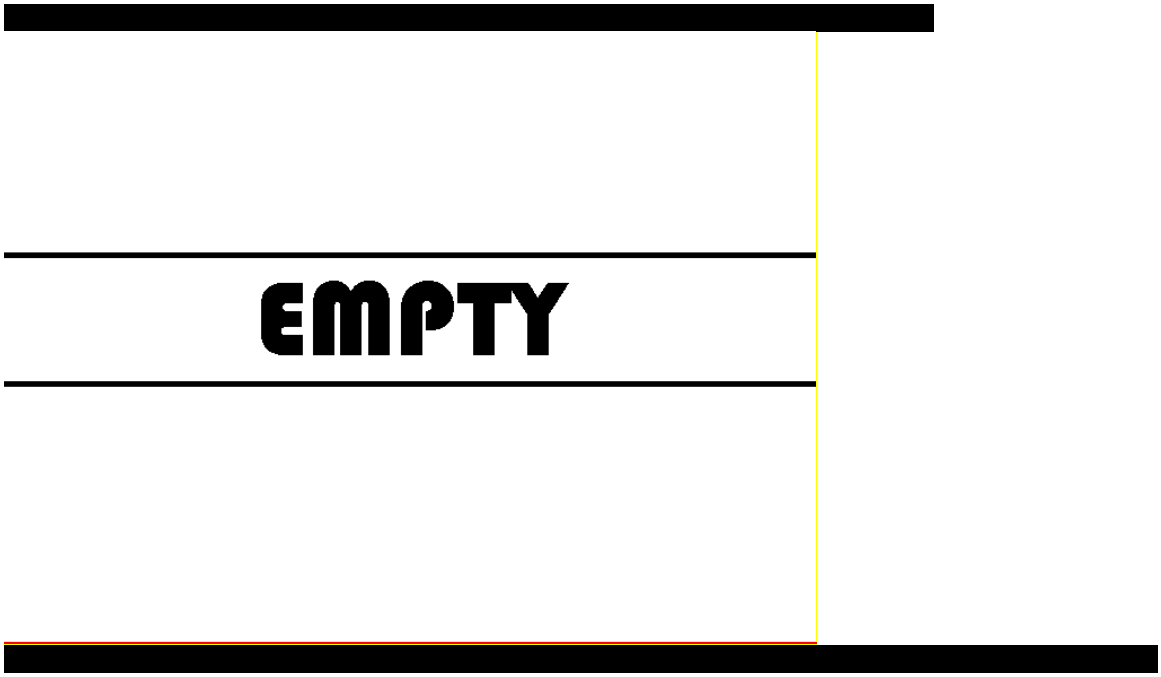
5.4.3 *Validation of mapping algorithms*

In order to identify the most appropriate mapping algorithm for use in the model, a validation study was performed. Published mapping algorithms from the HAQ-DI to EQ-5D utilities in RA were identified through searching the Health Economics Research Centre (HERC) database of mapping studies. Each study was reviewed and a mapping algorithm was deemed eligible for inclusion if it used EQ-5D utility values derived from the UK tariff and the mapping algorithms described were based on total HAQ-DI score (i.e. not based on single item responses or domain scores). Where a publication developed multiple mapping algorithms, only the ones recommended by the authors as having the best fit were included.

Each algorithm was then assessed on its ability to predict EQ-5D scores in the ORAL clinical trial data. The mean absolute error and root-mean squared error were calculated for each algorithm, and the mean absolute error was calculated on subsets of the EQ-5D range and for each possible HAQ score. The algorithms ability to predict QALYs in the dataset was also assessed.

5.4.3.1 Data source

Data from the ORAL clinical trial series has been used to validate the algorithms. All five trials (Scan; Sync; Standard; Solo, Step and Start) collected data on HAQ-DI, EQ-5D, age, gender and pain. The distributions of HAQ-DI and EQ-5D scores are presented in Figure 64 and Figure 65. There are a total of 18,100 observations of 4,215 patients with EQ-5D values.



EMPTY

5.4.3.2 Identified mapping algorithms

The HERC mapping database was reviewed to identify algorithms for mapping HAQ-DI to EQ-5D (300). Table 117 presents the details of the relevant algorithms. A total of 11 publications were identified, though two of these report the same algorithm, leaving 10 unique algorithms to be validated. However, the 2012 Hernandez publication (302) reports estimated utility values for a set of health states that could not be reproduced. Additionally, the later Hernandez publication (301) improves on the methods used; therefore, it was decided to exclude the Hernandez 2012 algorithm from the validation.

The majority of these algorithms use ordinary least squares regression methods, which have previously been deemed unsuitable for mapping to the EQ-5D. The Hernandez ALDVMM algorithm also uses VAS pain to estimate utility, which is not a variable that is tracked on an individual patient level in the tofacitinib model. In order for the ALDVMM algorithm to be incorporated into the model, three methods for estimating pain from HAQ-DI have also been included in the analysis, in addition to validating the algorithm using actual pain scores.

The first method is to apply the average pain by HAQ-DI score observed in the British Society for Rheumatology Biologics Register (BSRBR) data, as used by the ERG for TA375 (136). The second is to use the average pain by HAQ-DI score observed in the ORAL trial data and presented in Table 115. The third method is to use an ordinary least squares regression model to predict pain based on HAQ-DI, age and DAS28 at baseline. These options are summarised in Table 116.

Table 116: Options for applying the ALDVMM algorithm in the model

Algorithm	Source for pain scores
ALDVMM - est pain 1	Average pain score for HAQ-DI score from TA375
ALDVMM - est pain 1	Average pain score for HAQ-DI score from PLD
ALDVMM - est pain 1	OLS regression model

Table 117: List of algorithms identified from the HERC mapping database

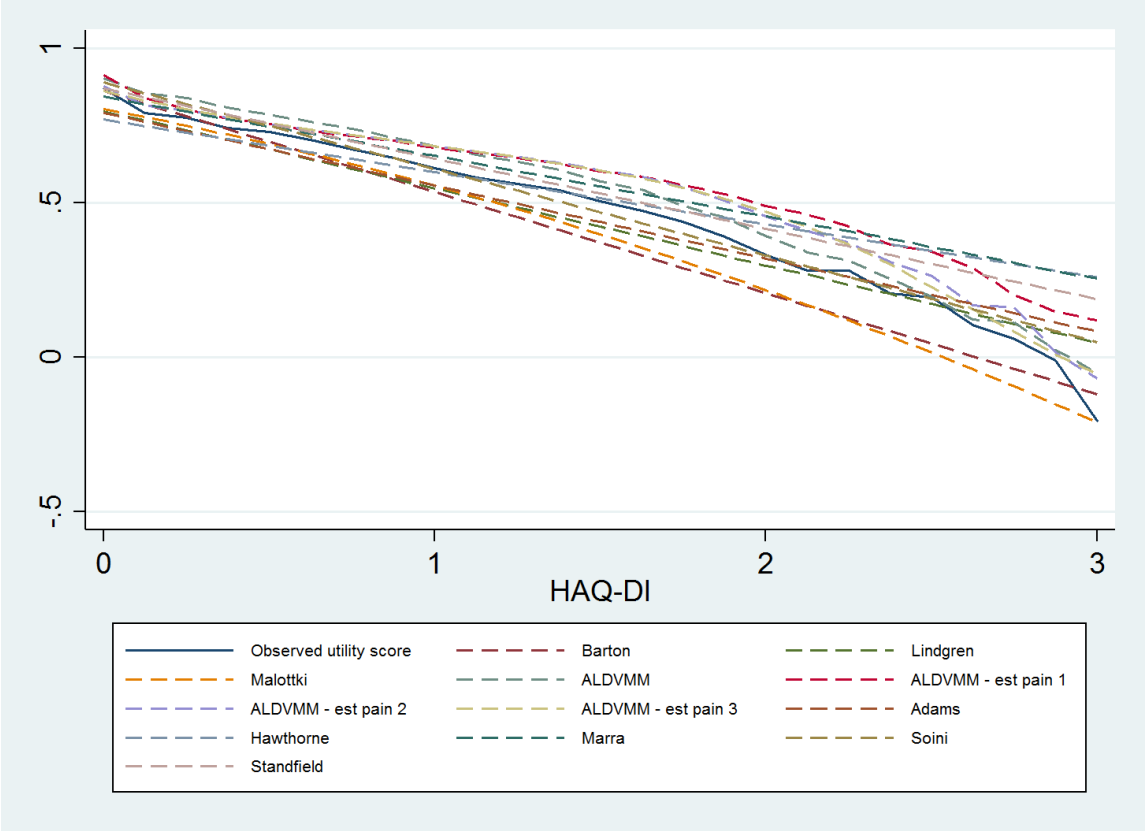
Publications	Year	Method	Comments
Adams 2010 (303)	2010	OLS	EQ-5D = 0.792 - 0.236*HAQ
Barton 2004 (291)	2004	OLS	EQ-5D = 0.862- 0.327*HAQ
Hawthorne 2000 (304)	2000	OLS	EQ-5D = 0.77 - 0.17*HAQ
Hernández 2012 (302)	2012	Multiple – preferred is ALDVMM	Use preferred fitting model only
Hernández 2013 (301)	2013	ALDVMM	This model includes pain, which is not being tracked in the model
Hurst 1997 (305)	1997	OLS	Same model as Barton
Lindgren 2009 (292)	2009	OLS	EQ-5D = 0.915- 0.252*HAQ
Malottki 2011 (306)	2011	OLS	EQ-5D = 0.804- 0.203*HAQ- 0.045*HAQ^2
Marra 2007 (307)	2007	OLS	EQ-5D = 0.72 - 0.2*HAQ + 0.25*age/100
Soini 2012 (308) and Ducournau 2009 (309)	2012	OLS	EQ-5D = 0.89 - 0.28*HAQ
Standfield 2010 (310)	2010	OLS	EQ-5D = 0.8711 - 0.2275*HAQ

Abbreviations: ALDVMM, adjusted limited dependent variable mixture models; EQ-5D, EuroQol five-dimension questionnaire; HAQ, Health Assessment Questionnaire; HERC, Health Economic Research Centre; LDVMM, limited dependent variable mixture models; OLS, ordinary least squares.

5.4.3.3 Algorithm review

The average EQ-5D score observed in the data set at each HAQ-DI score, as well as the average predicted value for each algorithm at each HAQ-DI score, is shown in Figure 66. Table 118 presents the average predicted utility, mean absolute error, root mean squared error, predicted QALYs and mean error in the predicted QALYs for each algorithm. Table 119 shows the average mean absolute error on ranges of the EQ-5D scale and Figure 67 shows the mean absolute error at each HAQ-DI score for each algorithm.

Figure 66: Average EQ-5D by HAQ-DI score



Abbreviations: EQ-5D, EuroQol five-dimension questionnaire; HAQ-DI, Health Assessment Questionnaire-Disability Index.

Table 118: Predictive properties of each mapping algorithm

Algorithm	Method applied	EQ-5D utility, mean (range)	MAE	RMSE	Mean QALYs	QALY error (p value)
Observed data	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Barton 2004 (291)	OLS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lindgren 2009 (292)	OLS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Malottki 2011 (306)	OLS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hernandez 2013 (301)	ALDVMM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hernandez 2013 – pain 1	ALDVMM (est. pain)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hernandez 2013 – pain 2	ALDVMM (est. pain 2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hernandez 2013 – pain 3	ALDVMM (est. pain 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adams 2010 (303)	OLS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hawthorne 2000 (304)	OLS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Marra 2007 (307)	OLS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Soini 2012 (308)	OLS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standfield 2010 (310)	OLS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

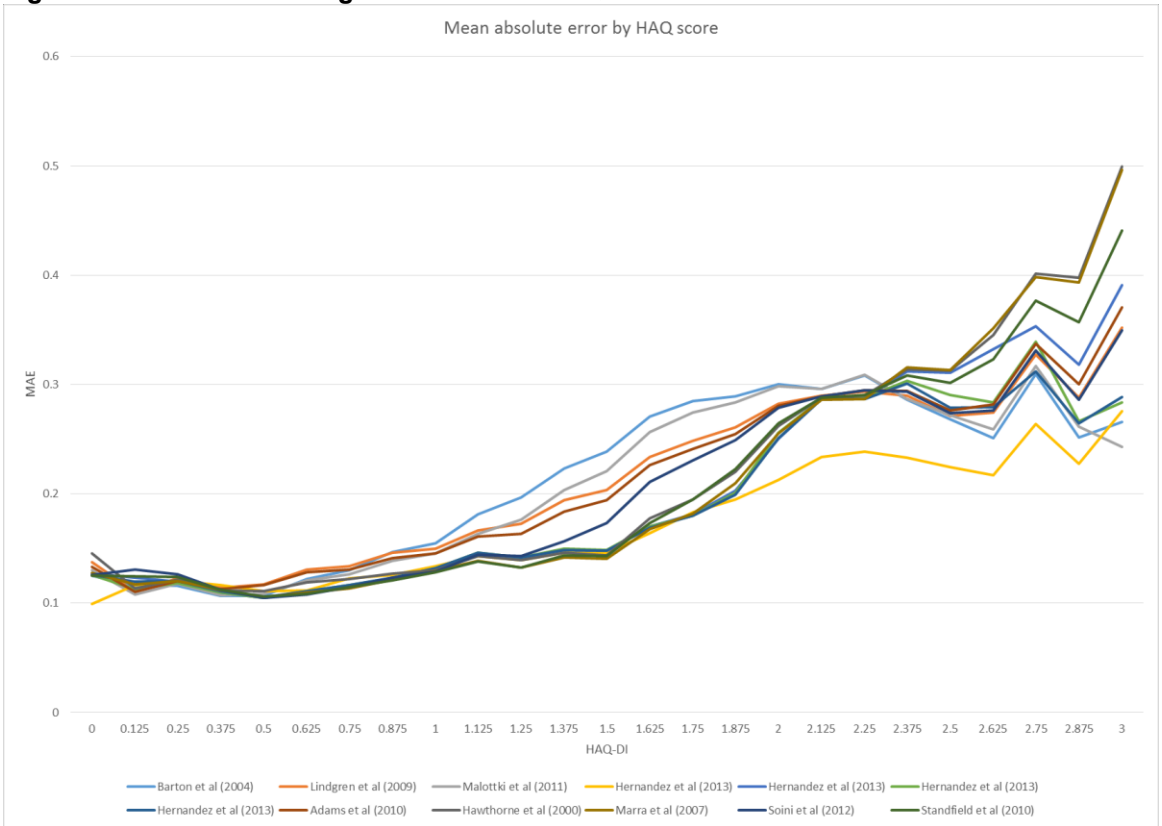
Abbreviations: ALDVMM, adjusted limited dependent variable mixture models; EQ-5D, EuroQol five-dimension questionnaire; MAE, mean absolute error; OLS, ordinary least squares; QALY, quality-adjusted life years; RSME, root mean squared error

Table 119: Mean absolute error for sections of the EQ-5D utility value range

Algorithm	≤0	>0, ≤0.5	>0.5, ≤0.75	>0.75, ≤1
Barton 2004 (291)	0.301	0.254	0.171	0.161
Lindgren 2009 (292)	0.389	0.283	0.133	0.178
Malottki 2011 (306)	0.302	0.268	0.153	0.169
Hernandez 2013 (301)	0.383	0.364	0.110	0.089
Hernandez 2013 – pain 1	0.558	0.437	0.088	0.107
Hernandez 2013 – pain 2	0.518	0.422	0.092	0.109
Hernandez 2013 – pain 3	0.511	0.422	0.092	0.110
Adams 2010 (303)	0.412	0.295	0.122	0.176
Hawthorne 2000 (304)	0.523	0.369	0.078	0.172
Marra 2007 (307)	0.544	0.406	0.084	0.123
Soini 2012 (308)	0.422	0.328	0.122	0.129
Standfield 2010 (310)	0.509	0.384	0.096	0.120

Abbreviations: EQ-5D, EuroQol five-dimension questionnaire.

Figure 67: MAE for each algorithm at each HAQ-DI score



Abbreviations: HAQ-DI, Health Assessment Questionnaire-Disability Index; MAE, mean absolute error.

5.4.3.4 Conclusions

The base-case analysis uses the ALDVMM model with pain estimated by taking the average pain score for each valid HAQ score from the ORAL clinical trials. This is the

ALDVMM – est pain 2 model in Table 116, which uses the HAQ/pain relationship presented in Table 115.

This model was chosen as it has a small MAE across the range of HAQ scores. The ALDVMM model using pain predicted by an OLS regression model also performs well, but it was judged that the OLS model introduces an extra layer of uncertainty without adding a significant amount of accuracy.

All algorithms perform worse as HAQ scores increase and EQ-5D scores decrease. There is little difference between any of the models when HAQ scores are below 1, and so it was decided to focus on prediction of with larger HAQ scores when selecting a preferred model.

The ALDVMM model using the HAQ/pain relationship from TA375 has also been considered as a scenario analysis. However, this approach appears to be less accurate than the ALDVMM models using ORAL clinical trial data to predict pain.

Additionally, the Soini model is tested in scenario analysis, as the Soini model is the best at predicting QALYs.

5.4.4 *Health-related quality-of-life studies*

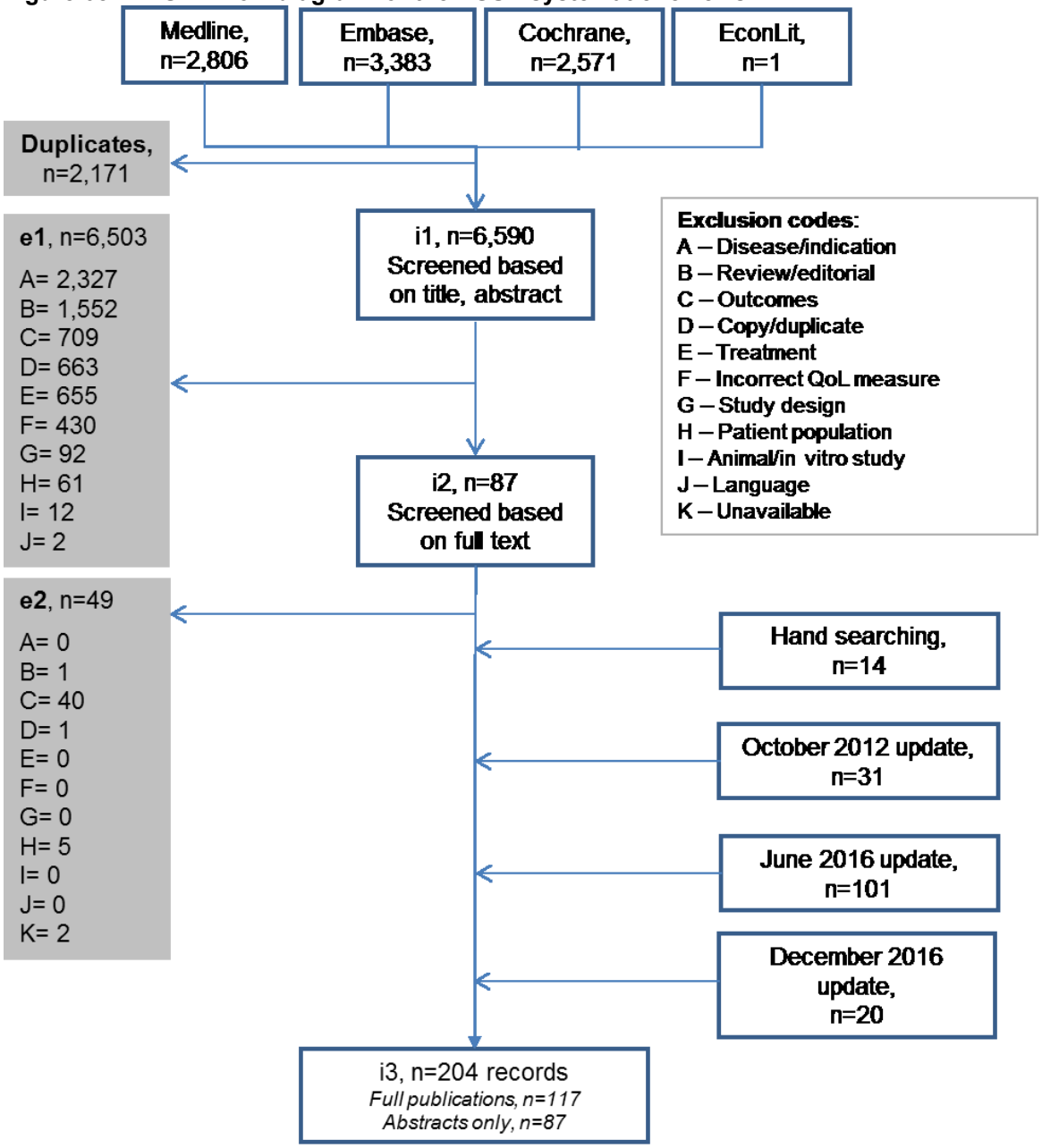
5.4.4.1 Identification of studies

A systematic review was conducted to identify HRQoL studies from the published literature relevant to the decision problem. In particular, studies reporting HSUVs relating to patients with RA were considered eligible for inclusion. Full details of the search are provided in Appendix 11.

Overall, a total of 206 publications were eligible for inclusion across the three subsequent reviews (full publications, n=119; abstracts, n=87). In addition, 16 relevant previous HTA submissions were identified. On completion of the June 2016 update, one abstract included in the original review (311), and three abstracts included in the October 2012 update (312-314) were found to have been superseded by full publications included in the most recent update (315-318). On completion of the December 2016 update, one abstract included in the June 2016 update was superseded by a full publication (319). For completeness, these abstracts have not been excluded.

A PRISMA diagram showing the overall flow of studies across the original review and the two updates is shown in Figure 68. Individual PRISMA flow diagrams showing the separate flow of studies through the original review, the October 2012 update, the June 2016 update and the December 2016 update are shown in Figure 121, Figure 122, Figure 123 and Figure 124 (Appendix 11), respectively.

Figure 68. PRISMA flow diagram for the HSUV systematic reviews



Abbreviations: HSUV, health-state utility values.

5.4.4.2 Description of studies

Full publications

Across the original review and two subsequent updates, a total of 119 eligible full publications reporting utilities for patients with RA were identified (original review, n=44; October 2012 update, n=14; June 2016 update, n=49; December 2016 update, n=12). Countries from which the utility data were derived included: the UK (n=25), the US (n=20), Sweden (n=12), the Netherlands (n=8), Japan (n=8), Canada (n=6), Norway (n=6), Denmark (n=5), Australia (n=3), Brazil (n=3), Korea (n=3), Spain (n=2), Ireland (n=2), France (n=2), Italy (n=2), Hungary (n=2), Greece (n=1), India (n=1), Morocco (n=1), Taiwan (n=1), Tunisia (n=1), Singapore (n=1), and Portugal (n=1). The remaining three studies were multi-national. A total of 33 studies enrolled patients with RA fulfilling ACR criteria, and three enrolled patients with RA diagnosed according to ICD-9. In terms of disease stage and severity, the following populations were considered across the included studies (note: some studies fall under more than one category):

- Patients with RA (no indication of disease severity) (n=95)
- Patients with active RA (n=9)
- Patients with early RA (n=6)
- Patients with stable or established RA (n=6)
- Patients with moderate-to-severe RA (n=2)
- Patients with moderate RA (n=1)
- Patients with active early RA and patients with active established RA (n=1)

With regards to details of previous/current treatments, the following populations were considered (note: some studies fall under more than one category):

- Patients with RA and no details regarding current/previous treatment (n=65)
- Patients with RA initiating/already receiving bDMARDs/anti-TNFs (n=24)
- Patients with RA previously treated with or receiving DMARDs (n=13)
- Patients with RA with an inadequate response to previous treatment with MTX (n=8)
- Patients with RA who are biologic-naïve (n=8)
- Patients with RA with an inadequate response to previous anti-TNF treatment (n=3)
- Patients with RA who are DMARD-naïve (n=2)
- Patients with RA not receiving DMARDs (n=1)

Intervention-specific utilities were reported by 18 publications. The interventions considered included the following:

- Adalimumab (ADA) vs etanercept (ETN) (n=3)
- First-, second-, or third-line anti-TNF therapy (n=2)
- Usual care vs hand exercise programme (including EXTRA) (n=2)

- Biologics vs non-biologics (n=1)
- Anti-TNF vs anti-TNF plus MTX (n=1)
- ETN, ADA, or infliximab (INF) (n=1)
- ADA vs placebo (n=1)
- INF vs SSZ plus hydrochloroquine (HCQ) (n=1)
- Usual care vs usual care plus an individualised exercise programme (n=1)
- cDMARD vs anti-TNF (n=1)
- Anakinra plus MTX vs MTX monotherapy (n=1)
- MTX, prednisolone (PSL), biologics, and combination therapies (n=1)
- MTX vs MTX plus ciclosporin vs MTX plus steroid vs triple therapy (n=1)
- Rituximab (RTX) vs anti-TNF therapy (n=1)

Study duration across the included publications ranged from 1 week (119) to economic analyses modelling over a patient lifetime. A total of 45 studies had a cross-sectional study design and thus derived utilities for a single time point.

- Utilities were also reported for a range of other health states, including but not limited to:
- Utilities by Health Assessment Questionnaire (HAQ) score (n=9)
- Utilities according to gender (n=8)
- Utilities by disease severity (n=5)
- Utilities by disease duration (including classification into early, late, or established disease) (n=4)
- Utilities by disease activity (n=4)
- Utilities according to presence/severity of adverse events (AEs) (n=3)
- Utilities according to presence of co-morbidities (n=3)
- Utilities by ACR (response/functional class) (n=2)
- Utilities according to patient expectations (n=2)
- Utilities according to patient age (n=2)
- Utilities according to EULAR response (n=1)

The following instruments were used to derive utilities across the studies:

- European Quality of Life-5 Dimensions (EQ-5D): n=95
- Short Form-6 Dimensions (SF-6D): n=21
- Health Utilities Index 2/3 (HUI2/3): n=7
- Direct time trade off (TTO): n=11
- Direct standard gamble (SG): n=4

- Assessment of Quality of Life (AQoL): n=2
- 15D: n=1
- Unclear: n=1

In addition, 21 studies reported mapping algorithms which may be used to convert disease-specific measures utilities. Health states were valued using the following value sets:

- UK tariff: n=34
- Danish tariff: n=6
- US tariff: n=5
- Japanese tariff: n=2
- European tariff: n=1
- Canadian tariff: n=1
- Dutch tariff: n=1
- French tariff: n=1
- Swedish tariff: n=1
- Spanish tariff: n=1
- Brazilian tariff: n=1
- Multiple tariffs (including UK tariff): n=3
- Unclear or not applicable: n=62

Overall, 34 of the studies fully met the requirements of the NICE reference case; that is, they derived utilities directly from patients using the preferred EQ-5D instrument, and UK societal preferences (elicited using the direct TTO method) were used to value health states. The remaining studies were either clearly inconsistent with the NICE reference case, or it was unclear if the studies met the reference case requirements. This was most often due to use of an instrument other than EQ-5D, use of an alternative country tariff, or lack of reporting regarding the use of societal preferences. A summary of the included full publications is shown in Table 255 of Appendix 11 (Section 8.11.4). A summary of the relevance of each publication to the NICE reference case is provided in Table 256 of Appendix 11 (Section 8.11.4).

Abstracts

Overall, 87 abstracts were identified as fulfilling the eligibility criteria of the review (original review, n=8; October 2012 update, n=17; June 2016 update, n=52; December 2016 update, n=10). A summary of the included abstracts is shown in Table 257 of Appendix 11 (Section 8.11.5).

Mapping algorithms

Overall, the review identified a total of 23 studies reporting the use of a mapping algorithm to derive utilities (full publications, n=21; abstracts, n=2). A summary of the included studies reporting mapping algorithms is shown in Table 258 of Appendix 11 (Section 8.11.6).

HTA submissions

A total of 16 relevant previous HTA submissions were identified by the reviews (Table 259 of Appendix 11 [Section 8.11.7]). All but one (TA195) of the six previous HTA submissions identified by the original review and October 2012 update were replaced or updated by the guidance in TA375, which was identified by the June 2016 update. In addition, the nine submissions identified from CADTH, PBAC and the SMC were cost-minimisation analyses and did not report the use of utility values in their analyses. Therefore, only TA195 and TA375 are summarised (Table 260 of Appendix 11 [Section 8.11.7]); both reported methods involving mapping algorithms to derive utilities for their analyses.

5.4.5 *Key differences*

The most relevant data identified from the literature review were NICE TA195 and TA375; both of these reported similar approach to utilities to the current model, i.e. mapping from patient-level data. This has been suggested by the ERG (TA225) as being a more appropriate model for RA due to the ability to allow more structural changes to the model and more varied sensitivity analyses (294).

5.4.6 *Adverse reactions*

5.4.6.1 Serious infections

The model considers the impact of serious infections on costs and quality of life only. The probability of experiencing an adverse event while on treatment is calculated and the QALY loss and incurred cost associated with an adverse event are weighted by this probability. It is assumed that if a patient experiences a serious infection, they will discontinue treatment; therefore, a patient may not experience more than one adverse event per treatment. Previous models have shown that adverse events are not a significant driver of cost-effectiveness and have therefore either taken a simplistic approach or assumed no impact and have not modelled them (293). The effect of removing adverse events is tested in scenario analysis, as is the effect of doubling the rate of serious infections. Ultimately, the simple approach used in the model was shown to be justified as the sensitivity analysis revealed little or no effect.

In this economic evaluation, the rate of serious infections for tofacitinib was taken from Strand et al, 2015 (320) and was used as the base probability of a serious infection. Odds ratio from also taken from Strand et al, 2015 were applied to estimate the relative occurrence for the other comparator biologic treatments (320).The cost and disutility associated with a serious infection were then multiplied by the probability of occurrence and the results applied to the patient's lifetime costs and QALYs.

Table 120: Serious infections

	Value	Source
6-month probability of serious infection for TOF	0.025	(320)
Disutility from serious infection	0.156	(321)
Duration of serious infection	28	(321)
QALY loss due to serious infection	0.012	-

Abbreviations: QALY, quality-adjusted life years; TOF, tofacitinib.

The probability (relative to tofacitinib) and associated yearly rate of serious infections is presented by therapy in Table 121.

Table 121: Probability and rate of serious infection per therapy

Therapy	Odds ratio vs TOF	SI rate (year)
Tofacitinib monotherapy	1.00	0.030
Tofacitinib + MTX	1.00	0.030
Adalimumab monotherapy	1.03	0.031
Adalimumab + MTX	1.03	0.031
Certolizumab monotherapy	0.99	0.030
Certolizumab + MTX	0.99	0.030
Etanercept monotherapy	0.45	0.014
Etanercept + MTX	0.45	0.014
Abatacept + MTX	0.53	0.016
Golimumab + MTX	0.59	0.018
Infliximab + MTX	0.38	0.011
Rituximab + MTX	0.46	0.014
Tocilizumab monotherapy	0.82	0.025
Tocilizumab + MTX	0.82	0.025
Ciclosporin	0.45	0.014
Leflunomide	0.45	0.014
MTX	0.45	0.014
Palliative care	0.45	0.014
Sulfasalazine	0.45	0.014
DMARD combination	0.45	0.014
Etanercept Biosimilar monotherapy	0.45	0.014
Etanercept Biosimilar + MTX	0.45	0.014
Infliximab Biosimilar + MTX	0.38	0.011

Abbreviations: DMARD, disease-modifying anti-rheumatic drug; MTX, methotrexate; SI, serious infection.

5.4.6.2 Disutility associated with injections and infusions

The disutility associated with injections and infusions is discussed in Appendix 12.

5.4.7 *Health-related quality-of-life data used in cost-effectiveness analysis*

HRQoL were unique to each patient and were mapped to the EQ-5D from HAQ-DI scores over the model time horizon (Section 5.4.2).

5.4.7.1 Clinical expert assessment of applicability of health state utility values

As outlined in 5.3.3 an expert panel was consulted which, in addition to the aforementioned points, recommended to use ORAL trial EQ5D data to confirm or validate the mapping assumptions made in TA375. Clinicians viewed the inclusion of the tofacitinib serious infection data in the model as a favourable approach in the light of previous EMA assessments.

5.5 *Cost and healthcare resource use identification, measurement and valuation*

5.5.1 *Resource identification, measurement and valuation studies*

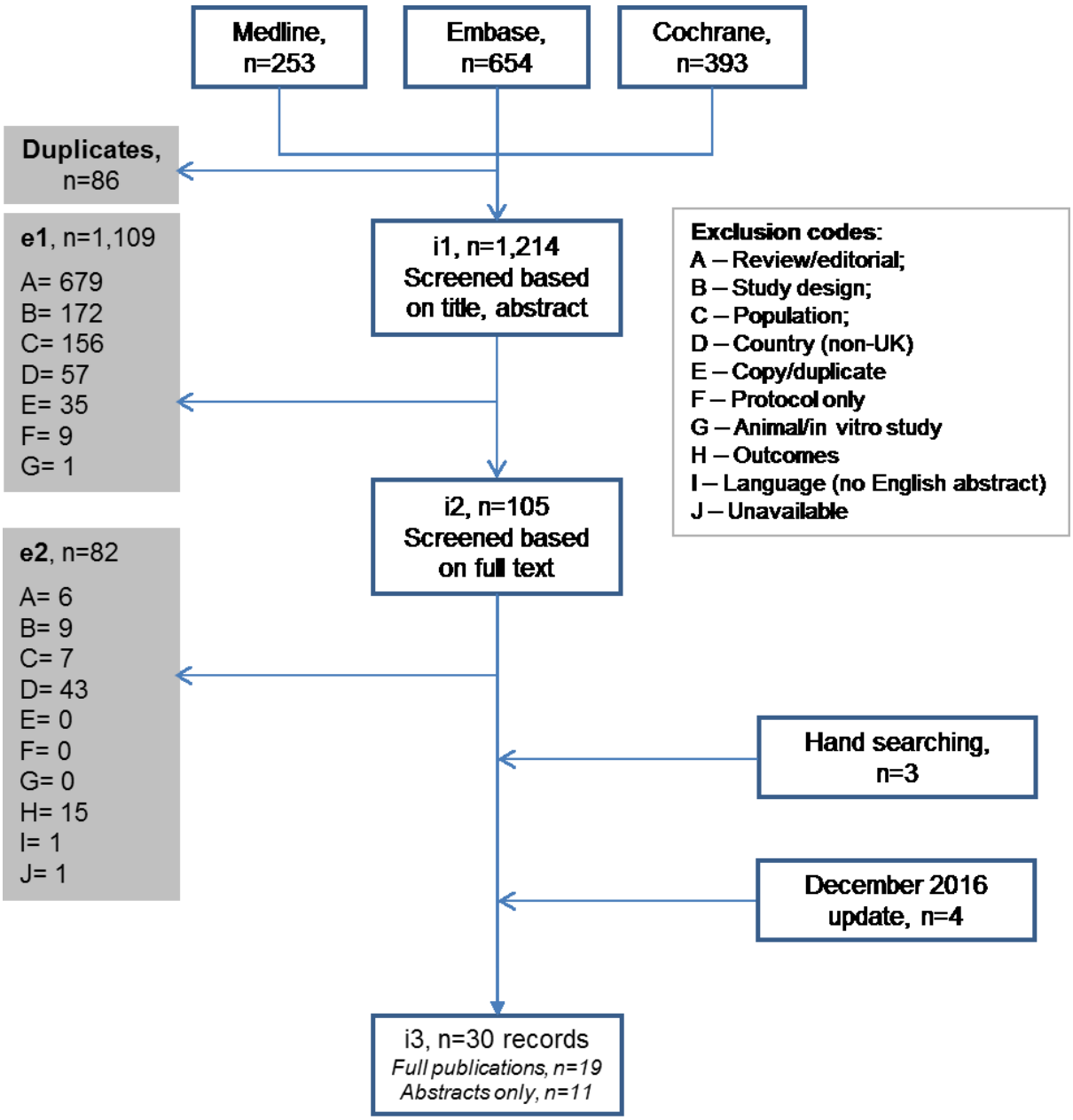
5.5.1.1 Identification of cost studies

A systematic review was conducted to identify resource data from the published literature relevant to the decision problem. Full details of the search are provided in Appendix 13.

In the original review, 1,300 papers were identified through the electronic database searches. Upon the removal of duplicate papers, 1,214 references were reviewed by title and abstract. A total of 105 citations were considered potentially relevant and were ordered for full publication review. Eighty-two publications were excluded at this stage. Hand searching yielded an additional three relevant publications, resulting in a total of 26 publications. In December 2016, the original systematic review (SR) was updated to identify relevant cost studies published since June 2016. Overall, 372 articles were identified by the electronic database searches. Upon removal of duplicate references, 49 citations were screened by title and abstract. A total of seven were deemed to be potentially relevant and were screened on the basis of full publication. A further three publications were excluded at this stage. Hand searching did not yield any additional papers for inclusion. Therefore, a total of four publications were included in the updated review (full publications, n=4). Overall, a total of 30 studies were eligible for inclusion across the original review and December 2016 update.

The flow of references through the review is captured in the PRISMA flow diagram in Figure 69. Individual PRISMA flow diagrams showing the separate flow of studies through the December 2016 update are shown in Figure 125. A summary of the included publications is provided in in Table 263 of Appendix 13 (Section 8.13.4).

Figure 69. PRISMA flow diagram for the cost and resource use systematic review



5.5.1.2 Description of included studies

Overall, 30 studies were identified which met the inclusion criteria of the review and are summarised in Table 263 of Section 8.13.4. Of these, 19 were full publications and 11 were abstracts. All of the included studies reported UK-specific cost/resource use data associated with RA. The populations considered in the included studies included the following:

- Patients with RA (no indication of disease stage/severity/diagnosis) (n=14)
- Patients with RA meeting the American Rheumatism Association (ARA)/ American College of Rheumatology (ACR) criteria for RA (n=5)
- Patients with early RA (n=4)
- Patients with early RA meeting the ACR criteria for RA (n=3)
- Patients with active RA (n=1)
- Patients with established RA (n=1)
- Patients with established RA diagnosed according to the ACR criteria for RA (n=1)
- Patients with early or established RA (n=1)

With regard to the treatment status of the patients included in the studies, the following populations were considered (note: studies may appear in more than one category):

- Patients who are DMARD naïve (n=3)
- Patients who are biologic naïve (n=3)
- Proportion of patients DMARD naïve (n=1)
- Proportion of patients non-steroidal anti-inflammatory drug (NSAID) naïve (n=1)
- Patients who have been previously treated:
    - Patients who have failed on prior MTX therapy (n=3)
    - Patients who have received biologic/anti-TNF therapy (n=2)
    - Second-line treatment of patients with ACR diagnosed RA (n=1)
    - Patients who have received 12 weeks of infliximab (IFX) therapy and considered IFX responders (n=1)

One study considered patients with both early or established RA and reported that the established RA patients were DMARD naïve, and those with active early disease were receiving MTX. Current treatment status of the patient cohort not reported (n=15). The following outcomes were reported across the included studies:

- Direct costs (medical or non-medical) (n=16)
- Indirect costs (n=7)
- Cost drivers of total costs (n=9)
- Resource use or disease burden data (including absenteeism, workforce withdrawal due to RA, length of stay) (n=16)

5.5.1.3 Appropriateness of NHS Ref costs/PbR tariffs

In line with previous NICE appraisals of treatments for RA the following cost inputs were considered:

- Drug acquisition costs (British National Formulary 2016) (322)
- Treatment monitoring (NHS Reference Costs 2015–16 (323, 324), Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care, 2016 (325) and Malottki et al, 2011 (306))
- Cost of serious infections (NHS Reference Costs 2010–11 (326) inflated using PSSRU Unit Costs of Health and Social Care, 2016 (325))

5.5.1.4 Clinical expert assessment of applicability of cost and healthcare resource use values

Clinical experts were not used to assess the applicability of values or to estimate values.

5.5.2 *Intervention and comparators' costs and resource use*

Four sets of costs are captured by the model: treatment costs; monitoring costs; background medical resource use and the cost of serious infections.

5.5.2.1 Cost of intervention and comparators

The cost of intervention and comparators are shown in Table 122 for the individual treatments, split into costs at 0–6 months and >6 months. Table 123 shows the cost of combination therapies used in the model. All patients incurred the cost of an intervention in the 0–6-month interval, unless they discontinued treatment. From Month 6 onwards, patients continued to incur the cost of treatment up until discontinuation. The option to account for vial wastage is included in the base case analysis. This method accounts for the difference in costs between the first 6 months and post 6 months, as some therapies require a loading dose, or are dosed differently in the first weeks of treatment. As rituximab is often administered every 9 months, rituximab administration is modelled as a recurring event in the base-case, which ensures accurate costing; this is consistent with the approach used in TA375 (22).

To incorporate the costs of cDMARDs it was assumed that cDMARD monotherapy incurs the cost of MTX and that combination strategies are costed as MTX and sulfasalazine. It is expected that the main source of costs for these strategies will be monitoring costs; therefore, simple assumptions around drug costs are deemed acceptable.

Table 122: Treatment costs

Treatment	Dose description	Cost per pack††	Mg per vial/ syringe/ capsule/ tablet††	Loading dose (mg) ††	Maintena-nce dose (mg) ††	Doses per pack/ mg per pack††	Admin costs per dose	Cost per vial/ syringe/ capsule/ tablet	Drug costs	
									Month 0–6	Subsequent annual drug costs
TOF	5 mg BD	List - £690.03 [redacted]	5	-	10	56	£0.00‡‡	[redacted]	[redacted]	[redacted]
ADA	40 mg Q2W, increased if necessary to 40 mg QW.	£704.28	40	-	40	2	£2.70§§	£352.14	£4,612.92	£9,225.84
CZP	Loading dose 400 mg Q2W for 3 doses, then maintenance 200 mg Q2W, once clinical response is confirmed.	£715.00	200	400	200	2	£2.70§§	£357.50	£2,153.10§	£9,365.20
Etanercept	25 mg BIW, alternatively 50 mg QW.	£715.00	50	-	50	4	£2.70§§	£178.75	£4,717.70	£9,435.40
Abatacept†	500 mg (up to 60 kg) / 750 mg (60–100kg) / 1 g (101+ kg) Q2W for 3 doses (loading dose),	£302.40	250	750	750	1	£159.20§§	£302.40	£9,064.40§	£13,863.20

Treatment	Dose description	Cost per pack††	Mg per vial/ syringe/ capsule/ tablet††	Loading dose (mg) ††	Maintena-nce dose (mg) ††	Doses per pack/ mg per pack††	Admin costs per dose	Cost per vial/ syringe/ capsule/ tablet	Drug costs	
									Month 0–6	Subsequent annual drug costs
	then (by IV) 500 mg / 750 mg / 1g Q4W.									
Golimumab†	Body weight up to 100kg: 50 mg once a month. Body-weight 100kg+: initially 50 mg once a month for 3–4 doses, on the same date each month.	£762.97	50	50	50	1	£2.70§§	£762.97	£4,594.02	£9,188.04
Infliximab†	Initially 3 mg/kg, then 3 mg/kg after 2 weeks, followed by 3 mg/kg after 4 weeks, then 3 mg/kg Q8W.	£377.66	100	-	214	1	£159.20§§	£377.66	£7,430.04	£8,399.17
Rituximab‡	1 g, then 1 g after 2 weeks, every 9 months	£873.15	500	-	1000	0.5	£159.20§§	£1,905.50	£7,622.00	£10,162.67
Tocilizumab†	8 mg/kg Q4W (maximum per dose 800 mg)	-	-	-	-	-	£159.20§§	£716.80	£5,694.00	£11,388.00
TOC80		£102.40	80	-	-	1	-	£102.40	-	-
TOC200		£256.00	200	-	-	1	-	£256.00	-	-

Treatment	Dose description	Cost per pack††	Mg per vial/ syringe/ capsule/ tablet††	Loading dose (mg) ††	Maintena-nce dose (mg) ††	Doses per pack/ mg per pack††	Admin costs per dose	Cost per vial/ syringe/ capsule/ tablet	Drug costs	
									Month 0–6	Subsequent annual drug costs
TOC400		£512.00	400	-	-	1	-	£512.00	-	-
Ciclosporin	Initially 2.5 mg/kg daily in 2 divided doses, increased if necessary up to 4 mg/kg daily after 6 weeks.	£48.50	100	179	286	30	£0.00‡‡	£1.62	£814.80	£1,765.40
Leflunomide	Initially 100 mg once daily for 3 days, then reduced to 10–20 mg once daily.	£4.59	20	100	20	30	£0.00‡‡	£0.15	£29.68	£55.69
MTX	Oral: 7.5 mg QW, adjusted according to response; maximum 20 mg per week. Injection: Initially 7.5 mg QW, then increased in steps of 2.5 mg QW, adjusted according to response; maximum 25 mg	£6.00	2.5	7.5	20	100	£0.00‡‡	£0.06	£11.58	£24.96

Treatment	Dose description	Cost per pack††	Mg per vial/ syringe/ capsule/ tablet††	Loading dose (mg) ††	Maintena-nce dose (mg) ††	Doses per pack/ mg per pack††	Admin costs per dose	Cost per vial/ syringe/ capsule/ tablet	Drug costs	
									Month 0–6	Subsequent annual drug costs
	per week.									
PaC	Assumed same as PRAM	-	-	-	-	-	-‡‡	-	£265.00	£530.00
Sulfasalazine	Initially 500 mg daily, increased in steps of 500 mg every 1 week, increased to 2–3 g daily in divided doses, enteric coated tablets to be administered.	£6.86	500	500	3000	112	£0.00‡‡	£0.06	£60.45	£133.77
DMARD combination	Assumed MTX + sulfasalazine	£0.00	-	-	-	0	£0.00‡‡		£72.03	£158.73
Benpali (ETNb)	N/A	£656.00	50	-	50	4	£2.70§§	£164.00	£4,334.20	£8,668.40
Inflectra (INFb)	N/A	£377.66	100	-	214	1	£159.20§§	£377.66	£7,430.04	£8,399.17

Abbreviations: ABA, abatacept; ADA, adalimumab; BD, twice a day; CZP, certolizumab pegol; ETN, etanercept; INF, infliximab; IR, inadequate response; IV, intravenous; MTX, methotrexate; PaC, palliative care; Q2W, every two weeks; Q4W, every four weeks; Q8W, every eight weeks; QW, once weekly; SC, subcutaneous; TOC, tocilizumab; TOC80, tocilizumab 80 mg; TOC200, tocilizumab 200 mg; TOC400, tocilizumab 400 mg; TOF, tofacitinib.

†Calculations shown here are average doses only – in the model these calculations are performed in the visual basic application to account for patient weight. ‡Calculations show here are approximate – in the model rituximab treatment is modelled as an event. § Loading dose at week 0, 2, 4. ¶Assumed to be 92% of tofacitinib cost, based on cost difference between etanercept/infliximab and their biosimilars. ††Source: British National Formulary January 2017(322). ‡‡Assumption based on TA375 (22). §§Assumed same as in TA375 (22), uplifted to 2014/15 values using PSSRU hospital and community health services index (325), assuming the base year is 2012/13.

Table 123: Cost of therapies by treatment cycles

Therapy	Modelled cost	
	0-6 months	Per year after
Tofacitinib monotherapy (PAS)	[redacted]	[redacted]
Tofacitinib + MTX (PAS)	[redacted]	[redacted]
Adalimumab monotherapy	£4,612.92	£9,225.84
Adalimumab + MTX	£4,624.50	£9,250.80
CZP monotherapy	£2,153.10	£9,365.20
CZP + MTX	£2,164.68	£9,390.16
Etanercept monotherapy	£4,717.70	£9,435.40
Etanercept + MTX	£4,729.28	£9,460.36
Abatacept + MTX	£9,075.98	£13,888.16
Golimumab + MTX	£4,605.60	£9,213.00
Infliximab + MTX	£8,153.85	£9,217.39
Rituximab + MTX	£7,633.58	£10,187.63
Tocilizumab monotherapy	£5,694.00	£11,388.00
Tocilizumab + MTX	£5,705.58	£11,412.96
Ciclosporin	£814.80	£1,765.40
Leflunomide	£29.68	£55.69
MTX	£11.58	£24.96
Palliative care	£265.00	£530.00
Sulfasalazine	£60.45	£133.77
DMARD combination	£72.03	£158.73
Etanercept Biosimilar monotherapy	£4,334.20	£8,668.40
Etanercept Biosimilar + MTX	£4,345.78	£8,693.36
Infliximab Biosimilar + MTX	£7,441.62	£8,424.13

Abbreviations: CZP, certolizumab pegol; DMARD, disease-modifying anti-rheumatic drug; MTX, methotrexate; PAS, patient access scheme.

5.5.2.2 Cost of monitoring

Monitoring costs were modelled in line with the AG's model for the review of TA375 (136). These are summarised per drug class in Table 124. In addition, outpatient contact cost was £143 (327). The time between monitoring visits was set as 0.17 years for tofacitinib, bDMARDs and cDMARDs.

Table 124: Monitoring costs at each visit

Test	Cost	Pre-treatment			On-treatment		
		TOF	bDMARD	cDMARD	TOF	bDMARD	cDMARD
Full blood count	£3.01 (323)	X	X	X	X	X	X
ESR	£3.01 (323)	X	X	X	X	X	X
Biochemical profile	£1.19 (324)	X	X	X	X	X	X
Chest x-ray	£19.67 (306, 325)	X	X	X			
Urinalysis	£1.19 (324)						
Hep B & Hep C	£6.02 (323)						
Lipid test	£3.01 (323)						
C-reactive protein	£3.01 (323)	X	X	X			
TB test	£3.01 (323)	X	X	X			

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; Hep B, hepatitis B; Hep C, hepatitis C; TB, tuberculosis; TOF, tofacitinib.

5.5.2.3 Background medical resource use

Background resource use is modelled on a cost per HAQ-DI band basis. This is in line with previous NICE submissions (TA375) (136). These costs were estimated based on data from the Norfolk Arthritis Register (NOAR) database (328, 329) and were multiplied by NHS reference costs and inflated to 2016 values.

5.5.3 *Health-state costs and resource use*

Costs for patients are defined on a per-patient basis based on their treatment sequence (Section 5.2.3.2 and 5.5.2.1) and their background resource use on a cost per HAQ-DI band basis (Section 5.5.2.3).

5.5.4 *Adverse reaction unit costs and resource use*

The impact of serious infections on costs is considered in this model (see Section 5.4.6.1 for rates for each treatment). The unit cost of a serious infection is £1,567 (325, 326).

5.5.5 *Miscellaneous unit costs and resource use*

No other costs were considered in the model.

5.6 *Summary of base-case de novo analysis inputs and assumptions*

5.6.1 *Summary of base-case de novo analysis inputs*

A list of all variables used in the economic analysis is provided in Table 125.

Table 125: Summary of variables applied in the economic model base case

Parameter	Source	Section
Clinical data		
Baseline patient characteristics	ORAL trials at an individual patient level: (Standard, Scan, Sync, Solo and Step) (122-124, 126, 129)	5.3.1
EULAR response at Month 6		
Treatment discontinuation		
Changes in HAQ-DI score at Month 6	BSRBR	5.3.2.2
Comparative relative treatment efficacy – OR of at least moderate EULAR response and good EULAR response	NMA	4.10
Long-term HAQ-DI progression • TOF and bDMARDs – *No progression* • cDMARDs – *Norton et al progression NICE and DSU analysis for rapid progressors*	NICE TA375 (24) Norton et al (297)	5.3.2.3
Mortality	NICE TA375 (22)	5.3.2.6
Serious infections	Strand et al, 2015 (320)	5.4.6.1
Utility data		
Disutility associated with serious infections	Oppong et al, 2013 (321)	5.4.6.1
Disutility associated with injections and/or infusions	Matza et al, 2013 (330)	5.4.6.2
Cost data		
Drug acquisition costs	British National Formulary (322)	5.5.2.1
Monitoring costs	NHS Reference Costs 2015–16 (323, 324), PSSRU Unit Costs of Health and Social Care, 2016 (325) and Malottki et al, 2011 (306)	5.5.2.2
Background medical resource use	Norfolk Arthritis Register database (328, 329)	5.5.2.3
Serious infections	NHS Reference Costs 2010–11 (326) inflated using PSSRU Unit Costs of Health and Social Care, 2016 (325)	5.5.4

Abbreviations: ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire-disability index; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Comparator treatment sequences which follow current NICE recommendations are summarised for:

- Base case 1 – severe cDMARD-IR (Table 96)

- Base case 2 – bDMARD-IR (Table 97)
- Scenario – moderate cDMARD-IR (Table 98)

Table 126: Treatment sequences considered by the economic evaluation for moderate-to-severe cDMARD-IR

Treatment sequence	Combination therapy											Monotherapy				
	DMC	ABT+ MTX	ADA+ MTX	CZP+ MTX	ETN+ MTX	GOL+ MTX	INF+M TX	TOC+ MTX	TOF+ MTX	ETNb+ MTX	INFb+ MTX	SSZ+ HQC	TOC	TOF	ETN	ADA
1	DMC	ABT+ MTX	ADA+ MTX	CZP+ MTX	ETN+ MTX	GOL+ MTX	INF+ MTX	TOC+ MTX	TOF+ MTX	ETNb+ MTX	INF+ MTX	SSZ+H QC	TOC	TOF	ETN	ADA
2	DMC	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	SSZ+H QC	ETN	ETN	ADA	ETN
3	DMC	TOC+ MTX	TOC+ MTX	TOC+ MTX	TOC+ MTX	TOC+ MTX	TOC+ MTX	ETN+ MTX	TOC+ MTX	TOC+ MTX	TOC+ MTX	SSZ+H QC	SSZ+H QC	SSZ+H QC	SSZ+H QC	SSZ+H QC
4	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	SSZ+H QC	SSZ+H QC	SSZ+H QC	SSZ+H QC	SSZ+H QC
5	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	SSZ+H QC	SSZ+H QC	SSZ+H QC	SSZ+H QC	SSZ+H QC
6	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF
7	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC

Abbreviations: ABA, abatacept; ADA, adalimumab; cDMARD, conventional disease modifying anti-rheumatic drug; CZP, certolizumab pegol; DMC, DMARD combination; ETN, etanercept; GOL, golimumab; INF, infliximab; PaC, palliative care; RTX, rituximab TOC, tocilizumab; TOF, tofacitinib.
‡This will reflect a combination of potential therapies, including monotherapy and combination therapy.

Table 127: Treatment sequences considered by the economic evaluation for bDMARD-IR

Treatment sequence	RTX tolerant (with RTX)				RTX intolerant				RTX tolerant (after) RTX)			
	RTX+MTX	TOF+MTX	ABT+MTX	GOL+MTX	TOF+MTX	ABT+MTX	TOC+MTX	GOL+MTX	RTX+MTX	TOF+MTX	ABT+MTX	GOL+MTX
1	RTX+MTX	TOF+MTX	ABT+MTX	GOL+MTX	TOF+MTX	ABT+MTX	TOC+MTX	GOL+MTX	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX
2	TOC+MTX	TOC+MTX	TOC+MTX	TOC+MTX	TOC+MTX	TOC+MTX	GOL+MTX	TOC+MTX	TOC+MTX	TOF+MTX	ABT+MTX	GOL+MTX
3	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	TOC+MTX	TOC+MTX	TOC+MTX
4	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC
5	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	LEF	DMC	DMC	DMC
6	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	LEF	LEF	LEF
7	-	-	-	-	-	-	-	-	-	PaC	PaC	PaC

Abbreviations: ABA, abatacept; ADA, adalimumab; cDMARD, conventional disease modifying anti-rheumatic drug; DMC, DMARD combination; GOL, golimumab; LEF, leflunomide; PaC, palliative care; RTX, rituximab TOC, tocilizumab; TOF, tofacitinib.
‡This will reflect a combination of potential therapies, including monotherapy and combination therapy.

Table 128: Treatment sequences considered by the economic evaluation for moderate cDMARD-IR

Treatment sequence†	Moderate sequence						Severe sequence	
	Combination TA375 sequence		Combination alternate sequence		Monotherapy			
	MTX	TOF+MTX	MTX	TOF+MTX	MTX	TOF	MTX	TOF+MTX
1	DMC	TOF+MTX	DMC	TOF+MTX	DMC	TOF	DMC	TOF+MTX
2	RTX+MTX	RTX+MTX	DMC	DMC	DMC	DMC	DMC	RTX+MTX
3	TOC+MTX	TOC+MTX	DMC	DMC	DMC	DMC	DMC	TOC+MTX
4	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC
5	DMC	DMC	DMC	DMC	DMC	DMC	DMC	DMC
6	LEF	LEF	PaC	DMC	LEF	LEF	LEF	LEF
7	PaC	PaC		PaC	PaC	PaC	PaC	PaC

Abbreviations: cDMARD, conventional disease modifying anti-rheumatic drug; PaC, palliative care; TOF, tofacitinib.
†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. ‡This will reflect a combination of potential therapies, including monotherapy and combination therapy. ¶Combination therapy will still be possible with cDMARD but will not include MTX.

5.6.2 *Assumptions*

Table 129: Assumptions used in the de novo economic model base case

Assumption	Rationale
On cessation of treatment, patients experience a worsening in HAQ-DI equal to their initial gain.	NICE has previously accepted this assumption in TA375 (291)
Changes of HAQ-DI score at month 6 are based on response and applied to all treatments in the same way (BSRBR flat rate).	NICE has previously accepted this assumption in TA375 (22).
It is assumed that patients who do not respond to treatment experience no change in HAQ-DI.	This assumption has been previously been used in TA375 (22).
In the base case, TOF is assumed to have no HAQ-DI progression.	The analysis of the long-term data used to model on-treatment HAQ-DI progression in the TOF arm essentially shows no progression.
When patients reach palliative care (add population descriptor) HAQ-DI scores are assumed to increase at a constant rate of 0.06 HAQ per year.	Assumption previously used in TA375 (22).
It is assumed that all patients will remain on therapy for at least 6 months, until response has been assessed.	NICE stopping criteria in TA375 (22).
To incorporate the costs of cDMARDs it is assumed that cDMARD monotherapy incurs the cost of methotrexate and that combination strategies will be costed as methotrexate and sulfasalazine.	It is expected that the main source of costs for these strategies will be monitoring costs; therefore, simplifying assumptions for drug costs have been made as a conservative approach. This may underestimate the costs of combination treatments.

Abbreviations: ADA, adalimumab; bDMARDs, biologic disease-modifying anti-rheumatic drugs; cDMARDs, conventional disease-modifying anti-rheumatic drugs; HAQ-DI, Health Assessment Questionnaire-disability index; TOF, tofacitinib.

5.7 *Results*

5.7.1 *Base case: cDMARD-IR combination therapy, PAS price*

5.7.1.1 Base case results

Base case results for Norton progression and rapid progression are presented in Table 130 and Table 131, respectively.

- The ICER for tofacitinib + MTX vs MTX ranged from £23,676–41,617 with rapid and Norton progression, respectively
- Tofacitinib + MTX dominated or extendedly dominated all other treatments using both progression assumptions with the exception of tocilizumab + MTX and infliximab biosimilar + MTX (rapid progression only
- The ICER for tocilizumab + MTX vs tofacitinib + MTX ranged from £88,129–139,113 with rapid and Norton progression, respectively

- The ICER for tofacitinib + MTX vs infliximab biosimilar + MTX with rapid progression was £34,201

Table 130: Base case results for patients who are cDMARD-IR receiving combination therapy, Norton progression

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]		
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£42,527	Ext. Dominated
INF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£43,481	Ext. Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£41,617	£41,617
ETNb+ MTX	[redacted]	[redacted]	[redacted]	[redacted]	£42,746	£127,228
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£44,904	Dominated
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£44,467	Dominated
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£44,331	Ext. Dominated
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£44,424	£139,113
ETN+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£45,275	Dominated
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£52,485	Dominated

Abbreviations: ADA, adalimumab; ABT, abatacept; b, biosimilar; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Table 131: Base case results for patients who are cDMARD-IR receiving combination therapy, rapid progression

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]		
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£23,412	£23,412
INF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£24,531	Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£23,676	£34,201
ETNb+ MTX	[redacted]	[redacted]	[redacted]	[redacted]	£24,644	Ext. Dominated
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£25,506	Dominated
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£25,389	Dominated
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£25,570	Ext. Dominated
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£25,589	£88,129
ETN+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£25,899	Dominated
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£29,717	Dominated

Abbreviations: ADA, adalimumab; ABT, abatacept; b, biosimilar; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

5.7.1.2 Clinical outcomes from the model

A summary of the clinical outcomes is provided for Norton progression and rapid progression in Table 132 and Table 133, respectively.

Table 132: Summary of clinical outcomes for cDMARD-IR combination therapy, Norton progression

Strategy	Age at death (years)	% EULAR – Moderate or Good (1ST RX)	Discounted costs	Discounted QALYs	Undiscounted costs	Undiscounted QALYs	HAQ at death	Time on 1st treatment (years)
MTX	78.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.24	[redacted]
ABT+MTX	78.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.68	[redacted]
ADA+MTX	78.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.68	[redacted]
CZP+MTX	78.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.65	[redacted]
ETN+MTX	78.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.65	[redacted]
GOL+MTX	78.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.67	[redacted]
INF+MTX	78.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.70	[redacted]
TOC+MTX	78.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.65	[redacted]
TOF+MTX	78.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.66	[redacted]
ETNb+MTX	78.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.66	[redacted]
INFb+MTX	78.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.71	[redacted]

Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Table 133: Summary of clinical outcomes for cDMARD-IR combination therapy, rapid progression

Strategy	Age at death (years)	% EULAR – Moderate or Good (1ST RX)	Discounted costs	Discounted QALYs	Undiscounted costs	Undiscounted QALYs	HAQ at death	Time on 1st treatment (years)
MTX	78.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.47	[redacted]
ABT+MTX	78.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.75	[redacted]
ADA+MTX	78.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.75	[redacted]
CZP+MTX	78.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.71	[redacted]
ETN+MTX	78.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.73	[redacted]
GOL+MTX	78.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.73	[redacted]
INF+MTX	78.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.78	[redacted]
TOC+MTX	78.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.73	[redacted]
TOF+MTX	78.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.74	[redacted]
ETNb+MTX	78.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.72	[redacted]
INFb+MTX	78.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.77	[redacted]

Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

5.7.1.3 Disaggregated results of the base case incremental cost effectiveness analysis

Table 134 and Table 135 present the disaggregated costs for Norton progression and rapid progression.

Table 134: Disaggregated costs for cDMARD-IR combination therapy, Norton progression

Strategy	Total cost	Primary therapy costs	Monitoring costs	Medical resource use	Adverse event costs
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Table 135: Disaggregated costs for cDMARD-IR combination therapy, rapid progression

Strategy	Total cost	Primary therapy costs	Monitoring costs	Medical resource use	Adverse event costs
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

5.7.1.4 Stability

10,000 patients have been passed through the model in the base case and scenario analyses. The model was run with up to 100,000 patients and 10,000 was decided to be a good trade-off between stability and run time. The model takes around 30 minutes to run 10,000 patients and 8 hours to run 100,000 patients. Total costs and QALYs appear stable after around 10,000 simulations. Figure 69 and Figure 70 present the incremental QALYs and costs with standard errors for the tofacitinib vs MTX comparison. The standard error in the incremental QALYs at 10,000 simulations is 0.019, compared to 0.006 for 100,000 simulations. The standard error in incremental costs at 10,000 simulations is £394, compared to £126 with 100,000 simulations. Figure 72 and Figure 73 present total QALYs and costs for all strategies with up to 100,000 simulations.

Figure 70: Incremental QALYs for tofacitinib vs MTX with standard errors

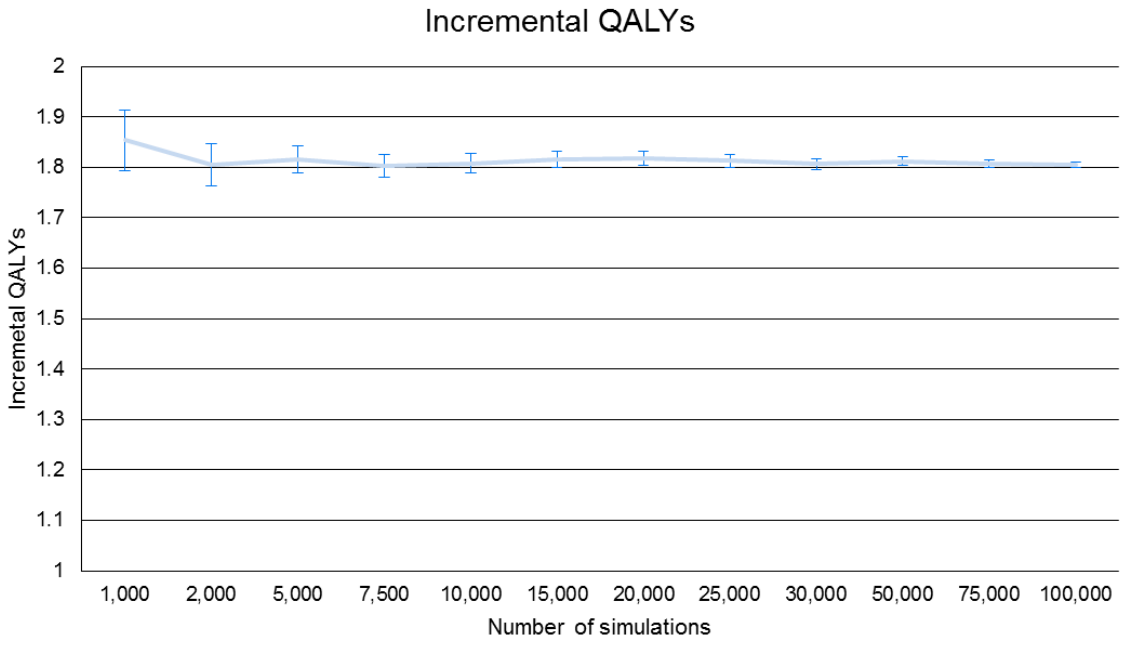


Figure 71: Incremental cost for tofacitinib vs MTX with standard errors

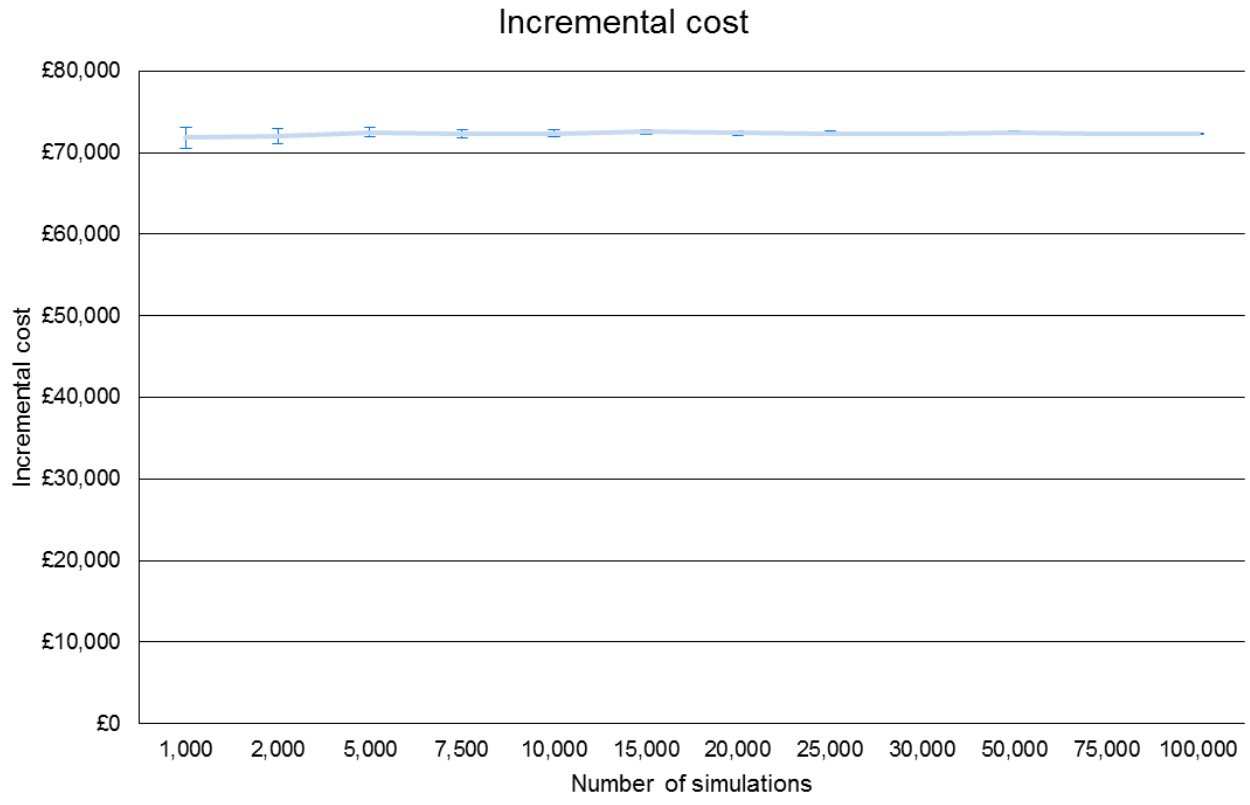
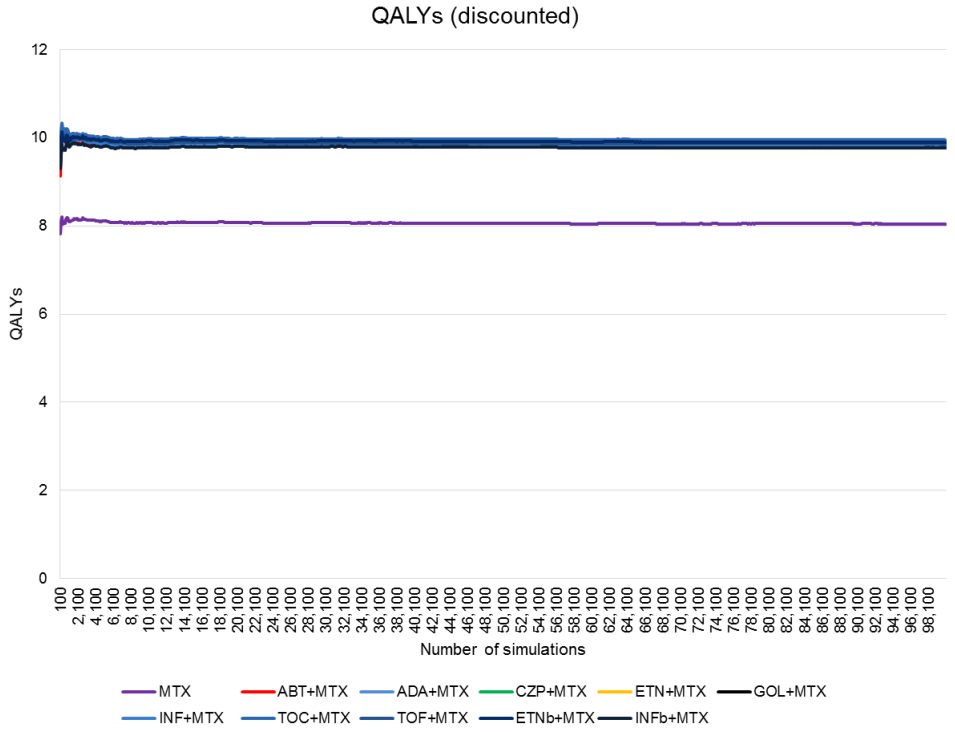
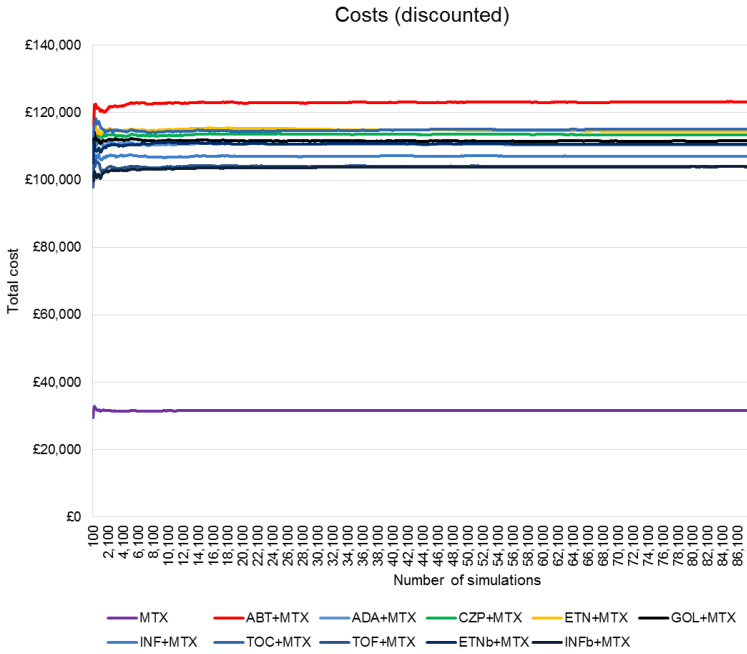


Figure 72: Total QALYs for all strategies



Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Figure 73: Total costs for all strategies



Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib

5.7.1.5 Probabilistic sensitivity analysis

Inputs

Parameters varied in the probabilistic sensitivity analysis (PSA) for the cDMARD-IR population include the baseline probability of response, odds ratios for response, HAQ-DI change at Month 6 and time to treatment discontinuation. The baseline probability of response and time to treatment discontinuation are calculated using multivariate regression models derived from patient-level data and in order to ensure the parameters in these models have been varied in a consistent way a multivariate normal distribution has been used to randomly sample parameter values.

Odds ratios for response have been taken directly from the coda used in the NMA. HAQ-DI change at month 6 has been varied using a normal distribution, and with standard errors taken from the BSRBR data. Table 136 summarises the distribution used in the PSA.

The population used in the PSA was resampled for each simulation. One hundred patients were used in each population run, compared to 10,000 in the base case. This has been done to reduce computational time. This is in line with NICE DSU guidance, which states that if there is a trade-off to be made between the number of patients simulated and number of PSA simulations run, the former is more appropriate.

HAQ-DI progression, HRQL and cost data have not been varied in the PSA. Instead, these parameters are varied in scenario analysis to assess the impact of changes in these variables.

Table 136: Distribution used to sample parameters for PSA: cDMARD-IR combination therapy

Parameter	Distribution used for PSA
EULAR moderate – Age	Multivariate normal distribution
EULAR moderate – Anti-CCP positive	Multivariate normal distribution
EULAR moderate – Female	Multivariate normal distribution
EULAR moderate – HAQ-DI	Multivariate normal distribution
EULAR moderate – DAS28	Multivariate normal distribution
EULAR moderate – Prior bDMARDs	Multivariate normal distribution
EULAR moderate – CDAI	Multivariate normal distribution
EULAR moderate – Constant	Multivariate normal distribution
EULAR good – Age	Multivariate normal distribution
EULAR good – Anti-CCP positive	Multivariate normal distribution
EULAR good – Female	Multivariate normal distribution
EULAR good – HAQ-DI	Multivariate normal distribution
EULAR good – DAS28	Multivariate normal distribution
EULAR good – Prior bDMARDs	Multivariate normal distribution
EULAR good – CDAI	Multivariate normal distribution
EULAR good – Constant	Multivariate normal distribution
Odds ratio for response: Tofacitinib monotherapy –	Coda

Parameter	Distribution used for PSA
Moderate	
Odds ratio for response: Tofacitinib monotherapy – Good	Coda
Odds ratio for response: Tofacitinib + MTX – Moderate	Coda
Odds ratio for response: Tofacitinib + MTX – Good	Coda
Odds ratio for response: Adalimumab monotherapy – Moderate	Coda
Odds ratio for response: Adalimumab monotherapy – Good	Coda
Odds ratio for response: Adalimumab + MTX – Moderate	Coda
Odds ratio for response: Adalimumab + MTX – Good	Coda
Odds ratio for response: Certolizumab monotherapy – Moderate	Coda
Odds ratio for response: Certolizumab monotherapy – Good	Coda
Odds ratio for response: Certolizumab + MTX – Moderate	Coda
Odds ratio for response: Certolizumab + MTX – Good	Coda
Odds ratio for response: Etanercept monotherapy – Moderate	Coda
Odds ratio for response: Etanercept monotherapy – Good	Coda
Odds ratio for response: Etanercept + MTX – Moderate	Coda
Odds ratio for response: Etanercept + MTX – Good	Coda
Odds ratio for response: Abatacept + MTX – Moderate	Coda
Odds ratio for response: Abatacept + MTX – Good	Coda
Odds ratio for response: Golimumab + MTX – Moderate	Coda
Odds ratio for response: Golimumab + MTX – Good	Coda
Odds ratio for response: Infliximab + MTX – Moderate	Coda
Odds ratio for response: Infliximab + MTX – Good	Coda
Odds ratio for response: Rituximab + MTX – Moderate	Coda
Odds ratio for response: Rituximab + MTX – Good	Coda
Odds ratio for response: Tocilizumab monotherapy – Moderate	Coda
Odds ratio for response: Tocilizumab monotherapy – Good	Coda
Odds ratio for response: Tocilizumab + MTX – Moderate	Coda
Odds ratio for response: Tocilizumab + MTX – Good	Coda
Odds ratio for response: Ciclosporin – Moderate	Coda
Odds ratio for response: Ciclosporin – Good	Coda
Odds ratio for response: Leflunomide – Moderate	Coda
Odds ratio for response: Leflunomide – Good	Coda
Odds ratio for response: MTX – Moderate	Coda
Odds ratio for response: MTX – Good	Coda
Odds ratio for response: Post-biologic therapy – Moderate	Coda
Odds ratio for response: Post-biologic therapy – Good	Coda
Odds ratio for response: Sulfasalazine – Moderate	Coda
Odds ratio for response: Sulfasalazine – Good	Coda
Odds ratio for response: DMARD combination – Moderate	Coda

Parameter	Distribution used for PSA
Odds ratio for response: DMARD combination – Good	Coda
Odds ratio for response: Etanercept biosimilar monotherapy – Good	Coda
Odds ratio for response: Etanercept biosimilar monotherapy – Moderate	Coda
Odds ratio for response: Etanercept biosimilar + MTX – Moderate	Coda
Odds ratio for response: Etanercept biosimilar + MTX – Good	Coda
EULAR Response – Moderate response	Normal distribution
EULAR Response – Good response	Normal distribution
Moderate responders: Lognormal – Age	Multivariate normal distribution
Moderate responders: Lognormal – Female	Multivariate normal distribution
Moderate responders: Lognormal – DAS28	Multivariate normal distribution
Moderate responders: Lognormal – Disease Duration (years)	Multivariate normal distribution
Moderate responders: Lognormal – Number of previous DMARDS	Multivariate normal distribution
Moderate responders: Lognormal – HAQ-DI	Multivariate normal distribution
Moderate responders: Lognormal – Constant	Multivariate normal distribution
Moderate responders: Lognormal – sigma	Multivariate normal distribution
Good responders: Lognormal – Age	Multivariate normal distribution
Good responders: Lognormal – Female	Multivariate normal distribution
Good responders: Lognormal – DAS28	Multivariate normal distribution
Good responders: Lognormal – Disease Duration (years)	Multivariate normal distribution
Good responders: Lognormal – Number of previous DMARDS	Multivariate normal distribution
Good responders: Lognormal – HAQ-DI	Multivariate normal distribution
Good responders: Lognormal – Constant	Multivariate normal distribution
Good responders: Lognormal – sigma	Multivariate normal distribution

Abbreviations: bDMARD, biological disease-modifying anti-rheumatic drug; CCP, cyclic citrullinated peptide; CDAI, clinical disease activity index; DAS28, Disease Activity Score in 28 joints; DMARD, disease-modifying anti-rheumatic drug; HAQ-DI, Health Assessment Questionnaire-disability index; MTX, methotrexate.

Results

The average results of the PSA for Norton progression are presented in Table 137, with a cost-effectiveness plane in Figure 74 and a cost-effectiveness acceptability curve in Figure 75.

The average results of the PSA for rapid progression are presented in Table 138, with a cost-effectiveness plane in Figure 77 and a cost-effectiveness acceptability curve in Figure 77.

Results in PSA do not differ significantly from the base case results for either progression setting. Tofacitinib was more costly and more effective than MTX in all scenarios. Tofacitinib becomes the optimal treatment option at a willingness-to-pay

threshold of approximately £25,000 and £40,000 per QALY for rapid and Norton progression, respectively.

With Norton progression, at a WTP threshold of £20,000 tofacitinib was the optimal treatment in 0% of scenarios, compared to 100% for MTX. At a WTP of £30,000 tofacitinib was the optimal treatment in 0% of scenarios, compared to 99% for MTX. At a WTP of £50,000 tofacitinib was the optimal treatment in 32% of scenarios, compared to 1% for MTX.

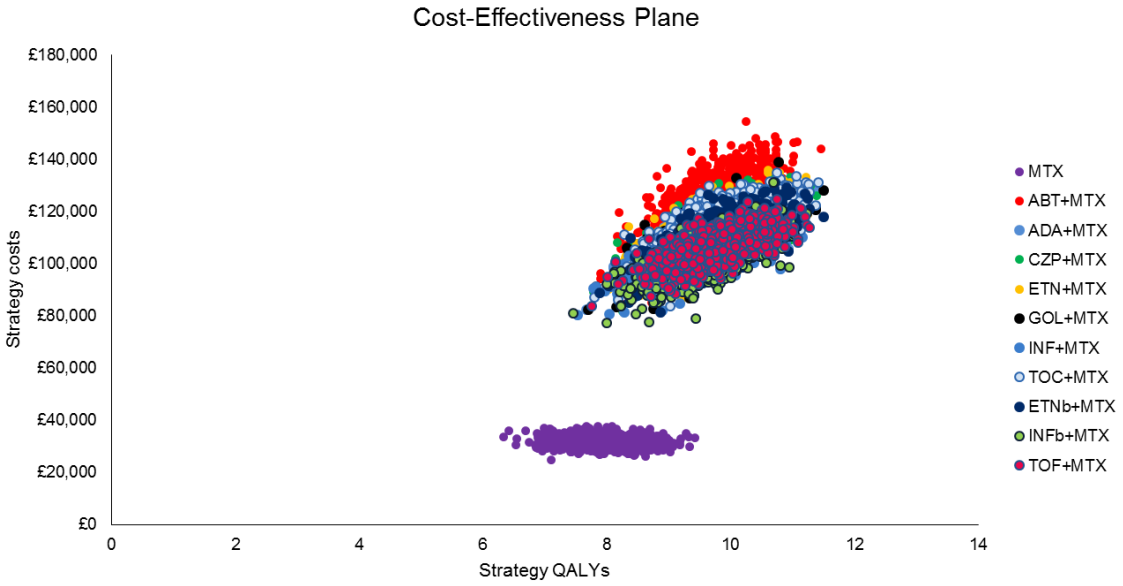
With rapid progression, at a WTP threshold of £20,000 tofacitinib was the optimal treatment in 1% of scenarios, compared to 99% for MTX. At a WTP of £30,000 tofacitinib was the optimal treatment in 39% of scenarios, compared to 0% for MTX. At a WTP of £50,000 tofacitinib was the optimal treatment in 28% of scenarios, compared to 0% for MTX.

Table 137: Average results from the PSA - cDMARD-IR combination therapy, Norton progression

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline
MTX	[redacted]	[redacted]	[redacted]	[redacted]	
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£41,389
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£40,610
INF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£42,994
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£41,782
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£43,643
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£43,214
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£43,317
ETN+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£43,747
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£42,747
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£51,524

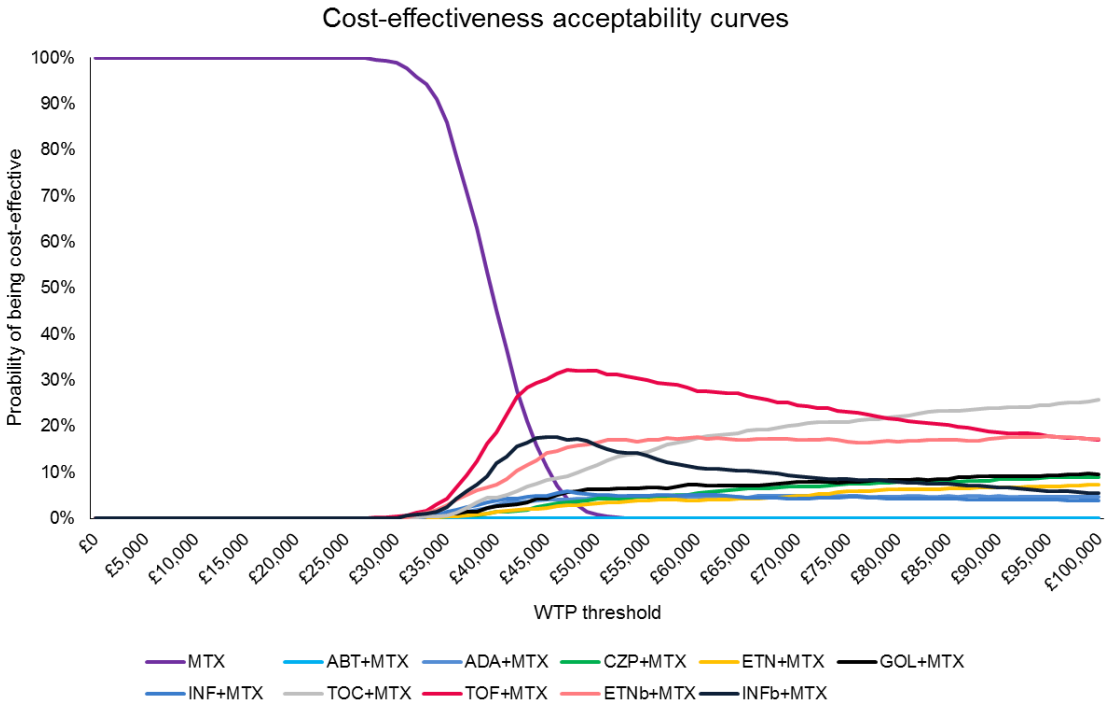
Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Figure 74: Cost-effectiveness plane for PSA, cDMARD-IR combination therapy, Norton progression



Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Figure 75: Cost-effectiveness acceptability curves for PSA, cDMARD-IR combination therapy, Norton progression



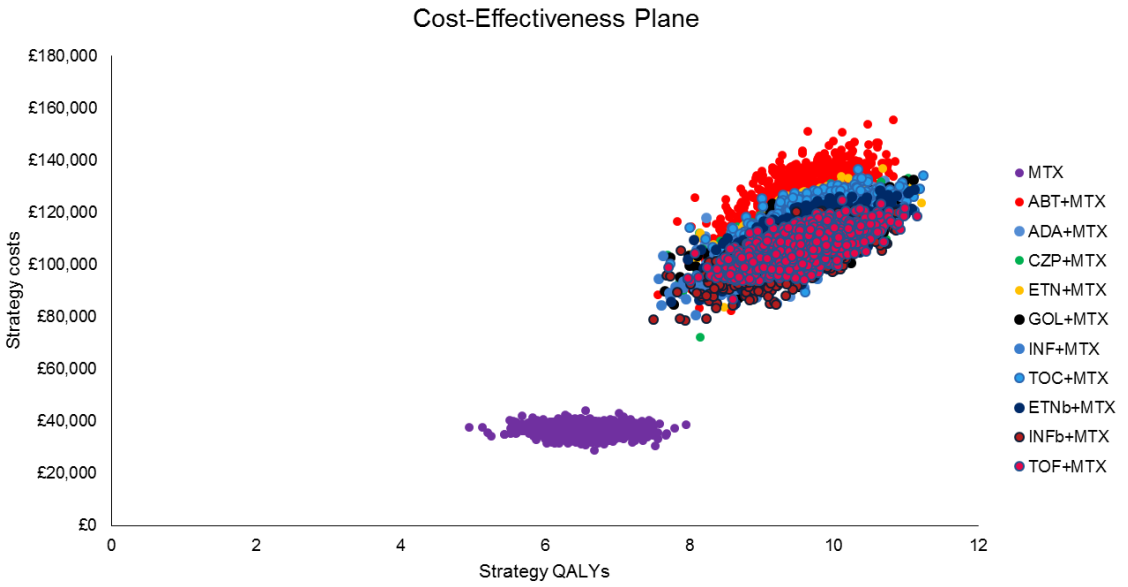
Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Table 138: Average results from the PSA - cDMARD-IR combination therapy, rapid progression

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline
MTX	[redacted]	[redacted]	[redacted]	[redacted]	
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£23,424
INF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£24,439
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£23,487
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£24,310
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£25,043
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£24,993
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£25,187
ETN+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£25,530
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£25,218
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£29,448

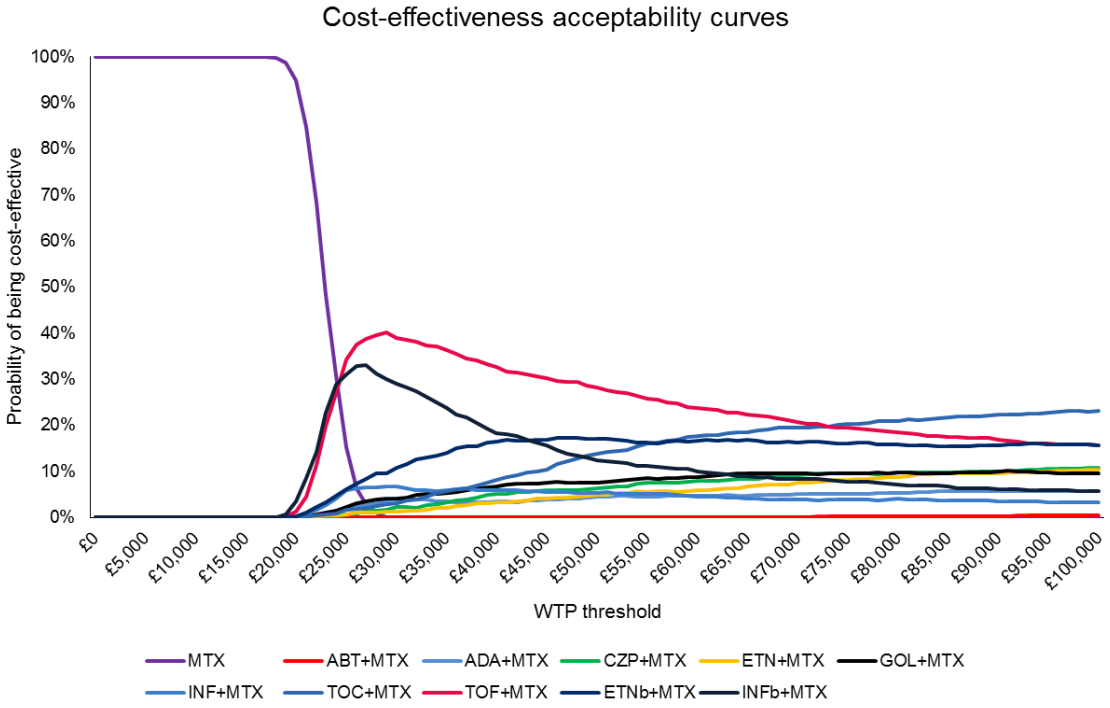
Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Figure 76: Cost-effectiveness plane for PSA, cDMARD-IR combination therapy, rapid progression



Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Figure 77: Cost-effectiveness acceptability curves for PSA, cDMARD-IR combination therapy, rapid progression



Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

5.7.1.6 Scenario analysis

Scenarios were performed which considered the impact of adjusting model inputs and settings as described in Table 139.

The severe strategy is the strategy used in the base case. In the TA375 strategy the MTX strategy is modelled in line with the bDMARD strategies, as is DMC → RTX+MTX → TOC+MTX → DMC → DMC → LEF → PBT. All other strategies remain the same. The BIO-only strategy does not model the MTX strategy. The YORK strategy is a sequence requested by the ERG. These strategies contain the same first-line therapies, which are the followed by 4 sets of DMC, then PBC. The RTX-IT strategy refers to the sequence used in patients who are rituximab intolerant. The set of treatment sequences used for each strategy is provided in Appendix 15.

In the NMA row, binomial refers to the base case binomial NMA, binomial alternate to the scenario analysis NMA using the binomial model, and probit refers to the NMA using the probit model for cDMARD-IR patients.

In the progression row, the linear scenarios models all cDMARDs as progressing in a linear fashion, with progression set to an increase in HAQ of 0.045 per year. The PaC lin only scenario only models PBC as having linear progression, thus LEF follows Norton progression. In the LTE scenario HAQ progression for tofacitinib is modelled using data from the LTE studies.

Table 139: Model settings/inputs varied in scenario analysis and relevant sections within the submission

Setting/input	Base case setting/input	Alternatives in SA	Section
Population	ORAL PLD	BSRBR data	5.3.1
Strategy	Severe	BIO-TA375 BIO-only YORK RTX-IT	5.2.3.2
NMA	Binomial Estimate 1	Binomial Estimate 2 Probit model	4.10
HAQ change	BSRBR	Patient-level data from ORAL trials	5.3.2.2
Progression	Rapid	Norton PaC lin only LTE	5.3.2.2
Discontinuation	Lognormal	Exponential Gompertz Weibull Loglogistic Generalised Gamma	5.3.2.4
IDU	No disutility applied for injections and infusions	Disutility applied for injections and infusions	Appendix 12
HRQL – Relationship between HAQ-DI and VAS pain	Patient-level data from ORAL trials	TA375	5.4.7
HRQL - Algorithm	ALDVMM	Soini	5.4.7
Cost of tofacitinib	[redacted]	List price (£690.03)	5.5.2.1
MRU and monitoring	TA375	MRU from Taylor et al (331) No monitoring costs No MRU	5.5.2.2 5.5.2.3

Abbreviations: BSRBR, British Society for Rheumatology; HAQ, Health Assessment Questionnaire; IDU, injection/infusion disutility; MRU, Medicines Resource Unit; NMA, network meta-analysis; PAS, patient access scheme; VAS, visual analogue scale.

The list of scenarios considered is provided in Table 140 and Table 141. In each table, changes to the basecase set up are highlighted by a yellow cell. A summary of the cost-effectiveness of tofacitinib in each scenario is also provided in this table, with full results in Appendix 14.

The ICER for tofacitinib + MTX vs MTX ranged from £25,241–48,915. Tofacitinib dominated or extendedly dominated treatments other than MTX in 16 of 21 scenarios, had ICERs ranging from £43,056–53,210 vs infliximab biosimilar + MTX in three scenarios and was extendedly dominated by infliximab biosimilar + MTX in two scenarios. In the scenarios representing the two base cases using the list price instead

of the PAS price the ICER for tofacitinib + MTX vs MTX was £25,241 using rapid progression and tofacitinib + MTX was dominated by MTX using Norton progression.

Scenarios 3 and 4 look at the impact of using an alternative NMA to find the probability of response for comparators. The results using the binomial estimate 2 show a small increase in QALYs across all strategies, which is expected as all therapies except tofacitinib will have an increased chance of response. However, this does not translate into a significant change in results. This indicates that the method used to account for early advancement in the ORAL clinical trials is not an important factor for determining cost-effectiveness.

Scenarios 6, 7 and 8 test the assumptions around HAQ progression. Scenarios 6 and 7 investigate the effect of changing the assumptions around cDMARD progression, neither of which have a large effect on the ICER. Scenario 8 investigates the effect of using LTE data for HAQ progression with tofacitinib. In this scenario tofacitinib dominates or extendedly dominates all other sequences except MTX. This is believed to be because the LTE data show a continued decrease in HAQ beyond month 6. The long-term data therefore extends a benefit to tofacitinib that biologics do not receive; it is consequently more conservative to assume no progression with tofacitinib.

Scenarios 9 through 12 test the effect of using an alternate distribution to define time to discontinuation. None of these scenarios result in a meaningful change in the results.

Scenario 13 tests the effect of including a QALY loss associated with subcutaneous injections and infusions. This results in a reduction in QALYs for all strategies, and tofacitinib and ETNb+MTX dominating all other strategies.

Scenario 14 tests the effect of using the TA375 HAQ/pain relationship in mapping HAQ-DI to the EQ-5D. As average pain scores are lower, QALYs increase for all strategies, and the ICER for tofacitinib vs MTX increases. This is likely due to the reduction in pain scores for patients with a HAQ score of 3. However, the results vs bDMARDs are unaffected.

Scenario 19 presents the results using the YORK strategy. Costs and QALYs are reduced for all strategies, with the exception of the costs in the MTX strategy. It can be seen that the incremental QALYs for TOC+MTX in this scenario are greatly increased, reducing the ICER vs tofacitinib to £51,449.

Scenario 21 presents the results using a population simulated using the average age, proportion of females, HAQ, DAS, weight, disease duration and previous number of DMARDs from the BSRBR. There is a reduction in costs and QALYs for all strategies, with the exception of the MTX strategy, where costs increase slightly.

This is likely due to patients in the BSRBR being slightly older, with higher HAQ scores. This translates into higher mortality rates and less time in the model, as well as generally higher HAQ scores throughout the model. Higher HAQ scores at baseline also mean fewer patients will have a ‘good’ EULAR response. However, this does not translate into a meaningful change in the ICERs, with the ICER for tofacitinib vs MTX slightly reduced. ETNb+MTX has an ICER of £64,652 vs tofacitinib + MTX and TOC+MTX has an ICER of £99,069 vs tofacitinib + MTX. All other treatments are dominated or extendedly dominated.

Table 140: Scenarios considered for the cDMARD-IR population receiving combination therapy (part 1)

Scenario	Basecase	1	2	3	4	5	6	7	8	9
Population	ORAL PLD	ORAL PLD	ORAL PLD	ORAL PLD	ORAL PLD	ORAL PLD	ORAL PLD	ORAL PLD	ORAL PLD	ORAL PLD
Strategy	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe
NMA	Estimate 1	Estimate 1	Estimate 1	Estimate 2	probit	Estimate 1	Estimate 1	Estimate 1	Estimate 1	Estimate 1
HAQ change	BSRBR	BSRBR	BSRBR	BSRBR	BSRBR	PLD	BSRBR	BSRBR	BSRBR	BSRBR
Progression	Norton	Norton	Rapid	Norton	Norton	Norton	PaC lin only	linear	LTE	Norton
Discontinuation	Lognormal	Lognormal	Lognormal	Lognormal	Lognormal	Lognormal	Lognormal	Lognormal	Lognormal	Exponential
IDU	Basecase	Basecase	Basecase	Basecase	Basecase	Basecase	Basecase	Basecase	Basecase	Basecase
HRQL – HAQ/Pain	PLD	PLD	PLD	PLD	PLD	PLD	PLD	PLD	PLD	PLD
HRQL - Algorithm	ALDVMM	ALDVMM	ALDVMM	ALDVMM	ALDVMM	ALDVMM	ALDVMM	ALDVMM	ALDVMM	ALDVMM
Cost of Tofacitinib	[redacted]	List - £690.03	List - £690.03	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRU and monitoring	TA375	TA375	TA375	TA375	TA375	TA375	TA375	TA375	TA375	TA375
TOF ICER vs MTX	£41,617	Dominated	**£25,241**	£44,790	£42,791	£45,087	£40,843	£46,127	£37,530	£40,831
TOF cost-effective vs non-MTX?†	Yes	No	No	No – ICER £53,210 vs INFb + MTX	No – ICER £43,056 vs INFb + MTX	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**

†Tofacitinib dominated or extendedly dominated the comparator, or the ICER for the comparator vs tofacitinib was >£30,000.
Abbreviations: BSRBR, British Society for Rheumatology; HAQ, Health Assessment Questionnaire; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ration; IDU, injection/infusion disutility; LTE, long-term extension; MRU, Medicines Resource Unit; NMA, network meta-analysis; PaC, palliative care; PAS, patient access scheme; PLD, patient-level data; VAS, visual analogue scale.

Table 141: Scenarios considered for the cDMARD-IR population receiving combination therapy (part 2)

Scenario	10	11	12	13	14	15	16	17	18	19	20	21
Population	ORAL PLD	ORAL PLD	ORAL PLD	ORAL PLD	ORAL PLD	ORAL PLD	ORAL PLD	ORAL PLD	ORAL PLD	ORAL PLD	ORAL PLD	BSRBR
Strategy	Severe	Severe	Severe	Severe	Severe	Severe	Severe	BIO-only	BIO-TA375	YORK	Severe	Severe
NMA	Estimate 1	Estimate 1	Estimate 1	Estimate 1	Estimate 1	Estimate 1	Estimate 1	Estimate 1	Estimate 1	Estimate 1	Estimate 1	Estimate 1
HAQ change	BSRBR	BSRBR	BSRBR	BSRBR	BSRBR	BSRBR	BSRBR	BSRBR	BSRBR	BSRBR	BSRBR	BSRBR
Progression	Norton	Norton	Norton	Norton	Norton	Norton	Norton	Norton	Norton	Norton	Norton	Norton
Discontinuation	Gompertz	Weibull	Generalised Gamma	Lognormal	Lognormal	Lognormal	Lognormal	Lognormal	Lognormal	Lognormal	Lognormal	Lognormal
AEs	Basecase	Basecase	Basecase	QALY loss	Basecase	Basecase	Basecase	Basecase	Basecase	Basecase	Basecase	Basecase
HRQL – HAQ/	PLD	PLD	PLD	PLD	TA375 HAQ/P	PLD	PLD	PLD	PLD	PLD	PLD	PLD
HRQL - Algorithm	ALDVMM	ALDVMM	ALDVMM	ALDVMM	ALDVMM	ALDVMM	ALDVMM	ALDVMM	ALDVMM	ALDVMM	Soini	ALDVMM
Cost of Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRU and monitoring	TA375	TA375	TA375	TA375	TA375	Taylor	TA375 - No monitoring	TA375	TA375	TA376	TA375	TA376
TOF ICER vs MTX	£36,374	£37,786	£42,434	£43,064	£48,915	£39,063	£38,963	£35,465	£51,972	£41,122	£39,266	£38,324
TOF cost-effective vs non-MTX?†	**Yes**	**Yes**	No – ICER £49,187 vs INFb + MTX	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**

†Tofacitinib dominated or extendedly dominated the comparator, or the ICER for the comparator vs tofacitinib was >£30,000.
Abbreviations: BSRBR, British Society for Rheumatology; HAQ, Health Assessment Questionnaire; HRQL, health-related quality of life; ICER, incremental cost-effectiveness

ration; IDU, injection/infusion disutility; LTE, long-term extension; MRU, Medicines Resource Unit; NMA, network meta-analysis; PaC, palliative care; PAS, patient access scheme; PLD, patient-level data; VAS, visual analogue scale.

5.7.2 *Base case: cDMARD-IR monotherapy, PAS price*

5.7.2.1 Base case results

Base case results for Norton progression and rapid progression are presented in Table 142 and Table 143, respectively.

- The ICER for tofacitinib vs MTX ranged from £25,807–56,231 for rapid progression and Norton progression, respectively
- Tofacitinib dominated or extendedly dominated all other treatments for both progression settings with the exception of tocilizumab
- The ICER for tocilizumab vs tofacitinib + MTX was £38,974–57,475 for rapid progression and Norton progression, respectively

Table 142: Base case results for patients who are cDMARD-IR receiving monotherapy, Norton progression

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]		
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£56,231	£56,231
ETN	[redacted]	[redacted]	[redacted]	[redacted]	£60,976	Ext. Dominated
ADA	[redacted]	[redacted]	[redacted]	[redacted]	£60,896	Ext. Dominated
TOC	[redacted]	[redacted]	[redacted]	[redacted]	£56,489	£57,475

Abbreviations: ADA, adalimumab; ETN, etanercept; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Table 143: Base case results for patients who are cDMARD-IR receiving monotherapy, rapid progression

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]		
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£25,807	£25,807
ADA	[redacted]	[redacted]	[redacted]	[redacted]	£28,199	Ext. Dominated
ETN	[redacted]	[redacted]	[redacted]	[redacted]	£28,890	Dominated
TOC	[redacted]	[redacted]	[redacted]	[redacted]	£27,858	£38,974

Abbreviations: ADA, adalimumab; ETN, etanercept; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

5.7.2.2 Clinical outcomes from the model

A summary of the clinical outcomes is provided for Norton progression and rapid progression in Table 144 and Table 145, respectively.

Table 144: Summary of clinical outcomes for cDMARD-IR monotherapy, Norton progression

Strategy	Age at death (years)	% EULAR – Moderate or Good (1ST RX)	Discounted costs	Discounted QALYs	Undiscounted costs	Undiscounted QALYs	HAQ at death	Time on 1st treatment (years)
MTX	78.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.19	[redacted]
TOC	78.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.84	[redacted]
TOF	78.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.91	[redacted]
ETN	78.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.89	[redacted]
ADA	78.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.89	[redacted]

Abbreviations: ADA, adalimumab; ETN, etanercept; HAQ, Health Assessment Questionnaire; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Table 145: Summary of clinical outcomes for cDMARD-IR monotherapy, rapid progression

Strategy	Age at death (years)	% EULAR – Moderate or Good (1ST RX)	Discounted costs	Discounted QALYs	Undiscounted costs	Undiscounted QALYs	HAQ at death	Time on 1st treatment (years)
MTX	78.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.48	[redacted]
TOC	78.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.01	[redacted]
TOF	78.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.08	[redacted]
ETN	78.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.06	[redacted]
ADA	78.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.07	[redacted]

Abbreviations: ADA, adalimumab; ETN, etanercept; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

5.7.2.3 Disaggregated results of the base case incremental cost effectiveness analysis

Table 146 and Table 147 presents the disaggregated costs for Norton progression and rapid progression.

Table 146: Disaggregated costs for cDMARD-IR monotherapy, Norton progression

Strategy	Total cost	Primary therapy costs	Monitoring costs	Medical resource use	Adverse event costs
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; ETN, etanercept; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Table 147: Disaggregated costs for cDMARD-IR monotherapy, rapid progression

Strategy	Total cost	Primary therapy costs	Monitoring costs	Medical resource use	Adverse event costs
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; ETN, etanercept; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

5.7.2.4 Probabilistic sensitivity analysis

See Section 5.7.1.4 for methods.

Results

The average results of the PSA for Norton progression are presented in Table 148, with a cost-effectiveness plane in Figure 78 and a cost-effectiveness acceptability curve in Figure 79.

The average results of the PSA for rapid progression are presented in Table 149, with a cost-effectiveness plane in Figure 80 and a cost-effectiveness acceptability curve in Figure 81.

Results in PSA were slightly higher than the base case results using Norton progression and slightly lower using rapid progression. Tofacitinib was more costly and more effective than MTX in all scenarios. Tofacitinib becomes the optimal treatment option at a willingness-to-pay threshold of approximately £25,000 and £50,000 per QALY for rapid and Norton progression, respectively.

With Norton progression, at a WTP threshold of £20,000 tofacitinib was the optimal treatment in 0% of scenarios, compared to 100% for MTX. At a WTP of £30,000 tofacitinib was the optimal treatment in 0% of scenarios, compared to 100% for MTX. At a WTP of £50,000 tofacitinib was the optimal treatment in 21% of scenarios, compared to 55% for MTX.

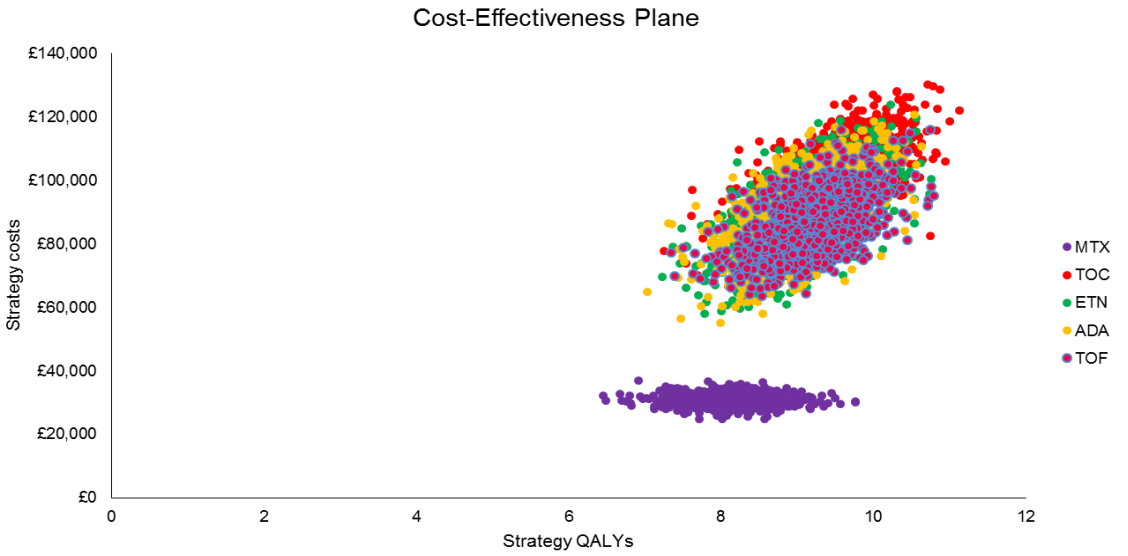
With rapid progression, at a WTP threshold of £20,000 tofacitinib was the optimal treatment in 2% of scenarios, compared to 98% for MTX. At a WTP of £30,000 tofacitinib was the optimal treatment in 65% of scenarios, compared to 4% for MTX. At a WTP of £50,000 tofacitinib was the optimal treatment in 33% of scenarios, compared to 0% for MTX.

Table 148: Average results from the PSA - cDMARD-IR monotherapy, Norton progression

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline
MTX	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£53,443
ADA	[redacted]	[redacted]	[redacted]	[redacted]	£63,937
ETN	[redacted]	[redacted]	[redacted]	[redacted]	£62,867
TOC	[redacted]	[redacted]	[redacted]	[redacted]	£53,110

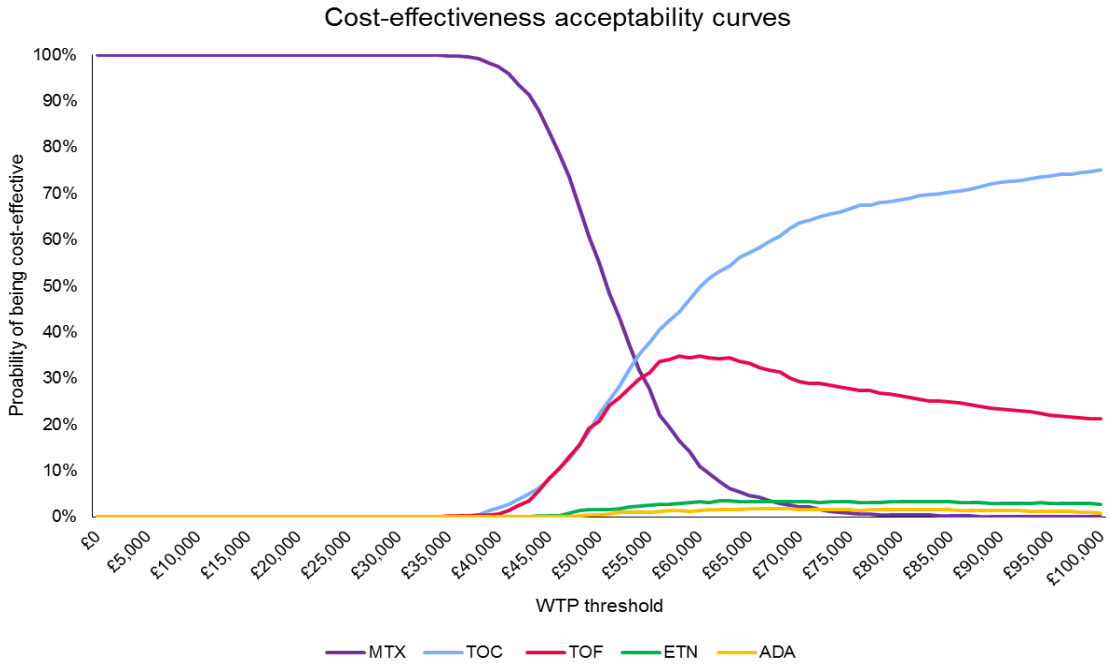
Abbreviations: ADA, adalimumab; ETN, etanercept; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Figure 78: Cost-effectiveness plane for PSA, cDMARD-IR monotherapy, Norton progression



Abbreviations: ADA, adalimumab; ETN, etanercept; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib

Figure 79: Cost-effectiveness acceptability curves for PSA, cDMARD-IR monotherapy, Norton progression



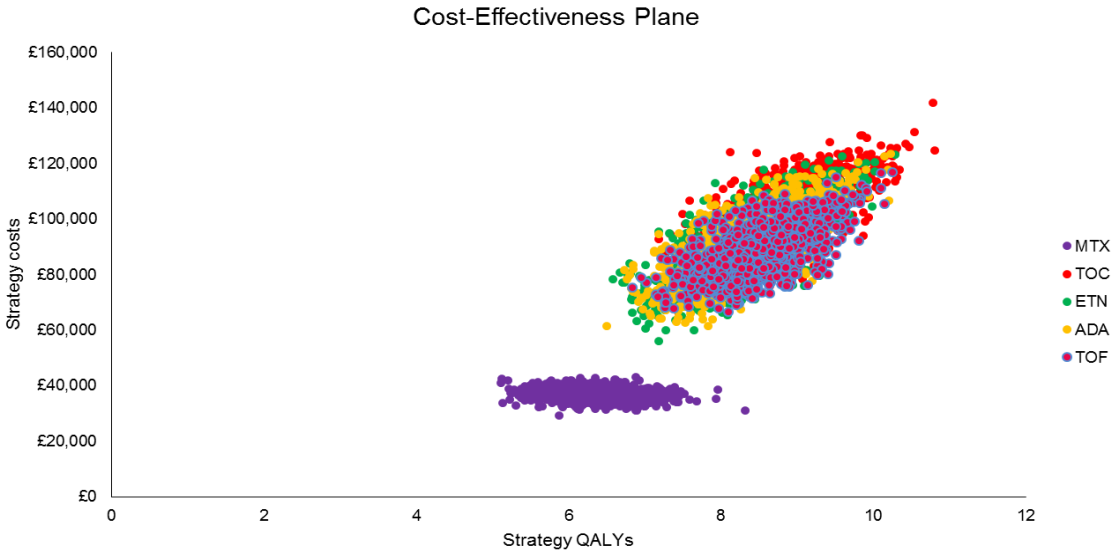
Abbreviations: ADA, adalimumab; ETN, etanercept; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Table 149: Average results from the PSA - cDMARD-IR monotherapy, rapid progression

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline
MTX	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£25,094
ADA	[redacted]	[redacted]	[redacted]	[redacted]	£28,514
ETN	[redacted]	[redacted]	[redacted]	[redacted]	£28,516
TOC	[redacted]	[redacted]	[redacted]	[redacted]	£27,125

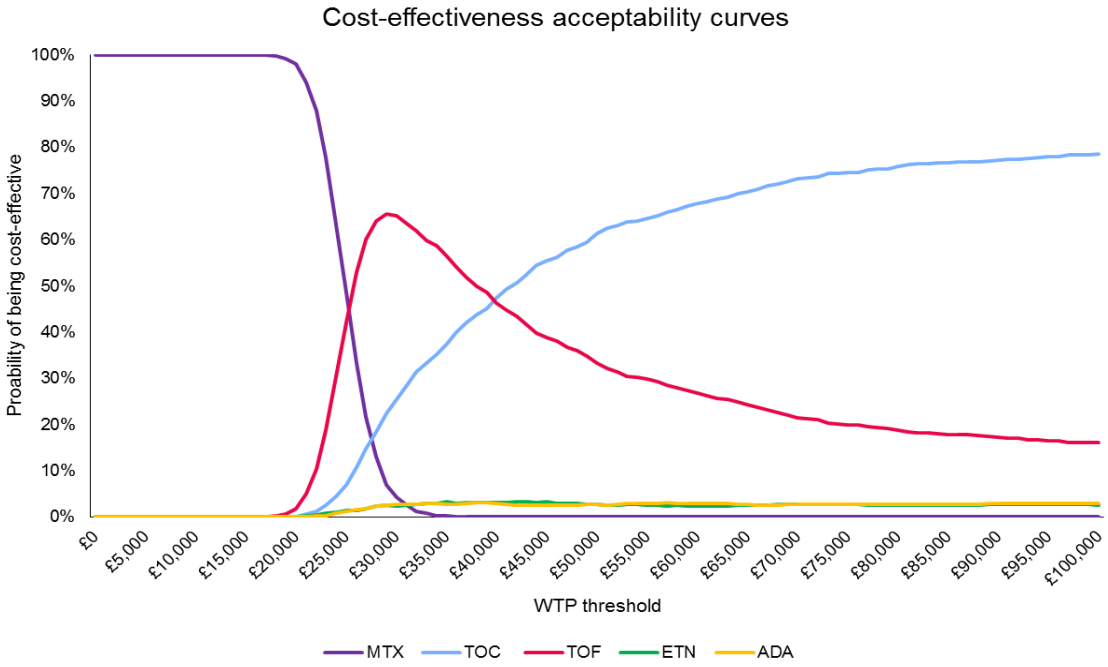
Abbreviations: ADA, adalimumab; ETN, etanercept; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Figure 80: Cost-effectiveness plane for PSA, cDMARD-IR monotherapy, rapid progression



Abbreviations: ADA, adalimumab; ETN, etanercept; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib

Figure 81: Cost-effectiveness acceptability curves for PSA, cDMARD-IR monotherapy, rapid progression



Abbreviations: ADA, adalimumab; ETN, etanercept; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

5.7.2.5 Scenario analysis

A list of scenarios considered is provided in Table 150 and Table 151. A summary of the cost-effectiveness of tofacitinib in each scenario is also provided in this table, with full results in Appendix 14.

The ICER for tofacitinib vs MTX ranged from £27,335–58,597 across the scenarios considered, and tofacitinib was extendedly dominated by MTX in 9 of the 17 scenarios. Tofacitinib dominated or extendedly dominated treatments other than MTX in 6 of 17 scenarios. In the scenarios representing the two base cases using the list price instead of the PAS price the ICER for tofacitinib vs MTX was £27,335 with rapid progression and tofacitinib was extendedly dominated by MTX using Norton progression. It should be noted that patients receiving tofacitinib as a monotherapy are likely to do so due to MTX intolerance; the comparison against MTX for monotherapy may therefore not be representative of clinical practice.

Table 150: Scenarios considered for the cDMARD-IR population receiving monotherapy (part 1)

Scenario	1	2	3	4	5	6	7	8
Strategy	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe
NMA	Estimate 1	Estimate 1	Estimate 2	probit	Estimate 1	Estimate 1	Estimate 1	Estimate 1
HAQ change	BSRBR	BSRBR	BSRBR	BSRBR	PLD	BSRBR	BSRBR	BSRBR
Progression	Norton	Rapid	Norton	Norton	Norton	PBT lin only	linear	LTE
Discontinuation	Lognormal	Lognormal	Lognormal	Lognormal	Lognormal	Lognormal	Lognormal	Lognormal
IDU	Basecase	Basecase	Basecase	Basecase	Basecase	Basecase	Basecase	Basecase
HRQL	PLD	PLD	PLD	PLD	PLD	PLD	PLD	PLD
Cost of Tofacitinib	List-£690.03	List-£690.03	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRU and monitoring	TA375	TA375	TA375	TA375	TA375	TA375	TA375	TA375
TOF ICER vs MTX	Ext dom	**£27,335**	£55,228	£48,404	Ext dom	Ext dom	Ext dom	£47,595
TOF cost-effective vs non-MTX?†	No	No – ICER for TOC vs TOF £27,368	**Yes**	**Yes**	No	No	No	**Yes**

†Tofacitinib dominated or extendedly dominated the comparator, or the ICER for the comparator vs tofacitinib was >£30,000.
Abbreviations: BSRBR, British Society for Rheumatology; HAQ, Health Assessment Questionnaire; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ration; IDU, injection/infusion disutility; LTE, long-term extension; MRU, Medicines Resource Unit; NMA, network meta-analysis; PaC, palliative care; PAS, patient access scheme; PLD, patient-level data; VAS, visual analogue scale.

Table 151: Scenarios considered for the cDMARD-IR population receiving monotherapy (part 2)

Scenario	9	10	11	12	13	14	15	16	17
Strategy	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	YORK
NMA	Estimate 1	Estimate 1	Estimate 1	Estimate 1	Estimate 1	Estimate 1	Estimate 1	Estimate 1	Estimate 1
HAQ change	BSRBR	BSRBR	BSRBR	BSRBR	BSRBR	BSRBR	BSRBR	BSRBR	BSRBR
Progression	Norton	Norton	Norton	Norton	Norton	Norton	Norton	Norton	Norton
Discontinuation	Exponential	Gompertz	Weibull	Generalised Gamma	Lognormal	Lognormal	Lognormal	Lognormal	Lognormal
AEs	Basecase	Basecase	Basecase	Basecase	QALY loss	Basecase	Basecase	Basecase	Basecase
HRQL	PLD	PLD	PLD	PLD	PLD	TA375 HAQ/P	PLD	PLD	PLD
Cost of Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRU and monitoring	TA375	TA375	TA375	TA375	TA375	TA375	Taylor	TA375 - No monitoring	TA375
TOF ICER vs MTX	Ext dom	£47,778	£49,454	Ext dom	£58,597	Ext dom	Ext dom	Ext dom	£44,514
TOF cost-effective vs non-MTX?†	No	**Yes**	No	No	**Yes**	No	No	No	**Yes**

†Tofacitinib dominated or extendedly dominated the comparator, or the ICER for the comparator vs tofacitinib was >£30,000.
Abbreviations: BSRBR, British Society for Rheumatology; HAQ, Health Assessment Questionnaire; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ration; IDU, injection/infusion disutility; LTE, long-term extension; MRU, Medicines Resource Unit; NMA, network meta-analysis; PaC, palliative care; PAS, patient access scheme; PLD, patient-level data; VAS, visual analogue scale.

5.7.3 *Base case: bDMARD-IR combination therapy*

5.7.3.1 Base case results

Base case results for rituximab contraindicated and rituximab non-contraindicated patients are presented in Table 152 and Table 153, respectively.

For rituximab non-contraindicated:

- Tofacitinib + MTX was not cost-effective

For rituximab contraindicated:

- Tofacitinib + MTX dominated or extendedly dominated all treatments

Table 152: Base case results for patients who are bDMARD-IR and are not contraindicated to rituximab

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]		
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: ABA, abatacept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab.

Table 153: Base case results for patients who are bDMARD-IR and are contraindicated to rituximab

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]		
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: ABA, abatacept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab.

5.7.3.2 Clinical outcomes from the model

A summary of the clinical outcomes is provided in Table 154 and Table 155.

Table 154: Summary of clinical outcomes for bDMARD-IR, rituximab non-contraindicated

Strategy	Age at death (years)	% EULAR – Moderate or Good (1ST RX)	Discounted costs	Discounted QALYs	Undiscounted costs	Undiscounted QALYs	HAQ at death	Time on 1st treatment (years)
RTX+MTX	77.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.94	[redacted]
TOF+MTX	77.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.96	[redacted]
ABT+MTX	77.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.96	[redacted]
GOL+MTX	77.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.98	[redacted]

Abbreviations: Abbreviations: ABA, abatacept; GOL, golimumab; HAQ, Health Assessment Questionnaire; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab.

Table 155: Summary of clinical outcomes for bDMARD-IR, rituximab contraindicated

Strategy	Age at death (years)	% EULAR – Moderate or Good (1ST RX)	Discounted costs	Discounted QALYs	Undiscounted costs	Undiscounted QALYs	HAQ at death	Time on 1st treatment (years)
TOF+MTX	77.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.96	[redacted]
ABT+MTX	77.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.97	[redacted]
TOC+MTX	77.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.98	[redacted]
GOL+MTX	77.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.99	[redacted]

Abbreviations: Abbreviations: ABA, abatacept; GOL, golimumab; HAQ, Health Assessment Questionnaire; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab.

5.7.3.3 Disaggregated results of the base case incremental cost effectiveness analysis

A summary of disaggregated costs is provided in Table 156 and Table 157.

Table 156: Disaggregated costs, bDMARD-IR, rituximab non-contraindicated

Strategy	Total cost	Treatment costs	Monitoring costs	Medical resource use	Adverse event costs
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Table 157: Disaggregated costs, bDMARD-IR, rituximab non-contraindicated

Strategy	Total cost	Treatment costs	Monitoring costs	Medical resource use	Adverse event costs
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

5.7.3.4 Probabilistic sensitivity analysis: base case - moderate-to-severe cDMARD-IR population

Inputs

As for cDMARD-IR, but using a different NMA for CODA inputs (Section 5.7.1.4).

Results

The average results of the PSA for rituximab non-contraindicated are presented in Table 158, with a cost-effectiveness plane in Figure 82 and a cost-effectiveness acceptability curve in Figure 83.

The average results of the PSA for rituximab contraindicated are presented in Table 159, with a cost-effectiveness plane in Figure 84 and a cost-effectiveness acceptability curve in Figure 85.

In PSA for rituximab non-contraindicated tofacitinib remained dominated by rituximab + MTX. For rituximab contraindicated tofacitinib + MTX again dominated all treatments. Tofacitinib was never the optimal treatment for rituximab non-contraindicated and was always the optimal treatment for rituximab contraindicated.

When patients were able to take rituximab, the TOF+MTX strategy has a 1% chance of being the optimal treatment at a WTP threshold of £20,000, a 1% chance of being the optimal treatment at a WTP threshold of £30,000, and a 4% chance of being the optimal treatment at a WTP threshold of £50,000.

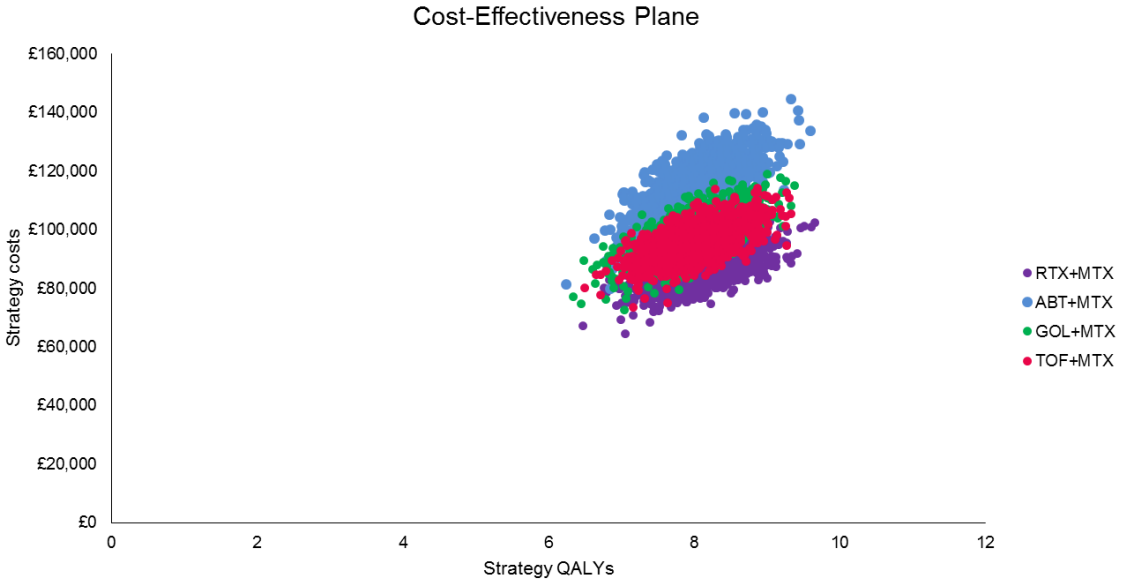
When patients were unable to take rituximab, the TOF+MTX strategy has an 75% chance of being the optimal treatment at a WTP threshold of £20,000, a 79% chance of being the optimal treatment at a WTP threshold of £30,000 and a 69% chance of being the optimal treatment at a WTP threshold of £50,000.

Table 158: Average results from the PSA - bDMARD-IR rituximab non-contraindicated

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

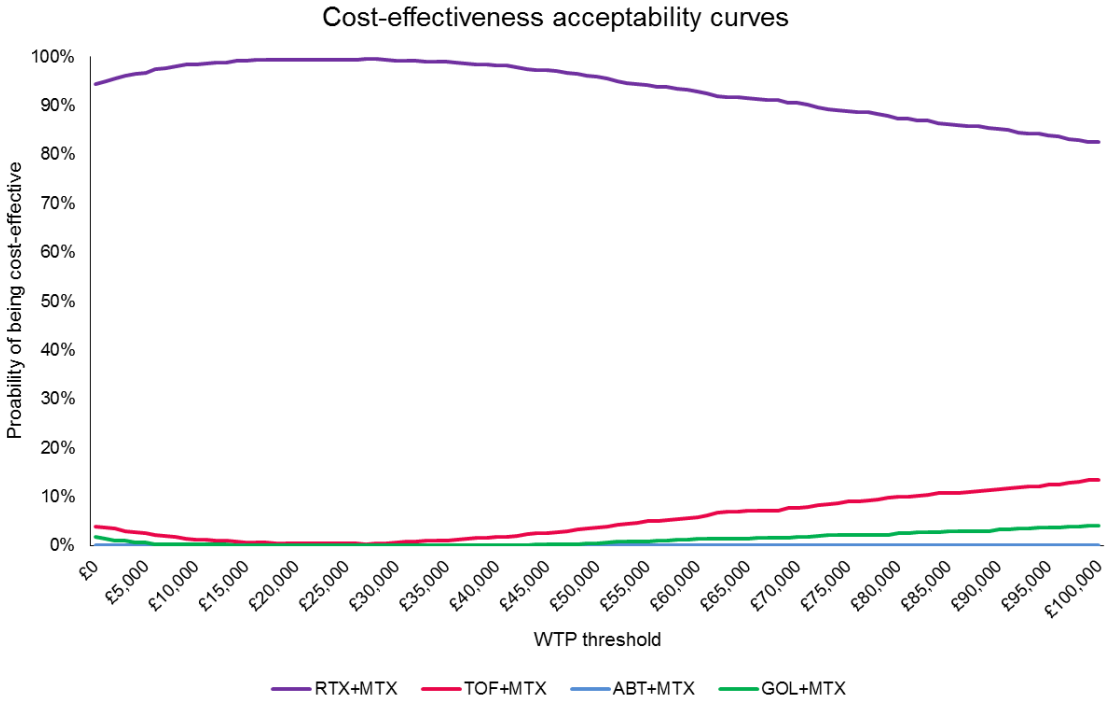
Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Figure 82: Cost-effectiveness plane for PSA, bDMARD-IR rituximab non-contraindicated



Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Figure 83: Cost-effectiveness acceptability curves for PSA, bDMARD-IR rituximab non-contraindicated



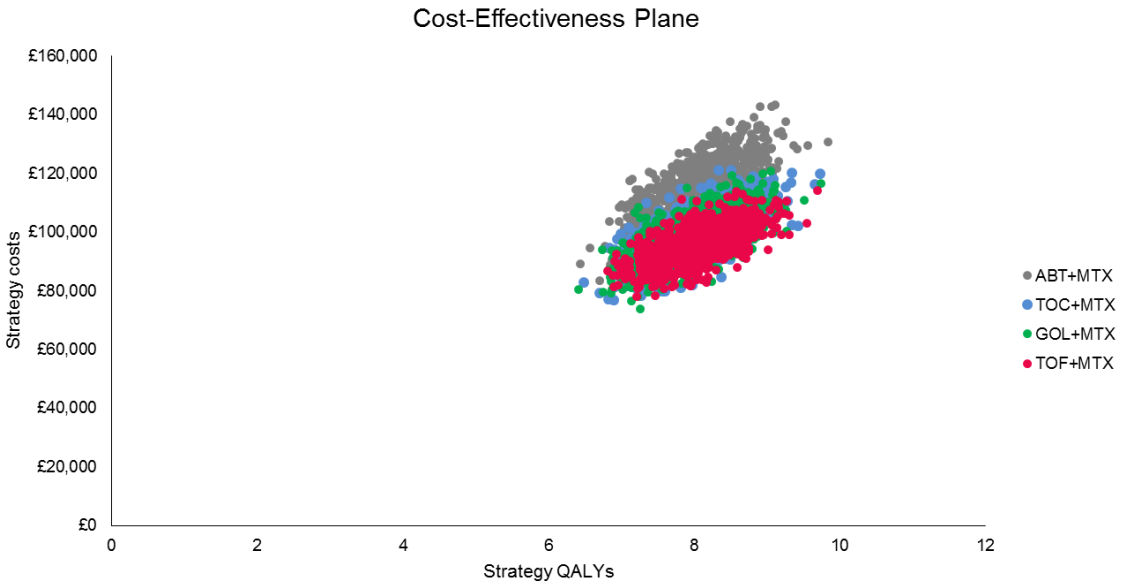
Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Table 159: Average results from the PSA - bDMARD-IR rituximab contraindicated

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

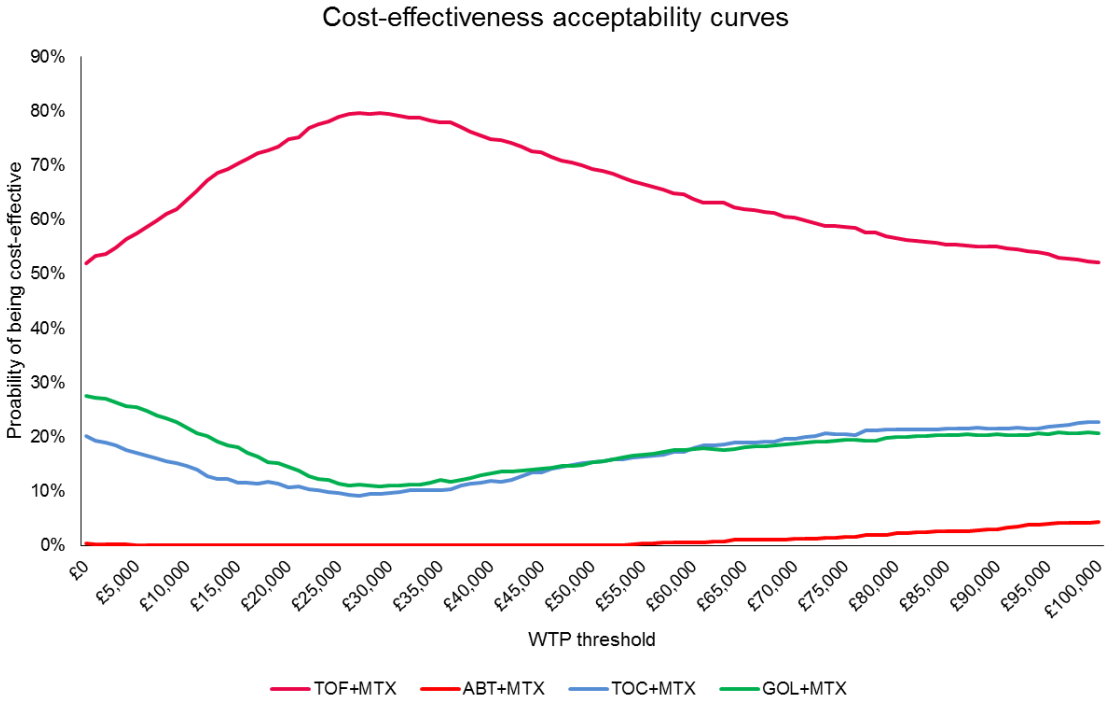
Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Figure 84: Cost-effectiveness plane for PSA, bDMARD-IR rituximab contraindicated



Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Figure 85: Cost-effectiveness acceptability curves for PSA, bDMARD-IR rituximab contraindicated



Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

5.7.3.5 Scenario analysis: rituximab non-contraindicated

A scenario analysis was performed for this population using the base case settings with the list price (Table 160). Tofacitinib + MTX was extendedly dominated by rituximab + MTX.

Table 160: Scenario analysis results for patients who are bDMARD-IR and are not contraindicated to rituximab, list price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]		
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: Abbreviations: ABA, abatacept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab.

5.7.3.6 Scenario analysis: rituximab contraindicated

A list of scenarios considered for is provided in Table 161 and Table 162. A summary of the cost-effectiveness of tofacitinib in each scenario is also provided in this table, with full results in Appendix 14.

Tofacitinib dominated or extendedly dominated all comparators, or the comparator had an ICER >£63,685 vs tofacitinib, in all scenarios.

Table 161: Scenarios considered for the bDMARD-IR population who are rituximab contraindicated (part 1)

Scenario	1	2	3	4	5	6
Strategy	RTX-IT	RTX-IT	RTX-IT	RTX-IT	RTX-IT	RTX-IT
HAQ change	BSRBR	PLD	BSRBR	BSRBR	BSRBR	BSRBR
Progression	Norton	Norton	linear	Norton	Norton	Norton
Discontinuation	Lognormal	Lognormal	Lognormal	Exponential	Gompertz	Weibull
IDU	Basecase	Basecase	Basecase	Basecase	Basecase	Basecase
HRQL	PLD	PLD	PLD	PLD	PLD	PLD
Cost of Tofacitinib	List-£690.03	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRU and monitoring	TA375	TA375	TA375	TA375	TA375	TA375
TOF cost-effective vs non-MTX?†	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**

†Tofacitinib dominated or extendedly dominated the comparator, or the ICER for the comparator vs tofacitinib was >£30,000.
Abbreviations: BSRBR, British Society for Rheumatology; HAQ, Health Assessment Questionnaire; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ration; IDU, injection/infusion disutility; LTE, long-term extension; MRU, Medicines Resource Unit; NMA, network meta-analysis; PaC, palliative care; PAS, patient access scheme; PLD, patient-level data; VAS, visual analogue scale.

Table 162: Scenarios considered for the bDMARD-IR population who are rituximab contraindicated (part 2)

Scenario	7	8	9	10	11	12
Strategy	RTX-IT	RTX-IT	RTX-IT	RTX-IT	RTX-IT	YORK
HAQ change	BSRBR	BSRBR	BSRBR	BSRBR	BSRBR	BSRBR
Progression	Norton	Norton	Norton	Norton	Norton	Norton
Discontinuation	Generalised Gamma	Lognormal	Lognormal	Lognormal	Lognormal	Lognormal
AEs	Basecase	QALY loss	Basecase	Basecase	Basecase	Basecase
HRQL	PLD	PLD	TA375 HAQ/P	PLD	PLD	PLD
Cost of Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRU and monitoring	TA375	TA375	TA375	Taylor	TA375 - No monitoring	TA375
TOF cost-effective vs non-MTX?†	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**

†Tofacitinib dominated or extendedly dominated the comparator, or the ICER for the comparator vs tofacitinib was >£30,000.
Abbreviations: BSRBR, British Society for Rheumatology; HAQ, Health Assessment Questionnaire; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ration; IDU, injection/infusion disutility; LTE, long-term extension; MRU, Medicines Resource Unit; NMA, network meta-analysis; PaC, palliative care; PAS, patient access scheme; PLD, patient-level data; VAS, visual analogue scale.

5.7.4 *Base case: bDMARD-IR monotherapy, MTX and rituximab intolerant*

5.7.4.1 Base case results

Base case results are presented in Table 163.

- The ICER for tofacitinib vs tocilizumab was £25,932

Table 163: Base case results for patients who are bDMARD-IR, MTX-intolerant, and are contraindicated to rituximab

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
TOC	[redacted]	[redacted]	[redacted]	[redacted]		
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£25,932	£25,932

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

5.7.4.2 Clinical outcomes from the model

A summary of the clinical outcomes is provided in Table 164.

Table 164: Summary of clinical outcomes for bDMARD-IR, MTX-intolerant, and contraindicated to rituximab

Strategy	Age at death (years)	% EULAR – Moderate or Good (1ST RX)	Discounted costs	Discounted QALYs	Undiscounted costs	Undiscounted QALYs	HAQ at death	Time on 1st treatment (years)
TOF	77.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.98	4.51
TOC	77.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.14	6.10

Abbreviations: HAQ, Health Assessment Questionnaire; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

5.7.4.3 *Disaggregated results of the base case incremental cost effectiveness analysis*

A summary of disaggregated costs is provided in Table 165.

Table 165: Disaggregated costs, bDMARD-IR, MTX-intolerant, and contraindicated to rituximab

Strategy	Total cost	Treatment costs	Monitoring costs	Medical resource use	Adverse event costs
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TOC, tocilizumab; TOF, tofacitinib.

5.7.4.4 *Scenario analysis*

A scenario analysis was performed for this population using the base case settings with the list price (Table 166). The ICER for tofacitinib vs tocilizumab was £31,536.

Table 166: Scenario analysis results for patients who are bDMARD-IR, MTX-intolerant, and are contraindicated to rituximab, list price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
TOC	[redacted]	[redacted]	[redacted]	[redacted]		
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£31,536	£31,536

Abbreviations: TOC, tocilizumab; TOF, tofacitinib.

5.7.5 *Base case: bDMARD-IR combination therapy, rituximab non-contraindicated, tofacitinib used after rituximab*

5.7.5.1 *Base case results*

Base case results for bDMARD-IR combination therapy in rituximab non-contraindicated patients in whom tofacitinib is used after rituximab patients are presented in Table 167.

- The ICER for tofacitinib + MTX after rituximab vs rituximab + MTX was £28,379
- Tofacitinib + MTX after rituximab dominated or extendedly dominated all other treatments with the exception of abatacept + MTX
- The ICER for abatacept + MTX vs tofacitinib + MTX was £1,544,810

Table 167: Base case results for bDMARD-IR combination therapy, rituximab non-contraindicated, tofacitinib used after rituximab

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]		
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£28,379	£28,379
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£36,880	Dominated
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£64,292	£1,544,810

Abbreviations: ABT, abatacept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab; TOF, tofacitinib.

5.7.5.2 Clinical outcomes from the model

A summary of the clinical outcomes is provided in Table 168.

Table 168: Summary of clinical outcomes for bDMARD-IR combination therapy, rituximab non-contraindicated, tofacitinib used after rituximab

Strategy	Age at death (years)	% EULAR – Moderate or Good (1ST RX)	Discounted costs	Discounted QALYs	Undiscounted costs	Undiscounted QALYs	HAQ at death	Time on 1st treatment (years)
RTX+MTX	77.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.94	[redacted]
TOF+MTX	77.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.80	[redacted]
ABT+MTX	77.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.79	[redacted]
GOL+MTX	77.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.80	[redacted]

Abbreviations: ABT, abatacept; GOL, golimumab; HAQ, Health Assessment Questionnaire; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab; TOF, tofacitinib.

5.7.5.3 Disaggregated results of the base case incremental cost effectiveness analysis

A summary of disaggregated costs is provided in Table 169.

Table 169: Disaggregated costs, bDMARD-IR combination therapy, rituximab non-contraindicated, tofacitinib used after rituximab

Strategy	Total cost	Treatment costs	Monitoring costs	Medical resource use	Adverse event costs
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, abatacept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab; TOF, tofacitinib.

5.7.5.4 Probabilistic sensitivity analysis

Inputs

As for cDMARD-IR, but using a different NMA for CODA inputs (Section 5.7.1.4).

Results

The average results of the PSA are presented in Table 170 with a cost-effectiveness plane in Figure 86 and a cost-effectiveness acceptability curve in Figure 87. The results of the PSA did not differ substantially vs the base case and tofacitinib + MTX became the optimal treatment strategy at a WTP threshold of approximately £25,000.

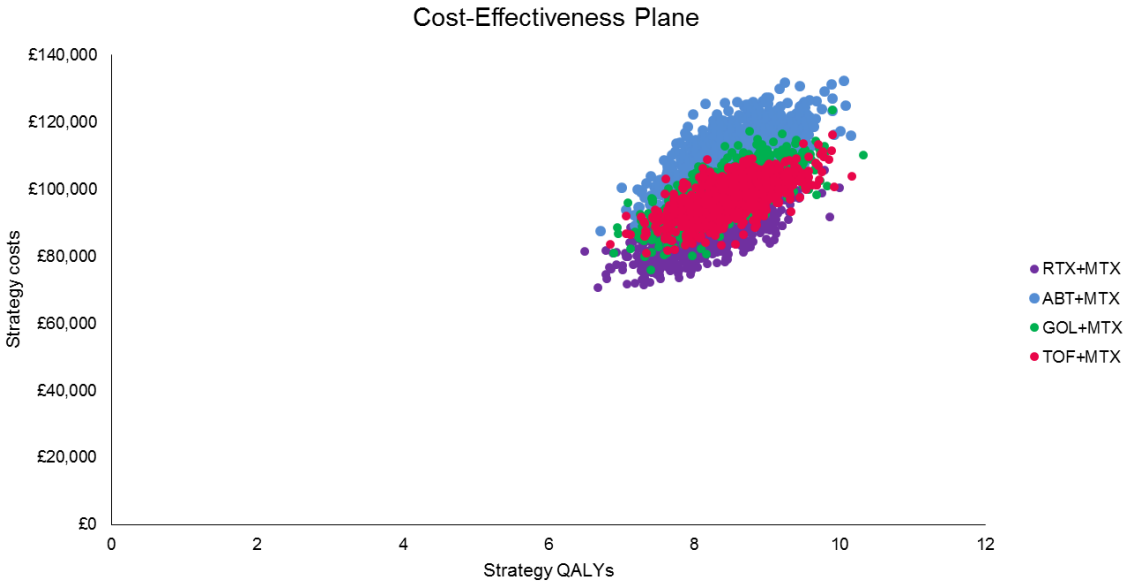
The TOF+MTX strategy has a 16% chance of being the optimal treatment at a WTP threshold of £20,000, a 43% chance of being the optimal treatment at a WTP threshold of £30,000 and a 65% chance of being the optimal treatment at a WTP threshold of £50,000.

Table 170: Average results from the PSA - bDMARD-IR combination therapy, rituximab non-contraindicated, tofacitinib used after rituximab

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£29,454
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£38,523
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£65,347

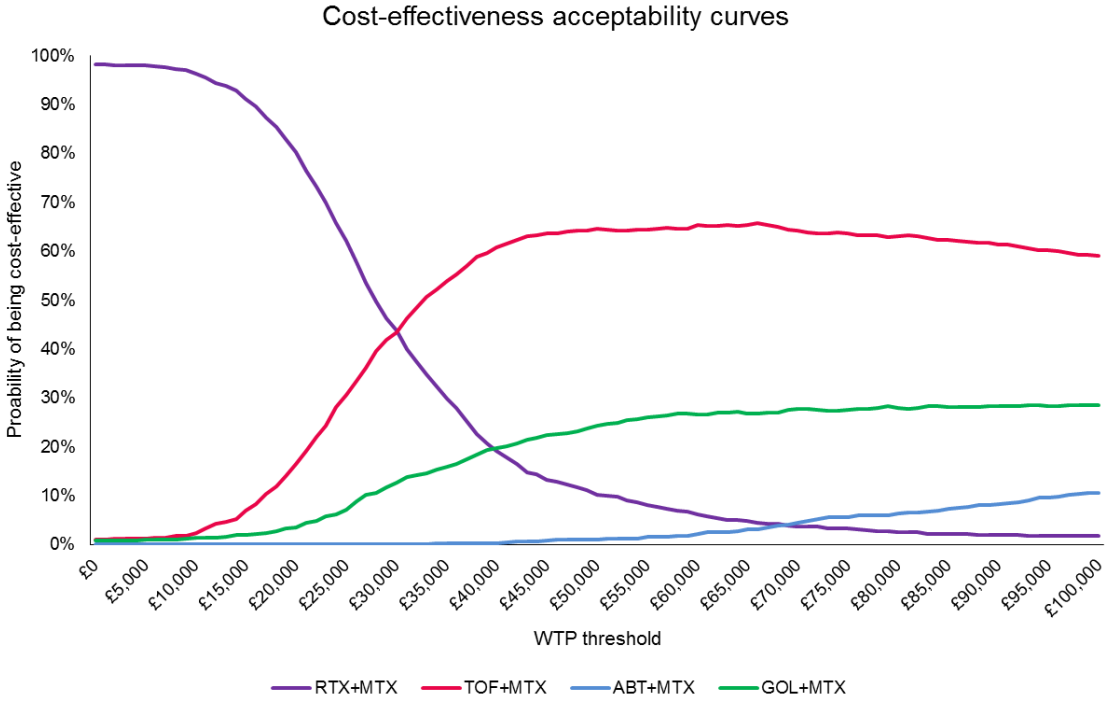
Abbreviations: ABT, abatacept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab; TOF, tofacitinib.

Figure 86: Cost-effectiveness plane for PSA, bDMARD-IR combination therapy, rituximab non-contraindicated, tofacitinib used after rituximab



Abbreviations: ABT, abatacept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab; TOF, tofacitinib.

Figure 87: Cost-effectiveness acceptability curves for PSA, bDMARD-IR combination therapy, rituximab non-contraindicated, tofacitinib used after rituximab



Abbreviations: ABT, abatacept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab; TOF, tofacitinib.

5.7.5.5 Scenario analysis

A scenario analysis was performed for this population using the base case settings with the list price (Table 171). The ICER for tofacitinib + MTX vs rituximab + MTX was £38,280.

Table 171: Scenario analysis results for bDMARD-IR combination therapy, rituximab non-contraindicated, tofacitinib used after rituximab, list price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]		
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£38,809	Ext. Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£38,280	£38,280
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£64,037	£720,355

Abbreviations: ABT, abatacept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab; TOF, tofacitinib.

5.7.6 *Scenario: cDMARD-IR moderate*

5.7.6.1 Severe model, combination therapy using the TA375 sequence

Results using Norton progression for list and PAS price are presented in Table 172 and Table 173, respectively, with results using rapid progression for list and PAS price in Table 174 and Table 175, respectively. The ICER for tofacitinib + MTX ranged from £31,397–52,549.

Table 172: Model results for moderate RA, cDMARD-IR combination therapy using the severe model and TA375 sequence with Norton progression and the PAS price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
DMC	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£50,169

Abbreviations: DMC, conventional disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

Table 173: Model results for moderate RA, cDMARD-IR combination therapy using the severe model and TA375 sequence with Norton progression and the list price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
DMC	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£52,549

Abbreviations: DMC, conventional disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

Table 174: Model results for moderate RA, cDMARD-IR combination therapy using the severe model and TA375 sequence with rapid progression and the PAS price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
DMC	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£31,397

Abbreviations: DMC, conventional disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

Table 175: Model results for moderate RA, cDMARD-IR combination therapy using the severe model and TA375 sequence with rapid progression and the list price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
DMC	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£33,444

Abbreviations: DMC, conventional disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

5.7.6.2 Severe model, combination therapy using the alternate sequence

Results using Norton progression for list and PAS price are presented in Table 176 and Table 177, respectively, with results using rapid progression for list and PAS price in Table 178 and Table 179, respectively. The ICER for tofacitinib + MTX ranged from £29,186–46,623.

Table 176: Model results for moderate RA, cDMARD-IR combination therapy using the severe model and alternate sequence with Norton progression and the PAS price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
DMC	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£40,523

Abbreviations: DMC, conventional disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

Table 177: Model results for moderate RA, cDMARD-IR combination therapy using the severe model and alternate sequence with Norton progression and the list price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
DMC	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£46,623

Abbreviations: DMC, conventional disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

Table 178: Model results for moderate RA, cDMARD-IR combination therapy using the severe model and alternate sequence with rapid progression and the PAS price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
DMC	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£29,186

Abbreviations: DMC, conventional disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

Table 179: Model results for moderate RA, cDMARD-IR combination therapy using the severe model and alternate sequence with rapid progression and the list price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
DMC	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£32,165

Abbreviations: DMC, conventional disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

5.7.6.3 Moderate model, combination therapy using the alternate sequence

Results using Norton progression for list and PAS price are presented in Table 180 and Table 181, respectively, with results using rapid progression for list and PAS price in Table 182 and Table 183, respectively. The ICER for tofacitinib + MTX ranged from £38,389–60,364.

Table 180: Model results for moderate RA, cDMARD-IR combination therapy using the moderate model and alternate sequence with Norton progression and the PAS price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
DMC	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£51,693

Abbreviations: DMC, conventional disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

Table 181: Model results for moderate RA, cDMARD-IR combination therapy using the moderate model and alternate sequence with Norton progression and the list price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
DMC	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£60,364

Abbreviations: DMC, conventional disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

Table 182: Model results for moderate RA, cDMARD-IR combination therapy using the moderate model and alternate sequence with rapid progression and the PAS price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
DMC	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£38,389

Abbreviations: DMC, conventional disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

Table 183: Model results for moderate RA, cDMARD-IR combination therapy using the moderate model and alternate sequence with rapid progression and the list price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
DMC	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£45,166

Abbreviations: DMC, conventional disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

5.7.6.4 Moderate model, monotherapy using the alternate sequence

Results using Norton progression for list and PAS price are presented in Table 180 and Table 181, respectively, with results using rapid progression for list and PAS price in Table 182 and Table 183, respectively. The ICER for tofacitinib + MTX ranged from £38,140–60,041.

Table 184: Model results for moderate RA, cDMARD-IR monotherapy using the moderate model and alternate sequence with Norton progression and the PAS price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
DMC	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£51,370

Abbreviations: DMC, conventional disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

Table 185: Model results for moderate RA, cDMARD-IR monotherapy using the moderate model and alternate sequence with Norton progression and the list price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
DMC	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£60,041

Abbreviations: DMC, conventional disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

Table 186: Model results for moderate RA, cDMARD-IR monotherapy using the moderate model and alternate sequence with rapid progression and the PAS price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
DMC	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£38,140

Abbreviations: DMC, conventional disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

Table 187: Model results for moderate RA, cDMARD-IR monotherapy using the moderate model and alternate sequence with rapid progression and the list price

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER
DMC	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£44,916

Abbreviations: DMC, conventional disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

5.8 *Validation*

5.8.1 *Validation of de novo cost-effectiveness analysis*

The model was validated internally with experienced health economists previously involved in AG reports on treatments for RA. In addition, the model structure, settings, inputs, and data were externally validated by an independent third-party health economic consultancy using established checklists and quality control procedures. This company reviewed the model from the perspective of a national payer such as NICE. The evaluation design, and methods employed were reviewed in terms of their suitability for submission to NICE, based on both previous submissions in RA (such as TA130), and current methods guidance such as that issued by NICE and the NICE Decision Support Unit.

The model was technically validated using standard procedures:

- Cell-by-cell (and line by line) checks of logic and consistency
- Logical checks based on model outputs
- Model behaviour checks
- Patient walkthroughs
    - i.e. tracking individuals through the model and ensuring that their modelled experiences are as expected

5.9 *Interpretation of the economic evidence*

5.9.1 *Overall conclusions*

The cost-effectiveness of tofacitinib has been appraised across a variety of populations and model settings. These have demonstrated that:

- Compared with MTX, tofacitinib (with or without MTX) is a cost-effective treatment in the severe cDMARD-IR population when rapid progression is assumed
- Compared with bDMARDs, tofacitinib (with or without MTX) is a cost-effective treatment for severe RA in both cDMARD-IR and bDMARD-IR patients, with the exception of when tofacitinib is assumed to be used alongside/instead of rituximab in bDMARD-IR patients
- In patients with moderate RA the ICER for tofacitinib + MTX vs DMC ranged from £29,186–60,364

The robustness of these results has been assessed through extensive scenario analysis and PSA which have demonstrated that the base case ICERs and conclusions for tofacitinib are relatively insensitive to changes. The greatest differences were seen for progression, with Norton progression leading tofacitinib to have an ICER >£30,000 per QALY for cDMARD-IR patients, while assuming rapid progression generally resulted in an ICER <£30,000 per QALY.

Of particular note is that the results of the model were not sensitive to the NMA used to inform efficacy comparisons; the ICER for tofacitinib + MTX vs MTX was £41,617 in the base case (Norton progression) and £42,791 and £44,790 using the alternate binomial model and probit models, respectively (no other changes applied). The binomial model was used in the base case for the reasons outlined in Section 4.10. The results of the scenario analysis therefore demonstrate that this has a minimal impact on the overall conclusions on the cost-effectiveness of tofacitinib.

5.9.2 *Relevance to patients with RA*

The results of the economic analysis demonstrate that tofacitinib is a cost-effective alternative to bDMARDs, which are currently restricted to patients with severe RA (DAS28>5.1). In addition, the results in the moderate population show an ICER for tofacitinib ranging from £29,186–60,364. There may therefore be a case for allowing use of tofacitinib in patients with moderate RA who must currently cycle through cDMARDs and reach severe disease before gaining access to more effective treatments.

5.9.3 *Strengths and limitations*

Strengths:

- The model structure follows that of other recent economic evaluations and follows clinical practice in the UK
- Makes use of a rich dataset from the ORAL trials and assesses the effect of heterogeneity in the patient population by adjusting outcomes based on patient characteristics
- The model makes use of long-term data to assess HAQ progression with tofacitinib
- The model uses conservative assumptions on the cost of comparators and presents results using both conservative and optimistic estimates of the efficacy of comparators
- The base case assumptions have been extensively tested in scenario analysis and the economic conclusions remain largely unchanged
- The model takes an innovative approach to modelling moderate patients and capturing their progression to severe disease, which has not been captured in any prior UK HTA submissions for RA

Limitations

- The use of early advancement in the ORAL clinical trials precluded a ‘clean’ comparison of EULAR response rates for tofacitinib vs placebo at month 6; however, alternate patient level data and NMA models exploring this were tested in scenario analysis in the economic model, with little impact on the economic conclusions
- The model assumes that factors affecting the probability of response and time to treatment discontinuation do not vary between therapies. This is in line with TA375
- [redacted]

[redacted]

6 Assessment of factors relevant to the NHS and other parties

6.1 *Population: people eligible for treatment*

In RA disease severity can be classified into 3 categories, based on the disease activity score (DAS28) scoring system. A DAS28 greater than 5.1 indicates high disease activity or severe disease, between 3.2 and 5.1 indicates moderate disease activity, and less than 3.2 indicates low disease activity. Under current NICE clinical guidance for the management of rheumatoid arthritis in adults (CG79) and it's referral to the NICE TA375 treamtment algorithm, biological DMARDs are recommentded for patients that have disease activity score (DAS28) greater than 5.1 and disease has not responded to intensive therapy with a combination of conventional disease‐modifying antirheumatic drugs (DMARDs) (22, 87). It is estimated that approximately 17,500 people are diagnosed with rheumatoid arthritis every year (1). Of these people NICE estimates that [redacted] are treated with bDMARDs, and approximately [redacted] of these patients will subsequently have an inadequate response to the bDMARD, requiring another bDMARD treament option (332). However, based on an alternative reference Pfizer believes the estimate is closer to [redacted], with but are in agreement on the estimated [redacted] subsequent inadequate bDMARD responders (333). Table 188 presents the annual number of patients eligible for tofacitinib patients.

Table 188: Estimation of patients eligible for treatment

	2017	2018	2019	2020	2021
Incident cases, n (1)	17,500	17,500	17,500	17,500	17,500
Proportion of these who have failed 2xcDMARDs, who will be eligible for bDMARDs under current guidance (CG79), n (332, 333)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of subsequent bDMARD failures eligible for further treatment, n (332, 333)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: bDMARD, biologic DMARD; cDMARD, conventional, DMARD; DMARD, disease-modifying anti-rheumatic drug; .

6.2 *Costs included*

Only the costs of tofacitinib tablet of 5mg BID at a discounted price of [redacted] per pack of 56 tablets of 5mg were considered within the budget impact calculations. The annual costs per patient taking tofacitinib is estimated as [redacted].

6.3 *Resource savings*

The budget impact analysis does not include any estimates of resource savings. However, potential cost savings can be achieved by switching from a more expensive treatment to tofacitinib. Alternatively, as tofacitinib is a novel oral tsDMARD, no

administrative costs of up to £159.20 per administration or cold-chain costs are required, which can lead to further cost savings (22).

6.4 *Budget impact*

Table 189 presents the estimated budget impact to the NHS in England of introducing tofacitinib, assuming positive NICE guidance in Pfizer's proposed patient population.

Based on the submitted price for tofacitinib and uptake assumptions, [redacted]. These calculations do not consider the costs displaced by prescribing tofacitinib ni palce of one of the seven NICE approved bDMARDs. Consequenctly, with the PAS applied, the introduction of tofacitinib is not expected to increase the cost incurred by the NHS for treating a patient with severe RA.

Table 189: Budget impact on NHS with introduction of tofacitinib

	2017	2018	2019	2020	2021
% uptake	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate to severe RA cDMARD-IR patients eligible for treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
severe RA bDMARD-IR patients eligible for treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients eligible for tofacitinib, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual discounted costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative discounted cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.5 *Additional factors not included in analysis*

The budget impact calculations do not consider costs associated with current biologics DMARDs available for the treatment of RA, predominantly administration costs or cold-chain requirements. The budget impact analysis does also not include the annual rate of discontinuations for tofactinib, which is estimated as 7.2% per year based on the 8.5 year long-term tofacitinib trial data (12).

6.6 *Limitations of the analysis*

The analysis does not consider any displacement of comparators, which is likely to incur additional cost savings for the NHS, given that tofacitinib has one of the least expensive list prices, whilst demonstrating comparable efficacy and safety profile.

7 References

1. National Institute for Health and Care Excellence. Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs. Final Scope. 2017.
2. McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. Nat Rev Immunol. 2007;7(6):429-42.
3. O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A. Janus kinase inhibitors in autoimmune diseases. Ann Rheum Dis. 2013;72 Suppl 2:ii111-5.
4. Lundquist LM, Cole SW, Sikes ML. Efficacy and safety of tofacitinib for treatment of rheumatoid arthritis. World J Orthop. 2014;5(4):504-11.
5. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017.
6. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. New England Journal of Medicine. 2012;367(6):495-507.
7. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med. 2014;370(25):2377-86.
8. Strand V, Kremer J, Wallenstein G, Kanik KS, Connell C, Gruben D, et al. Effects of tofacitinib monotherapy on patient-reported outcomes in a randomized phase 3 study of patients with active rheumatoid arthritis and inadequate responses to DMARDs. Arthritis Res Ther. 2015;17:307.
9. van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum. 2013;65(3):559-70.
10. Pfizer I. Pfizer Provides Update on Global Regulatory Approvals and Launches of XELJANZ® (tofacitinib citrate) for the Treatment of Rheumatoid Arthritis. Available at: http://www.pfizer.com/news/press-release/press-release-detail/pfizer_provides_update_on_global_regulatory_approvals_and_launches_of_xeljanz_tofacitinib_citrate_for_the_treatment_of_rheumatoid_arthritis Accessed: April 2017. 2013.
11. Pfizer I. XELJANZ – tofacitinib citrate tablet, film coated and XELJANZ XR – tofacitinib citrate tablet, film coated US prescribing information. 2016.
12. Cohen SB, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P, et al. Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. Ann Rheum Dis. 2017.
13. Pfizer Inc. Data on file - Patients treated with tofacitinib worldwide. 2017.
14. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis. 2016;75(1):3-15.
15. Singh JA, Saag KG, Bridges SL, Jr., Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis & Rheumatology. 2016;68(1):1-26.

16. Radner H, Alasti F, Smolen JS, Aletaha D. Physical function continues to improve when clinical remission is sustained in rheumatoid arthritis patients. Arthritis Res Ther. 2015;17:203.
17. Ariza-Ariza R, Hernandez-Cruz B, Carmona L, Dolores Ruiz-Montesinos M, Ballina J, Navarro-Sarabia F. Assessing utility values in rheumatoid arthritis: a comparison between time trade-off and the EuroQol. Arthritis Rheum. 2006;55(5):751-6.
18. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum. 1993;36(6):729-40.
19. Gossec L, Dougados M, Dixon W. Patient-reported outcomes as end points in clinical trials in rheumatoid arthritis. RMD Open. 2015;1(1):e000019.
20. Kalyoncu U, Dougados M, Daures JP, Gossec L. Reporting of patient-reported outcomes in recent trials in rheumatoid arthritis: a systematic literature review. Ann Rheum Dis. 2009;68(2):183-90.
21. National institute for Health and Care Excellence. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. TA195. 2010.
22. National Institute for Health and Care Excellence. Adalimumab, etanercept, inflfliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (TA375). Technology appraisal guidance. 2016.
23. National Institute for Health and Care Excellence. Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor. TA415. 2016.
24. Davis S, Stevenson M, Tappenden P, Wailoo A. NICE DSU TECHNICAL SUPPORT DOCUMENT 15: COST-EFFECTIVENESS MODELLING USING PATIENT-LEVEL SIMULATION. 2014.
25. Dias S, Sutton AJ, Welton NJ, Ades AE. Nice DSU technical support document 6: Embedding evidence synthesis in probabilistic cost-effectiveness analysis: Software choices. National Institute for Health and Clinical Excellence, London, UK. 2011.
26. Kearns B, Ara R, Wailoo A. A REVIEW OF THE USE OF STATISTICAL REGRESSION MODELS TO INFORM COST EFFECTIVENESS ANALYSES WITHIN THE NICE TECHNOLOGY APPRAISALS PROGRAMME. 2012.
27. Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data. Sheffield: Report by the Decision Support Unit. 2011.
28. Curtis JR, Xie F, Yun H, Bernatsky S, Winthrop KL. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. Ann Rheum Dis. 2016;75(10):1843-7.
29. Curtis JR, Zhang R, Krishnaswami S, Anisfeld A, Chen Y, Strengholt S, et al. Use of a risk characterisation approach to contextualise the safety profile of new rheumatoid arthritis treatments: a case study using tofacitinib. Clin Rheumatol. 2017;36(3):683-8.
30. AbbVie Ltd. Summary of product characteristics. Humira 40 mg/0.8 ml vial for paedriatric use. 2017.
31. Bristol-Myers Squibb Pharmaceutical Ltd. Summary of product characteristics. ORENCIA 125 mg solution for injection (pre-filled syringe). 2016.
32. UCB Pharma Ltd. Summary of product characteristics. Cimzia 200 mg solution for injection in pre-filled syringe. 2016.
33. Merck Sharp & Dohme Ltd. Summary of product characteristics. Remicade 100mg powder for concentrate for solution for infusion. 2016.

34. Roche Ltd. Summary of product characteristics. RoActemra 20mg/ml Concentrate for Solution for Infusion. 2016.
35. Pfizer I. Summary of product characteristics. Enbrel 25 mg powder and solvent for solution for injection. 2016.
36. Merck Sharp & Dohme Ltd. Summary of product characteristics. Simponi 50 mg solution for injection. 2017.
37. Barton JL. Patient preferences and satisfaction in the treatment of rheumatoid arthritis with biologic therapy. Patient Prefer Adherence. 2009;3:335-44.
38. Louder AM, Singh A, Saverno K, Cappelleri JC, Aten AJ, Koenig AS, et al. Patient Preferences Regarding Rheumatoid Arthritis Therapies: A Conjoint Analysis. Am Health Drug Benefits. 2016;9(2):84-93.
39. Boonen A, Severens JL. The burden of illness of rheumatoid arthritis. Clin Rheumatol. 2011;30 Suppl 1:S3-8.
40. Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch MH, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). Ann Rheum Dis. 2014;73(1):62-8.
41. British Society for Rheumatology. Simple Tasks. Rheumatic conditions in the UK: The problem. The impact. The answers. 2013.
42. Pollard LC, Choy EH, Gonzalez J, Khoshaba B, Scott DL. Fatigue in rheumatoid arthritis reflects pain, not disease activity. Rheumatology (Oxford). 2006;45(7):885-9.
43. Wolfe F, Hawley DJ, Wilson K. The prevalence and meaning of fatigue in rheumatic disease. J Rheumatol. 1996;23(8):1407-17.
44. Belza BL, Henke CJ, Yelin EH, Epstein WV, Gilliss CL. Correlates of fatigue in older adults with rheumatoid arthritis. Nurs Res. 1993;42(2):93-9.
45. Luyster FS, Chasens ER, Wasko MC, Dunbar-Jacob J. Sleep quality and functional disability in patients with rheumatoid arthritis. J Clin Sleep Med. 2011;7(1):49-55.
46. Lubeck DP. Patient-reported outcomes and their role in the assessment of rheumatoid arthritis. Pharmacoeconomics. 2004;22(2 Suppl 1):27-38.
47. Dikranian A, Galloway J, Kekow J, Maniccia A, Spurden D, Bananis E, et al., editors. Understanding the important of a patient's role in the management of rheumatoid arthritis: results form a patient-based survey. American College of Rheumatology 2015 Annual Meeting; 2015; San Francisco, CA.
48. Brouwer WB, van Exel NJ, van de Berg B, Dinant HJ, Koopmanschap MA, van den Bos GA. Burden of caregiving: evidence of objective burden, subjective burden, and quality of life impacts on informal caregivers of patients with rheumatoid arthritis. Arthritis Rheum. 2004;51(4):570-7.
49. Rubbert-Roth A, Finckh A. Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: a critical review. Arthritis Res Ther. 2009;11 Suppl 1:S1.
50. Conaghan PG, Hensor EM, Keenan AM, Morgan AW, Emery P, Consortium Y. Persistently moderate DAS-28 is not benign: loss of function occurs in early RA despite step-up DMARD therapy. Rheumatology (Oxford). 2010;49(10):1894-9.
51. Gibofsky A. Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. Am J Manag Care. 2012;18(13 Suppl):S295-302.
52. Strand V, Kimberly R, Isaacs JD. Biologic therapies in rheumatology: lessons learned, future directions. Nat Rev Drug Discov. 2007;6(1):75-92.
53. Uhlig T, Moe RH, Kvien TK. The burden of disease in rheumatoid arthritis. Pharmacoeconomics. 2014;32(9):841-51.
54. Prete M, Racanelli V, Digiglio L, Vacca A, Dammacco F, Perosa F. Extra-articular manifestations of rheumatoid arthritis: An update. Autoimmun Rev. 2011;11(2):123-31.

55. Vela P. Extra-articular manifestations of rheumatoid arthritis, now. EMJ Rheumatol. 2014;1:103-12.
56. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365(23):2205-19.
57. Matcham F, Scott IC, Rayner L, Hotopf M, Kingsley GH, Norton S, et al. The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis. Semin Arthritis Rheum. 2014;44(2):123-30.
58. National audit office. Services for people with rheumatoid arthritiss: Report by the comptroller and auditor General. HC 823 Session 2008-2009. 2009.
59. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1316-22.
60. Rindfleisch JA, Muller D. Diagnosis and management of rheumatoid arthritis. Am Fam Physician. 2005;72(6):1037-47.
61. Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet. 2001;358(9285):903-11.
62. Wolfe F. The natural history of rheumatoid arthritis. J Rheumatol Suppl. 1996;44:13-22.
63. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ. 2003;81(9):646-56.
64. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69(9):1580-8.
65. Norton S, Koduri G, Nikiphorou E, Dixey J, Williams P, Young A. A study of baseline prevalence and cumulative incidence of comorbidity and extra-articular manifestations in RA and their impact on outcome. Rheumatology (Oxford). 2013;52(1):99-110.
66. Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2013;159(4):253-61.
67. Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV, et al. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum. 2005;52(2):412-20.
68. Smitten AL, Simon TA, Hochberg MC, Suissa S. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Res Ther. 2008;10(2):R45.
69. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum. 2002;46(9):2287-93.
70. Dickens C, Creed F. The burden of depression in patients with rheumatoid arthritis. Rheumatology (Oxford). 2001;40(12):1327-30.
71. Nicassio PM. Arthritis and psychiatric disorders: disentangling the relationship. J Psychosom Res. 2010;68(2):183-5.
72. Leino M, Tuominen S, Pirila L, Tuominen R. Effects of rheumatoid arthritis on household chores and leisure-time activities. Rheumatol Int. 2015;35(11):1881-8.
73. Ware JE, Jr., Keller SD, Hatoum HT, Kong SX. The SF-36 Arthritis-Specific Health Index (ASHI): I. Development and cross-validation of scoring algorithms. Med Care. 1999;37(5 Suppl):MS40-50.
74. Ware JE, Kosinski M. Interpreting SF-36 summary health measures: a response. Qual Life Res. 2001;10(5):405-13; discussion 15-20.
75. Hill J. Effects of rheumatoid arthritis on sexual activity and relationships. Rheumatology. 2003;42(2):280-6.
76. Wiles NJ, Scott DG, Barrett EM, Merry P, Arie E, Gaffney K, et al. Benchmarking: the five year outcome of rheumatoid arthritis assessed using a pain score, the

Health Assessment Questionnaire, and the Short Form-36 (SF-36) in a community and a clinic based sample. Ann Rheum Dis. 2001;60(10):956-61.
77. Jacobi CE, van den Berg B, Boshuizen HC, Rupp I, Dinant HJ, van den Bos GA. Dimension-specific burden of caregiving among partners of rheumatoid arthritis patients. Rheumatology (Oxford). 2003;42(10):1226-33.
78. Alfaro N, Lazaro P, Gabriele G, Garcia-Vicuna R, Jover JA, Sevilla J. Perceptions, attitudes and experiences of family caregivers of patients with musculoskeletal diseases: a qualitative approach. Reumatol Clin. 2013;9(6):334-9.
79. National Rheumatoid Arthritis Society. Family Matters: A major UK wide survey on the impacts on the family of living with rheumatoid arthritis. 2012.
80. Eriksson JK, Johansson K, Askling J, Neovius M. Costs for hospital care, drugs and lost work days in incident and prevalent rheumatoid arthritis: how large, and how are they distributed? Ann Rheum Dis. 2015;74(4):648-54.
81. Gulacsi L, Brodszky V, Baji P, Kim H, Kim SY, Cho YY, et al. Biosimilars for the management of rheumatoid arthritis: economic considerations. Expert Rev Clin Immunol. 2015;11 Suppl 1:S43-52.
82. Kobelt G, Kasteng F. Access to innovative treatments in rheumatoid arthritis in Europe. Available at: http://www.comparatorreports.se/ Accessed: April 2017. 2009.
83. Hockley T, Costa-Font J, McGuire A. A Common Disease With Uncommon Treatment. European Guideline Variations and Access to Innovative Therapies for Rheumatoid Arthritis. . Policy analysis centre. London School of Economics and Political Science. 2012.
84. Birnbaum H, Pike C, Kaufman R, Cifaldi M. Employer model of workplace impacts of anti-TNF therapy for rheumatoid arthritis. J Occup Environ Med. 2009;51(10):1167-76.
85. Filipovic I, Walker D, Forster F, Curry AS. Quantifying the economic burden of productivity loss in rheumatoid arthritis. Rheumatology (Oxford). 2011;50(6):1083-90.
86. Jacobs P, Bissonnette R, Guenther LC. Socioeconomic burden of immune-mediated inflammatory diseases--focusing on work productivity and disability. J Rheumatol Suppl. 2011;88:55-61.
87. National institute for Health and Care Excellence. Rheumatoid arthritis in adults: management (CG79). Clinical guideline. 2009.
88. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. Rheum Dis Clin North Am. 2009;35(4):745-57, vii-viii.
89. Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. Clin Exp Rheumatol. 2008;26(5 Suppl 51):S35-61.
90. Carmona L, Cross M, Williams B, Lassere M, March L. Rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2010;24(6):733-45.
91. Listing J, Kekow J, Manger B, Burmester GR, Pattloch D, Zink A, et al. Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFalpha inhibitors and rituximab. Ann Rheum Dis. 2015;74(2):415-21.
92. Humphreys JH, Warner A, Chipping J, Marshall T, Lunt M, Symmons DP, et al. Mortality trends in patients with early rheumatoid arthritis over 20 years: results from the Norfolk Arthritis Register. Arthritis Care Res (Hoboken). 2014;66(9):1296-301.
93. Molina E, del Rincon I, Restrepo JF, Battafarano DF, Escalante A. Mortality in Rheumatoid Arthritis (RA): factors associated with recording RA on death certificates. BMC Musculoskelet Disord. 2015;16:277.
94. Chehata JC, Hassell AB, Clarke SA, Mattey DL, Jones MA, Jones PW, et al. Mortality in rheumatoid arthritis: relationship to single and composite measures of disease activity. Rheumatology (Oxford). 2001;40(4):447-52.

95. Gordon P, West J, Jones H, Gibson T. A 10 year prospective followup of patients with rheumatoid arthritis 1986-96. J Rheumatol. 2001;28(11):2409-15.
96. Naz SM, Farragher TM, Bunn DK, Symmons DP, Bruce IN. The influence of age at symptom onset and length of followup on mortality in patients with recent-onset inflammatory polyarthritis. Arthritis Rheum. 2008;58(4):985-9.
97. Symmons DP, Jones MA, Scott DL, Prior P. Longterm mortality outcome in patients with rheumatoid arthritis: early presenters continue to do well. J Rheumatol. 1998;25(6):1072-7.
98. Watson DJ, Rhodes T, Guess HA. All-cause mortality and vascular events among patients with rheumatoid arthritis, osteoarthritis, or no arthritis in the UK General Practice Research Database. J Rheumatol. 2003;30(6):1196-202.
99. National Institute for Health and Care Excellence. Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs. TA225. 2011.
100. National Institute for Health and Care Excellence. Tocilizumab for the treatment of rheumatoid arthritis. TA247. 2012.
101. National institute for Health and Care Excellence. Rheumatoid arthritis in over 16s (QS33). Quality Standard. 2013.
102. National Institute for Health and Care Excellence. Drug treatment for rheumatoid arthritis. Pathway. 2016.
103. National Institute for Health and Care Excellence. Rheumatoid arthritis. Scenario: Confirmed rheumatoid arthritis. Clinical Knowledge Summaries. 2013.
104. Ledingham JG, N.; Irving, K.; Gorodkin, R.; Aris, M.; Burke, J.; Gordon, P.; Christidis, D.; Galloway, S.; Hayes, E.; Jeffries, A.; Mercer, S.; Mooney, J.; van Leuven, S.; Galloway, J. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Rheumatology. 2017.
105. Deighton C, Hyrich K, Ding T, Ledingham J, Lunt M, Luqmani R, et al. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. Rheumatology (Oxford). 2010.
106. British Society for Rheumatology BHPiRSG. The State of Play in UK Rheumatology: Insights into service pressures and solutions. 2015.
107. Rendas-Baum R, Wallenstein GV, Koncz T, Kosinski M, Yang M, Bradley J, et al. Evaluating the efficacy of sequential biologic therapies for rheumatoid arthritis patients with an inadequate response to tumor necrosis factor-alpha inhibitors. Arthritis Res Ther. 2011;13(1):R25.
108. Moots RJ, Naisbett-Groet B. The efficacy of biologic agents in patients with rheumatoid arthritis and an inadequate response to tumour necrosis factor inhibitors: a systematic review. Rheumatology (Oxford). 2012;51(12):2252-61.
109. Katchamart W, Trudeau J, Phumethum V, Bombardier C. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. Cochrane Database Syst Rev. 2010 (4):CD008495.
110. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis. 2009;68(7):1100-4.
111. Blom M, Kievit W, Fransen J, Kuper IH, den Broeder AA, De Gendt CM, et al. The reason for discontinuation of the first tumor necrosis factor (TNF) blocking agent does not influence the effect of a second TNF blocking agent in patients with rheumatoid arthritis. J Rheumatol. 2009;36(10):2171-7.
112. Bolge SC, Goren A, Tandon N. Reasons for discontinuation of subcutaneous biologic therapy in the treatment of rheumatoid arthritis: a patient perspective. Patient Prefer Adherence. 2015;9:121-31.
113. Chilton F, Collett RA. Treatment choices, preferences and decision-making by patients with rheumatoid arthritis. Musculoskeletal Care. 2008;6(1):1-14.

114. Brorsson S, Nilsdotter A, Thorstensson C, Bremander A. Differences in muscle activity during hand-dexterity tasks between women with arthritis and a healthy reference group. BMC Musculoskelet Disord. 2014;15:154.
115. Keininger D, Coteur G. Assessment of self-injection experience in patients with rheumatoid arthritis: psychometric validation of the Self-Injection Assessment Questionnaire (SIAQ). Health Qual Life Outcomes. 2011;9:2.
116. Wolfe F. A reappraisal of HAQ disability in rheumatoid arthritis. Arthritis Rheum. 2000;43(12):2751-61.
117. Callahan LF, Bloch DA, Pincus T. Identification of work disability in rheumatoid arthritis: physical, radiographic and laboratory variables do not add explanatory power to demographic and functional variables. J Clin Epidemiol. 1992;45(2):127-38.
118. Wolfe F, Kleinheksel SM, Cathey MA, Hawley DJ, Spitz PW, Fries JF. The clinical value of the Stanford Health Assessment Questionnaire Functional Disability Index in patients with rheumatoid arthritis. J Rheumatol. 1988;15(10):1480-8.
119. Pincus T, Callahan LF. Rheumatology function tests: grip strength, walking time, button test and questionnaires document and predict longterm morbidity and mortality in rheumatoid arthritis. J Rheumatol. 1992;19(7):1051-7.
120. Landewe RB, Connell CA, Bradley JD, Wilkinson B, Gruben D, Strengholt S, et al. Is radiographic progression in modern rheumatoid arthritis trials still a robust outcome? Experience from tofacitinib clinical trials. Arthritis Res Ther. 2016;18(1):212.
121. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367(6):508-19.
122. Pfizer I. Clinical Study Report A3921064: Phase 3 Randomized, Double-Blind, Active Comparator, Placebo-Controlled Study of the Efficacy and Safety of 2 Doses of CP-690,550 in Patients with Active Rheumatoid Arthritis on Background Methotrexate. 2012.
123. Pfizer I. Clinical Study Report A3921044: Phase 3 Randomized, Double Blind, Placebo Controlled Study of the Efficacy and Safety of 2 Doses of CP-690,550 in Patients With Active Rheumatoid Arthritis on Background Methotrexate (1-Year Analysis). 2012.
124. Pfizer I. Clinical Study Report A3921046: Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of 2 Doses of CP-690,550 in Patients with Active Rheumatoid Arthritis on Background DMARDs. 2012.
125. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med. 2012;367(6):495-507.
126. Pfizer I. Clinical Study Report A3921045: Phase 3, Randomized, Double Blind, Placebo Controlled Study of the Efficacy and Safety of 2 Doses of CP-690,550 Monotherapy in Patients with Active Rheumatoid Arthritis. 2012.
127. Pfizer I. Clinical Study Report A3921069: Phase 3 Randomized, Double Blind Study of the Efficacy and Safety of 2 Doses of CP-690,550 Compared to Methotrexate in Methotrexate Naïve Patients with Rheumatoid Arthritis. 2015.
128. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. The Lancet. 2013;381(9865):451-60.
129. Pfizer I. Clinical Study Report A3921032: Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of 2 Doses of CP-690,550 in Patients With Active Rheumatoid Arthritis on Background Methotrexate With Inadequate Response to TNF Inhibitors. 2012.

130. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315-24.
131. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995;38(6):727-35.
132. Stein CM, Pincus T. Placebo-controlled studies in rheumatoid arthritis: ethical issues. Lancet. 1999;353(9150):400-3.
133. NICE Decision Support Unit. NICE DSU technical support document 16: adjusting survival time estimates in the presence of treatment switching. 2014.
134. Singh JA, Hossain A, Tanjong Ghogomu E, Kotb A, Christensen R, Mudano AS, et al. Biologics or tofacitinib for rheumatoid arthritis in incomplete responders to methotrexate or other traditional disease-modifying anti-rheumatic drugs: a systematic review and network meta-analysis. The Cochrane Library. 2016.
135. Thorlund K, Druyts E, Avina-Zubieta JA, Wu P, Mills EJ. Why the findings of published multiple treatment comparison meta-analyses of biologic treatments for rheumatoid arthritis are different: an overview of recurrent methodological shortcomings. Ann Rheum Dis. 2013;72(9):1524-35.
136. Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J, et al. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: Systematic review and economic evaluation. Health Technology Assessment. 2016;20(35).
137. Dougados M, Kissel K, Sheeran T, Tak PP, Conaghan PG, Mola EM, et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Annals of the Rheumatic Diseases. 2013;72(1):43-50.
138. Dougados M, Kissel K, Conaghan PG, Mola EM, Schett G, Gerli R, et al. Clinical, radiographic and immunogenic effects after 1 year of tocilizumab-based treatment strategies in rheumatoid arthritis: the ACT-RAY study. Annals of the Rheumatic Diseases. 2014;73(5):803-9.
139. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. The Lancet.381(9877):1541-50.
140. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti–tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: The ARMADA trial. Arthritis & Rheumatism. 2003;48(1):35-45.
141. Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Annals of the Rheumatic Diseases. 2008;67(8):1096-103.
142. van Vollenhoven RF, Kinnman N, Vincent E, Wax S, Bathon J. Atacicept in patients with rheumatoid arthritis and an inadequate response to methotrexate: Results of a phase II, randomized, placebo-controlled trial. Arthritis & Rheumatism. 2011;63(7):1782-92.
143. Smolen JS, Emery P, Ferraccioli GF, Samborski W, Berenbaum F, Davies OR, et al. Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomised, placebo-controlled trial. Annals of the Rheumatic Diseases. 2015;74(5):843-50.

144. Miyasaka N, The CSI. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Modern Rheumatology. 2008;18(3):252-62.
145. Choe J-Y, Prodanovic N, Niebrzydowski J, Staykov I, Dokoupilova E, Baranauskaite A, et al. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. Annals of the Rheumatic Diseases. 2015.
146. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti–tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: A randomized, placebo-controlled, 52-week trial. Arthritis & Rheumatism. 2004;50(5):1400-11.
147. Emery P, Vencovský J, Sylwestrzak A, Leszczyński P, Porawska W, Baranauskaite A, et al. A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. Annals of the Rheumatic Diseases. 2015.
148. Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum. 2012;64(3):617-29.
149. Tanaka Y, Harigai M, Takeuchi T, Yamanaka H, Ishiguro N, Yamamoto K, et al. Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study. Annals of the Rheumatic Diseases. 2012;71(6):817-24.
150. Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumour necrosis factor α given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Annals of the Rheumatic Diseases. 2009;68(6):789-96.
151. Bingham CO, Weinblatt M, Han C, Gathany TA, Kim L, Lo KH, et al. The effect of intravenous golimumab on health-related quality of life in rheumatoid arthritis: 24-week results of the phase III GO-FURTHER trial. The Journal of Rheumatology. 2014;41(6):1067-76.
152. Bae S-C, Kim J, Choe J-Y, Park W, Lee S-H, Park Y-B, et al. A phase III, multicentre, randomised, double-blind, active-controlled, parallel-group trial comparing safety and efficacy of HD203, with innovator etanercept, in combination with methotrexate, in patients with rheumatoid arthritis: the HERA study. Annals of the Rheumatic Diseases. 2016.
153. Kameda H, Ueki Y, Saito K, Nagaoka S, Hidaka T, Atsumi T, et al. Etanercept (ETN) with methotrexate (MTX) is better than ETN monotherapy in patients with active rheumatoid arthritis despite MTX therapy: a randomized trial. Modern Rheumatology. 2010;20(6):531-8.
154. Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. Mod Rheumatol. 2014;24(5):715-24.
155. Kim H-Y, Lee S-K, Song YW, Yoo D-H, Koh E-M, Yoo B, et al. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR Journal of Rheumatology. 2007;10(1):9-16.

156. Kremer JM, Cohen S, Wilkinson BE, Connell CA, French JL, Gomez-Reino J, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. Arthritis Rheum. 2012;64(4):970-81.
157. Machado DA, Guzman RM, Xavier RM, Simon JA, Mele L, Pedersen R, et al. Open-label observation of addition of etanercept versus a conventional disease-modifying antirheumatic drug in subjects with active rheumatoid arthritis despite methotrexate therapy in the Latin American region. Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases. 2014;20(1):25-33.
158. Li Z, Zhang F, Kay J, Fei K, Han C, Zhuang Y, et al. Efficacy and safety results from a Phase 3, randomized, placebo-controlled trial of subcutaneous golimumab in Chinese patients with active rheumatoid arthritis despite methotrexate therapy. International Journal of Rheumatic Diseases. 2015.
159. Kremer JM, Blanco R, Brzosko M, Burgos-Vargas R, Halland A-M, Vernon E, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: Results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis & Rheumatism. 2011;63(3):609-21.
160. Fleischmann RM, Halland A-M, Brzosko M, Burgos-Vargas R, Mela C, Vernon E, et al. Tocilizumab Inhibits Structural Joint Damage and Improves Physical Function in Patients with Rheumatoid Arthritis and Inadequate Responses to Methotrexate: LITHE Study 2-year Results. The Journal of Rheumatology. 2013;40(2):113-26.
161. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. The Lancet. 2008;371(9617):987-97.
162. Strand V, van Vollenhoven RF, Lee EB, Fleischmann R, Zwillich SH, Gruben D, et al. Tofacitinib or adalimumab versus placebo: patient-reported outcomes from a phase 3 study of active rheumatoid arthritis. Rheumatology. 2016;55(6):1031-41.
163. Yoo DH, Hrycaj P, Miranda P, Ramiterre E, Piotrowski M, Shevchuk S, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: The PLANETRA study. Annals of the Rheumatic Diseases. 2013;72(10):1613-20.
164. Keystone E, Heijde DVD, Mason D, Landewé R, Vollenhoven RV, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: Findings of a fifty-two–week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis & Rheumatism. 2008;58(11):3319-29.
165. Strand V, Mease P, Burmester GR, Nikaï E, Coteur G, van Vollenhoven R, et al. Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. Arthritis Research & Therapy. 2009;11(6):R170-R.
166. Smolen J, Landewé RB, Mease P, Brzezicki J, Mason D, Luijtens K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Annals of the Rheumatic Diseases. 2009;68(6):797-804.
167. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis

patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Modern Rheumatology. 2009;19(1):12-9.
168. Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: A large, randomized, placebo-controlled trial. Arthritis & Rheumatism. 2006;54(4):1075-86.
169. Kaneko Y, Atsumi T, Tanaka Y, Inoo M, Kobayashi-Haraoka H, Amano K, et al. Comparison of adding tocilizumab to methotrexate with switching to tocilizumab in patients with rheumatoid arthritis with inadequate response to methotrexate: 52-week results from a prospective, randomised, controlled study (SURPRISE study). Annals of the Rheumatic Diseases. 2016;75(11):1917-23.
170. Takeuchi T, Yamanaka H, Tanaka Y, Sakurai T, Saito K, Ohtsubo H, et al. Evaluation of the pharmacokinetic equivalence and 54-week efficacy and safety of CT-P13 and innovator infliximab in Japanese patients with rheumatoid arthritis. Modern Rheumatology. 2015;25(6):817-24.
171. Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: The tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis & Rheumatism. 2008;58(10):2968-80.
172. van de Putte LBA, Atkins C, Malaise M, Sany J, Russell A, van Riel PLCM, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Annals of the Rheumatic Diseases. 2004;63(5):508-16.
173. van Vollenhoven RF, Ernestam S, Geborek P, Petersson IF, Coster L, Waltbrand E, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet. 2009;374(9688):459-66.
174. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005;353(11):1114-23.
175. Smolen JS, Kay J, Doyle MK, Landewe R, Matteson EL, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009;374(9685):210-21.
176. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008;67(11):1516-23.
177. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54(9):2793-806.
178. Gottenberg JE, Brocq O, Perdriger A, Lassoued S, Berthelot JM, Wendling D, et al. Non-TNF-Targeted Biologic vs a Second Anti-TNF Drug to Treat Rheumatoid Arthritis in Patients With Insufficient Response to a First Anti-TNF Drug: A Randomized Clinical Trial. Jama. 2016;316(11):1172-80.
179. Combe B, Dougados M, Logeart I, Lukas C, Mariette X, Puechal X, et al. AB0516 An open-label randomized controlled study to evaluate the efficacy of etanercept (ETN) versus rituximab (RTX), in patients with active rheumatoid arthritis

previously treated with RTX and TNF blockers. Annals of the Rheumatic Diseases. 2013;71(Suppl 3):667-.
180. Manders SH, Kievit W, Adang E, Brus HL, Moens HJ, Hartkamp A, et al. Cost-effectiveness of abatacept, rituximab, and TNFi treatment after previous failure with TNFi treatment in rheumatoid arthritis: a pragmatic multi-centre randomised trial. Arthritis Res Ther. 2015;17:134.
181. Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe DJ, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis. Cochrane Database Syst Rev. 2016 (8):CD010227.
182. Singh JA, Hossain A, Tanjong Ghogomu E, Mudano AS, Tugwell P, Wells GA. Biologic or tofacitinib monotherapy for rheumatoid arthritis in people with traditional disease-modifying anti-rheumatic drug (DMARD) failure: a Cochrane Systematic Review and network meta-analysis (NMA). The Cochrane Library. 2016.
183. Keystone EC, Taylor PC, Drescher E, Schlichting DE, Beattie SD, Berclaz PY, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Annals of the Rheumatic Diseases. 2015;74(2):333-40.
184. Abe T, Takeuchi T, Miyasaka N, Hashimoto H, Kondo H, Ichikawa Y, et al. A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. J Rheumatol. 2006;33(1):37-44.
185. Genovese MC, Covarrubias A, Leon G, Mysler E, Keiserman M, Valente R, et al. Subcutaneous abatacept versus intravenous abatacept: A phase IIIb noninferiority study in patients with an inadequate response to methotrexate. Arthritis & Rheumatism. 2011;63(10):2854-64.
186. van Riel PLCM, Taggart AJ, Sany J, Gaubitz M, Nab HW, Pedersen R, et al. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. Annals of the Rheumatic Diseases. 2006;65(11):1478-83.
187. van Riel PLCM, Freundlich B, MacPeek D, Pedersen R, Foehl JR, Singh A, et al. Patient-reported health outcomes in a trial of etanercept monotherapy versus combination therapy with etanercept and methotrexate for rheumatoid arthritis: the ADORE trial. Annals of the Rheumatic Diseases. 2008;67(8):1104-10.
188. Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: A randomized trial. Annals of Internal Medicine. 2006;144(12):865-76.
189. Russell AS, Wallenstein GV, Li T, Martin MC, Maclean R, Blaisdell B, et al. Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. Annals of the Rheumatic Diseases. 2007;66(2):189-94.
190. Kennedy WP, Simon JA, Offutt C, Horn P, Herman A, Townsend MJ, et al. Efficacy and safety of pateclizumab (anti-lymphotoxin-[alpha]) compared to adalimumab in rheumatoid arthritis: a head-to-head phase 2 randomized controlled study (The ALTARA Study). Arthritis Research & Therapy. 2014;16(5):467.
191. Weinblatt ME, Schiff M, Valente R, van der Heijde D, Citera G, Zhao C, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: Findings of a phase IIIb, multinational, prospective, randomized study. Arthritis & Rheumatism. 2013;65(1):28-38.
192. Kim H-Y, Hsu P-N, Barba M, Sulaiman W, Robertson D, Vlahos B, et al. Randomized comparison of etanercept with usual therapy in an Asian population

with active rheumatoid arthritis: the APPEAL trial. International Journal of Rheumatic Diseases. 2012;15(2):188-96.
193. Conaghan PG, Durez P, Alten RE, Burmester G-R, Tak PP, Klareskog L, et al. Impact of intravenous abatacept on synovitis, osteitis and structural damage in patients with rheumatoid arthritis and an inadequate response to methotrexate: the ASSET randomised controlled trial. Annals of the Rheumatic Diseases. 2013;72(8):1287-94.
194. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. The Lancet.354(9194):1932-9.
195. Lipsky PE, van der Heijde DMFM, St. Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and Methotrexate in the Treatment of Rheumatoid Arthritis. New England Journal of Medicine. 2000;343(22):1594-602.
196. Kivitz A, Olech E, Borofsky M, Zazueta BM, Navarro-Sarabia F, Radominski SC, et al. Subcutaneous tocilizumab versus placebo in combination with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. Arthritis care & research. 2014;66(11):1653-61.
197. Maini RN, Taylor PC, Szechinski J, Pavelka K, Bröll J, Balint G, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis & Rheumatism. 2006;54(9):2817-29.
198. Chen DY, Chou SJ, Hsieh TY, Chen YH, Chen HH, Hsieh CW, et al. Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. J Formos Med Assoc. 2009;108(4):310-9.
199. Chen X-X, Li Z-g, Wu H-x, Zhao D-b, Li X-f, Xu J-h, et al. A randomized, controlled trial of efficacy and safety of Anbainuo, a bio-similar etanercept, for moderate to severe rheumatoid arthritis inadequately responding to methotrexate. Clinical Rheumatology. 2016;35(9):2175-83.
200. Choy E, McKenna F, Vencovsky J, Valente R, Goel N, VanLunen B, et al. Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. Rheumatology. 2012;51(7):1226-34.
201. Cohen SB, Moreland LW, Cush JJ, Greenwald MW, Block S, Shergy WJ, et al. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. Annals of the Rheumatic Diseases. 2004;63(9):1062-8.
202. Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Annals of the Rheumatic Diseases. 2006;65(10):1357-62.
203. Durez P, Nzeusseu Toukap A, Lauwerys BR, Manicourt DH, Verschueren P, Westhovens R, et al. A randomised comparative study of the short term clinical and biological effects of intravenous pulse methylprednisolone and infliximab in patients with active rheumatoid arthritis despite methotrexate treatment. Annals of the Rheumatic Diseases. 2004;63(9):1069.
204. Yamanaka H, Nagaoka S, Lee S-K, Bae S-C, Kasama T, Kobayashi H, et al. Discontinuation of etanercept after achievement of sustained remission in patients with rheumatoid arthritis who initially had moderate disease activity—results from the ENCOURAGE study, a prospective, international, multicenter randomized study. Modern Rheumatology. 2016;26(5):651-61.

205. Smolen JS, Burmester G-R, Combe B, Curtis JR, Hall S, Haraoui B, et al. Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. The Lancet.388(10061):2763-74.
206. Fleischmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Annals of the Rheumatic Diseases. 2009;68(6):805-11.
207. Genovese MC, Cohen S, Moreland L, Lium D, Robbins S, Newmark R, et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis & Rheumatism. 2004;50(5):1412-9.
208. Gerlag DM, Hollis S, Layton M, Vencovský J, Szekanecz Z, Braddock M, et al. Preclinical and clinical investigation of a CCR5 antagonist, AZD5672, in patients with rheumatoid arthritis receiving methotrexate. Arthritis & Rheumatism. 2010;62(11):3154-60.
209. Hobbs K, Deodhar A, Wang B, Bitman B, Nussbaum J, Chung J, et al. Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of etanercept in patients with moderately active rheumatoid arthritis despite DMARD therapy. Springerplus. 2015;4:113.
210. Huang F, Zhang FC, Bao CD, Tao Y, Gu JR, Xu JH, et al. [Adalimumab plus methotrexate for the treatment of rheumatoid arthritis: a multi-center randomized, double-blind, placebo-controlled clinical study.]. Chung-Hua Nei Ko Tsa Chih Chinese Journal of Internal Medicine. 2009;48(11):916-21.
211. Iwahashi M, Inoue H, Matsubara T, Tanaka T, Amano K, Kanamono T, et al. Efficacy, safety, pharmacokinetics and immunogenicity of abatacept administered subcutaneously or intravenously in Japanese patients with rheumatoid arthritis and inadequate response to methotrexate: a Phase II/III, randomized study. Mod Rheumatol. 2014;24(6):885-91.
212. Jani RH, Gupta R, Bhatia G, Rathi G, Ashok Kumar P, Sharma R, et al. A prospective, randomized, double-blind, multicentre, parallel-group, active controlled study to compare efficacy and safety of biosimilar adalimumab (Exemptia; ZRC-3197) and adalimumab (Humira) in patients with rheumatoid arthritis. International Journal of Rheumatic Diseases. 2015.
213. Johnsen AK, Schiff MH, Mease PJ, Moreland LW, Maier AL, Coblyn JS, et al. Comparison of 2 doses of etanercept (50 vs 100 mg) in active rheumatoid arthritis: a randomized double blind study. The Journal of Rheumatology. 2006;33(4):659-64.
214. Kang YM, Park W, Park YE, Choe JY, Bae S-C, Cho CS, et al. AB0501 Efficacy and safety of certolizumab pegol (CZP) with concomitant methotrexate (MTX) in korean rheumatoid arthritis (RA) patients (PTS) with an inadequate response to MTX. Annals of the Rheumatic Diseases. 2013;71(Suppl 3):666.
215. Kay J, Matteson EL, Dasgupta B, Nash P, Durez P, Hall S, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: A randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis & Rheumatism. 2008;58(4):964-75.
216. Kay J, Chopra A, Chandrashekara S, Olakkengil DJ, Bhojani KS, Bhatia G, et al. A phase 3, randomized, double-blind, active comparator study of the efficacy and safety of BOW015, a biosimilar infliximab, in patients with active rheumatoid arthritis on stable methotrexate doses. Annals of the Rheumatic Diseases. 2014;73(11).
217. Kay J, Weinblatt M, Keystone E, Genovese MC, Baranauskaite A, Cheong SY, et al. THU0138 Secondary Efficacy Results Up To Week 24 from A Phase III Study Comparing SB5 (An Adalimumab Biosimiar) with Adalimumab Reference Product

in Patients with Moderate To Severe Rheumatoid Arthritis despite Methotrexate Therapy. Annals of the Rheumatic Diseases. 2016;75(Suppl 2):231.
218. Kim J, Ryu H, Yoo DH, Park SH, Song GG, Park W, et al. A clinical trial and extension study of infliximab in Korean patients with active rheumatoid arthritis despite methotrexate treatment. Journal of Korean medical science. 2013;28(12):1716-22.
219. Kremer JM, Westhovens R, Leon M, Di Giorgio E, Alten R, Steinfeld S, et al. Treatment of Rheumatoid Arthritis by Selective Inhibition of T-Cell Activation with Fusion Protein CTLA4Ig. New England Journal of Medicine. 2003;349(20):1907-15.
220. Lan JL, Chou SJ, Chen DY, Chen YH, Hsieh TY, Young M, Jr. A comparative study of etanercept plus methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis: a 12-week, double-blind, randomized, placebo-controlled study. J Formos Med Assoc. 2004;103(8):618-23.
221. Li Z, Zhang F, Kay J, Fei K, Han C, Zhuang Y, et al. FRI0211 Safety and efficacy of subcutaneous golimumab in chinese patients with active rheumatoid arthritis despite mtx therapy: results from a randomized, placebo-controlled, phase 3 trial. Annals of the Rheumatic Diseases. 2013;72(Suppl 3):A444-A.
222. Lim MJ, Park SH, Shim S-C, Baek HJ, Yoo D-H, Kim HA, et al. AB0562 A double-blind, placebo-controlled, multicenter trial of tocilizumab in moderate to severe active RA patients with inadequate response to methotrexate in korean population. Annals of the Rheumatic Diseases. 2013;71(Suppl 3):670.
223. MacIsaac KD, Baumgartner R, Kang J, Loboda A, Peterfy C, DiCarlo J, et al. Pre-Treatment Whole Blood Gene Expression Is Associated with 14-Week Response Assessed by Dynamic Contrast Enhanced Magnetic Resonance Imaging in Infliximab-Treated Rheumatoid Arthritis Patients. PLoS One. 2014;9(12):e113937.
224. Matsumoto AK, Pavelka K, Rizzo W, Gupta R, Shergy W, Heycaj P, et al. Secondary efficacy endpoints: Results from a phase 3 study comparing ABP 501 with adalimumab in subjects with moderate to severe rheumatoid arthritises. Arthritis and Rheumatology. Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP. 2015;67(no pagination).
225. Huizinga TW, Fleischmann RM, Jasson M, Radin AR, van Adelsberg J, Fiore S, et al. Sarilumab, a fully human monoclonal antibody against IL-6R[alpha] in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. Annals of the Rheumatic Diseases. 2014;73(9):1626-34.
226. Genovese MC, Fleischmann R, Kivitz AJ, Rell-Bakalarska M, Martincova R, Fiore S, et al. Sarilumab Plus Methotrexate in Patients With Active Rheumatoid Arthritis and Inadequate Response to Methotrexate: Results of a Phase III Study. Arthritis & rheumatology (Hoboken, N.J.). 2015;67(6):1424-37.
227. Burmester GR, Lin Y, Patel R, van Adelsberg J, Mangan EK, Graham NMH, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. Annals of the Rheumatic Diseases. 2016.
228. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis: A randomized, controlled trial. Annals of Internal Medicine. 1999;130(6):478-86.
229. Mathias SD, Colwell HH, Miller DP, Moreland LW, Buatti M, Wanke L. Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. Clinical Therapeutics.22(1):128-39.

230. Ogata A, Tanimura K, Sugimoto T, Inoue H, Urata Y, Matsubara T, et al. Phase III study of the efficacy and safety of subcutaneous versus intravenous tocilizumab monotherapy in patients with rheumatoid arthritis. Arthritis care & research. 2014;66(3):344-54.
231. Kaeley GS, Evangelisto AM, Nishio MJ, Goss SL, Liu S, Kalabic J, et al. Methotrexate Dosage Reduction Upon Adalimumab Initiation: Clinical and Ultrasonographic Outcomes from the Randomized Noninferiority MUSICA Trial. The Journal of Rheumatology. 2016;43(8):1480.
232. Taylor PC, Keystone EC, Van Der Heijde D, Tanaka Y, Ishii T, Emoto K, et al. Baricitinib versus placebo or adalimumab in patients with active rheumatoid arthritis (RA) and an inadequate response to background methotrexate therapy: Results of a phase 3 study. Arthritis and Rheumatology. Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP. 2015;67(no pagination).
233. Dougados M, Van Der Heijde D, Chen YC, Greenwald M, Drescher E, Liu J, et al. Baricitinib, an oral janus kinase (jak)1/jak2 inhibitor, in patients with active rheumatoid arthritis (RA) and an inadequate response to cDMARD therapy: Results of the phase 3 Ra-build study. Annals of the Rheumatic Diseases. 2015;74:79-80.
234. Emery P, Gaich CL, DeLozier AM, De Bono S, Liu J, Chang C, et al. Patient-reported outcomes from a phase 3 study of baricitinib in patients with rheumatoid arthritis with inadequate response to conventional synthetic disease-modifying antirheumatic drugs. Arthritis and Rheumatology. Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP. 2015;67(no pagination).
235. Shi Q, Zhao Y, Bao C, Li XF, Huang F, Zhu P, et al. The efficacy and safety of tocilizumab combined with disease-modifying anti-rheumatoid drugs in the treatment of active rheumatoid arthritis: a multi-center, randomized, double-blinded, placebo-controlled trial. [Chinese]. Zhonghua nei ke za zhi. 2013;52(4):323-9.
236. Bingham C III TY, Karpouzas G, Takeuchi T, Aletaha D, Thorne C, Sheng S, Xu W, Rao R, Fei K, Hsu B, Agarwal P, Popik S, Kurrasch R, Peterson S, Ganguly R, Han C, McQuarrie K. Treatment with Sirukumab, an Anti-IL6 Cytokine Monoclonal Antibody, Improves Fatigue and Health-Related Physical and Emotional Well Being in Patients with Active Rheumatoid Arthritis Refractory to Conventional or Biologic Therapy: Results of 2 Global, Placebo-Controlled, Phase 3 Trials. Arthritis & Rheumatology. 2016;68(suppl 10).
237. Taylor PC SM, Wang Q, Jiang Y, Kurrasch R, Daga S, Rao R, Hsu B, Tak PP. Efficacy and Safety of Monotherapy with Sirukumab, an Anti–IL-6 Cytokine Monoclonal Antibody, Compared with Adalimumab Monotherapy in Biologic-Naive Patients with Active Rheumatoid Arthritis: Results of a Global, Randomized, Double-Blind, Parallel-Group, Phase 3 Study. Arthritis & Rheumatology. 2016;68(10).
238. Smolen JS, Weinblatt ME, Sheng S, Zhuang Y, Hsu B. Sirukumab, a human anti-interleukin-6 monoclonal antibody: a randomised, 2-part (proof-of-concept and dose-finding), phase II study in patients with active rheumatoid arthritis despite methotrexate therapy. Annals of the Rheumatic Diseases. 2014;73(9):1616-25.
239. Nishimoto N, Yoshizaki K, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Treatment of rheumatoid arthritis with humanized anti–interleukin-6 receptor antibody: A multicenter, double-blind, placebo-controlled trial. Arthritis & Rheumatism. 2004;50(6):1761-9.
240. Burmester GR, Rubbert-Roth A, Cantagrel A, Hall S, Leszczynski P, Feldman D, et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to

severe rheumatoid arthritis (SUMMACTA study). Annals of the Rheumatic Diseases. 2014;73(1):69-74.
241. Takeuchi T, Matsubara T, Nitobe T, Suematsu E, Ohta S, Honjo S, et al. Phase II dose–response study of abatacept in Japanese patients with active rheumatoid arthritis with an inadequate response to methotrexate. Modern Rheumatology. 2013;23(2):226-35.
242. Tanaka Y, Suzuki M, Nakamura H, Toyoizumi S, Zwillich SH, Tofacitinib Study I. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. Arthritis Care Res (Hoboken). 2011;63(8):1150-8.
243. Tanaka Y, Takeuchi T, Yamanaka H, Nakamura H, Toyoizumi S, Zwillich S. Efficacy and safety of tofacitinib as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study. Mod Rheumatol. 2015;25(4):514-21.
244. Tanaka Y, Emoto K, Cai Z, Aoki T, Schlichting D, Rooney T, et al. Efficacy and safety of baricitinib in Japanese patients with active rheumatoid arthritis receiving background methotrexate therapy: A 12-week, double-blind, randomized placebo-controlled study. Journal of Rheumatology. 2016;43(3):504-11.
245. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A Trial of Etanercept, a Recombinant Tumor Necrosis Factor Receptor:Fc Fusion Protein, in Patients with Rheumatoid Arthritis Receiving Methotrexate. New England Journal of Medicine. 1999;340(4):253-9.
246. Weinblatt ME, Mease P, Mysler E, Takeuchi T, Drescher E, Berman A, et al. The Efficacy and Safety of Subcutaneous Clazakizumab in Patients With Moderate-to-Severe Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Results From a Multinational, Phase IIb, Randomized, Double-Blind, Placebo/Active-Controlled, Dose-Ranging Study. Arthritis & Rheumatology. 2015;67(10):2591-600.
247. Weinblatt ME, Baranauskaite A, Niebrzydowski J, Dokoupilova E, Zielinska A, Sitek-Ziolkowska K, et al. A phase III, randomized, double-blind clinical study comparing SB5, an adalimumab biosimilar, with adalimumab reference product (humira) in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy (24-week results). Arthritis and Rheumatology. Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP. 2015;67(no pagination).
248. Zhang F-C, Hou Y, Huang F, Wu D-H, Bao C-D, Ni L-Q, et al. Infliximab versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a preliminary study from China. APLAR Journal of Rheumatology. 2006;9(2):127-30.
249. Weinblatt ME, Kremer J, Cush J, Rigby W, Teng LL, Devenport J, et al. Tocilizumab as monotherapy or in combination with nonbiologic disease-modifying antirheumatic drugs: twenty-four-week results of an open-label, clinical practice study. Arthritis Care Res (Hoboken). 2013;65(3):362-71.
250. Emery P, Rondon J, Garg A, van Hoogstraten H, Graham N, Liu M, et al. Safety and tolerability of subcutaneous sarilumab compared to intravenous tocilizumab in patients with RA. Arthritis & Rheumatology. 2015;67:1268-9.
251. Eremeeva A, Chernyaeva E, Ivanov R, Nasonov E, Knyazeva L. FRI0224 Comparison of Efficacy and Safety of Rituximab Biosimilar, BCD-020, and Innovator Rituximab in Patients with Active Rheumatoid Arthritis Refractory To TNFA Inhibitors. Annals of the Rheumatic Diseases. 2016;75(Suppl 2):513-4.
252. Smolen JS, Burmester GR, Combe B, Curtis JR, Hall S, Haraoui B, et al. Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. Lancet. 2016;388(10061):2763-74.

253. Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, et al. Baricitinib in Patients with Refractory Rheumatoid Arthritis. N Engl J Med. 2016;374(13):1243-52.
254. Williams JH, Hutmacher MM, Zierhut ML, Becker JC, Gumbiner B, Spencer-Green G, et al. Comparative assessment of clinical response in patients with rheumatoid arthritis between PF-05280586, a proposed rituximab biosimilar, and rituximab. Br J Clin Pharmacol. 2016;82(6):1568-79.
255. Aletaha D, Bingham CI, Tanaka Y, Agarwal P, Kurrasch R, Tak P, et al. Efficacy and Safety of Sirukumab, an Anti-IL-6 Cytokine Monoclonal Antibody, in Patients with Active Rheumatoid Arthritis Despite Anti-TNF Therapy: Results from a Randomized, Double-Blind, Placebo-Controlled, Global, Phase 3 Study [abstract]. Arthritis Rheumatol. 2016;68 (Suppl 10)(http://acrabstracts.org/abstract/efficacy-and-safety-of-sirukumab-an-anti-il-6-cytokine-monoclonal-antibody-in-patients-with-active-rheumatoid-arthritis-despite-anti-tnf-therapy-results-from-a-randomized-double-blind-pla/. Accessed March 21, 2017.).
256. Fleischmann R, van Adelsberg J, Lin Y, Castelar-Pinheiro GD, Brzezicki J, Hrycaj P, et al. Sarilumab and Nonbiologic Disease-Modifying Antirheumatic Drugs in Patients With Active Rheumatoid Arthritis and Inadequate Response or Intolerance to Tumor Necrosis Factor Inhibitors. Arthritis & Rheumatology. 2017;69(2):277-90.
257. Genovese MC, Fleischmann R, Furst D, Janssen N, Carter J, Dasgupta B, et al. Efficacy and safety of olokizumab in patients with rheumatoid arthritis with an inadequate response to TNF inhibitor therapy: outcomes of a randomised Phase IIb study. Ann Rheum Dis. 2014;73(9):1607-15.
258. Schiff MH, von Kempis J, Goldblum R, Tesser JR, Mueller RB. Rheumatoid arthritis secondary non-responders to TNF can attain an efficacious and safe response by switching to certolizumab pegol: a phase IV, randomised, multicentre, double-blind, 12-week study, followed by a 12-week open-label phase. Ann Rheum Dis. 2014;73(12):2174-7.
259. Aletaha D, Alasti F, Smolen JS. Rheumatoid factor determines structural progression of rheumatoid arthritis dependent and independent of disease activity. Ann Rheum Dis. 2013;72(6):875-80.
260. Boers M. Does sex of rheumatoid arthritis patients matter? Lancet. 1998;352(9126):419-20.
261. Canhao H, Rodrigues AM, Mourao AF, Martins F, Santos MJ, Canas-Silva J, et al. Comparative effectiveness and predictors of response to tumour necrosis factor inhibitor therapies in rheumatoid arthritis. Rheumatology (Oxford). 2012;51(11):2020-6.
262. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
263. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. 2008.
264. Dias S, Welton, N.J., Sutton, A.J., Caldwell, D.M., Lu, G. & Ades, A.E. . NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials. available from http://www.nicedsu.org.uk. 2011; last updated April 2014.
265. Wollenhaupt J, Silverfield J, Lee EB, Curtis JR, Wood SP, Soma K, et al. Safety and efficacy of tofacitinib, an oral janus kinase inhibitor, for the treatment of rheumatoid arthritis in open-label, longterm extension studies. J Rheumatol. 2014;41(5):837-52.
266. Charles-Schoeman C, Fleischmann R, Davignon J, Schwartz H, Turner SM, Beysen C, et al. Potential mechanisms leading to the abnormal lipid profile in

patients with rheumatoid arthritis versus healthy volunteers and reversal by tofacitinib. Arthritis & Rheumatology. 2015;67(3):616-25.
267. Kremer JM, Kivitz AJ, Simon-Campos JA, Nasonov EL, Tony HP, Lee SK, et al. Evaluation of the effect of tofacitinib on measured glomerular filtration rate in patients with active rheumatoid arthritis: results from a randomised controlled trial. Arthritis Res Ther. 2015;17:95.
268. Kremer JM, Bloom BJ, Breedveld FC, Coombs JH, Fletcher MP, Gruben D, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. Arthritis Rheum. 2009;60(7):1895-905.
269. Conaghan PG, Ostergaard M, Bowes MA, Wu C, Fuerst T, van der Heijde D, et al. Comparing the effects of tofacitinib, methotrexate and the combination, on bone marrow oedema, synovitis and bone erosion in methotrexate-naive, early active rheumatoid arthritis: results of an exploratory randomised MRI study incorporating semiquantitative and quantitative techniques. Ann Rheum Dis. 2016;75(6):1024-33.
270. Boyle DL, Soma K, Hodge J, Kavanaugh A, Mandel D, Mease P, et al. The JAK inhibitor tofacitinib suppresses synovial JAK1-STAT signalling in rheumatoid arthritis. Ann Rheum Dis. 2015;74(6):1311-6.
271. McInnes IB, Kim HY, Lee SH, Mandel D, Song YW, Connell CA, et al. Open-label tofacitinib and double-blind atorvastatin in rheumatoid arthritis patients: a randomised study. Ann Rheum Dis. 2014;73(1):124-31.
272. Winthrop KL, Silverfield J, Racewicz A, Neal J, Lee EB, Hrycaj P, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. Ann Rheum Dis. 2016;75(4):687-95.
273. Howlader N, Noone A, Krapcho M, Garshell J, Miller D, Altekruse S, et al. SEER Cancer Statistics Review, 1975–2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014.
274. Rahman MU, Buchanan J, Doyle MK, Hsia EC, Gathany T, Parasuraman S, et al. Changes in patient characteristics in anti-tumour necrosis factor clinical trials for rheumatoid arthritis: results of an analysis of the literature over the past 16 years. Ann Rheum Dis. 2011;70(9):1631-40.
275. Schwartzman SS, P.; Takiya, L.; Snyder, M.; Fan, H.; Lukic, T.; Roberts, J.; Rigby, W. F. C. COMPARISON OF TOFACITINIB EFFICACY IN PATIENTS WITH MODERATE VS SEVERE RHEUMATOID ARTHRITIS: POOLED ANALYSIS OF PHASE 3 STUDIES. [Abstract in submission]. 2017.
276. Pfizer I. Protocol A3921187. A phase 3b/4 randomized double blind study of 5 mg of tofacitinib with and without methotrexate in comparison to adalimumab with methotrexate in subjects with moderately to severely active rheumatoid arthritis. Statistical analysis plan. 2014.
277. Beresniak A BC, Zeidler H, Gromnica-Ihle E, Kruger K, Neubauer AS. Value Health. [Conference Abstract]. 2009 October; Conference: ISPOR 12th Annual European Congress Paris France. Conference Start: 20091024 Conference End: 20091027. Conference Publication: (var.pagings). 12 (7):A440.
278. Carlson JJ OS, Dejonckheere F, Sullivan S. Cost-effectiveness of tocilizumab monotherapy vs. adalimumab monotherapy in the treatment of severe active rheumatoid arthritis. ACR conference. 2012:abstract number: 2463.
279. Krieckaert C NS, Nurmohamed MT, Van Dongen CJ, Lems WF, Lafeber FP. Evaluating the cost-effectiveness of personalized treatment with adalimumab using serum drug level and anti-adalimumab antibodies in rheumatoid arthritis patients. Annals of the Rheumatic Diseases. 2012;71(Supplement 3):104; EULAR abstract OP0149.

280. Tanaka E IE, Hoshi D, Kobayashi A, Sugimoto N, Shidara K. Cost-effectiveness of a humanized anti-interleukin-6 (IL-6) receptor monoclonal antibody, tocilizumab, in rheumatoid arthritis using IORRA cohort. Annals of the Rheumatic Diseases. 2012;71(Supplement 3):668; EULAR abstract AB0528.
281. Valle-Mercado C CM, Parra-Torrado M, Rosselli D. . Cost-effectiveness of biologic agents compared with methotrexate in the treatment of rheumatoid arthritis in Colombia. Value in Health. 2011 November;Conference: ISPOR 14th Annual European Congress Madrid Spain. Conference Start: 20111105 Conference End: 20111108. Conference Publication: (var.pagings). 14 (7):A311.
282. Villoro R HA, Ferro B, Talavera P. . Cost-utility analysis of certolizumab pegol versus alternative tumor necrosis factor-inhibitors, for the treatment of moderateto-severe rheumatoid arthritis in Spain. Value in Health. 2011 November;Conference: ISPOR 14th Annual European Congress Madrid Spain. Conference Start: 20111105 Conference End: 20111108. Conference Publication: (var.pagings). 14 (7):A310-A1.
283. Carlson JJ, Ogale S, Dejonckheere F, Sullivan SD. Economic evaluation of tocilizumab monotherapy compared to adalimumab monotherapy in the treatment of severe active rheumatoid arthritis. Value in Health. 2015;18(2):173-9.
284. Krieckaert CL, Nair SC, Nurmohamed MT, van Dongen CJ, Lems WF, Lafeber FP, et al. Personalised treatment using serum drug levels of adalimumab in patients with rheumatoid arthritis: an evaluation of costs and effects. Annals of the Rheumatic Diseases. 2015;74(2):361-8.
285. Tanaka E, Inoue E, Hoshi D, Shimizu Y, Kobayashi A, Sugimoto N, et al. Cost-eff ectiveness of tocilizumab, a humanized anti-interleukin-6 receptor monoclonal antibody, versus methotrexate in patients with rheumatoid arthritis using real-world data from the iorra observational cohort study. Modern Rheumatology. 2015;25(4):503-13.
286. Valle-Mercado C, Cubides MF, Parra-Torrado M, Rosselli D. Cost-effectiveness of biological therapy compared with methotrexate in the treatment for rheumatoid arthritis in Colombia. Rheumatology International. 2013;33(12):2993-7.
287. Beresniak A, Baerwald C, Zeidler H, Kruger K, Neubauer AS, Dupont D, et al. Cost-effectiveness simulation model of biologic strategies for treating to target rheumatoid arthritis in Germany. Clinical and Experimental Rheumatology. 2013;31(3):400-8.
288. Hidalgo-Vega A, Villoro R, Blasco JA, Talavera P, Ferro B, Purcaru O. Cost-utility analysis of certolizumab pegol versus alternative tumour necrosis factor inhibitors available for the treatment of moderate-to-severe active rheumatoid arthritis in Spain. Cost Effectiveness and Resource Allocation. 2015;13 (1) (no pagination)(11).
289. Claxton L, Taylor M, Jenks M, Wallenstein G, Mendelsohn A, Bourret J, et al. An economic evaluation of tofacitinib (xeljanz) treatment in rheumatoid arthritis: Modeling the cost of treatment strategies in the us. Arthritis and Rheumatology. Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP. 2015;67(no pagination).
290. Tanaka E, Inoue E, Shimizu Y, Kobayashi A, Sugimoto N, Hoshi D, et al. Optimal rheumatoid arthritis patient selection for biological treatment from pharmacoeconomic perspectives based on the institute of rheumatology, rheumatoid arthritis (IORRA) cohort. Arthritis and Rheumatism. 2013;65:S568.
291. Barton P, Jobanputra P, Wilson J, Bryan S, Burls A. The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis. Health Technol Assess. 2004;8(11):iii, 1-91.

292. Lindgren P, Geborek P, Kobelt G. Modeling the cost-effectiveness of treatment of rheumatoid arthritis with rituximab using registry data from Southern Sweden. Int J Technol Assess Health Care. 2009;25(2):181-9.
293. Tosh J, Brennan A, Wailoo A, Bansback N. The Sheffield rheumatoid arthritis health economic model. Rheumatology. 2011;50 Suppl 4:iv26-31.
294. Jackson R, Tosh J, Davies S, Wong R, Stevenson M, Stevens J. Golimumab for the treatment of rheumatoid arthritis after failure of previous disease-modifying antirheumatic drugs: A Single Technology Appraisal. ScHARR, The University of Sheffield. 2010.
295. Bansback N, Ara R, Karnon J, Anis A. Economic Evaluations in Rheumatoid Arthritis: A Critical Review of Measures Used to Define Health States. Pharmacoeconomics. 2008;26(5):395-408.
296. Kearns B, Ara R, Wailoo A, Manca A, Alava MH, Abrams K, et al. Good practice guidelines for the use of statistical regression models in economic evaluations. Pharmacoeconomics. 2013;31(8):643-52.
297. NICE Decision Support Unit. Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2013.
298. Norton S, Fu B, Scott DL, Deighton C, Symmons DP, Wailoo AJ, et al. Health Assessment Questionnaire disability progression in early rheumatoid arthritis: systematic review and analysis of two inception cohorts. Semin Arthritis Rheum. 2014;44(2):131-44.
299. Gibson L, Hernandez Alava M, Wailoo A. Progression of Disease in People with Rheumatoid Arthritis Treated with Non-Biologic Therapies. Report by the Decision Support Unit. 2015.
300. Dakin H. Review of studies mapping from quality of life or clinical measures to EQ-5D: an online database. Health and Quality of Life Outcomes. 11:151. 2013.
301. Hernandez Alava M, Wailoo A, Wolfe F, Michaud K. The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis. Rheumatology. 2013;52(5):944-50.
302. Hernandez Alava M, Wailoo AJ, Ara R. Tails from the peak district: adjusted limited dependent variable mixture models of EQ-5D questionnaire health state utility values. Value in Health. 2012;15(3):550-61.
303. Adams R, Walsh C, Veale D, Bresnihan B, FitzGerald O, Barry M. Understanding the relationship between the EQ-5D, SF-6D, HAQ and disease activity in inflammatory arthritis. Pharmacoeconomics. 2010;28(6):477-87.
304. Hawthorne GB, R.; Defina, J. . Functional status and health-related quality of life assessment in patients with rheumatoid arthritis. . Centre for Health Program Evaluation, working paper 116. 2000.
305. Hurst NP, Kind P, Ruta D, Hunter M, Stubbings A. Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). British Journal of Rheumatology. 1997;36(5):551-9.
306. Malottki K, Barton P, Tsourapas A, Uthman AO, Liu Z, Routh K, et al. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. Health Technol Assess. 2011;15(14):1-278.
307. Marra CA, Marion SA, Guh DP, Najafzadeh M, Wolfe F, Esdaile JM, et al. Not all "quality-adjusted life years" are equal. J Clin Epidemiol. 2007;60(6):616-24.
308. Soini EJ, Hallinen TA, Puolakka K, Vihervaara V, Kauppi MJ. Cost-effectiveness of adalimumab, etanercept, and tocilizumab as first-line treatments for moderate-to-severe rheumatoid arthritis. J Med Econ. 2012;15(2):340-51.
309. Ducournau P, Kielhorn A, Wintfeld N. Comparison of linear and nonlinear utility mapping between HAQ and the EQ-5D using pooled data from the tocilizumab trials OPTION and LITHE. Annual Meeting of the British Society of Rheumatology (BSR), Glasgow. 2009:Poster 258.

310. Standfield L, Norris S, Harvey C, Elliot L, Riordan J, Hall S, et al. Relationship between rheumatoid arthritis disease severity, health-related utility, and resource use in Australian patients: A cross-sectional, multicenter study. Clin Ther. 2010;32(7):1329-42.
311. Hoshi D, Inoue A, Tsutani K, Shidara Y. Euro Qol (Eq-5d) Based QoL in 5,023 Japanese Patients with Rheumatoid Arthritis in an Observational Cohort IORRA. Ann Rheum Dis. 2009;68(Suppl 3):224.
312. Gulacsi L. Subjective health expectations of rheumatoid arthritis patients starting biological therapy. Value in Health. 2011;14(7):A312-A3.
313. Linde L, Hetland ML, Ostergaard M. Predictors of differences in quality adjusted life years in patients with rheumatoid arthritis treated with biologcs for one year. Ann Rheum Dis. 2011;70(Suppl 3):642.
314. Nakajima A. Impact of comorbidities on both disease activity and treatment strategy in patients with rheumatoid arthritis: analysis of the IORRA cohort database. Ann Rheum Dis. 2012;71(Suppl 3):105.
315. Pentek M, Gulacsi L, Rojkovich B, Brodszky V, van Exel J, Brouwer WB. Subjective health expectations at biological therapy initiation: a survey of rheumatoid arthritis patients and rheumatologists. The European journal of health economics : HEPAC : health economics in prevention and care. 2014;15:S83-S92.
316. Linde L, Sorensen J, Ostergaard M, Hetland ML. Gain in quality-adjusted life-years in patients with rheumatoid arthritis during 1 year of biological therapy: a prospective study in clinical practice.[Erratum appears in J Rheumatol. 2013 Sep;40(9):1634 Note: Merete, Lund Hetland [corrected to Hetland, Merete Lund]]. Journal of Rheumatology. 2013;40(9):1479-86.
317. Nakajima A, Inoue E, Shimizu Y, Kobayashi A, Shidara K, Sugimoto N, et al. Presence of comorbidity affects both treatment strategies and outcomes in disease activity, physical function, and quality of life in patients with rheumatoid arthritis. Clinical Rheumatology. 2015;34(3):441-9.
318. Hoshi D, Tanaka E, Igarashi A, Inoue E, Kobayashi A, Sugimoto N, et al. Profiles of EQ-5D utility scores in the daily practice of Japanese patients with rheumatoid arthritis; Analysis of the IORRA database. Modern Rheumatology. 2016;26(1):40-5.
319. Bae S, Koh H, Kim Y. Factors associated with quality of life and functional disability among rheumatoid arthritis patients treated with disease-modifying anti-rheumatic drugs for at least six-months. Value in Health. 2016;19 (3):A236.
320. Strand V, Ahadieh S, French J, Geier J, Krishnaswami S, Menon S, et al. Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. Arthritis Res Ther. 2015;17:362.
321. Oppong R, Kaambwa B, Nuttall J, Hood K, Smith RD, Coast J. The impact of using different tariffs to value EQ-5D health state descriptions: an example from a study of acute cough/lower respiratory tract infections in seven countries. Eur J Health Econ. 2013;14(2):197-209.
322. British National Formulary. BNF online. Available at: http://www.bnf.org/ [Last accessed January 2017].
323. Department of Health. NHS reference Costs 2015–16: Direct Access: Pathology Services, Haematology, DAPS05. 2016.
324. Department of Health. NHS reference Costs 2015–16: Clinical Biochemistry, DAPS04. 2016.
325. Personal Social Services Research Unit. Unit costs of health and social care. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2016/. 2016.
326. Department of Health. NHS Reference Costs 2010-11. NHS Trusts and PCTs combined. Average cost of WA03Y (Septicaemia without CC: £1,752). DZ23C (Bronchopneumonia without CC: £1,438), LA04F (Kidney or Urinary Tract

Infections with length of stay 2 days or more without CC: £1,408), PA16B (Major Infections without CC: £2,623), DZ22C (Unspecified Acute Lower Respiratory Infection without CC: £1,079), DZ21K (Chronic Obstructive Pulmonary Disease or Bronchitis without NIV without Intubation without CC: £1,266). 2011.
327. Department of Health. National Schedule of Reference Costs 2015-16 for NHS Trusts. Total average cost of outpatient attendance for Service Code 410 (Rheumatology). Sheet: Total Outpatient Attendances. 2016.
328. Symmons DP, Barrett EM, Bankhead CR, Scott DG, Silman AJ. The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk Arthritis Register. British Journal of Rheumatology. 1994;33(8):735-9.
329. Wiles NJ, Dunn G, Barrett EM, Harrison BJ, Silman AJ, Symmons DP. One year followup variables predict disability 5 years after presentation with inflammatory polyarthritis with greater accuracy than at baseline. J Rheumatol. 2000;27(10):2360-6.
330. Matza LS, Cong Z, Chung K, Stopeck A, Tonkin K, Brown J, et al. Utilities associated with subcutaneous injections and intravenous infusions for treatment of patients with bone metastases. Patient Prefer Adherence. 2013;7:855-65.
331. Taylor MS, R.; Ganderton, M.; Conway, P.; Lebmeier, M.; Packham J. The relationship between Health Assessment Questionnaire score and resource use in the management of rheumatoid arthritis. . In: European League Against Rheumatism (EULAR). Paris. 2008.
332. National Institute for Health and Care Excellence. Costing template for TA195. 2010.
333. Pfizer Inc. Data on file - Decision Resources. 2015.
334. Weinblatt ME, Bingham CO, Mendelsohn AM, Kim L, Mack M, Lu J, et al. Intravenous golimumab is effective in patients with active rheumatoid arthritis despite methotrexate therapy with responses as early as week 2: results of the phase 3, randomised, multicentre, double-blind, placebo-controlled GO-FURTHER trial. Annals of the Rheumatic Diseases. 2013;72(3):381-9.
335. Genovese MC, Schiff M, Luggen M, Becker JC, Aranda R, Teng J, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis. 2008;67(4):547-54.
336. Genovese MC, Schiff M, Luggen M, Le Bars M, Aranda R, Elegbe A, et al. Longterm safety and efficacy of abatacept through 5 years of treatment in patients with rheumatoid arthritis and an inadequate response to tumor necrosis factor inhibitor therapy. J Rheumatol. 2012;39(8):1546-54.
337. Combe B, Dougados M, Logeart I, Lukas C, Mariette X, Puechal X, et al. An open-label randomized controlled study to evaluate the efficacy of etanercept (ETN) versus rituximab (RTX), in patients with active rheumatoid arthritis previously treated with RTX and TNF blockers [Abstract]. Ann Rheum Dis. 2012;71:667.
338. Smolen JS, Kay J, Doyle M, Landewe R, Matteson EL, Gaylis N, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor alpha inhibitors: findings with up to five years of treatment in the multicenter, randomized, double-blind, placebo-controlled, phase 3 GO-AFTER study. Arthritis Res Ther. 2015;17:14.
339. Smolen JS, Kay J, Doyle MK, Landewe R, Matteson EL, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009;374(9685):210-21.
340. Smolen JS, Kay J, Landewe RB, Matteson EL, Gaylis N, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis who have previous experience with tumour necrosis factor inhibitors: results of a long-term extension

of the randomised, double-blind, placebo-controlled GO-AFTER study through week 160. Ann Rheum Dis. 2012;71(10):1671-9.
341. Smolen J, Kay J, Landewe R, Matteson EL, Gaylis NB, Wollenhaupt JJ, et al., editors. Golimumab use and sustained clinical response in patients with active rheumatoid arthritis previously treated with anti-tumor necrosis factor alpha agents. Annual Scientific Meeting of the American College of Rheumatology and Association of Rheumatology Health Professionals; 2011. Arthritis and Rheumatism.
342. Smolen JS, Kay J, Doyle MK, Landewe R, Matteson E, Wollenhaupt J, et al., editors. Golimumab in rheumatoid arthritis patients previously treated with anti-TNF alpha agents: 2 year results from go-after study; 2011. Rheumatology.
343. Manders SH, Kievit W, Adang E, Brus HL, Bernelot Moens H, Hartkamp A, et al. Effectiveness of Abatacept, Rituximab or A TNFI after Failure of the First Tnfi: Results of A MultiCentered Pragmatic RCT [Abstract 1635 EULAR 2014]. Ann Rheum Dis. 2014;73(Suppl 2):509.
344. Manders SH, Kievit W, Brus HL, Bernelot Moens H, Hartkamp A, Bos R, et al. Mode Of Action Change Not Necessary After Failing The First Tumornecrosisfactor Inhibitor: Preliminary Results Of a Randomized Controlled Trial [Abstract 1419 presented at the 2013 ACR/ARHP annual meeting]. Available from http://acrabstracts.org/abstract/mode-of-action-change-not-necessary-after-failing-the-first-tumornecrosisfactor-inhibitor-preliminary-results-of-a-randomized-controlled-trial/ Accessed Janulary 2017. 2013.
345. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet. 2013;381(9865):451-60.
346. Strand V, Burmester GR, Zerbini CA, Mebus CA, Zwillich SH, Gruben D, et al. Tofacitinib with methotrexate in third-line treatment of patients with active rheumatoid arthritis: patient-reported outcomes from a phase III trial. Arthritis Care Res (Hoboken). 2015;67(4):475-83.
347. Strand V, Burmester GR, Ogale S, Devenport J, John A, Emery P. Improvements in health-related quality of life after treatment with tocilizumab in patients with rheumatoid arthritis refractory to tumour necrosis factor inhibitors: results from the 24-week randomized controlled RADIATE study. Rheumatology (Oxford). 2012;51(10):1860-9.
348. Emery P, Keystone E, Tony H-P, Law A, Woodworth T, Kremer J. Tocilizumab Significantly Improves Patient Outcomes Regardless Of Prior Inadequate Response To Tumour Necrosis Factor Antagonists In Rheumatoid Arthritis [Abstract]. 2009.
349. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54(9):2793-806.
350. Cohen SB, Keystone E, Genovese MC, Emery P, Peterfy C, Tak PP, et al. Continued inhibition of structural damage over 2 years in patients with rheumatoid arthritis treated with rituximab in combination with methotrexate. Ann Rheum Dis. 2010;69(6):1158-61.
351. Keystone E, Burmester GR, Furie R, Loveless JE, Emery P, Kremer J, et al. Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum. 2008;59(6):785-93.
352. Keystone EC, Cohen SB, Emery P, Kremer JM, Dougados M, Loveless JE, et al. Multiple courses of rituximab produce sustained clinical and radiographic efficacy and safety in patients with rheumatoid arthritis and an inadequate response to 1

or more tumor necrosis factor inhibitors: 5-year data from the REFLEX study. J Rheumatol. 2012;39(12):2238-46.
353. Allaart CF, Breedveld FC, Dijkmans BA. Treatment of recent-onset rheumatoid arthritis: lessons from the BeSt study. J Rheumatol Suppl. 2007;80:25-33.
354. Bansback NJ, Brennan A, Ghatnekar O. Cost effectiveness of adalimumab in the treatment of patients with moderate to severe rheumatoid arthritis in Sweden. Ann Rheum Dis. 2005;64(7):995-1002.
355. Barbieri M, Wong JB, Drummond M. The cost effectiveness of infliximab for severe treatment-resistant rheumatoid arthritis in the UK. Pharmacoeconomics. 2005;23(6):607-18.
356. Barra L, Pope JE, Payne M. Real-world anti-tumor necrosis factor treatment in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: cost-effectiveness based on number needed to treat to improve health assessment questionnaire. J Rheumatol. 2009;36(7):1421-8.
357. Benucci M, Li Gobbi F, Sabadini L, Saviola G, Baiardi P, Manfredi M. The economic burden of biological therapy in rheumatoid arthritis in clinical practice: cost-effectiveness analysis of sub-cutaneous anti-TNFalpha treatment in Italian patients. Int J Immunopathol Pharmacol. 2009;22(4):1147-52.
358. Brennan A, Bansback N, Reynolds A, Conway P. Modelling the cost-effectiveness of etanercept in adults with rheumatoid arthritis in the UK. Rheumatology (Oxford). 2004;43(1):62-72.
359. Brennan A, Bansback N, Nixon R, Madan J, Harrison M, Watson K, et al. Modelling the cost effectiveness of TNF-alpha antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry. Rheumatology (Oxford). 2007;46(8):1345-54.
360. Chen YF, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technol Assess. 2006;10(42):iii-iv, xi-xiii, 1-229.
361. Chiou CF, Choi J, Reyes CM. Cost-effectiveness analysis of biological treatments for rheumatoid arthritis. Expert Rev. 2004;4(3):307-15.
362. Choi HK, Seeger JD, Kuntz KM. A cost-effectiveness analysis of treatment options for patients with methotrexate-resistant rheumatoid arthritis. Arthritis Rheum. 2000;43(10):2316-27.
363. Choi HK, Seeger JD, Kuntz KM. A cost effectiveness analysis of treatment options for methotrexate-naive rheumatoid arthritis. J Rheumatol. 2002;29(6):1156-65.
364. Coyle D, Judd M, Blumenauer B, Cranney A, Maetzel A, Tugwell P, et al. Infliximab and Etanercept in Patients with Rheumatoid Arthritis: A Systematic Review and Economic Evaluation. Canadian Coordinating Office for Health Technology Assessment. 2006.
365. Davies A, Cifaldi MA, Segurado OG, Weisman MH, Davies A, Cifaldi MA, et al. Cost-effectiveness of sequential therapy with tumor necrosis factor antagonists in early rheumatoid arthritis. Journal of Rheumatology. 2009;36(1):16-26.
366. Farahani P, Levine M, Goeree R. A comparison between integrating clinical practice setting and randomized controlled trial setting into economic evaluation models of therapeutics. J Eval Clin Pract. 2006;12(4):463-70.
367. Finckh A, Bansback N, Marra CA, Anis AH, Michaud K, Lubin S, et al. Treatment of very early rheumatoid arthritis with symptomatic therapy, disease-modifying antirheumatic drugs, or biologic agents: a cost-effectiveness analysis. Ann Intern Med. 2009;151(9):612-21.
368. Hallinen TA, Soini EJ, Eklund K, Puolakka K. Cost-utility of different treatment strategies after the failure of tumour necrosis factor inhibitor in rheumatoid arthritis in the Finnish setting. Rheumatology (Oxford). 2010;49(4):767-77.

369. Jobanputra P, Barton P, Bryan S, Burls A. The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess. 2002;6(21):1-110.
370. Kielhorn A, Porter D, Diamantopoulos A, Lewis G. UK cost-utility analysis of rituximab in patients with rheumatoid arthritis that failed to respond adequately to a biologic disease-modifying antirheumatic drug. Curr Med Res Opin. 2008;24(9):2639-50.
371. Kobelt G, Jonsson L, Young A, Eberhardt K. The cost-effectiveness of infliximab (Remicade) in the treatment of rheumatoid arthritis in Sweden and the United Kingdom based on the ATTRACT study. Rheumatology (Oxford). 2003;42(2):326-35.
372. Kobelt G, Eberhardt K, Geborek P. TNF inhibitors in the treatment of rheumatoid arthritis in clinical practice: costs and outcomes in a follow up study of patients with RA treated with etanercept or infliximab in southern Sweden. Ann Rheum Dis. 2004;63(1):4-10.
373. Kobelt G, Lindgren P, Lindroth Y, Jacobson L, Eberhardt K. Modelling the effect of function and disease activity on costs and quality of life in rheumatoid arthritis. Rheumatology (Oxford). 2005;44(9):1169-75.
374. Kobelt G, Lindgren P, Singh A, Klareskog L. Cost effectiveness of etanercept (Enbrel) in combination with methotrexate in the treatment of active rheumatoid arthritis based on the TEMPO trial. Ann Rheum Dis. 2005;64(8):1174-9.
375. Kobelt G, Lindgren P, Geborek P. Costs and outcomes for patients with rheumatoid arthritis treated with biological drugs in Sweden: a model based on registry data. Scand J Rheumatol. 2009;38(6):409-18.
376. Lekander I, Borgstrom F, Svarvar P, Ljung T, Carli C, van Vollenhoven RF. Cost-effectiveness of real-world infliximab use in patients with rheumatoid arthritis in Sweden. Int J Technol Assess Health Care. 2010;26(1):54-61.
377. Merkesdal S, Kirchhoff T, Wolka D, Ladinek G, Kielhorn A, Rubbert-Roth A. Cost-effectiveness analysis of rituximab treatment in patients in Germany with rheumatoid arthritis after etanercept-failure. Eur J Health Econ. 2010;11(1):95-104.
378. Russell A, Beresniak A, Bessette L, Haraoui B, Rahman P, Thorne C, et al. Cost-effectiveness modeling of abatacept versus other biologic agents in DMARDS and anti-TNF inadequate responders for the management of moderate to severe rheumatoid arthritis. Clin Rheumatol. 2009;28(4):403-12.
379. Sany J, Cohen JD, Combescure C, Bozonnat MC, Roch-Bras F, Lafon G, et al. Medico-economic evaluation of infliximab in rheumatoid arthritis--prospective French study of a cohort of 635 patients monitored for two years. Rheumatology (Oxford). 2009;48(10):1236-41.
380. Saraux A, Gossec L, Goupille P, Bregman B, Boccard E, Dupont D, et al. Cost-effectiveness modelling of biological treatment sequences in moderate to severe rheumatoid arthritis in France. Rheumatology (Oxford). 2010;49(4):733-40.
381. Schulze-Koops H, Deeg M, Runge C, Volmer T, Brecht JG. [Health-economic assessment of combination therapy for rheumatoid arthritis with methotrexat and etanercept based on the TEMPO Study]. Z Rheumatol. 2009;68(10):836-41.
382. Spalding JR, Hay J. Cost effectiveness of tumour necrosis factor-alpha inhibitors as first-line agents in rheumatoid arthritis. Pharmacoeconomics. 2006;24(12):1221-32.
383. Tanno M, Nakamura I, Ito K, Tanaka H, Ohta H, Kobayashi M, et al. Modeling and cost-effectiveness analysis of etanercept in adults with rheumatoid arthritis in Japan: a preliminary analysis. Mod Rheumatol. 2006;16(2):77-84.
384. van den Hout WB, Goekoop-Ruiterman YP, Allaart CF, de Vries-Bouwstra JK, Hazes JM, Kerstens PJ, et al. Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. Arthritis Rheum. 2009;61(3):291-9.

385. Vera-Llonch M, Massarotti E, Wolfe F, Shadick N, Westhovens R, Sofrygin O, et al. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to tumor necrosis factor-alpha antagonists. J Rheumatol. 2008;35(9):1745-53.
386. Vera-Llonch M, Massarotti E, Wolfe F, Shadick N, Westhovens R, Sofrygin O, et al. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to methotrexate. Rheumatology (Oxford). 2008;47(4):535-41.
387. Virkki LM, Konttinen YT, Peltomaa R, Suontama K, Saario R, Immonen K, et al. Cost-effectiveness of infliximab in the treatment of rheumatoid arthritis in clinical practice. Clin Exp Rheumatol. 2008;26(6):1059-66.
388. Wailoo A. Modeling the Cost Effectiveness of Etanercept, Adalimumab and Anakinra Compared to Infliximab in the Treatment of Patients in the Medicare Program. Agency for Healthcare Research and Quality. 2006.
389. Wailoo AJ, Bansback N, Brennan A, Michaud K, Nixon RM, Wolfe F. Biologic drugs for rheumatoid arthritis in the Medicare program: a cost-effectiveness analysis. Arthritis Rheum. 2008;58(4):939-46.
390. Walsh CA, Minnock P, Slattery C, Kennedy N, Pang F, Veale DJ, et al. Quality of life and economic impact of switching from established infliximab therapy to adalimumab in patients with rheumatoid arthritis. Rheumatology (Oxford). 2007;46(7):1148-52.
391. Welsing PM, Severens JL, Hartman M, van Riel PL, Laan RF. Modeling the 5-year cost effectiveness of treatment strategies including tumor necrosis factor-blocking agents and leflunomide for treating rheumatoid arthritis in the Netherlands. Arthritis Rheum. 2004;51(6):964-73.
392. Wong JB, Singh G, Kavanaugh A. Estimating the cost-effectiveness of 54 weeks of infliximab for rheumatoid arthritis. Am J Med. 2002;113(5):400-8.
393. Yuan Y, Trivedi D, Maclean R, Rosenblatt L. Indirect cost-effectiveness analyses of abatacept and rituximab in patients with moderate-to-severe rheumatoid arthritis in the United States. J Med Econ. 2010;13(1):33-41.
394. Benucci M, Saviola G, Baiardi P, Manfredi M. Cost-effectiveness treatment with Rituximab in patients with rheumatoid arthritis in real life. Rheumatol Int. 2011;31(11):1465-9.
395. Beresniak A, Ariza-Ariza R, Garcia-Llorente JF, Ramirez-Arellano A, Dupont D. Modelling cost-effectiveness of biologic treatments based on disease activity scores for the management of rheumatoid arthritis in Spain. Int J Inflam. 2011;2011:727634.
396. Cimmino MA, Leardini G, Salaffi F, Intorcia M, Bellatreccia A, Dupont D, et al. Assessing the cost-effectiveness of biologic agents for the management of moderate-to-severe rheumatoid arthritis in anti-TNF inadequate responders in Italy: a modelling approach. Clin Exp Rheumatol. 2011;29(4):633-41.
397. Diamantopoulos A, Benucci M, Capri S, Berger W, Wintfeld N, Giuliani G, et al. Economic evaluation of tocilizumab combination in the treatment of moderate-to-severe rheumatoid arthritis in Italy. Journal of Medical Economics. 2012;15(3):576-85.
398. Kobelt G, Lekander I, Lang A, Raffeiner B, Botsios C, Geborek P. Cost-effectiveness of etanercept treatment in early active rheumatoid arthritis followed by dose adjustment. Int J Technol Assess Health Care. 2011;27(3):193-200.
399. Puolakka K, Blafield H, Kauppi M, Luosujarvi R, Peltomaa R, Leikola-Pelho T, et al. Cost-effectiveness modelling of sequential biologic strategies for the treatment of moderate to severe rheumatoid arthritis in Finland. Open Rheumatol J. 2012;6:38-43.
400. Schipper LG, Kievit W, den Broeder AA, van der Laar MA, Adang EM, Fransen J, et al. Treatment strategies aiming at remission in early rheumatoid arthritis

patients: starting with methotrexate monotherapy is cost-effective. Rheumatology (Oxford). 2011;50(7):1320-30.
401. Wu B, Wilson A, Wang FF, Wang SL, Wallace DJ, Weisman MH, et al. Cost effectiveness of different treatment strategies in the treatment of patients with moderate to severe rheumatoid arthritis in china. PLoS One. 2012;7(10):e47373.
402. Ahmadiani S, Nikfar S, Karimi S, Jamshidi AR, Akbari-Sari A, Kebriaeezadeh A. Rituximab as first choice for patients with refractory rheumatoid arthritis: cost-effectiveness analysis in Iran based on a systematic review and meta-analysis. Rheumatol Int. 2016.
403. Athanasakis K, Tarantilis F, Tsalapati K, Konstantopoulou T, Vritzali E, Kyriopoulos J. Cost-utility analysis of tocilizumab monotherapy in first line versus standard of care for the treatment of rheumatoid arthritis in Greece. Rheumatology International. 2015;35(9):1489-95.
404. Curtis JR, Chastek B, Becker L, Quach C, Harrison DJ, Yun H, et al. Cost and effectiveness of biologics for rheumatoid arthritis in a commercially insured population. Journal of Managed Care and Specialty Pharmacy. 2015;21(4):318-28.
405. Diamantopoulos A, Finckh A, Huizinga T, Sungher DK, Sawyer L, Neto D, et al. Tocilizumab in the treatment of rheumatoid arthritis: A cost-effectiveness analysis in the UK. Pharmacoeconomics. 2014;32(8):775-87.
406. Eriksson JK, Karlsson JA, Bratt J, Petersson IF, Van Vollenhoven RF, Ernestam S, et al. Cost-effectiveness of infliximab versus conventional combination treatment in methotrexate-refractory early rheumatoid arthritis: 2-year results of the register-enriched randomised controlled SWEFOT trial. Annals of the Rheumatic Diseases. 2015;74(6):1094-101.
407. Fagnani F, Pham T, Claudepierre P, Berenbaum F, De Chalus T, Saadoun C, et al. Modeling of the clinical and economic impact of a risk-sharing agreement supporting a treat-to-target strategy in the management of patients with rheumatoid arthritis in France. J Med Econ. 2016;19(8):812-21.
408. Fitzpatrick R, Scott DG, Keary I. Cost-minimisation analysis of subcutaneous methotrexate versus biologic therapy for the treatment of patients with rheumatoid arthritis who have had an insufficient response or intolerance to oral methotrexate. Clinical Rheumatology. 2013;32(11):1605-12.
409. Fragoulakis V, Vitsou E, Hernandez AC, Maniadakis N. Economic evaluation of anti-TNF agents for patients with rheumatoid arthritis in Greece. ClinicoEconomics and Outcomes Research. 2015;7:85-93.
410. Gissel C, Gotz G, Repp H. Cost-effectiveness of adalimumab for rheumatoid arthritis in Germany. Z Rheumatol. 2016.
411. Hashemi-Meshkini A, Nikfar S, Glaser E, Jamshidi A, Hosseini SA. Cost-Effectiveness Analysis of Tocilizumab in Comparison with Infliximab in Iranian Rheumatoid Arthritis Patients with Inadequate Response to tDMARDs: A Multistage Markov Model. Value in Health Regional Issues. 2016;9:42-8.
412. Jalal H, O'Dell JR, Bridges SL, Jr., Cofield S, Curtis JR, Mikuls TR, et al. Cost-Effectiveness of Triple Therapy versus Etanercept Plus Methotrexate in Early Aggressive Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2016.
413. Kobelt G. Treating to target with etanercept in rheumatoid arthritis: Cost-effectiveness of dose reductions when remission is achieved. Value in Health. 2014;17(5):537-44.
414. Kostic M, Jovanovic S, Tomovic M, Milenkovic MP, Jankovic SM. Cost-effectiveness analysis of tocilizumab in combination with methotrexate for rheumatoid arthritis: a Markov model based on data from Serbia, country in socioeconomic transition. Vojnosanitetski pregled. 2014;71(2):144-8.
415. Kvamme MK, Lie E, Uhlig T, Moger TA, Kvien TK, Kristiansen IS. Cost-effectiveness of TNF inhibitors vs synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: A Markov model study based on two

longitudinal observational studies. Rheumatology (United Kingdom). 2015;54(7):1226-35.
416. Lee MY, Park SK, Park SY, Byun JH, Lee SM, Ko SK, et al. Cost-effectiveness of Tofacitinib in the Treatment of Moderate to Severe Rheumatoid Arthritis in South Korea. Clinical Therapeutics. 2015;37(8):1662-76.
417. Lekander I, Borgstrom F, Lysholm J, Van Vollenhoven RF, Lindblad S, Geborek P, et al. The cost-effectiveness of TNF-inhibitors for the treatment of rheumatoid arthritis in Swedish clinical practice. European Journal of Health Economics. 2013;14(6):863-73.
418. Lekander I, Kobelt G, Svarvar P, Ljung T, Van Vollenhoven R, Borgstrom F. The comparison of trial data-based and registry data-based cost-effectiveness of infliximab treatment for rheumatoid arthritis in Sweden using a modeling approach. Value in Health. 2013;16(2):251-8.
419. Nguyen CM, Bounthavong M, Mendes MA, Christopher ML, Tran JN, Kazerooni R, et al. Cost utility of tumour necrosis factor-alpha inhibitors for rheumatoid arthritis: an application of Bayesian methods for evidence synthesis in a Markov model. Pharmacoeconomics. 2012;30(7):575-93.
420. Quartuccio L, Di Bidino R, Ruggeri M, Schiavon F, Biasi D, Adami S, et al. Cost-effectiveness analysis of two rituximab retreatment regimens for longstanding rheumatoid arthritis. Arthritis Care and Research. 2015;67(7):947-55.
421. Said C, Coleiro B, Zarb Adami M, Azzopardi LM, Serracino Inglott A. Cost effectiveness of TNF- alpha inhibitors in rheumatoid arthritis. International Journal of Inflammation. 2013;2013 (no pagination)(581409).
422. Stephens S, Botteman MF, Cifaldi MA, Van Hout BA. Modelling the cost-effectiveness of combination therapy for early, rapidly progressing rheumatoid arthritis by simulating the reversible and irreversible effects of the disease. BMJ Open. 2015;5 (6) (no pagination)(06560).
423. Tran-Duy A, Boonen A, Kievit W, van Riel PL, van de Laar MA, Severens JL. Modelling outcomes of complex treatment strategies following a clinical guideline for treatment decisions in patients with rheumatoid arthritis. Pharmacoeconomics. 2014;32(10):1015-28.
424. Wu B, Song Y, Leng L, Bucala R, Lu L. Treatment of moderate rheumatoid arthritis with different strategies in a health resource-limited setting: a cost-effectiveness analysis in the era of biosimilars. Clinical and Experimental Rheumatology. 2015;33(1):20-6.
425. Claxton L, Jenks M, Taylor M, Wallenstein G, Mendelsohn AM, Bourret JA, et al. An Economic Evaluation of Tofacitinib Treatment in Rheumatoid Arthritis: Modeling the Cost of Treatment Strategies in the United States. Journal of Managed Care & Specialty Pharmacy. 2016;22(9):1088-102.
426. de Jong PH, Hazes JM, Buisman LR, Barendregt PJ, van Zeben D, van der Lubbe PA, et al. Best cost-effectiveness and worker productivity with initial triple DMARD therapy compared with methotrexate monotherapy in early rheumatoid arthritis: cost-utility analysis of the tREACH trial. Rheumatology. 2016;55(12):2138-47.
427. Joensuu JT, Aaltonen KJ, Aronen P, Sokka T, Puolakka K, Tuompo R, et al. Cost-effectiveness of biologic compared with conventional synthetic disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis: A register study. Rheumatology (United Kingdom). 2016;55(10):1803-11.
428. Kievit W, van Herwaarden N, van den Hoogen FH, van Vollenhoven RF, Bijlsma JW, van den Bemt BJ, et al. Disease activity-guided dose optimisation of adalimumab and etanercept is a cost-effective strategy compared with non-tapering tight control rheumatoid arthritis care: analyses of the DRESS study. Annals of the Rheumatic Diseases. 2016;75(11):1939-44.
429. Park SK, Park SH, Lee MY, Park JH, Jeong JH, Lee EK. Cost-effectiveness Analysis of Treatment Sequence Initiating With Etanercept Compared With

Leflunomide in Rheumatoid Arthritis: Impact of Reduced Etanercept Cost With Patent Expiration in South Korea. Clinical Therapeutics. 2016;38(11):2430-46.e3.
430. Porter D, van Melckebeke J, Dale J, Messow CM, McConnachie A, Walker A, et al. Tumour necrosis factor inhibition versus rituximab for patients with rheumatoid arthritis who require biological treatment (ORBIT): an open-label, randomised controlled, non-inferiority, trial. Lancet. 2016;388(10041):239-47.
431. Tanaka E, Inoue E, Yamaguchi R, Shimizu Y, Kobayashi A, Sugimoto N, et al. Pharmacoeconomic analysis of biological disease modifying antirheumatic drugs in patients with rheumatoid arthritis based on real-world data from the IORRA observational cohort study in Japan. Modern Rheumatology. 2016:1-10.
432. Aagren M DA, Pang F, Winding B. . The Cost-Utility of Adalimumab (Humira) in Patients with Rheumatoid Arthritis (RA) in Denmark. ISPOR Conference. 2007.
433. Agarwal SJ SS, Johnson ML. . Value Health. [Conference Abstract]. 2009 May; Conference: ISPOR 14th Annual International Meeting Orlando, FL United States. Conference Start: 20090516 Conference End: 20090520. Conference Publication: (var.pagings). 12 (3):A67-A8.
434. Aguirre A GE, Bierschwale H, Arce CA. . Value Health. [Conference Abstract]. 2009 October; Conference: ISPOR 12th Annual European Congress Paris France. Conference Start: 20091024 Conference End: 20091027. Conference Publication: (var.pagings). 12 (7):A522-A3.
435. Alves M CF, Litalien G. . Cost-Effectiveness of Abatacept in Patients with Moderately to Severely Active Rheumatoid Arthritis and Inadequate Response to Methotrexate in Brazil. ISPOR Conference. 2008.
436. Brodszky V PM, Karpati K, Boncz I, Sebestyen A, Gulacsi L. . Cost-Utility Analysis of Rituximab Treatment in Rheumatoid Arthritis after Anti-TNF-Alpha Therapy in Hungary. ISPOR Conference. 2007.
437. F. C. Cost-Effectiveness of Rituximab Versus Alternative Anti-Tumor Necrosis Factor (TNF) Therapy After Previous Failure of One Anti-TNF Agent for Treatment of Rheumatoid Arthritis in Costa Rica. ISPOR Conference. 2010.
438. F. C. Cost-Effectiveness of Rituximab Versus Alternative Anti-Tumor Necrosis Factor (TNF) Therapy After Previous Failure of One Anti-TNF Agent for Treatment of Rheumatoid Arthritis in Mexico. ISPOR Conference. 2010.
439. F. C. Cost-Effectiveness of Tocilizumab for the Management of Patients with Active Rheumatoid Arthritis despite Previous DMARD Therapy in Costa Rica. ISPOR Conference. 2010.
440. F. C. Cost-Effectiveness of Tocilizumab for the Management of Patients with Active Rheumatoid Arthritis Despite Previous DMARD Therapy in Mexico. 2010.
441. Carter C TR. A Cost-efficacy Analysis of Anti-Tumor Necrosis Factor Therapy in the Treatment of Rheumatoid Arthritis using Radiologic Outcomes. Ann Rheum Dis. 2010;69(Supple3):532.
442. Creemers MC KW, Van Den Hoogen F, De Jong A, Van Riel P. . Cost-Effectiveness of Two TNF Inhibitors, Etanercept and INfliximab, in Patients with Rheumatoid Arthritis in Daily Clinical Practice in the Netherlands. Ann Rheum Dis. 2005;65(Suppl III):430.
443. Davies A. Cost Effectiveness of Five Biologics in the Treatment of Long-Standing Moderate to Severe Rheumatoid Arthritis. ACR Conference. 2006.
444. Deeg M ES, Runge C. . Cost-Effectiveness of Etanercept and Infliximab in the Real-World Setting - An estimate Based on Published German Data on Response and Adherence. ISPOR Conference. 2007.
445. Deeg M ES, Runge C. . Adalimumab, Etanercept or Infliximab: What is the Most Cost-Effective Anti-TNF-a Therapy in RA in a Real-World Setting? ISPOR Conference. 2008.
446. Diamantopoulos A WN, Giuliani G. . Value Health. [Conference Abstract]. 2009 October; Conference: ISPOR 12th Annual European Congress Paris France.

Conference Start: 20091024 Conference End: 20091027. Conference Publication: (var.pagings). 12 (7):A443.
447. Dolezal T PA, Pavelka K. . Value Health. [Conference Abstract]. 2009 October; Conference: ISPOR 12th Annual European Congress Paris France. Conference Start: 20091024 Conference End: 20091027. Conference Publication: (var.pagings). 12 (7):A441.
448. Fautrel B MM, Daures JP, Miadi-Fargier H, Le Pen C. . Cost-Effectiveness Simulation Model of Abatacept versus Anti-TNF Treatment Strategies in Rheumatoid Arthritis in France. ACR Conference. 2008.
449. Gandhi P SJ, Viraparia P, Kauf T. . A Cost-Effectiveness Analysis of Biological Agents for Patients with Moderate to Severe Rheumatoid Arthritis Following Inadequate Response to Methotrexate. ISPOR Conference. 2008.
450. Gao X HS, Carpiuc KT, Stephens JM, Sato R, Singh A. Value Health. [Conference Abstract]. 2009 May; Conference: ISPOR 14th Annual International Meeting Orlando, FL United States. Conference Start: 20090516 Conference End: 20090520. Conference Publication: (var.pagings). 12 (3):A67.
451. Gil-Hurle D CS. Cost-Efficacy Analysis of TNF Alpha Antagonists in the Treatment of Rheumatoid Arthritis. ISPOR Conference. 2010.
452. Giuliani G DVS, Diamantopoulos A, Brown B, Kielhorn A. . Modelling of the Cost-Effectiveness of Rituximab for Treatment of Rheumatoid Arthritis in Italy. ISPOR Conference. 2006.
453. Gossec L GP, Saraux A, Bregman B, Boccard E, Dupont D. Cost-Effectiveness Simulation Model of Abatacept Versus Rituximab in Rheumatoid Arthritis in France. ISPOR Conference. 2008.
454. Hallinen TA SE, Eklund K, Puolakka K. . Value Health. [Conference Abstract]. 2009 October; Conference: ISPOR 12th Annual European Congress Paris France. Conference Start: 20091024 Conference End: 20091027. Conference Publication: (var.pagings). 12 (7):A444.
455. Kielhorn A AC, Aristides M, Diamantopoulos A. . Using Mabthera in Patients with Rheumatic Arthritis in Spain: Results of Cost-Effectiveness Data Based on Micro-Simulation. ISPOR Conference. 2006.
456. Kobelt G. Cost-Effectiveness of Rituximab as Second-Line Biological Treatment Compared to Registry Data. 2008.
457. Lebmeier P, Drost P, Ouwens, Bergman G, Baig MS. . The Cost-Effectiveness of Abatacept in Combination with Methotrexate for the Treatment of Patient with Active Rheumatoid Arthritis after an Inadequate Response to Methotrexate in the United Kingdom. ISPOR Conference. 2010.
458. Lee EK PE, Sung Y, K., Park S, J., Kimm JJ, Bae HG. . Cost-Effectiveness Analysis of Treatment Options for Methotrexate-Resistant Rheumatoid Arthritis in Korea. ISPOR Conference. 2006.
459. Lekander I BF, Carli C, Svarvar P, Ljung L, Van Vollenhoven R. . A Cost Effectiveness Analysis of Infliximab Treatment in Patients with Rheumatoid Arthritis (RA) in Sweden, Based on Data from the STURE Registry. ISPOR Conference. 2008.
460. Lewis G KA, Diamantopoulos A. . Cost-Effectiveness of Rituximab (Mabthera) Compared with Abatacept (Orencia) for the Treatment of Moderate/Severe Rheumatoid Arthritis (RA) in the UK. ISPOR Conference. 2007.
461. Lin HY CD, Chen DY, Cheng A, Huang X, Lou SF. Cost-Effectiveness Analysis of Rituximab for Rheumatoid Arthritis in Taiwan. ISPOR Conference. 2008.
462. Malone D, Ortmeier B. Cost Effectiveness Analysis of Etanercept (ENBREL) Versus Infliximab (Remicade) in the treatment of Rheumatoid Arthritis Patients. Arthritis Rheum. 2002;46(Suppl):S95.
463. McNamara S, Papadakis K, Wintfeld N, Diamantopoulos A. An economic evaluation on the use of tocilizumab (Roactemra) with methotrexate in the treatment of adults with moderate to severe active rheumatoid arthritis who have

failed to respond adequately to an anti-TNF drug in Scotland. Ann Rheum Dis. 2010;69(Suppl3):1516-23.
464. Miadi-Fargier H FB, Maravic M, Daures JP, Ollivier AL, Le Pen C. Cost-Effectiveness of Using Etanercept as First Line in Severe and Highly Active Rheumatoid Arthritis (RA). ISPOR Conference. 2008.
465. Minda K HN, Parry D, Hines P, Yuan Y. . Cost-Utility of Abatacept, A New Biologic Treatment for Patients with Rheumatoid Arthritis who Failed Anti-TNF Therapy. ISPOR Conference. 2007.
466. Mistry B MJ, Diamantopoulos A, Kielhorn A. . Cost-Utility Analysis of Rituximab as a New Therapeutic Option for Rheumatoid Arthritis Patients in Canada. ISPOR Conference. 2007.
467. Nguyen C MM, Bounthavong M, Christopher M. . Cost-Utility Analysis of Tumor Necrosis Factor-Alpha inhibitors for the Treatment of Rheumatoid Arthritis using a Markov Model. ISPOR Conference. 2010.
468. Papadakis K MS, Wintfeld N, Diamantopoulos A. . A UK Cost-Effectiveness Analysis on the use of Tocilizumab (Roactemra) with Methotrexate in the Treatment of Adults with Moderate to Severe Active Rheumatoid Arthritis Who Have Failed to Respond Adequately to One or More DMARDs. Ann Rheum Dis. 2010;58(10):2968-80.
469. Plisko R KJ, Przemyslaw R, Russel-Szymczyk M. . Cost-Effectiveness of Rituximab (Mabthera) Compared with TNF Inhibitors For the Treatment of Rheumatoid Arthritis (RA) in Polan. ISPOR Conference. 2008.
470. Plisko R KJ, Lis J, Rys P. . Value Health. [Conference Abstract]. 2009 October; Conference: ISPOR 12th Annual European Congress Paris France. Conference Start: 20091024 Conference End: 20091027. Conference Publication: (var.pagings). 12 (7):A442.
471. Pompen M DA, Kievit J, Kielhorn A. . Economic Consequences of Providing Rituximab as a Treatment Alternative for Rheumatoid Arthritis in the Netherlands. ISPOR Conference. 2007.
472. Porter D LG, Brown B, Diamantopoulos A, Kielhorn A. . Cost-Effectiveness Analysis of Rituximab as a New therapeutic Option for Rheumatoid Arthritis in the UK. ISPOR Conference. 2007.
473. Purcaru O TP, Emery P, Palmer S. . Cost-Effectiveness of Certolizumab Pegol plus Methotrexate or as Monotherapy for the Treatment of Active Rheumatoid Arthritis in the United Kingdom. ISPOR Conference. 2010.
474. Puolakka K BH, Kauppi M, Luosujarvi R, Peltomaa R, Leikola-Pelho T. Scand J Rheumatol. [Conference Abstract]. Conference: 33rd Scandinavian Congress of Rheumatology, SCR 2010 Bergen Norway. Conference Start: 20100509 Conference End: 20100512. Conference Publication: (var.pagings). 39:34.
475. Rubbert A KA, Schach S, Brown B, Aristides M. . Cost-Effectiveness of Rituximab as a New Treatment Modality for Rheumatoid Arthritis in Germany. ISPOR Conference. 2007.
476. Saggia MG, Pina F. Cost-Effectiveness Analysis of Etnaercept vs Infliximab for Treatment of Severe Rheumatoid Arthritis in Brazil. ISPOR Conference. 2007.
477. Saraux A GP, Gossec L, Bregman B, Boccard E, Dupont D. Cost-Effectiveness Simulation Model of Abatacept versus Anti-TNF Treatment Strategies in Rheumatoid Arthritis in France. ACR Conference. 2008.
478. Schach S RA, Kielhorn A. . Cost-Benefit Comparison of Biologic DMARDs Using a Non-Modelling Approach. Ann Rheum Dis 2007. 2007;66(Suppl II):437.
479. Soini EJ HT, Taihi M, Honkanen V. . Cost-Effectiveness, Value of Information and Budget Impact of Certolizumab Pegol Compared to Subcutaneous Tumor Necrosis Factor (TNF) Inhibitors and Methotrexate in the treatment of Moderate-to-Severe rheumatoid Arthritis in Finland. ISPOR Conference. 2010.
480. Soini EJ KM, Vihervaara V, Puolakka K. . Cost-Utility and Multinomial Expected Value of Perfect Information of Sequenced Treatment with Biologics in Moderate-

to-Severe Rheumatoid Arthritis: Analysis Based on Clinically Meaningful Responses. ISPOR Conference. 2010.
481. Sole JP OG, Kielhorn A. . Cost-Benefit of Rituximab for Rheumatoid Arthritis Patients in Argentina. ISPOR Conference. 2007.
482. Taylor M TP, Conway P, Pearce DJ, Reynolds A. . Economic Benefits of Etanercept for Achieving Clinical and Radiographic Remission in Patients with Rheumatoid Arthritis: An Analysis using TEMPO Data. Ann Rheum Dis. 2006;65(Suppl II):505.
483. Taylor M TP, Reynolds A, Conway P. . Costs and Benefits of Etanercept Followed by Rituximab at Different Stages of the Treatment Sequence in Patients with Rheumatoid Arthritis. BSR Conference. 2007.
484. Taylor M TP, Reynolds A, Conway P. . Economic Benefits of Etanercept Following Anti-TNF Treatment in Patients with Rheumatoid Arthritis: An Analysis using TEMPO data. BSR Conference. 2007.
485. Taylor M CP, Lebmeier M, Ganderton M. . The Cost-Effectiveness of Sequential Use of Anti-Tumor Necrosis Factor Agents in the Treatment of Rheumatoid Arthritis. ISPOR Conference. 2008.
486. Vorobyev P LM, Avksentyeva M, Alekseyeva Y, Karateyev D. . Economical Evaluation of Adalimumab in Patients with Rheumatoid Arthritis. ISPOR Conference. 2010.
487. Woods B JJ, Morris J, Punekar Y, Davies A, Hawkins N. . Cost-effectiveness of biological therapy in the UK for the treatment of Rheumatoid Arthritis following exposure to a previous Tumour Necrosis Factor Alpha inhibitor: a patient level simulation model. Ann Rheum Dis. 2010;69(Suppl3):203.
488. Yuan Y WZ, Kim M. . Modeling Cost-Effectiveness of Abatacept versus Infliximab in Patients with Rheumatoid Arthritis (RA) in the US. ACR Conference. 2007.
489. Yunger S MB. Value Health. [Conference Abstract]. 2009 May; Conference: ISPOR 14th Annual International Meeting Orlando, FL United States. Conference Start: 20090516 Conference End: 20090520. Conference Publication: (var.pagings). 12 (3):A70.
490. Zapata L MG, Mucino E, Rivas R. . Cost-Effectiveness of the Treatment for Early Rheumatoid Arthritis in Mexico: Infliximab vs Adalimumab. ISPOR Conference. 2008.
491. Zou D DO, Tsao N, Goeree R. . Canadian Cost-Effectiveness Analysis of Abatacept (Orencia) for the Management of Moderately to Severely Active Rheumatoid Arthritis in Patients with Inadequate Response to Methotrexate. ISPOR Conference. 2010.
492. Adams RC WC, Schmitz S, Barton P, Barry M. . A cost utility analysis of anti-TNF agents for the treatment of rheumatoid arthritis. Value in Health. 2011 November;Conference: ISPOR 14th Annual European Congress Madrid Spain. Conference Start: 20111105 Conference End: 20111108. Conference Publication: (var.pagings). 14 (7):A311-A2.
493. Alfonso-Cristancho AR AE, Roa CN. . Cost-effectiveness of abatacept or infliximab in rheumatoidarthritis in colombi. Value in Health. 2011 May;Conference: 16th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2011 Baltimore, MD United States. Conference Start: 20110521 Conference End: 20110525. Conference Publication: (var.pagings). 14 (3):A127.
494. Alfonso-Cristancho R AE, Roa CN, Valencia JE. . What is the value of the new kid on the block?: Tocilizumab versus abatacept for rheumatoid arthritis in Colombia. Value in Health. 2011 November;Conference: ISPOR 3rd Latin America Conference Mexico City Mexico. Conference Start: 20110908 Conference End: 20110910. Conference Publication: (var.pagings). 14 (7):A563.
495. Alfonso-Cristancho R SN, Aiello EC, Roa CN. . Abatacept or infliximab for rheumatoid arthritis in venezuela? Acost-effectiveness analysis. Value in Health.

2011 May; Conference: 16th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2011 Baltimore, MD United States. Conference Start: 20110521 Conference End: 20110525. Conference Publication: (var.pagings). 14 (3):A126-A7.
496. Becerra Rojas F BCC, Aiello EC, Zingoni C, Bergman G, Drost P. Cost effectiveness of abatacept in comparison with other biologictherapies for the treatment of moderate to severe activerheumatoid arthritis patients who have failed to methotrexatebased treatment at essalud in 2010. Value in Health. 2011 May;Conference: 16th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2011 Baltimore, MD United States. Conference Start: 20110521 Conference End: 20110525. Conference Publication: (var.pagings). 14 (3):A129.
497. Benedict A KT, Shaw JW, Marcellusi A, Vanness DJ, Gitto L. Economic evaluation of adalimumab for the treatment of early and late-stage rheumatoid arthritis in Italy. Value in Health. 2012;15(Supplement 7):A447; ISPOR EU abstract PMS46.
498. Benucci M SW, Gilloteau I, Crocchiolo D, Sennfalt K, Leclerc A. Abatacept or infliximab for patients with rheumatoid arthritis and inadequate response to methotrexate: A trial-based and reallife cost-consequence analysis. Value in Health. 2011 November;Conference: ISPOR 14th Annual European Congress Madrid Spain. Conference Start: 20111105 Conference End: 20111108. Conference Publication: (var.pagings). 14 (7):A307.
499. Bynum LA JN. Cost-effectiveness of Rituximab vs Adalimumab in the treatment of moderate to severe rheumatoid arthritis. Value in Health. 2010 May;Conference: 15th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2010 Atlanta, GA United States. Conference Start: 20100515 Conference End: 20100519. Conference Publication: (var.pagings). 13 (3 SUPPL. 3):A126.
500. Carlos F CP. Economic evaluation of rituximab versus alternative anti-tumor necrosis factor (TNF) therapy after failure of anti-TNF for treatment of rheumatoid arthritis in Mexico. Arthritis and Rheumatism. 2010;Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP 10 Philadelphia, PA United States. Conference Start: 20091016 Conference End: 20091021. Conference Publication: (var.pagings). 62:767.
501. Chen HF LH, Lang HC. . Cost-effectiveness of biological treatments in patients with rheumatoid arthritis in Taiwan. Value in Health. 2012;15(Supplement 7):A673; ISPOR Asia-Pacific abstract PMS13.
502. Desai RJ RJ, Biddle AK. . Cost-effectiveness analysis of golimumab for the treatment of rheumatoid arthritis. Value in Health. 2012 June;Conference: 17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2012 Washington, DC United States. Conference Start: 20120602 Conference End: 20120606. Conference Publication: (var.pagings). 15 (4):A39.
503. Diamantopoulos A AS, Bernardo A, Branco J, Ines L, Pereira Da Silva JA. Cost-effectiveness of tocilizumab compared to standard therapeutic sequences for the treatment of moderate/severe rheumatoid arthritis (RA) patients in Portugal. Value in Health. 2011 November;Conference: ISPOR 14th Annual European Congress Madrid Spain. Conference Start: 20111105 Conference End: 20111108. Conference Publication: (var.pagings). 14 (7):A307.
504. Diamantopoulos A KW, De Vries R, Pompen M. . Cost-effectiveness of Rituximab in the treatment of RA patients in the Netherlands. Value in Health. 2011 November;Conference: ISPOR 14th Annual European Congress Madrid Spain. Conference Start: 20111105 Conference End: 20111108. Conference Publication: (var.pagings). 14 (7):A311; PMS49.

505. I. E. Cost-effectiveness of tocilizumab for the treatment of active rheumatoid arthritis (RA) patients with inadequate response to anti-TNF treatment in Turkey. Value in Health. 2012;15(Supplement 7):A445; ISPOR EU abstract PMS35.
506. Fernandes RA BV, Mould JF. . Economic analysis of etanercept in rheumatoid arthritis from a public perspective in Venezuela. Value in Health. 2011 November;Conference: ISPOR 14th Annual European Congress Madrid Spain. Conference Start: 20111105 Conference End: 20111108. Conference Publication: (var.pagings). 14 (7):A308.
507. Fernandes RA TD, Mould JF. . Economic analysis of etanercept in rheumatoid arthritis from a public perspective in Colombia. Value in Health. 2011 November;Conference: ISPOR 14th Annual European Congress Madrid Spain. Conference Start: 20111105 Conference End: 20111108. Conference Publication: (var.pagings). 14 (7):A308-A9.
508. Fernandes RA TM, Tolentino ACM, Takemoto MMS, Santos PML, Mould JF. . Economic evaluation of etanercept in rheumatoid arthritis from the public payer perspective in Brazil. Value in Health. 2011 November;Conference: ISPOR 14th Annual European Congress Madrid Spain. Conference Start: 20111105 Conference End: 20111108. Conference Publication: (var.pagings). 14 (7):A309.
509. Gibbons C DA, Pang H, Huertas C, Dejonckheere F. . Tocilizumab in methotrexate-intolerant or contraindicated patients - a cost-utility model for Scotland. Annals of the Rheumatic Diseases. 2012;71(Supplement 3):454; EULAR abstract FRI0414.
510. Guijarro P CC, Brosa M. . Cost-effectiveness analysis of etanercept and infliximab in the treatment of rheumatoid arthritis (RA) in Spain. Value in Health. 2012;15(Supplement 7):A448; ISPOR EU abstract PMS49.
511. Jalal H MK, Choi HK, Rho YH, Kuntz K. . Are biologics cost-effective? Analysis based on real-life rheumatoid arthritis patients. Arthritis and Rheumatism. Conference: Annual Scientific Meeting of the American College of Rheumatology and Association of Rheumatology Health Professionals. 2011;63(10 SUPPL. 1).
512. Krieckaert CLM NS, Nurmohamed MT, Van Dongen CJ, Lems WF, Lafeber FPJG. Evaluating the cost-effectiveness of personalized treatment with adalimumab using serum drug levels in rheumatoid arthritis patients. ACR conference. 2012:abstract number 1832.
513. Launois R LMJ, Huynh TMT. . Mixed treatment comparison, cost-effectiveness analysis and budget impact model in the treatment of rheumatoid arthritis after failure of conventional DMARD therapy using comprehensive bayesian decision analytical modelling. Value in Health. 2012 June;Conference: 17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2012 Washington, DC United States. Conference Start: 20120602 Conference End: 20120606. Conference Publication: (var.pagings). 15 (4):A50.
514. Lechuga D AM. Cost minimization analysis with rituximab in the management of Rheumatoid Arthritis (RA) from the mexican public perspective. Value in Health. 2012 June;Conference: 17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2012 Washington, DC United States. Conference Start: 20120602 Conference End: 20120606. Conference Publication: (var.pagings). 15 (4):A40.
515. Lutz M CG, Morales G. . Cost-effectiveness analysis of etanercept versus available antitnf and IL-6 blockers for treating rheumatoid arthritis in Guatemala. Value in Health. 2011 November;Conference: ISPOR 3rd Latin America Conference Mexico City Mexico. Conference Start: 20110908 Conference End: 20110910. Conference Publication: (var.pagings). 14 (7):A562-A3.
516. Maniadakis N BD, Kourlaba G, Christou P, Anargiros I, Smets E. Cost-utility and budget impact analysis of certolizumab pegol plus methotrexate for the treatment of moderate-to-severe active rheumatoid arthritis in Greece. Value in Health.

2011 November;Conference: ISPOR 14th Annual European Congress Madrid Spain. Conference Start: 20111105 Conference End: 20111108. Conference Publication: (var.pagings). 14 (7):A310.
517. McNamara S PK, Wintfeld N, Diamantopoulos A. . An economic evaluation on the use of tocilizumab (RoActemra®) with methotrexate in the treatment of adults with moderate to severe active rheumatoid arthritis who have failed to respond adequately to an anti-TNF drug in Scotland. Annals of the Rheumatic Diseases. 2010;69(Supplement 3):389; EULAR abstract FRI0220.
518. Monteiro I CA, Encarnacao R, Diamantopoulos A, Dejonckheere F. . Cost-utility of tocilizumab monotherapy in methotrexate intolerant/contra-indicated, moderate/severe rheumatoid arthritis patients in Portugal. Value in Health. 2012;15(Supplement 7):A447; ISPOR EU abstract PMS42.
519. F. NS. Pharmacoeconomic evaluation of tocilizumab monotherapy vs. adalimumab monotherapy in reducing disease activity in patients with rheumatoid arthritis. ACR conference. 2012:abstract number: 2173.
520. Papadakis K MS, Wintfeld N, Diamantopoulos AA. . A UK cost-effectiveness analysis on the use of tocilizumab (Roactemra®) with methotrexate in the treatment of adults with moderate to severe active rheumatoid arthritis who have failed to respond adequately to one or more DMARDs. Annals of the Rheumatic Diseases. 2010;69(Supplement 3):389; EULAR abstract FRI0219.
521. Pericleous L LM. Cost-effectiveness of abatacept for the treatment of rheumatoid arthritis (RA) after the failure of a first tnf inhibitor in the United Kingdom. Value in Health. 2011 November;Conference: ISPOR 14th Annual European Congress Madrid Spain. Conference Start: 20111105 Conference End: 20111108. Conference Publication: (var.pagings). 14 (7):A307-A8.
522. Piha T ME, Kuriki W, Miranda PA. . Cost-effectiveness analysis of certolizumab pegol in patients with rheumatoid arthritis from a Brazilian private perspective. Value in Health. 2012;15(Supplement 7):A446; ISPOR EU abstract PMS39.
523. Quartuccio L MP, Corazza L, Fabro C, Benucci M, Pellerito R. Clinical and pharmacogenetic characterization to predict cost-effectiveness of rituximab (RTX) therapy in rheumatoid arthritis (RA). Annals of the Rheumatic Diseases. 2011;70(Supplement 3):423; EULAR abstract FRI0239.
524. Quartuccio L SF, Biasi D, Carraro V, Ravagnani V, Dal Forno I. 12 month-retrospective analysis of two different rituximab retreatment regimens in rheumatoid arthritis: retreatment at clinical relapse vs 6th month fixed retreatment. Arthritis Rheum. 2011;63(10Supplement):S868; ACR abstract 2221.
525. Quintana G RJ, Caceres HA, Rueda JD, Rosselli D. . Economic evaluation of the treatment of rheumatoid arthritiswith anti-tnf biological therapies in colombia. Value in Health. 2011 May;Conference: 16th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2011 Baltimore, MD United States. Conference Start: 20110521 Conference End: 20110525. Conference Publication: (var.pagings). 14 (3):A129.
526. Ramirez de Arellano A GLJ, Ariza R, López-Belmonte Claver JL, Beresniak A. . Cost-effectiveness model of abatacept for management of moderate to severe rheumatoid arthritis in Spain. Annals of the Rheumatic Diseases. 2011;70(Supplement 3):459; EULAR abstract FRI0344.
527. Salazar JC CJ, Santos-Moreno P, Casas N, Rondon F, Fernandez F. Cost-utility and cost-benefit of biological treatments for rheumatoid arthritis in Colombia. Annals of the Rheumatic Diseases. 2011;70(Supplement 3):203; EULAR abstract THU0070.
528. Soini EJO HT, Kauppi MJ, Vihervaara V, Puolakka K. . Comprehensive Health economic Assessment of sequenced treatment with biologics in moderate-to-severe rheumatoid arthritis: Analysis based on ACR50 and ACR70 responses. Arthritis and Rheumatism. 2010; Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual

Scientific Meeting, ACR/ARHP 10 Philadelphia, PA United States. Conference Start: 20091016 Conference End: 20091021. Conference Publication: (var.pagings). 62:759.
529. Takemoto M FR, Fujii RK, Mould J, Tang B. . Etanercept in early rheumatoid arthritis: economoic evaluation from the public payer perspective in Brazil. Value in Health. 2012;15(Supplement 7):A512; ISPOR EU abstract PSY25.
530. Tanaka E IE, Hoshi D, Kobayashi A, Sugimoto N, Shidara K. Evaluation of the cost-effectiveness of rheumatoid arthritis treatment with biologic agents using the IORRA cohort database. ACR conference. 2012:abstract number: 1831.
531. Taylor M RC, Conway P, Lebmeier M. . Economic evaluation of therapeutic approaches for rheumatoid arthritis: The case for sequential anti-TNF use. Rheumatology. 2009 April;Conference: British Society for Rheumatology and British Health Professionals in Rheumatology Annual Meetings 2009, Rheumatology'09 Glasgow United Kingdom. Conference Start: 20090428 Conference End: 20090501. Conference Publication: (var.pagings). 48:i112.
532. Turesson C TA, Bengtsson A, Sennfalt K, Dupont D, Beresniak A. . Sequential pharmacoeconomic model of biologic strategies for rheumatoid arthritis in sweden based on disease activity. Arthritis and Rheumatism. 2009;Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP 09 Atlanta, GA United States. Conference Start: 20101106 Conference End: 20101111. Conference Publication: (var.pagings). 60:1003.
533. Van den Hout W KN, Dirven L, Kerstens P, Huizinga T, Lems W. Long-term cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis - 5 year follow-up data from the BEST study. Annals of the Rheumatic Diseases. 2012;71(Supplement 3):363; EULAR abstract FRI0155.
534. Vargas-Valencia J S-GM, Mould-Quevedo JF, Mucino-Ortega E, Galindo-Suarez RM. . Cost-effectiveness analysis of etanercept in the treatment of rheumatoid arthritis in Mexico. Value in Health. 2011 May;Conference: 16th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2011 Baltimore, MD United States. Conference Start: 20110521 Conference End: 20110525. Conference Publication: (var.pagings). 14 (3):A127.
535. Vermeer M KW, Kuper I, Braakman-Jansen A, Bernelot Moens H, Zijlstra T. Cost-effectiveness and cost-utility analysis of treat-to-target versus usual care in early rheumatoid arthritis: results of the DREAM registry. Annals of the Rheumatic Diseases. 2012;71(Supplement 3):92; EULAR abstract OP0116.
536. Woods B JJ, Morris J, Punekar Y, Davies A, Hawkins N. . Cost-effectiveness of biological therapy in the UK for the treatment of rheumatoid arthritis following exposure to a previous tumour necrosis factor alpha inhibitor: a patient level simulation model. Annals of the Rheumatic Diseases. 2010;69(Supplement 3):203; EULAR abstract THU0174.
537. Zhang Y YL, Dong P, Xie X, Tang B. . Cost-effectiveness analysis of etanercept in the treatment of rheumatoid arthritis in China. Value in Health. 2012;15(Supplement 7):A673; ISPOR Asia-Pacific abstract PMS14.
538. Ahmadiani S, Nikfar S, Karimi S, Jamshidi AR, Akbari-Sari A, Kebriaeezadeh A. Rituximabas first choice for patients with refractory rheumatoid arthritis: Cost-effectiveness analysis in Iran based on a systematic review and meta-analysis. Value in Health. 2014;17 (7):A382.
539. Ahmadiani S, Nikfar S, Karimi S, Jamshidi AR, Kebriaeezadeh A, Akbari-Sari A. Rituximab as first choice for patients with refractory rheumatoid arthritis: A systematic review and cost-effectiveness analysis. Value in Health. 2014;17 (3):A47.

540. Albuja MF, Torres FG, Mould J, Estevez C. Cost-effectiveness analysis of etanercept in the treatment of rheumatoid arthritis in institutional market in Ecuador. Value in Health. 2013;16 (7):A717.
541. Almeida R, AlcivarAlcivar I, Cabezas M, Fornasini M, Albert A. Cost-effectiveness of biologic therapies for rheumatoid arthritis in a large public hospital in Ecuador. Value in Health. 2016;19 (3):A233.
542. Ariza R, Van Walsem A, Canal C, Roldan C, Betegon L, Oyaguez I, et al. Cost-minimization analysis of subcutaneous abatacept in the treatment of rheumatoid arthritis in Spain. [Spanish]. Farmacia Hospitalaria. 2014;38(4):257-65.
543. Athanasakis K, Konstantopoulou T, Tarantilis F, Tsalapati K, Vritzali E, Kyriopoulos J. Cost-utility analysis of tocilizumab in combination with methotrexate versus standard of care for the treatment of rheumatoid arthritis in Greece. Value in Health. 2013;16 (7):A565.
544. Bansback N, Phibbs C, Sun H, O'Dell JR, Brophy M, Keystone EC, et al. Cost-effectiveness of adding etanercept vs. Sulfasalazine and hydroxychloroquine to methotrexate therapy: A randomized noninferiority trial. Arthritis and Rheumatology. 2014;66:S1214-S5.
545. Bektur C, Kayir F, Nurgozhin T. Cost-Effectiveness Analysis of Tocilizumab Verse Infliximab for the Patients With Rheumatoid Arthritis in Kazakhstan. Value in Health. 2014;17(7):A379.
546. Benito Ruiz P, Navarro Sarabia F, Gomez Reino J, Poveda J, Alvaro Gracia J, Rubio-Rodriguez D, et al. Cost-utility of rheumatoid arthritis monotherapy with tocilizumab in Spain. Value in Health. 2013;16 (7):A565.
547. Bonafede MM, Johnson BH, Princic N, Shah N, Harrison DJ. Cost-effectiveness of RA biologics in the two years following initiation using a validated claims-based algorithm in a united states commercially insured population. Value in Health. 2014;17 (3):A46-A7.
548. Buschinelli CT. Analysing costs per clinical remission of tocilizumab monotherapy versus adalimumab monotherapy in rheumatoid arthritis from a public perspective in Brazil. Value in Health. 2013;16(7):A716.
549. Buschinelli CT, Tsuchiya CT, Maximo MFM, Tobaruella FS, Goncalves TM. Comparing costs per clinical remission of tocilizumab monotherapy versus adalimumab monotherapy in patients with rheumatoid arthritis: A Brazilian private perspective. Value in Health. 2013;16 (7):A716.
550. Cardenas M, De La Fuente S, Font-Ugalde P, Castro-Villegas MC, Romero-Gomez M, Ruiz-Vilchez D, et al. Long-term cost-effectiveness analysis of the treatment with infliximab, etanercept and adalimumab in rheumatoid arthritis patients in real-life clinical practice. Annals of the Rheumatic Diseases. 2015;74:703.
551. Carlson J. Cost-Effectiveness of Tocilizumab Monotherapy Versus Adalimumab Monotherapy in the Treatment of Severe Active RA. Value in Health. 2012;15:A277-A575.
552. Chang S, Sawyer L, Dejonckheere F, Grichova L, Diamantopoulos A. Tocilizumab in methotrexate-naive rheumatoid arthritis-a cost-utility model for Slovakia. Value in Health. 2015;18 (7):A648.
553. Claxton L, Taylor M, Moynagh D, Gruben D, Wallenstein G, Singh A. Modelling the costs and outcomes associated with sequence of treatment with and without tofacitinib for the treatment of moderate to severe rheumatoid arthritis in the us. Annals of the Rheumatic Diseases. 2015;74:319-20.
554. Codreanu C, Mogosanu C, Joita M, Purcaru O. Cost-effectiveness of certolizumab pegol in the treatment of active rheumatoid arthritis, axial spondyloarthritis, and psoriatic arthritis in Romania. Value in Health. 2014;17 (7):A379.

555. Elgart JF, Gonzalez L, Aiello EC. Abatacept for the treatment of patients with rheumatoid arthritis in argentina: A cost-effectiveness analysis. Value in Health. 2013;16 (3):A223-A4.
556. Elgart JF, Gonzalez L, Aiello EC. Cost-effectiveness of abatacept for the treatment of patients with rheumatoid arthritis after an inadequate response to methotrexate in chile. Value in Health. 2013;16 (3):A223.
557. Fagnani F, Pham T, Claudepierre P, Berenbaum F, De Chalus T, Saadoun C, et al. Cost-effectiveness modelling of a 3-month tight control patient management of rheumatoid arthritis with certolizumab pegol in France. Value in Health. 2013;16 (7):A562.
558. Ferreira CN, Rufino CS, Amaral LM, Fernandes RA. Economic analysis of biologic alternatives in the management of rheumatoid arthritis, psoriasis and ankylosing spondylitis from public and private perspectives in Brazil. Value in Health. 2015;18 (3):A162.
559. Ferreira CN, Rufino CS, Santana CF, Dulcine M. Assessment of tofacitinib for rheumatoid arthritis from the perspective of the Brazilian healthcare system. Value in Health. 2015;18 (7):A646.
560. Fuchs PA, Lal L, Fuchs HA, Swint J. Cost-effectiveness and cost-utility analyses comparing strategies for initial treatment of rheumatoid arthritis using published outcomes: Economic lessons from the tear trial. Value in Health. 2015;18 (7):A671.
561. Gamboa O, Barbosa D, Parada L, Latorre M. Cost-effectiveness analysis of tocilizumab in rheumatoid arthritis, in Colombia. Value in Health. 2013;16 (7):A563.
562. Garita M, Peralta M, Munoz-Louis R. Cost-effectiveness analysis of etanercept versus other available. Value in Health. 2014;17 (3):A47.
563. Gissel C. Cost-effectiveness of adalimumab for rheumatoid arthritis in Germany. Value in Health. 2014;17 (3):A48.
564. Han X, Hay JW. Cost-effectiveness analysis of certolizumab, etanercept, golimumab and tofacitinib for the treatment of moderately to severely active rheumatoid arthritis. Value in Health. 2015;18 (3):A162.
565. Hansen RN, Best JH, Sullivan SD, Carlson JJ. Cost-effectiveness of tocilizumab for the management of inadequately responding rheumatoid arthritis patients. Value in Health. 2015;18 (3):A161.
566. Kowalik K, Krysinski J, Bialecka U, Kolossa K, Jeka S. Pharmacoeconomic evaluation of rheumatoid arthritis treatment with selected biological drugs. [Polish]. Reumatologia. 2012;50(6):472-7.
567. Li J, Wen Z, Tian F, Zhang L, Luo Y, Deng L, et al. Real-world health outcomes, economic impacts, and cost effectiveness associated with infliximab for rheumatoid arthritis in a medium-sized city of China. Value in Health. 2016;19 (3):A235.
568. Lutz MA. Cost-effectiveness analysis of etanercept versus available anti-TNF and IL-6 blockers for treating rheumatoid arthritis in Costa Rica. Value in Health. 2013;16(3).
569. Lutz MA. Cost-effectiveness analysis of etanercept versus available anti-TNF and IL-6 blockers for treating rheumatoid arthritis in El Salvador. Value in Health. 2013;16(3).
570. Lutz MA, Alonzo H, Bogantes JP, Cuesta G. Cost-effectiveness analysis of etanercept versus available anti-TNF and IL-6 blockers for treating rheumatoid arthritis in honduras. Value in Health. 2013;16 (3):A224.
571. Marino J, Diamantopoulos A, Duong M, Boam JM. Tocilizumab monotherapy in patients where methotrexate is considered inappropriate: A Canadian cost-utility analysis. Value in Health. 2016;19 (3):A235.
572. Mateus C, Moura A. Cost-effectiveness analysis of etanercept in the treatment of rheumatoid arthritis in Portugal. Value in Health. 2014;17 (7):A380-A1.

573. Navarro Sarabia F, Blanco FJ, Alvaro Gracia JM, Garcia Meijide JA, Poveda JL, Rubio-Rodriguez D, et al. [Economic evaluation of rheumathoid arthritis monotherapy with tocilizumab and adalimumab]. Revista Espanola de Salud Publica. 2013;87(4):343-50.
574. Ngo P, Sorathia R, Todd C, Jones G, Nash P. Australian economic evaluation of tocilizumab (TCZ) monotherapy vs. adalimumab (ADA) monotherapy in patients with rheumatoid arthritis (RA) based on the ADACTA trial. Internal Medicine Journal. 2013;43:12.
575. Pichardo-Pina CA, Sanchez-Casillas JL, Pozos-Espindola JC. Cost-minimization analyses of adalimumab compared with selective immunosuppressive cytokines blockers and inhibitors of tumor necrosis factor alpha indicated for the treatment of rheumatoid arthritis, psoriasis and Crohn's disease in the private market in Mexico. Value in Health. 2015;18 (7):A843.
576. Rantalaiho V, Martikainen J, Kautiainen H, Puolakka K, Leirisalo-Repo M. Initial infliximab is not cost-effective added on to a remission-targeted combination therapy in early rheumatoid arthritis: The 2-year results of the randomized clinical NEO-RACo trial. Scandinavian Journal of Rheumatology. 2014;43:1.
577. Rantalaiho V, Martikainen J, Kautiainen H, Puolakka K, Leirisalo-Repo M. Initial infliximab is not cost-effective in otherwise actively treated early rheumatoid arthritis. The 2-year follow-up results of the randomized clinical NEO-RACo trial. Annals of the Rheumatic Diseases. Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR. 2014;73(no pagination).
578. Rantalaiho V, Puolakka K, Martikainen J, Kautiainen H, Leirisalo-Repo M. Adding an initial six-month course of infliximab to an active combination treatment is cost saving in working-aged early rheumatoid arthritis patients. Arthritis and Rheumatology. 2014;66:S1083-S4.
579. Ravera S, Batticciotto A, Riva M, Donati C, Sarzi-Puttini P. Economic evaluation of tocilizumab monotherapy vs adalimumab monotherapy in patients with rheumatoid arthritis in Italy. Value in Health. 2015;18 (7):A640.
580. Ryazhenov VV, Emchenko IV. Cost-effectiveness analysis of biological disease-modifying antirheumatic drugs in the treatment of Russian patients with rheumatoid arthritis who failed previous anti-TNF-alfa therapy. Value in Health. 2013;16 (7):A562-A3.
581. Ryazhenov VV, Gorokhova SG, Maximkin SA. Pharmacoeconomic evaluation of biologic therapies in Russian patients with rheumatoid arthritis and intolerance or inadequate response to conventional basic Therap. Value in Health. 2014;17 (7):A375.
582. Ryazhenov VV, Gorokhova SG. Pharmacoeconomic analysis of different strategies of monotherapy with biologic therapies in Russian patients with rheumatoid arthritis. Value in Health. 2015;18 (7):A645.
583. Salinas-Escudero G, Vargas-Valencia J, Garcia-Garcia EG, Muncino-Ortega E, Galindo-Suarez RM. [Cost-effectiveness analysis of etanercept compared with other biologic therapies in the treatment of rheumatoid arthritis]. [Spanish]. Revista medica del Instituto Mexicano del Seguro Social. 2013;51(5):514-21.
584. Sanchez R, Restovic G, Planellas L. Biological agents for patients with rheumatoid arthritis who had failed treatment with methotrexate in the Spanish clinical setting: A cost-effectiveness analysis. Value in Health. 2015;18 (7):A645-A6.
585. Scaccabarozzi L. Cost-minimization analysis of anti-TNF biologics in the treatment of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis under the Brazilian public health care system (SUS) perspective. Value in Health. 2014;17 (3):A229.
586. Scaccabarozzi L. Cost-minimization analysis of anti-TNF biologics in the treatment of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis

under the Brazilian private health care system perspective. Value in Health. 2014;17(3):A229.
587. Scaccabarozzi L, Asano E, Monteiro AC. Cost-minimization analyses of biological therapies in the treatment of rheumatoid arthritis under the Brazilian public health system perspective. Value in Health. 2016;19 (3):A234-A5.
588. Scaccabarozzi L, Asano E, Monteiro AC. Cost-minimization analysis of biological drugs in the treatment of rheumatoid arthritis under the Brazilian private health system perspective. Value in Health. 2016;19 (3):A234.
589. Schabert VF. Long-Term Effectiveness and Cost Per Effectively Treated Patient With Biologics Used In Rheumatoid Arthritis. 2013 ACR/ARHP Annual Meeting Conference Abstract.
590. Soini EJ, Hallinen T, Vihervaara V, Kauppi MJ. Cost-utility of first-line adalimumab and tocilizumab monotherapies in rheumatoid arthritis based on head-to-head data. Value in Health. 2013;16 (7):A566.
591. Tanaka E, Inoue E, Hoshi D, Nakajima A, Momohara S, Taniguchi A, et al. Pharmaeconomic analysis of biological agents in rheumatoid arthritis based on analysis of prospective observational cohort data in Japan. [Japanese]. Japanese Pharmacology and Therapeutics. 2013;41(4):347-62.
592. Tanaka E, Inoue E, Hoshi D, Shidara K, Sato E, Inoue Y, et al. Optimal timing for tocilizumab administration to patients with rheumatoid arthritis in Japan based on a cost-effectiveness analysis using the IORRA cohort study. Annals of the Rheumatic Diseases. Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR. 2013;72(no pagination).
593. Tangwongsiri D, Leartsakulpanitch J. Cost utility analysis of infliximab for the treatment of severe rheumatoid arthritis in Thailand. Value in Health. 2014;17 (7):A774.
594. Trueman D, Bird A, Mumby-Croft J. The cost-effectiveness of alternative treatment sequences in rheumatoid arthritis. Value in Health. 2014;17 (3):A48.
595. Tzanetakos C, Maniadakis N, Kourlaba G, Tzioufas A, Goules A, Theodoratou T, et al. Cost-utility analysis of certolizumab pegol plus methotrexate for the treatment of moderate-to-severe active rheumatoid arthritis in Greece. Value in Health. 2014;17 (7):A382.
596. Vanier A, Tubach F, Alfaiate T, Mariette X, Fautrel B. Step-down strategy of spacing TNF-blockers injections for established rheumatoid arthritis in remission: A cost-utility analysis based on the strass trial. Annals of the Rheumatic Diseases. 2015;74:178.
597. Velasquez ZM, Bustos Medina L, De la Puente AC, Zaror SC, Gutierrez-Ardila MV. Economic evaluation of tofacitinib as initial medication in adults with rheumatoid arthritis after failure to methotrexate in Chile. Value in Health. 2015;18 (3):A161.
598. Wolff M, Zhou ZY, Signorovitch J, Shaw JW, Ganguli A. Cost-effectiveness of different treatment sequences including adalimumab in the treat-to-target framework for early rheumatoid arthritis in Germany. Arthritis and Rheumatism. 2013;65:S753.
599. Woolcott JC, Blackhouse G, Claxton L, Wallenstein G, Tran T, Goeree R, et al. The economic value of tofacitinib 5 mg bid in the treatment of moderate to severe rheumatoid arthritis: A Canadian analysis. Annals of the Rheumatic Diseases. 2015;74:785.
600. Athanasakis K, Tarantilis F, Skroumpelos A, Kyriopoulos J. Cost-effectiveness analysis of tocilizumab subcuta neouscombotherapy first line for the management of rheumatoid arthritis in Greece. Value in Health. 2016;19 (7):A538.
601. Bonafede M. Claims-based analysis of cost-effectiveness among patients with rheumatoid arthritis who switched from a tumor necrosis factor inhibitor to another targeted disease-modifying antirheumatic drug. Abstract: ACR 2016. 2016.

602. Huoponen S, Aaltonen KJ, Joensuu JT, Rutanen J, Relas H, Taimen K, et al. A cost-effectiveness analysis of abatacept, tocilizumab, and TNF-inhibitor compared with rituximab as a second-line therapy for treatment of rheumat oid arthritis. Value in Health. 2016;19 (7):A538.
603. Li C, Chou P, Chang C, Fann CS. The comparisons of biologics with methotrexate for treating rheumatoid arthritis patients in Taiwan: The use of cost-utility analysis and budget impact analysis. Value in Health. 2016;19 (7):A915.
604. Villa S, Ravasio R, Rossetti F, Bianchino L. Economic evaluation of tocilizumab vs abatacept in methotrexat e-experienced patients with rheumat oid arthritis in Italy. Value in Health. 2016;19 (7):A538.
605. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ. 1996;313(7052):275-83.
606. Arne M, Janson C, Janson S, Boman G, Lindqvist U, Berne C, et al. Physical activity and quality of life in subjects with chronic disease: chronic obstructive pulmonary disease compared with rheumatoid arthritis and diabetes mellitus. Scand J Prim Health Care. 2009;27(3):141-7.
607. Bansback N, Marra C, Tsuchiya A, Anis A, Guh D, Hammond T, et al. Using the health assessment questionnaire to estimate preference-based single indices in patients with rheumatoid arthritis. Arthritis Rheum. 2007;57(6):963-71.
608. Bejia I, Salem KB, Touzi M, Bergaoui N. Measuring utilities by the time trade-off method in Tunisian rheumatoid arthritis patients. Clin Rheumatol. 2006;25(1):38-41.
609. Boggs R. 1.UT3 ESTIMATING HEALTH UTILITY FROM A PHYSICAL FUNCTION ASSESSMENT IN RHEUMATOID ARTHRITIS (RA) PATIENTS TREATED WITH ADALIMUMAB (D2E7). Value in Health. 2002;5(6):452-3.
610. Carreno A, Fernandez I, Badia X, Varela C, Roset M. Using HAQ-DI to estimate HUI-3 and EQ-5D utility values for patients with rheumatoid arthritis in Spain. Value in Health. 2011;14(1):192-200.
611. Chiou CF, Weisman M, Sherbourne CD, Reyes C, Dylan M, Ofman J, et al. Measuring preference weights for American college of rheumatology response criteria for patients with rheumatoid arthritis. J Rheumatol. 2005;32(12):2326-9.
612. Conner-Spady B, Suarez-Almazor ME. Variation in the estimation of quality-adjusted life-years by different preference-based instruments. Med Care. 2003;41(7):791-801.
613. Harrison MJ, Davies LM, Bansback NJ, McCoy MJ, Verstappen SM, Watson K, et al. The comparative responsiveness of the EQ-5D and SF-6D to change in patients with inflammatory arthritis. Qual Life Res. 2009;18(9):1195-205.
614. Harrison MJ, Lunt M, Verstappen SM, Watson KD, Bansback NJ, Symmons DP. Exploring the validity of estimating EQ-5D and SF-6D utility values from the health assessment questionnaire in patients with inflammatory arthritis. Health Qual Life Outcomes. 2010;8:21.
615. Hurst NP, Jobanputra P, Hunter M, Lambert M, Lochhead A, Brown H. Validity of Euroqol--a generic health status instrument--in patients with rheumatoid arthritis. Economic and Health Outcomes Research Group. British Journal of Rheumatology. 1994;33(7):655-62.
616. Kaplan RM, Groessl EJ, Sengupta N, Sieber WJ, Ganiats TG. Comparison of measured utility scores and imputed scores from the SF-36 in patients with rheumatoid arthritis. Med Care. 2005;43(1):79-87.
617. Kobelt G, Eberhardt K, Jonsson L, Jonsson B. Economic consequences of the progression of rheumatoid arthritis in Sweden. Arthritis Rheum. 1999;42(2):347-56.
618. Lillegraven S, Kristiansen IS, Kvien TK. Comparison of utility measures and their relationship with other health status measures in 1041 patients with rheumatoid arthritis. Ann Rheum Dis. 2010;69(10):1762-7.

619. Linde L, Sorensen J, Ostergaard M, Horslev-Petersen K, Hetland ML. Health-related quality of life: validity, reliability, and responsiveness of SF-36, 15D, EQ-5D [corrected] RAQoL, and HAQ in patients with rheumatoid arthritis. J Rheumatol. 2008;35(8):1528-37.
620. Linde L, Sorensen J, Ostergaard M, Horslev-Petersen K, Hetland ML. Does clinical remission lead to normalization of EQ-5D in patients with rheumatoid arthritis and is selection of remission criteria important? J Rheumatol. 2010;37(2):285-90.
621. Marra CA, Esdaile JM, Guh D, Kopec JA, Brazier JE, Koehler BE, et al. A comparison of four indirect methods of assessing utility values in rheumatoid arthritis. Med Care. 2004;42(11):1125-31.
622. Marra CA, Woolcott JC, Kopec JA, Shojania K, Offer R, Brazier JE, et al. A comparison of generic, indirect utility measures (the HUI2, HUI3, SF-6D, and the EQ-5D) and disease-specific instruments (the RAQoL and the HAQ) in rheumatoid arthritis. Soc Sci Med. 2005;60(7):1571-82.
623. Peeters Y, Stiggelbout AM. Valuing health: does enriching a scenario lead to higher utilities? Med Decis Making. 2009;29(3):334-42.
624. Rashidi AA, Anis AH, Marra CA. Do visual analogue scale (VAS) derived standard gamble (SG) utilities agree with Health Utilities Index utilities? A comparison of patient and community preferences for health status in rheumatoid arthritis patients. Health Qual Life Outcomes. 2006;4:25.
625. Russell AS, Conner-Spady B, Mintz A, Maksymowych WP. The responsiveness of generic health status measures as assessed in patients with rheumatoid arthritis receiving infliximab. J Rheumatol. 2003;30(5):941-7.
626. Salaffi F, Stancati A, Carotti M. Responsiveness of health status measures and utility-based methods in patients with rheumatoid arthritis. Clin Rheumatol. 2002;21(6):478-87.
627. Scott DL, Khoshaba B, Choy EH, Kingsley GH. Limited correlation between the Health Assessment Questionnaire (HAQ) and EuroQol in rheumatoid arthritis: questionable validity of deriving quality adjusted life years from HAQ. Ann Rheum Dis. 2007;66(11):1534-7.
628. Suarez-Almazor ME, Conner-Spady B. Rating of arthritis health states by patients, physicians, and the general public. Implications for cost-utility analyses. J Rheumatol. 2001;28(3):648-56.
629. Tijhuis GJ, Jansen SJ, Stiggelbout AM, Zwinderman AH, Hazes JM, Vliet Vlieland TP. Value of the time trade off method for measuring utilities in patients with rheumatoid arthritis. Ann Rheum Dis. 2000;59(11):892-7.
630. Wailoo A. Modeling the Cost Effectiveness of Etanercept, Adalimumab and Anakinra Compared to Infliximab in the Treatment of Paitents with Rheumatoid Arthritis in the Medicare Program. Agency for Healthcare Research and Quality. 2006.
631. Witney AG, Treharne GJ, Tavakoli M, Lyons AC, Vincent K, Scott DL, et al. The relationship of medical, demographic and psychosocial factors to direct and indirect health utility instruments in rheumatoid arthritis. Rheumatology (Oxford). 2006;45(8):975-81.
632. Wolfe F, Hawley DJ. Measurement of the quality of life in rheumatic disorders using the EuroQol. British Journal of Rheumatology. 1997;36(7):786-93.
633. Wolfe F, Michaud K. The loss of health status in rheumatoid arthritis and the effect of biologic therapy: a longitudinal observational study. Arthritis Res Ther. 2010;12(2):R35.
634. Wolfe F, Michaud K, Wallenstein G. Scale characteristics and mapping accuracy of the US EQ-5D, UK EQ-5D, and SF-6D in patients with rheumatoid arthritis. J Rheumatol. 2010;37(8):1615-25.
635. Wolfe F, Michaud K, Li T, Katz RS. EQ-5D and SF-36 quality of life measures in systemic lupus erythematosus: comparisons with rheumatoid arthritis,

noninflammatory rheumatic disorders, and fibromyalgia. J Rheumatol. 2010;37(2):296-304.
636. Adams R, Craig BM, Walsh CD, Veale DJ, Bresnihan B, FitzGerald O, et al. The impact of a revised EQ-5D population scoring on preference-based utility scores in an inflammatory arthritis cohort. Value in Health. 2011;14(6):921-7.
637. Buitinga L, Braakman-Jansen LM, Taal E, Kievit W, Visser H, van Riel PL, et al. Comparative responsiveness of the EuroQol-5D and Short Form 6D to improvement in patients with rheumatoid arthritis treated with tumor necrosis factor blockers: results of the Dutch Rheumatoid Arthritis Monitoring registry. Arthritis Care Res (Hoboken). 2012;64(6):826-32.
638. Heiberg T, Austad C, Kvien TK, Uhlig T. Performance of the Rheumatoid Arthritis Impact of Disease (RAID) score in relation to other patient-reported outcomes in a register of patients with rheumatoid arthritis. Ann Rheum Dis. 2011;70(6):1080-2.
639. Inotai A, Rojkovich B, Fulop A, Jaszay E, Agh T, Meszaros A. Health-related quality of life and utility in patients receiving biological and non-biological treatments in rheumatoid arthritis. Rheumatol Int. 2012;32(4):963-9.
640. Jobanputra P, Maggs F, Deeming A, Carruthers D, Rankin E, Jordan AC, et al. A randomised efficacy and discontinuation study of etanercept versus adalimumab (RED SEA) for rheumatoid arthritis: a pragmatic, unblinded, non-inferiority study of first TNF inhibitor use: outcomes over 2 years. BMJ Open. 2012;2(6).
641. Karlsson JA, Nilsson JA, Neovius M, Kristensen LE, Gulfe A, Saxne T, et al. National EQ-5D tariffs and quality-adjusted life-year estimation: comparison of UK, US and Danish utilities in south Swedish rheumatoid arthritis patients. Ann Rheum Dis. 2011;70(12):2163-6.
642. Kievit W, Fransen J, Adang EM, den Broeder AA, Bernelot Moens HJ, Visser H, et al. Long-term effectiveness and safety of TNF-blocking agents in daily clinical practice: results from the Dutch Rheumatoid Arthritis Monitoring register. Rheumatology (Oxford). 2011;50(1):196-203.
643. Kobelt G, Texier-Richard B, Mimoun S, Woronoff AS, Bertholon DR, Perdriger A, et al. Rheumatoid arthritis and sexuality: a patient survey in France. BMC Musculoskelet Disord. 2012;13:170.
644. Kontodimopoulos N, Bozios P, Yfantopoulos J, Niakas D. Longitudinal predictive ability of mapping models: examining post-intervention EQ-5D utilities derived from baseline MHAQ data in rheumatoid arthritis patients. European Journal of Health Economics. 2013;14(2):307-14.
645. Salaffi F, Carotti M, Ciapetti A, Gasparini S, Grassi W. A comparison of utility measurement using EQ-5D and SF-6D preference-based generic instruments in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2011;29(4):661-71.
646. Sorensen J, Linde L, Ostergaard M, Hetland ML. Quality-adjusted life expectancies in patients with rheumatoid arthritis--comparison of index scores from EQ-5D, 15D, and SF-6D. Value in Health. 2012;15(2):334-9.
647. Staples MP, March L, Lassere M, Reid C, Buchbinder R. Health-related quality of life and continuation rate on first-line anti-tumour necrosis factor therapy among rheumatoid arthritis patients from the Australian Rheumatology Association Database. Rheumatology (Oxford). 2011;50(1):166-75.
648. Wade AG, Crawford GM, Pumford N, Koscielny V, Maycock S, McConnachie A. Baseline characteristics and patient reported outcome data of patients prescribed etanercept: web-based and telephone evaluation. BMC Med Res Methodol. 2011;11:91.
649. Alemao E, Joo S, Kawabata H, Al MJ, Allison PD, Rutten-Van Molken MPMH, et al. Effects of Achieving Target Measures in Rheumatoid Arthritis on Functional Status, Quality of Life, and Resource Utilization: Analysis of Clinical Practice Data. Arthritis Care and Research. 2016;68(3):308-17.

650. Austad C, Kvien TK, Olsen IC, Uhlig T. Health status has improved more in women than in men with rheumatoid arthritis from 1994 to 2009: Results from the Oslo rheumatoid arthritis register. Annals of the Rheumatic Diseases. 2013;74(1):148-55.
651. Watts R, Mooney J, Barton G, Macgregor AJ, Shepstone L, Irvine L, et al. The outcome and cost-effectiveness of nurse-led care in the community for people with rheumatoid arthritis: A non-randomised pragmatic study. BMJ Open. 2015;5 (8) (no pagination)(e007696).
652. Buitinga L, Braakman-Jansen LM, Taal E, van de Laar MA. Construct validity of the interview time trade-off and computer time trade-off in patients with rheumatoid arthritis: a cross-sectional observational pilot study. BMC Musculoskeletal Disorders. 2012;13:112.
653. Bujkiewicz S, Thompson JR, Sutton AJ, Cooper NJ, Harrison MJ, Symmons DPM, et al. Use of bayesian multivariate meta-analysis to estimate the HAQ for mapping onto the EQ-5D questionnaire in rheumatoid arthritis. Value in Health. 2014;17(1):109-15.
654. Chen JS, Makovey J, Lassere M, Buchbinder R, March LM. Comparative effectiveness of anti-tumor necrosis factor drugs on health-related quality of life among patients with inflammatory arthritis. Arthritis Care and Research. 2014;66(3):464-72.
655. Cho SK, Kim D, Jun JB, Bae SC, Sung YK. Factors influencing quality of life (QOL) for Korean patients with rheumatoid arthritis (RA). Rheumatology International. 2013;33(1):93-102.
656. Crilly MA, Johnston MC, Black C. Relationship of EQ-5D quality of life with the presence of co-morbidity and extra-articular features in patients with rheumatoid arthritis. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2014;23(5):1435-43.
657. Dasgupta B, Combe B, Louw I, Wollenhaupt J, Zerbini CAF, Beaulieu A, et al. Patient and physician expectations of add-on treatment with golimumab for rheumatoid arthritis: Relationships between expectations and clinical and quality of life outcomes. Arthritis Care and Research. 2014;66(12):1799-807.
658. Oliveira Junior HA, Almeida AM, Acurcio FA, Santos JB, Kakehasi AM, Alvares J, et al. Profile of patients with rheumatic diseases undergoing treatment with anti-TNF agents in the Brazilian public health system (SUS), belo horizonte - MG. Brazilian Journal of Pharmaceutical Sciences. 2015;51(3):709-20.
659. De Oliveira Junior HA, Dos Santos JB, Acurcio FA, Almeida AM, Kakehasi AM, Alvares J, et al. Poorer functionality is related to better quality of life response following the use of biological drugs: 6-month outcomes in a prospective cohort from the Public Health System (Sistema Unico de Saude), Minas Gerais, Brazil. Expert Review of Pharmacoeconomics and Outcomes Research. 2015;15(3):403-12.
660. Ferreira LN, Ferreira PL, Pereira LN. Comparing the performance of the SF-6D and the EQ-5D in different patient groups. Acta Medica Portuguesa. 2014;27(2):236-45.
661. Fevang BT, Lygre SH, Bertelsen G, Skredderstuen A, Havelin LI, Furnes O. Good function after shoulder arthroplasty. Acta Orthopaedica. 2012;83(5):467-73.
662. Fukuda W, Omoto A, Ohta T, Majima S, Kimura T, Tanaka T, et al. Low body mass index is associated with impaired quality of life in patients with rheumatoid arthritis. International Journal of Rheumatic Diseases. 2013;16(3):297-302.
663. Garcia I, Portugal C, Chu LH, Kawatkar AA. Response rates of three modes of survey administration and survey preferences of rheumatoid arthritis patients. Arthritis care & research. 2014;66(3):364-70.
664. Gaujoux-Viala C, Fautrel B, Guillemin F, Flipo RM, Bourgeois P, Rat AC. Who are the patients with early arthritis with worse than death scores on the EQ-5D? Results from the ESPOIR cohort. Rheumatology. 2013;52(5):832-8.

665. Hernandez Alava M, Wailoo A, Wolfe F, Michaud K. A comparison of direct and indirect methods for the estimation of health utilities from clinical outcomes. Medical Decision Making. 2014;34(7):919-30.
666. Horslev-Petersen K, Hetland ML, Junker P, Podenphant J, Ellingsen T, Ahlquist P, et al. Adalimumab added to a treat-to-target strategy with methotrexate and intra-articular triamcinolone in early rheumatoid arthritis increased remission rates, function and quality of life. The OPERA Study: an investigator-initiated, randomised, double-blind, parallel-group, placebo-controlled trial. Annals of the Rheumatic Diseases. 2014;73(4):654-61.
667. Iqbal I, Dasgupta B, Taylor P, Heron L, Pilling C. Elicitation of health state utilities associated with differing durations of morning stiffness in rheumatoid arthritis. Journal of Medical Economics. 2012;15(6):1192-200.
668. Jobanputra P, Maggs F, Deeming A, Carruthers D, Rankin E, Jordan A, et al. Randomized efficacy and discontinuation study of etanercept versus adalimumab (Red sea): A pragmatic, open-label, non-inferiority study of first TNF inhibitor use in rheumatoid arthritis: 1-year data. Rheumatology (United Kingdom). 2012;51:iii116-iii7.
669. Karlsson JA, Neovius M, Nilsson JA, Petersson IF, Bratt J, van Vollenhoven RF, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in early rheumatoid arthritis: 2-year quality-of-life results of the randomised, controlled, SWEFOT trial. Annals of the Rheumatic Diseases. 2013;72(12):1927-33.
670. Kim HL, Kim D, Jang EJ, Lee MY, Song HJ, Park SY, et al. Mapping health assessment questionnaire disability index (HAQ-DI) score, pain visual analog scale (VAS), and disease activity score in 28 joints (DAS28) onto the EuroQol-5D (EQ-5D) utility score with the KORean Observational study Network for Arthritis (KORONA) registry data. Rheumatology International. 2016;36(4):505-13.
671. Kwan YH, Koh ET, Leong KP, Wee HL. Association between helplessness, disability, and disease activity with health-related quality of life among rheumatoid arthritis patients in a multiethnic Asian population. Rheumatology International. 2014;34(8):1085-93.
672. Lamb SE, Williamson EM, Heine PJ, Adams J, Dosanjh S, Dritsaki M, et al. Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet. 2015;385(9966):421-9.
673. LoVerde ZJ, Mandl LA, Johnson BK, Figgie MP, Boettner F, Lee YY, et al. Rheumatoid Arthritis Does Not Increase Risk of Short-term Adverse Events after Total Knee Arthroplasty: A Retrospective Case-control Study. Journal of Rheumatology. 2015;42(7):1123-30.
674. Manning VL, Kaambwa B, Ratcliffe J, Scott DL, Choy E, Hurley MV, et al. Economic evaluation of a brief education, self-management and upper limb exercise training in people with rheumatoid arthritis (EXTRA) programme: a trial-based analysis. Rheumatology. 2015;54(2):302-9.
675. Mukka S, Berg G, Hassany HR, Koye AK, Sjoden G, Sayed-Noor AS. Semiconstrained total elbow arthroplasty for rheumatoid arthritis patients: clinical and radiological results of 1-8 years follow-up. Archives of Orthopaedic & Trauma Surgery. 2015;135(5):595-600.
676. Nair SC, Welsing PM, Marijnissen AK, Sijtsma P, Bijlsma JW, van Laar JM, et al. Does disease activity add to functional disability in estimation of utility for rheumatoid arthritis patients on biologic treatment? Rheumatology. 2016;55(1):94-102.
677. Pavelka K, Szekanecz Z, Damjanov N, Majdan M, Nasonov E, Mazurov V, et al. Induction of response with etanercept-methotrexate therapy in patients with moderately active rheumatoid arthritis in Central and Eastern Europe in the PRESERVE study. Clinical Rheumatology. 2013;32(9):1275-81.

678. Peeters Y, Vliet Vlieland TP, Stiggelbout AM. Focusing illusion, adaptation and EQ-5D health state descriptions: the difference between patients and public. Health Expectations. 2012;15(4):367-78.
679. Radner H, Smolen JS, Aletaha D. Remission in rheumatoid arthritis: benefit over low disease activity in patient-reported outcomes and costs. Arthritis Research & Therapy. 2014;16(1):R56.
680. Radner H, Yoshida K, Mjaavatten MD, Aletaha D, Frits M, Lu B, et al. Development of a multimorbidity index: Impact on quality of life using a rheumatoid arthritis cohort. Seminars in Arthritis and Rheumatism. 2015;45(2):167-73.
681. Scott DL, Ibrahim F, Farewell V, O'Keeffe AG, Walker D, Kelly C, et al. Tumour necrosis factor inhibitors versus combination intensive therapy with conventional disease modifying anti-rheumatic drugs in established rheumatoid arthritis: TACIT non-inferiority randomised controlled trial. BMJ. 2015;350:h1046.
682. Scott IC, Ibrahim F, Simpson G, Kowalczyk A, White-Alao B, Hassell A, et al. A randomised trial evaluating anakinra in early active rheumatoid arthritis. Clinical & Experimental Rheumatology. 2016;34(1):88-93.
683. Seegobin SD, Ma MH, Dahanayake C, Cope AP, Scott DL, Lewis CM, et al. ACPA-positive and ACPA-negative rheumatoid arthritis differ in their requirements for combination DMARDs and corticosteroids: secondary analysis of a randomized controlled trial. Arthritis Research & Therapy. 2014;16(1):R13.
684. Seto Y, Inoue E, Shidara K, Hoshi D, Sugimoto N, Sato E, et al. Functional disability can deteriorate despite suppression of disease activity in patients with rheumatoid arthritis: a large observational cohort study. Modern Rheumatology. 2013;23(6):1179-85.
685. Sorensen J, Primdahl J, Horn HC, Horslev-Petersen K. Shared care or nurse consultations as an alternative to rheumatologist follow-up for rheumatoid arthritis (RA) outpatients with stable low disease-activity RA: cost-effectiveness based on a 2-year randomized trial. Scandinavian Journal of Rheumatology. 2015;44(1):13-21.
686. Tanaka E, Hoshi D, Igarashi A, Inoue E, Shidara K, Sugimoto N, et al. Analysis of direct medical and nonmedical costs for care of rheumatoid arthritis patients using the large cohort database, IORRA. Modern Rheumatology. 2013;23(4):742-51.
687. Tarride JE, Haq M, Nakhai-Pour HR, O'Reilly DJ, Xie F, Dolovich L, et al. The excess burden of rheumatoid arthritis in Ontario, Canada. Clinical & Experimental Rheumatology. 2013;31(1):18-24.
688. Traki L, Rostom S, Tahiri L, Bahiri R, Harzy T, Abouqal R, et al. Responsiveness of the EuroQol EQ-5D and Hospital Anxiety and Depression Scale (HADS) in rheumatoid arthritis patients receiving tocilizumab. Clinical Rheumatology. 2014;33(8):1055-60.
689. Uehara M, Takahashi J, Hirabayashi H, Ogihara N, Mukaiyama K, Kuraishi S, et al. Evaluation of clinical results and quality of life after surgical reconstruction for rheumatoid cervical spine. Spine Journal: Official Journal of the North American Spine Society. 2013;13(4):391-6.
690. Wailoo A, Hernandez Alava M, Scott IC, Ibrahim F, Scott DL. Cost-effectiveness of treatment strategies using combination disease-modifying anti-rheumatic drugs and glucocorticoids in early rheumatoid arthritis. Rheumatology. 2014;53(10):1773-7.
691. Williams MA, Williamson EM, Heine PJ, Nichols V, Glover MJ, Dritsaki M, et al. Strengthening And stretching for Rheumatoid Arthritis of the Hand (SARAH). A randomised controlled trial and economic evaluation. Health Technol Assess. 2015;19(19):1-222.

692. Austad C, Kvien T, Olsen I, Uhlig T. Sleep disturbance in patients with rheumatoid arthritis is related to fatigue, disease activity, and other patient-reported outcomes. Scandinavian Journal of Rheumatology. 2016:1-9.
693. Bae SC, Cho SK, Won S, Lee HS, Kang YM, Lee SH, et al. Factors associated with quality of life and functional disability among rheumatoid arthritis patients treated with disease-modifying anti-rheumatic drugs for at least 6 months. International Journal of Rheumatic Diseases. 2016.
694. Chen HH, Chen DY, Chen YM, Lai KL. Health-related quality of life and utility: comparison of ankylosing spondylitis, rheumatoid arthritis, and systemic lupus erythematosus patients in Taiwan. Clinical Rheumatology. 2016:1-10.
695. Cooper A, Wallman J, Gulfe A. What PASSes for good? Experience-based Swedish and hypothetical British EuroQol 5-Dimensions preference sets yield markedly different point estimates and patient acceptable symptom state cut-off values in chronic arthritis patients on TNF blockade. Scandinavian Journal of Rheumatology. 2016;45(6):470-3.
696. Dos Santos JBR, Almeida AM, Acurcio FDA, De Oliveira HA, Kakehasi AM, Guerra AA, et al. Comparative effectiveness of adalimumab and etanercept for rheumatoid arthritis in the Brazilian Public Health System. Journal of Comparative Effectiveness Research. 2016;5(6):539-49.
697. Mian AN, Ibrahim F, Scott DL, Galloway J. Optimal responses in disease activity scores to treatment in rheumatoid arthritis: Is a DAS28 reduction of >1.2 sufficient? Arthritis Research and Therapy. 2016;18 (1) (no pagination)(142).
698. Pal S, Veeravalli SCM, Das SK, Shobha V, Uppuluri RR, Dharmanand BG, et al. Efficacy and safety of golimumab in Indian patients with rheumatoid arthritis: Subgroup data from GO-MORE study. International Journal of Rheumatic Diseases. 2016.
699. Rome K, Clark H, Gray J, McMeekin P, Plant M, Dixon J. Clinical effectiveness and cost-effectiveness of foot orthoses for people with established rheumatoid arthritis: an exploratory clinical trial. Scand J Rheumatol. 2016:1-7.
700. Uhlig T, Bjorneboe O, Kroll F, Palm O, Olsen IC, Grotle M. Involvement of the multidisciplinary team and outcomes in inpatient rehabilitation among patients with inflammatory rheumatic disease Rehabilitation, physical therapy and occupational health. BMC Musculoskeletal Disorders. 2016;17 (1) (no pagination)(18).
701. Wallman JK, Eriksson JK, Nilsson JA, Olofsson T, Kristensen LE, Neovius M, et al. Costs in Relation to Disability, Disease Activity, and Health-related Quality of Life in Rheumatoid Arthritis: Observational Data from Southern Sweden. Journal of Rheumatology. 2016;43(7):1292-9.
702. Yoshizawa K, Kobayashi H, Fujie M, Ogawa Y, Yajima T, Kawai K. Estimation of minimal clinically important change of the Japanese version of EQ-5D in patients with chronic noncancer pain: A retrospective research using real-world data. Health Qual Life Outcomes. 2016;14 (1) (no pagination)(35).
703. Burstrom K, Johannesson M, Diderichsen F. Swedish population health-related quality of life results using the EQ-5D. Qual Life Res. 2001;10(7):621-35.
704. Greiner W, Weijnen T, Nieuwenhuizen M, Oppe S, Badia X, Busschbach J, et al. A single European currency for EQ-5D health states. Results from a six-country study. Eur J Health Econ. 2003;4(3):222-31.
705. Dolan P, Gudex C, Kind P, Williams A. A social tariff for EuroQol: results from a UK general population survey. York: Centre for Health Economics, University of York. 1995.
706. Wittrup-Jensen KU, Lauridsen J, Gudex C, Pedersen KM. Generation of a Danish TTO value set for EQ-5D health states. Scand J Public Health. 2009;37(5):459-66.
707. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35(11):1095-108.

708. Feeny D, Furlong W, Torrance GW, Goldsmith CH, Zhu Z, DePauw S, et al. Multiattribute and single-attribute utility functions for the health utilities index mark 3 system. Med Care. 2002;40(2):113-28.
709. Dolan P, Gudex C, Kind P, Williams A. A social tariff for EuroQol. York: Publications Unit, Centre for Health Economics, University of York. 1996.
710. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care. 2005;43(3):203-20.
711. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002;21(2):271-92.
712. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. Med Care. 2004;42(9):851-9.
713. Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D. Discussion paper 172. Centre for Health Economics. York; University of York. 1999.
714. Benito-Garcia E, Pedro S, Vasconcelos JC, Marques R. HAQ-based utilities using EuroQoL, Brazier's Short Form-6D, and VAS-QoL have different values and may not all discriminate across disease severity among a Portuguese cohort of rheumatoid arthritis patients. ISPOR 12th Annual European Congress. 2009.
715. Chang H, Chen L, Tsai WC. Assessing health-related quality of life in Taiwanese rheumatoid arthritis patients by applying time trade-off and EQ-5D methods. ISPOR 15th Annual International Meeting. 2010.
716. Radner H, Aletaha D, Smolen J. Work productivity ,quality of life, and health states of different disease activity states in patients with rheumatoid arthritis (RA). Ann Rheum Dis. 2009;68(Suppl 3):396.
717. Smolen J, Combe B, Hammond B, Vlahos B, Singh A, Koenig A. Improvement in patient-reported outcomes with etanercept-methotrexate therapy in moderately active rheumatoid arthritis: interim results of the preserve trial. Ann Rheum Dis. 2011;70(Suppl 3):260.
718. Varela C. Using HAQ to estimate HUI3 and EQ-5D utility values in Spanish rheumatoid arthritis patients. ISPOR 11th Annual European Congress. 2008.
719. Bird H. Impact of etanercept-methotrexate therapy on patient-reported outcomes in a randomized controlled trial in moderately active rheumatoid arthritis patients. Ann Rheum Dis. 2012;71(Suppl 3):633.
720. Britsemmer K. The impact of morning stiffness on quality of life in early rheumatoid arthritis. Value in Health. 2011;63.
721. Fleischmann R, Bolce R, Wang J, Ingham M, Dehoratius R, Decktor D. Improved quality of life and productivity in patients with moderate or severe rheumatoid arthritis actively switched to treatment with infliximab from adalimumab or etanercept therapy. Arthritis and Rheumatism. 2011;63(Suppl 1):10.
722. Ghosh P. Investigation of comparative clinical outcomes profiles and cost effectiveness of four classes of anti arthritic drugs using HAQ-DI, DAS-28 and EQ5D3L in a tertiary care hospital in western India. Value in Health. 2012;15(7):A674.
723. Koenig A. Profile of an under-studied rheumatoid arthritis (ra) population: characteristics of patients with moderately active rheumatoid arthritis despite methotrexate use. Ann Rheum Dis. 2012;71(Suppl 3):652.
724. Lee AT. Differences in cost-of-illness and quality of life between rheumatoid arthritis and ankylosing spondylitis in south korea. Value in Health. 2011:A23-A510.
725. Pogozheva E. Postoperative complications in rheumatoid arthritis patients receiving biologic and nonbiologic disease-modifying antirheumatic drugs. Ann Rheum Dis. 2012;71(Suppl 3):374.
726. Pumford N, Wade A, Crawford G, McConnachie A. Sensitivity of pro's to detect changes in quality of life in patients treated with a biologic agent. Value in Health. 2011;14(7):A314.

727. Rappaport H. Quality of life among patients with self-reported rheumatoid arthritis: a nationally representative sample. Value in Health. 2012;15(4):A43-A4.
728. Settas L, Papadopoulos N, Pikazis D, Vasilopoulos D, Katsounaros M, Latsou D, et al. Measuring the health-related quality of life in patients with rheumatoid arthritis treated with adalimumab in Greece: comparing the results of one generic (EQ-5D) and one disease-specific (HAQ) instrument. Value in Health. 2011;14(7):A315.
729. Soliman MM. Impact of rituximab on the quality of life and physical function of patients with rheumatoid arthritis: results from the British Society for Rheumatology biologics register. Arthritis and Rheumatism. 2011;63(November 2011 abstract suppl).
730. Waimann C. The Burden of Early Arthritis in Latin America: Utility Analysis Using Patient-Level Data From the Argentinian Consortium for Early Arthritis. American College of Rheumatology. 2012;60.
731. Westhovens R, Weinblatt M, Han C, Gathany T, Kim L, Mack M, et al. Intravenously administered golimumab significantly improves health related quality of life and work productivity in patients with rheumatoid arthritis: results of a phase III, placebo-controlled trial. Value in Health. 2012;15(4):A42.
732. Alemao E, Joo S, Allison P, Al M, Rutten-van Molken M, Banerjee S, et al. Comparisons of quality of life, resource use and physical functioning in ra patients classified as high, moderate or low risk for rapid radiographic progression. Arthritis and Rheumatology. 2014;66:S501.
733. Alemao E, Joo S, Kawabata H, Al M, Allison P, Rutten-van Molken M, et al. Quality of life and economic benefits of remission/low disease activity in patients with rheumatoid arthritis in clinical practice setting. Annals of the Rheumatic Diseases. Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR. 2014;73(no pagination).
734. Alemao E, Joo S, Kawabata H, Banerjee S, Frits M, Iannaccone C, et al. Benefits of early onset of DAS28 (CRP). Arthritis and Rheumatology. 2014;66:S920.
735. Alemao E, Joo S, Frits M, Iannaccone C, Shadick N, Weinblatt M. Baseline characteristics and changes in disease activity at 12 months in patients treated with abatacept versus other biologic disease-modifying antirheumatic drugs in clinical practice setting-results from the brass registry. Annals of the Rheumatic Diseases. 2015;74:1045.
736. Anno S, Inui K, Mamoto K, Okano T, Sugioka Y, Tada M, et al. Work ability and work disability evaluation in patients with rheumatoid arthritis-from the tomorrow study. Annals of the Rheumatic Diseases. 2015;74:329.
737. Codreanu C, Mogosan C, Enache L, Stanciu D, Ionescu R, Opris D, et al. Romanian registry of rheumatic diseases: Efficacy and safety of biologic therapy in rheumatoid arthritis. Annals of the Rheumatic Diseases. 2015;74:458.
738. Cooper A, Karlsson JA, Gurlfe A. Marked differences in euro-qol-5-dimensions preference sets based on hypothetical or experience based valuation. Arthritis and Rheumatology. 2014;66:S505.
739. Dasgupta B, Bertin P, Settas L, Fonseca JE, Wolff V, Yao R, et al. Golimumab improves patient-reported outcomes in patients with active rheumatoid arthritis. Arthritis and Rheumatism. 2013;65:S209.
740. Dasgupta B, Combe B, Louw I, Wollenhaupt J, Zerbini C, Beaulieu A, et al. Attainment of remission, functional, and quality of life improvements with golimumab treatment in rheumatoid arthritis are associated with patient expectations. Arthritis and Rheumatism. 2013;65:S210.
741. Dusad A, Pedro S, Garvin K, Hartman C, O'Dell J, Mikuls TR, et al. Patient reported outcomes following total knee arthroplasty in rheumatoid arthritis and osteoarthritis. Arthritis and Rheumatology. 2014;66:S46.
742. Emery P, Wiland P, Spieler W, Dudler J, Gaylord S, Williams T, et al. Impact of etanercept-methotrexate therapy on patient-reported outcomes in rheumatoid

arthritis patients with up to 12 months of symptoms. Arthritis and Rheumatism. 2012;64:S160.
743. Gaujoux-Viala C, Rat AC, Guillemin F, Etcheto A, Dougados M, Fautrel B. Who are the patients with rheumatoid arthritis with "worse than death" scores on the Eq-5D? Results from the comedra study. Annals of the Rheumatic Diseases. Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR. 2014;73(no pagination).
744. Gaujoux-Viala C, Hosseini K, Rat AC, Guillemin F, Etcheto A, Soubrier M, et al. Impact of comorbidities on measuring indirect utility by the SF-6D or the EQ-5D in rheumatoid arthritis: An analysis of 962 patients enrolled in Comedra. Annals of the Rheumatic Diseases. Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR. 2014;73(no pagination).
745. Hallert E, Husberg M, Skogh T, Rahmqvist M. Socioeconomic and demographic characteristics among two cohorts of patients with early rheumatoid arthritis in Sweden, enrolled 1996-98 and 2006-09. Annals of the Rheumatic Diseases. Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR. 2013;72(no pagination).
746. Han C, Bingham CO, Westhovens R, Weinblatt ME, Kim L, Baker D, et al. A comparison of EQ5D index from the UK, US, and Japan preference weights model, and mapping algorithm from clinical outcomes in patients with rheumatoid arthritis: Results of from simponi aria study. Annals of the Rheumatic Diseases. 2015;74:225-6.
747. Hope H, Hyrich K, Anderson J, Cordingley L, Verstappen S. Early adherence to methotrexate in rheumatoid arthritis (RA) is high: A prospective longitudinal study of new users. Arthritis and Rheumatology. 2014;66:S892.
748. Hoshi D, Tanaka E, Inoue E, Shidara K, Shimizu Y, Kobayashi A, et al. Minimally important difference in the European quality of life-five dimensions in patients with rheumatoid arthritis. Arthritis and Rheumatology. 2014;66:S183-S4.
749. Ishikawa H, Abe A, Murasawa A, Kojima T, Kojima M, Ishiguro N, et al. Patient-reported outcome and disease activity after orthopedic intervention in the disabled patients with long-standing established rheumatoid arthritis. A prospective cohort study of 136 patients. Annals of the Rheumatic Diseases. 2015;74:980.
750. Jorgensen TS, Turesson C, Kapetanovic M, Englund M, Turkiewicz A, Christensen R, et al. EQ-5D utility, response and drug adherence in rheumatoid arthritis patients on biologic monotherapy: A prospective observational study of patients registered in the south swedish SSATG registry. Annals of the Rheumatic Diseases. 2015;74:793.
751. Jorgensen TS, Turesson C, Kapetanovic MC, Englund M, Turkiewicz A, Christensen R, et al. Is mode of action important when switching biologic monotherapy in rheumatoid arthritis? Drug adherence results from the swedish ssatg registry. Arthritis and Rheumatology. Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP. 2015;67(no pagination).
752. Kavati A, Rappaport H. Impact of rheumatoid arthritis (RA) on quality of life (QOL) in a nationally representative population in the united states. Value in Health. 2013;16 (3):A227.
753. Kim D, Sung YK, Cho SK, Won S, Han M, Bang SY, et al. Factors associated with impairment on quality of life in early or established ra patients. Arthritis and Rheumatology. 2014;66:S465-S6.
754. Koroleva MV, Raskina TA. Effect of rituximab therapy on life quality with rheumatoid arthritis patients. Osteoporosis International. 2014;25:S365-S6.

755. Koroleva MV, Raskina TA, Malyshenko OS. Effect of rituximab on quality of life with rheumatoid arthritis patients to baseline bone mineral density. Osteoporosis International. 2015;1):S277-S8.
756. Kover K, Meszaros A. Functional observ ation with TTO in chronic diseases. Value in Health. 2013;16 (7):A597.
757. Lee JY, Jung S, Lee EK. Health-related quality of life of patients with rheumatoid arthritis in Korea: The Korea national health and nutrition examination survey. Value in Health. 2014;17 (3):A52.
758. Lie E, Lillegraven S, Fagerli KM, Uhlig T, Kvien TK. TNF inhibitor treatment in rheumatoid arthritis (RA) patients with moderate versus high disease activity at baseline: A comparison of utility gains, response and remission rates. Arthritis and Rheumatism. 2012;64:S220.
759. Linde L, Sorensen J, Ostergaard M, Hetland ML. Predictors of gain in quality adjusted life years in RA patients treated with biologics for one year. Annals of the Rheumatic Disease. Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR. 2012;71(no pagination).
760. Lipina M, Makarov M, Amirdjanova V, Makarov S, Pavlov V, Vardicova G, et al. Quality of life and knee function of the patients with rheumatoid arthritis after arthroscopic synovectomy. Annals of the Rheumatic Disease. Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR. 2012;71(no pagination).
761. Mlcoch T, Jircikova J, Mandelikova M, Kruntoradova K, Dolezal T. The impact of anti-TNF (etanercept) therapy on work productivity in patients with rheumatoid arthritis, psoriatic arthritis and psoriasis in the Czech republic. Value in Health. 2015;18 (7):A649.
762. Moots J. Burden of rheumatoid arthritis in emerging and developed countries. Conference abstract. EULAR 2014.
763. Nafees B, Lloyd A, Gaich CL, Birt J, Hughes RA. Patient preferences for biologic treatments in rheumatoid arthritis. Arthritis and Rheumatism. 2012;64:S213.
764. Nordberg LB, Lie E, Aga AB, Maehlen MT, Inge Olsen C, Uhlig T, et al. The rheumatoid arthritis impact of disease score is associated with disease activity by clinical, laboratory and ultrasonographic measures: Validation in an inception cohort of DMARD naive patients with rheumatoid arthritis. Arthritis and Rheumatology. 2014;66:S150.
765. Pamuk ON, Cetin P, Solmaz D, Ertenli I, Akar S, Karaaslan Y, et al. Work producivity in rheumatoid arthritis: Analysis from multicenter Turkish study. Annals of the Rheumatic Diseases. 2015;74:233.
766. Panasyuk E, Nasonov E, Nasonova VA. Tocilizumab improved of the quality of the life patients with severe/moderate RA (LORNET Study). Annals of the Rheumatic Diseases. 2015;74:722-3.
767. Pedersini R, Karateev DE, Vasilescu RS, Alvir JM, Spurden D, Smolen JS. The burden of rheumatoid arthritis in Russia. Value in Health. 2015;18 (7):A651.
768. Roskidaylo A, Lipina M, Makarov S, Makarov M, Amirdjanova V. Arthroscopic synovectomy for the rheumatoid elbow (short-term outcome). Annals of the Rheumatic Diseases. Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR. 2013;72(no pagination).
769. Roskidaylo A, Logunov A, Makarov S, Amirdjanova V. Total elbow replacement coonrad-morrey in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR. 2013;72(no pagination).
770. Shidara K, Nakajima A, Inoue E, Hoshi D, Tanaka E, Inoue Y, et al. Sustaining remission as defined by the new ACR/EULAR criteria leads to better quality of life in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases.

Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR. 2013;72(no pagination).
771. Shimizu Y, Nakajima A, Inoue E, Tanaka E, Kobayashi A, Seto Y, et al. Functional disability and quality of life are more likely improved in patients with rheumatoid arthritis who achieved the new ACR/EULAR remission criteria compared to DAS28 remission in daily practice. Arthritis and Rheumatism. 2013;65:S566.
772. Strand V, Genovese M, Mallya U, Richards H, Mpofu S. Improvements in health-related quality of life (HRQOL) in patients with rheumatoid arthritis (RA) receiving secukinumab: Results of a dose-finding study. Annals of the Rheumatic Disease. Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR. 2012;71(no pagination).
773. Strandberg-Larsen M, Hansen BB, Gothberg M, Valencia X. Outcome differences in algorithms used for indirect mapping of utility values from HAQ-DI: An assessment based on phase 2A clinical trial data in patients with rheumatoid arthritis after treatment with NNC0109-0012 (anti-II-20 MAB). Value in Health. 2012;15 (7):A476.
774. Sung YK, Yoshida K, Prince FHM, Frits MA, Choe JY, Chung WT, et al. Quality of life in rheumatoid arthritis: Cross-national comparison study between us and South Korea. Arthritis and Rheumatism. 2013;65:S438-S9.
775. Tanaka Y, Shinmura Y, Nakajima R, Muramatsu T, Komatsu S, Kubo T, et al. Economic impact of adalimumab treatment in japanese patients with rheumatoid arthritis: Analysis of 24 weeks data from the anouveau study. Arthritis and Rheumatism. 2013;65:S1011-S2.
776. Tang CH, Hsu PN, Hsu JY, Fang CH. Health-state utilities in measuring health-related quality of life among patients with rheumatoid arthritis in Taiwan. Value in Health. 2013;16 (7):A568.
777. Tang CH, Hsu JY, Hsu PN. Using health assessment questionnaire-disability index to estimate EQ-5D utility values for patients with rheumatoid arthritis in Taiwan. Value in Health. 2014;17 (7):A374.
778. Tatangelo M, Tomlinson G, Bombardier C. Derivation and comparison of utility scores for economic evaluation in large datasets: Modelling patient level EQ-5D using the Ontario best practices research initiative. Journal of Rheumatology. 2015;42 (7):1318.
779. Taylor PC, Gomez-Reino JJ, Caporali R, Alten R, Bertin P, Sullivan E, et al. Correlation of rheumatologists' perceptions of RA severity with observed disease activity, patient impact and treatment patterns. Arthritis and Rheumatology. Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP. 2015;67(no pagination).
780. Verstappen SM, Lunt M, Barton A, Anderson J, Hadfield K, Hyrich KL. Patient acceptable symptom state in rheumatoid arthritis patients starting methotrexate correlates with age and patient reported outcomes. Annals of the Rheumatic Disease. Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR. 2012;71(no pagination).
781. Yalakki L. Comparing quality of life in low disease activity: rheumatoid arthritis patients, receiving biologics and combination DMARD. Rheumatology 2015 BSR Conference.
782. Andersson M, Larsson I. Reasons to stop drinking alcohol among patients with rheumatoid arthritis-a mixed method study. Annals of the Rheumatic Diseases. 2016;75:1295.
783. Efthymiadou O, Kanavos P, Mossman J. Differentiation of health related quality of life outcomes between patient populations; results from patients with breast cancer, rheumatoid arthritis, multiple sclerosis, rare cancers and rare diseases. Value in Health. 2016;19 (7):A478.

784. Ishikawa H, Abe A, Murasawa A, Kojima T, Kojima M, Ishiguro N, et al. Orthopedic surgical intervention aiming at higher level of quality of life and mental wellness for the patients with rheumatoid arthritis. A prospective cohort study of 276 surgicallytreated patients. Annals of the Rheumatic Diseases. 2016;75:195-6.
785. Ishikawa H, Abe A, Murasawa A, Kojima T, Kojima M, Ishiguro N, et al. Systemic effect of wrist surgery on quality of life and mental wellness for the patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2016;75:213.
786. Laires PA, Mourao AF, Ribeiro C, Borges J, Goncalves MJ, Bernardes JM, et al. Real-world quality-adjusted life-years gains in Portuguese patients with rheumatoid arthritis following 1 year of golimumab treatment. Value in Health. 2016;19 (7):A530.
787. Malm K, Bremander A, Andersson MLE, Bergman S, Larsson I. Quality of life in patient with established rheumatoid arthritis: A qualitative study. Annals of the Rheumatic Diseases. 2016;75:1308.
788. Pongmesa T, Munchey R. Health-related quality of life in patients with rheumatoid arthritis at uttaradit hospital, Thailand. Value in Health. 2016;19 (7):A917.
789. Rosa-Goncalves D, Bernardes M, Costa L. Determinants of functional capacity in patients with established rheumatoid arthritis-a cross-sectional study. Annals of the Rheumatic Diseases. 2016;75:1241.
790. Takeuchi T, Karpouzas G, Thorne C, McQuarrie K, Sheng S, Xu W, et al. Work productivity/interference and general health status improvements with sirukumab, an anti-IL-6 cytokine monoclonal antibody, in patients with active rheumatoid arthritis despite treatment with disease-modifying anti-rheumatic drugs: Results from the phase 3 sirround-d study. Value in Health. 2016;19 (7):A542.
791. Triantafyllias K, Leiss R, Lauter A, De Blasi M, Hesse M, Schwarting A. Quality of life indexes in patients with very early rheumatoid arthritis (VERA): A two center subgroup analysis from the ADAPTHERA cohort. Annals of the Rheumatic Diseases. 2016;75:969.
792. Joint Formulary Committee. British National Formulary. Available at: http://www.bnf.org/bnf/index.htm (Accessed April 2017).
793. Bansback N, Zhang W, Walsh D, Kiely P, Williams R, Guh D, et al. Factors associated with absenteeism, presenteeism and activity impairment in patients in the first years of RA. Rheumatology. 2012;51(2):375-84.
794. Barrett EM, Scott D, Wiles NJ. The impact of rheumatoid arthritis on employment status in the early years of disease: a UK community-based study. Rheumatology. 2000;39:1403-9.
795. Bedenbaugh AV, Qizilbash N, Dunkel J, San Jose B, Mendez I. Real-World Utilization Of Certolizumab Pegol (Czp) For The Treatment Of Rheumatoid Arthritis (Ra) In The United Kingdom. Value in Health. 2014;17(3):A42.
796. Bykerk VP. Reduction of Disease Burden on Workplace and Household Productivity Following 52 Weeks of Treatment with Certolizumab Pegol in Combination with Methotrexate in DMARD-Naïve Patients with Active, Severe, Progressive Rheumatoid Arthritis. 2015 ACR/ARHP Annual Meeting Conference Abstract.
797. Callaghan R, Prabu A, Allan RB, Clarke AE, Sutcliffe N, Pierre YS, et al. Direct healthcare costs and predictors of costs in patients with primary Sjogren's syndrome. Rheumatology. 2007;46(1):105-11.
798. Cooper NJ, Mugford M, Scott DG, Barrett EM, Symmons DP. Secondary health service care and second line drug costs of early inflammatory polyarthritis in Norfolk, UK. Journal of Rheumatology. 2000;27(9):2115-22.
799. Currie CJ, Poole CD, Singh A, Reynolds A. Estimation of costs of health care for people with rheumatoid arthritis for varying degrees of disability as measured by

the health assessment questionnaire in the United Kingdom. Value in Health. 2010;13 (3):A125.
800. Fitzpatrick R, Buchan S. Optimising methotrexate therapy and reducing total treatment costs in rheumatoid arthritis. Rheumatology. 2011;50:iii66.
801. Fitzpatrick R, Keary IP. The impact of service delivery options on the cost of subcutaneous methotrexate for the management of rheumatoid arthritis patients. Rheumatology. 2011;50:iii64.
802. Kennedy N, Stokes E, O'Shea E, Murphy TB, Bresnihan B, FitzGerald O. Inpatient and outpatient rehabilitation for patients with rheumatoid arthritis: A clinical and economic assessment. Journal of Medical Economics. 2007;10(4):515-28.
803. Kobelt G, Jonsson L, Lindgren P, Young A, Eberhardt K. Modeling the progression of rheumatoid arthritis: a two-country model to estimate costs and consequences of rheumatoid arthritis. Arthritis & Rheumatism. 2002;46(9):2310-9.
804. Kronisch C, McLernon DJ, Dale J, Paterson C, Ralston SH, Reid DM, et al. Brief Report: Predicting Functional Disability: One-Year Results From the Scottish Early Rheumatoid Arthritis Inception Cohort. Arthritis & Rheumatology. 2016;68(7):1596-602.
805. Lambert CM, Hurst NP, Lochhead A, McGregor K, Hunter M, Forbes J. A pilot study of the economic cost and clinical outcome of day patient vs inpatient management of active rheumatoid arthritis. British Journal of Rheumatology. 1994;33(4):383-8.
806. Mattila K, Buttgereit F, Tuominen R. Influence of rheumatoid arthritis-related morning stiffness on productivity at work: results from a survey in 11 European countries. Rheumatology International. 2015;35(11):1791-7.
807. McIntosh E. The cost of rheumatoid arthritis. British Journal of Rheumatology. 1996;35(8):781-90.
808. McWilliams DF, Young A, Kiely P, Walsh DA. Self-reported patterns of job loss and social security benefits claims in early rheumatoid arthritis: The eran cohort. Annals of the Rheumatic Disease. Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR. 2012;71(no pagination).
809. Nikiphorou E, Dixey J, Williams P, Morris S, Young A. Osteoporotic fracture in rheumatoid arthritis (RA): A study of incidence, predictive factors and economic burden from a 25 year RA inception cohort. Osteoporosis International. 2012;23:S159.
810. Nikiphorou E, Carpenter L, Dixey J, Williams P, Kiely P, Walsh D, et al. A study of incidence, risk factors and economic burden of osteoporotic fracture in rheumatoid arthritis (RA): Results from two UK inception cohorts. Annals of the Rheumatic Diseases. Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR. 2013;72(no pagination).
811. Nikiphorou E, Morris S, MacGregor A, Cooper N, Chipping J, Symmons D, et al. A prospective, multi-centre, prevalence-based cost-of-illness study of RA in the UK. Relative costs of biologics and orthopaedic surgery in established disease. Annals of the Rheumatic Diseases. Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR. 2013;72(no pagination).
812. Nikiphorou E, Davies C, Mugford M, Cooper N, Brooksby A, Bunn DK, et al. Direct health costs of inflammatory polyarthritis 10 years after disease onset: Results from the norfolk arthritis register. Journal of Rheumatology. 2015;42(5):794-8.
813. Poole CD, Currie CJ, Holden S, Singh A. Impact of disease severity on the total, health-related, financial costs of treatment of people with rheumatoid arthritis in the United Kingdom. Value in Health. 2012;15 (4):A36-A7.

814. Pugner KM, Scott DI, Holmes JW, Hieke K. The costs of rheumatoid arthritis: an international long-term view. Seminars in Arthritis & Rheumatism. 2000;29(5):305-20.
815. Pullar T, Capell HA, Millar A, Brooks RG. Alternative medicine: Cost and subjective benefit in rheumatoid arthritis. British Medical Journal. 1982;285(6355):1629-31.
816. Van Haselen RA, Graves N, Dahiha S. The costs of treating rheumatoid arthritis patients with complementary medicine: Exploring the issue. Complementary Therapies in Medicine. 1999;7(4):217-21.
817. Young A, Prouse P, Williams P, Devlin J, Koduri G, Pattison D, et al. The effect of rheumatoid arthritis (RA) on job loss & work productivity. Results from an inception cohort with 10 year follow up. Rheumatology. 2009;48:i111.
818. Emery P, Solem C, Majer I, Cappelleri JC, Tarallo M. A European chart review study on early rheumatoid arthritis treatment patterns, clinical outcomes, and healthcare utilization. Rheumatol Int. 2015;35(11):1837-49.
819. Holden SE, Currie CJ, Lennon M, Reynolds AV, Moots RJ. Cost of dose escalation in people with rheumatoid arthritis treated with tumour necrosis factor inhibitors across Europe. Clin Exp Rheumatol. 2016;34(4):679-84.
820. Molinier L, Bauvin E, Combescure C, Castelli C, Rebillard X, Soulie M, et al. Methodological considerations in cost of prostate cancer studies: a systematic review. Value in Health. 2008;11(5):878-85.

Pfizer Limited
Walton Oaks, Dorking Road, Walton on the Hill,
Tadworth, Surrey KT20 7NS, UK
Telephone: +44 (0)1304 616161

Worldwide Biopharmaceutical Businesses

Meindert Boysen

Programme Director Technology Appraisals
National Institute for Health and Care Excellence
Level 1A | City Tower | Piccadilly Plaza
Manchester M1 4BT
United Kingdom

14 July 2017

CONFIDENTIAL

Single Technology Appraisal
Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease modifying anti-rheumatic drugs [ID526]

Dear Meindert,

Pfizer would like to thank NICE for its continued engagement and dialogue. In particular, we would like to convey our appreciation for NICE's flexibility in recent months when scheduling the assessment of tofacitinib (Xeljanz), in light of receiving a marketing authorisation from the European medicines Agency (EMA) earlier than expected on 31st March 2017.

During the recent fact check of the ERG report for the single technology appraisal of tofacitinib, we identified an error in Section 4.8 of our submission when quality assuring the ERG reporting of tofacitnib data. The data in Table 57, which presented patient level data analyses of the ORAL clinical trial programme for Estimate 2 of the ORAL Sync trial, are incorrect. Consequently, the efficacy data of tofactinib relative to the control are underestimated, which are used to inform the network meta-analyses (NMA) presented in our submission, and response to the ERG clarification questions.

We have included an appendix below, which outlines how the error occurred, and presents the corrected values, NMA and economic analyses. The values of all other ORAL trial patient level data remained unchanged.

Overall the error correction does not change the conclusions of the cost-effectiveness analyses presented in the STA, Pfizer's ERG clarification response, nor that of the ERG as outlined in their report. However, the change is clinically meaningful, as it affects the overall ranking of tofacitinib within the network meta-analysis efficacy ranking. Therefore, we would like the ERG and the Appraisal Committee to consider this within their assessment of tofacitinib.

Please do not hesitate to get in touch for any further information or analyses you would like to obtain from Pfizer in order to facilitate the NICE decision making process.

Yours sincerely,

Angela Blake
Head of UK Health and Value
Pfizer UK

Registered in England: No 526209
Registered Office: Ramsgate Road
Sandwich, Kent CT13 9NJ, UK

Appendix A

1 *Tofacitinib Estimate 2 error in the company submission (CS) and Evidence Review Group (ERG) report*

During our review of the ERG report, and in particular Figures 2 to 6 (pages 83 to 86), Pfizer identified an error in the ORAL Sync patient level data Estimate 2, which was presented in Table 57 of the CS (page 160). This estimate value was unfortunately used in the NMA and subsequently in the economic analyses in the CS and the ERG clarification response analyses. All other values presented in CS tables 56 and 57 are correct. Below, Pfizer would like to summarise the error and provide revised tables, network meta-analysis (NMA) results and key economic analyses.

1.1 *Summary of error*

In the absence of comparative 6 month data due to the early escape design, these two estimates are presented as the possible range of clinical efficacy for tofacitinib compared to placebo within the ORAL trials. As part of the patient level data analyses, Pfizer conducted several scenarios using non-responder imputations (NRI) with and without advancement penalty (AP). Table 1 and 2 (below) present the values from the original Table 56 and 57 of the CS (section 4.8.1.2, pages 159-160). Table 1 presents Estimate 1 based on NRI applied at month 3 to placebo, but not to tofactinib. In Estimate 2 (Table 2) NRI with AP was applied to both treatment arms.

During the patient level data analyses, a copy and paste error occurred in the calculation of Estimate 2 for ORAL Sync. For the placebo arm this effectively resulted in including all placebo-randomised patients who received tofacitinib from month 3 to 6. Therefore the efficacy values for placebo in Table 2 are confounded by patients receiving active treatment with tofacitinib between the months 3 and 6. Additionally, the analysis was performed on the full data set of the Oral Sync trial, including bDMARD experienced patients, rather than exclusively on the cDMARD-IR population.

This simple copy and paste error at the patient level data analysis stage unfortunately carried through to the NMA and CS write up.

Table 3 presents the correct patient level data analysis values for ORAL Sync; NRI with AP for tofacitinib and for placebo, excluding bDMARD experienced patients, which is reflected in the matching total patient numbers of Estimate 1 (Table 1) for the ORAL Sync analyses. The values of all other ORAL trial patient level data remains unchanged.

Correcting for the ORAL Sync Estimate 2 error does not change the cost-effectiveness conclusion as presented in the CS or by the ERG.

1.2 *Patient level data analyses results*

- *Table 1: Estimate 1 for second-line combination therapy trials (NRI no AP) – (Table 56 of CS)*
- *Table 2: Estimate 2 for second-line combination therapy trials (NRI with AP) – (Table 57 of CS)*
- *Table 3: Estimate 2 for second-line combination therapy trials (NRI with AP), including corrected ORAL Sync estimate - (replacing Table 57 of CS)*

Table 1: Estimate 1 for second-line combination therapy trials

	No response	*Moderate*	*Good*	*Moderate & Good*	*Total*
ORAL Scan					
Tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo to tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORAL Sync					
Tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo to tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORAL Standard					
Tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo to tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BD, twice daily.

Table 2: Estimate 2 for second-line combination therapy trials

	No response	*Moderate*	*Good*	*Moderate & Good*	*Total*
ORAL Scan					
Tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo to tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORAL Sync					
Tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo to tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORAL Standard					
Tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo to tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BD, twice daily.

Table 3 Estimate 2 for second-line combination therapy trials, with corrected ORAL Sync estimate

	No response	*Moderate*	*Good*	*Moderate & Good*	*Total*
ORAL Scan					
Tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo to tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORAL Sync – corrected					
Tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo to tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORAL Standard					
Tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo to tofacitinib 5 mg BD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BD, twice daily.

1.3 *Network meta-analysis (NMA) results*

Pfizer updated the NMA using the corrected Estimate 2 for Oral Sync (note: the values of the other ORAL trials remained unchanged).
For a better comparison of the magnitude of change, the results are conveniently presented below by listing the ERG clarification response tables based on the incorrect Estimate 2 first, followed by the Pfizer Estimate 2 corrected tables.

1.3.1 *NMA results based on incorrect ORAL Sync Estimate 2*

Table 4 and 5 present the NMA results provided by Pfizer on the 22nd of May at the ERG clarification response stage, applying the ERG requested changes.
The results were based on the incorrect ORAL Sync Estimate 2 PLD value on the following ERG requested set up:

- *A random effects probit model with an informative prior*
- *EULAR response for ORAL trials derived using DAS ESR with all trial data by applying non-responder imputation Estimate 2.*
- *Use the individual EULAR results from trials in the NMA, i.e. not pooling individual patient-level data from ORAL trials.*
- *Including the SWEFOT trial*
- *Based on evidence network figure 1*

Figure 1: cDMARD-IR – evidence network for both EULAR moderate response and EULAR good response (as separate analyses)

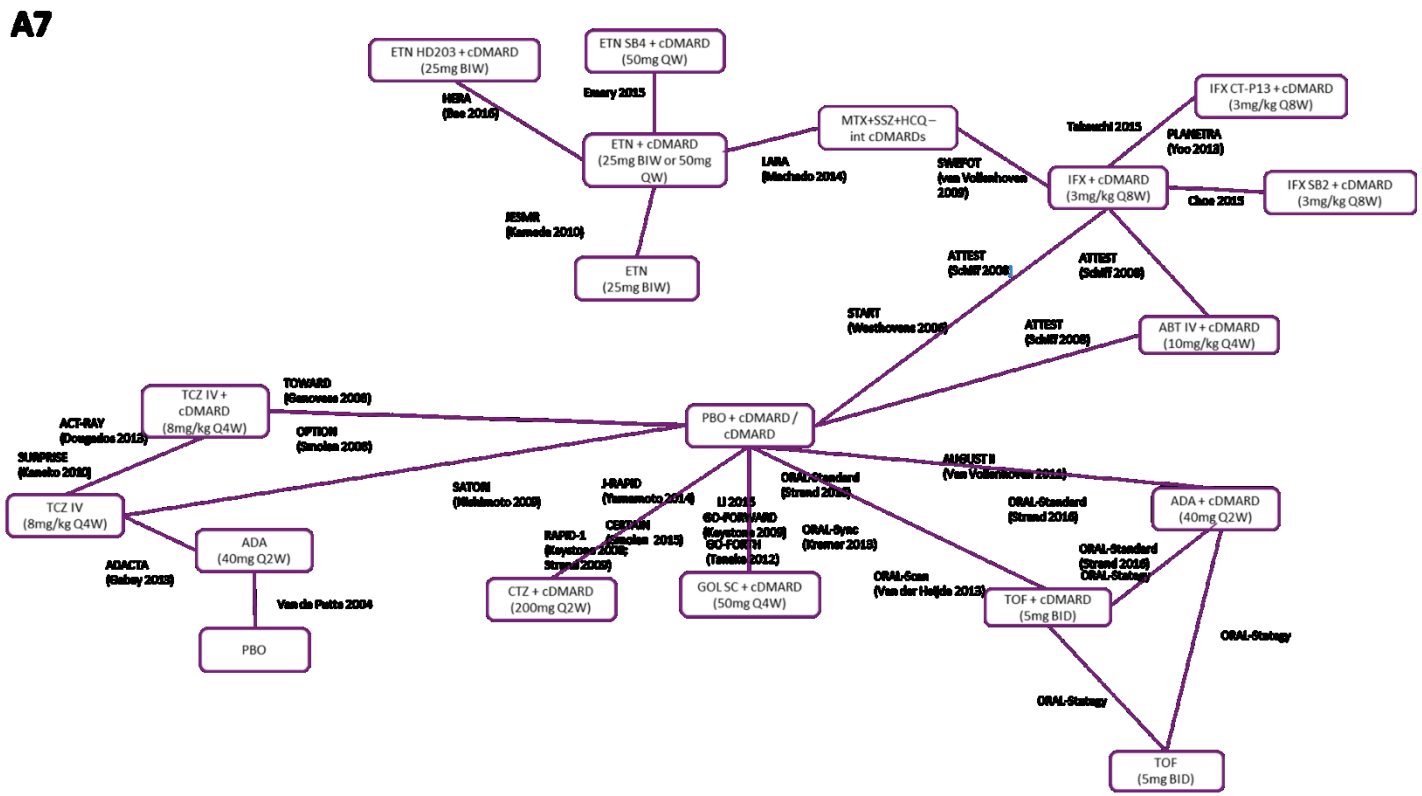


Table 4: cDMARD-IR EULAR response (containing incorrect ORAL Sync Estimate 2) – effects of interventions relative to placebo + cDMARD on the probit scale (random effects)

Intervention	*Log odds of no response vs placebo + csDMARD*				
	Mean	*SD*	*Median*	*95% CrI*	
				Lower	*Higher*
ABT + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CZP 200 mg Q2W SC + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN HD203 25 mg BIW + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN SB4 50 mg QW SC + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX CT-P13 3 mg/kg Q8W + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX SB2 + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOC + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF 5 mg BID + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN 25 mg SC BIW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF 5 mg BID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intensified csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A negative value indicates that the treatment is better than placebo + csDMARD at increasing the probability of an improved EULAR response. Grey cells indicate a significant result, shown by CrIs which exclude the null value. Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CZP, certolizumab pegol; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; LEF, leflunomide; MTX, methotrexate; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; SFZ, sulfasalazine; TOC, tocilizumab; TOF, tofacitinib.

Table 5: cDMARD-IR EULAR response (containing incorrect ORAL Sync Estimate 2) – probability of achieving a good response or at least a moderate response

Treatment	*Good EULAR response*					*At least a moderate EULAR response*				
	Mean	*SD*	*Median*	*95% CrI*		*Mean*	*SD*	*Median*	*95% CrI*	
				Lower	*Upper*				*Lower*	*Upper*
PBO + cDMARD	[redacted]									
ABT + cDMARD	[redacted]									
ADA + cDMARD	[redacted]									
CTZ 200mg Q2W SC + cDMARD	[redacted]									
ETN + cDMARD	[redacted]									
ETN HD203 25 mg BIW + cDMARD	[redacted]									
ETN SB4 50mg QW SC + cDMARD	[redacted]									
GOL + cDMARD	[redacted]									
IFX + cDMARD	[redacted]									
IFX CT-P13 3mg/kg Q8W + cDMARD	[redacted]									
IFX SB2 + cDMARD	[redacted]									
TCZ + cDMARD	[redacted]									
TOF 5mg BID + cDMARD	[redacted]									
PBO	[redacted]									
ADA	[redacted]									
TCZ	[redacted]									
ETN 25mg SC BIW	[redacted]									
TOF 5 mg BID	[redacted]									
intensified cDMARD	[redacted]									

Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; TCZ, tocilizumab; TOF, tofacitinib.

1.3.2 *NMA results based on correct ORAL Sync Estimate 2*

Table 6 and 7 present the NMA results using the correct ORAL Sync Estimate 2 PLD value on the following ERG requested set up:

- *A random effects probit model with an informative prior*
- *EULAR response for ORAL trials derived using DAS ESR with all trial data by applying non-responder imputation Estimate 2.*
- *Use the individual EULAR results from trials in the NMA, i.e. not pooling individual patient-level data from ORAL trials.*
- *Including the SWEFOT trial*
- *Based on evidence network figure 1*

Table 6: csDMARD-IR NMA EULAR response – effects of interventions relative to placebo + csDMARD on the probit scale (random effects) - containing correct ORAL Sync Estimate 2

Intervention	*Log odds of no response vs placebo + csDMARD*				
	Mean	*SD*	*Median*	*95% CrI*	
				Lower	*Higher*
ABT + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CZP 200 mg Q2W SC + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN HD203 25 mg BIW + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN SB4 50 mg QW SC + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX CT-P13 3 mg/kg Q8W + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX SB2 + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOC + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF 5 mg BID + csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN 25 mg SC BIW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF 5 mg BID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intensified csDMARD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A negative value indicates that the treatment is better than placebo + csDMARD at increasing the probability of an improved EULAR response. Grey cells indicate a significant result, shown by CrIs which exclude the null value. Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CZP, certolizumab pegol; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; LEF, leflunomide; MTX, methotrexate; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; SFZ, sulfasalazine; TOC, tocilizumab; TOF, tofacitinib.

Table 7: csDMARD-IR EULAR response – probability of achieving a good response or at least a moderate response - containing correct ORAL Sync Estimate 2

Treatment	Good EULAR response					At least a moderate EULAR response				
	Mean	SD	Median	95% CrI		Mean	SD	Median	95% CrI	
				Lower	Upper				Lower	Upper
PBO + csDMARD	[redacted]									
ABT + csDMARD	[redacted]									
ADA + csDMARD	[redacted]									
CZP 200 mg Q2W SC + csDMARD	[redacted]									
ETN + csDMARD	[redacted]									
ETN HD203 25 mg BIW + csDMARD	[redacted]									
ETN SB4 50 mg QW SC + csDMARD	[redacted]									
GOL + csDMARD	[redacted]									
IFX + csDMARD	[redacted]									
IFX CT-P13 3 mg/kg Q8W + csDMARD	[redacted]									
IFX SB2 + csDMARD	[redacted]									
TOC + csDMARD	[redacted]									
TOF 5 mg BID + csDMARD	[redacted]									
PBO	[redacted]									
ADA	[redacted]									
TOC	[redacted]									
ETN 25 mg SC BIW	[redacted]									
TOF 5 mg BID	[redacted]									
Intensified csDMARD	[redacted]									

Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CZP, certolizumab pegol; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; TOC, tocilizumab; TOF, tofacitinib.

1.3.3 *Conclusion*

Correcting for the Estimate 2 ORAL Sync error only marginally affects the comparative efficacy results of the biologics compared to cDMARD, with only infliximab biosilimars and adalimumab monotherapy changing statistical significance levels. However, the efficacy compared to cDMARD for adalimumab + cDMARD, tofacitinib + cDMARD and tofacitinib monotherapy markedly change from [redacted] to [redacted], respectively. Therefore the possible range of clinical efficacy between Estimate 1 and corrected Estimate 2 has narrowed.

1.4 *Cost-effectiveness analysis results*

The updated economic results for tofacitinib combination therapy and monotherapy in the cDMARD-IR population are presented below. The results were derived by using the revised NMA results from Tables 6 and 7 (above), with the corrected model provided to ERG at the ERG clarification stage.

Again, for a better comparison of the magnitude of change, the results are conveniently presented as economic analyses results based on the incorrect Estimate 2 NMA first (Table 8 and 9), followed by the economic analyses results based on the corrected Estimate 2 (table 10 and 11), for combi-therapy and monotherapy respectively .

Both sets of results were based on corrected model provided to ERG at the ERG clarification stage.

1.4.1 *CE results based on NMA using incorrect ORAL Sync Estimate 2*

Table 8 Base-case results for patients who are cDMARD-IR receiving combination therapy, Norton progression – based on NMA (table 4 + 5) containing incorrect ORAL Sync Estimate 2

Strategy	*Cost*	*QALYs*	*Inc. Cost*	*Inc QALY*	*ICER vs baseline*	*ICER*
MTX	[redacted]	[redacted]	[redacted]	[redacted]		
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*Ext. Dominated*
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*Ext. Dominated*
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*£33,635*
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*Dominated*
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*£55,624*
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*Dominated*
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*£261,468*
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*Dominated*

Table 9 Base-case results for patients who are cDMARD-IR receiving monotherapy, Norton progression - based on NMA (table 4 + 5) containing incorrect ORAL Sync Estimate 2

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
SUL	[redacted]	[redacted]	[redacted]	[redacted]		
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,799
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,851

1.4.2 *CE results based on NMA using correct ORAL Sync Estimate 2*

Table 10 Base-case results for patients who are cDMARD-IR receiving combination therapy, Norton progression – based on NMA (table 6 + 7) containing correct ORAL Sync Estimate 2

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]		
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,864
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,469
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£107,710
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 11 Base-case results for patients who are cDMARD-IR receiving monotherapy, Norton progression - based on NMA (table 6 + 7) containing correct ORAL Sync Estimate 2

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
SUL	[redacted]	[redacted]	[redacted]	[redacted]		
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,729
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,759

1.5 *Conclusions*

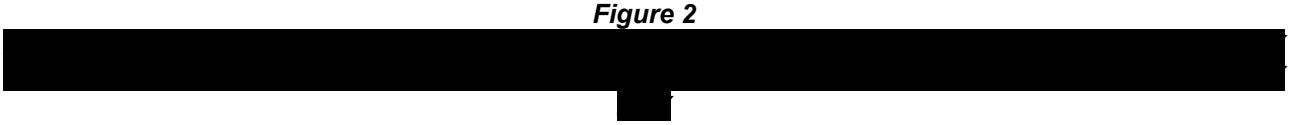
Correcting for the ORAL Sync Estimate 2 error does not change the cost-effectiveness conclusion as presented in the CS or by the ERG.

However, the correction of this error affects the efficacy ranking as presented in the ERG report Figures 2 and 3, and 5 and 6 (pages 83 to 86). This would apply to Estimate 2 values of tofacitinib + cDMARD, adalimumab + cDMARD and tofactinib monotherapy. The revised graphics are presented in Appendix 2, and can be used by the ERG to directly replace the current graphics in ERG report.

Appendix 2

- *Figure 2 presents the revised combi-therapy rankogram graphic based on Estimate 1 and Estimate 2 (incl. corrected ORAL Sync values) NMAs to replace figure 2 of the ERG report on page 83*
- *Figure 3 presents the revised combi-therapy rankogram graphic based on Estimate 2 (incl. corrected ORAL Sync values) NMAs, with and without prior-biologics trials included, to replace figure 5 of the ERG report on page 85*
- *Figure 4 presents the revised monotherapy rankogram graphic based on Estimate 1 and Estimate 2 (incl. corrected ORAL Sync values) NMAs to replace figure 3 of the ERG report on page 84*
- *Figure 5 presents the revised monotherapy rankogram graphic based on Estimate 2 (incl. corrected ORAL Sync values) NMAs, with and without prior-biologics trials included, to replace figure 6 of the ERG report on page 86*

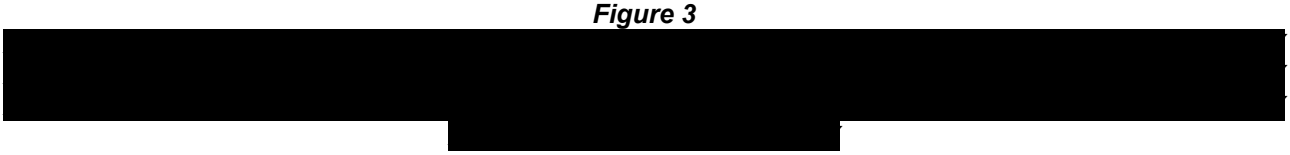
Figure 2



EMPTY

* statistically significant compared to cDMARD

Figure 3



EMPTY

* statistically significant compared to cDMARD

Registered in England: No 526209
Registered Office: Ramsgate Road
Sandwich, Kent CT13 9NJ, UK

Figure 4

[redacted]

* statistically significant compared to cDMARD

Figure 5

[redacted]

Registered in England: No 526209
Registered Office: Ramsgate Road
Sandwich, Kent CT13 9NJ, UK

ADDENDUM

Contents

1 Odd ratios (OR) for all treatments including monotherapies compared to TOF+MTX.

Table 1 ORs and probabilities of good and moderate EULAR response for each treatment used in the cDMARD-IR population vs TOF+MTX

Therapy	based on NMA using ORAL trial Estimate 1					based on NMA using ORAL trial Estimate 2					based on NMA using ORAL trial corrected Estimate 2				
	ORs compared with TOF+MTX		Probabilities of EULAR response*			ORs compared with TOF+MTX		Probabilities of EULAR response*			ORs compared with TOF+MTX		Probabilities of EULAR response*		
	Moderate or good	Good	No response	Moderate or good	Good response	Moderate or good	Good	No response	Moderate or good	Good response	Moderate or good	Good	No response	Moderate or good	Good response
TOF + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTZ + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABT + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOC + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN#	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SUL†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TOF: tofacitinib; ABT: abatacept; TOC: tocilizumab; ADA: adalimumab; CTZ: certolizumab pegol; ETN: etanercept; GOL: golimumab; IFX: infliximab; RTX: rituximab; MTX: methotrexate;
*Average probabilities based on the full population of ORAL trials (Scan, Standard, Sync)
Biosimilars assumed to have same efficacy
†Assumed equal to MTX

Table 2 ORs and probabilities of good and moderate EULAR response for each treatment used in the bDMARD-IR population vs TOF+MTX

Therapy	based on NMA using ORAL trial Estimate 1					based on NMA using ORAL trial Estimate 2				
	ORs compared with TOF+MTX		Probabilities of EULAR response*			ORs compared with TOF+MTX		Probabilities of EULAR response*		
	Moderate or good	Good	No response	Moderate or good	Good response	Moderate or good	Good	No response	Moderate or good	Good response
TOF + MTX†										
ABT + MTX										
ETN + MTX#†										
GOL + MTX										
TOC + MTX†										
RTX + MTX										
MTX										

Abbreviations: TOF: tofacitinib; ABT: abatacept; TOC: tocilizumab; ETN: etanercept; GOL: golimumab; MTX: methotrexate; RTX: rituximab

*Average probabilities based on the full population of ORAL trials (Step)

Biosimilars assumed to have same efficacy

†Monotherapy to be assumed to be the same as combination therapy

2 Deterministic rounding to nearest HAQ-DI score

HAQ-DI scores range from 0 to 3, with higher scores indicating greater disability. HAQ-DI scores lie on a discrete scale with step values of 0.125, resulting in 25 points. In the model, patients start with a baseline HAQ-DI score and the HAQ-DI progression of patients is modified reflecting treatment response, loss of treatment efficacy or disease progression over time. Changes applied to the HAQ-DI score are usually estimates based on average changes observed in trials or registries and therefore are rarely exact multiples of 0.125. Thus, after applying such a change, the resulting HAQ-DI score of a patient has to be assigned to a valid HAQ-DI score. The company approached this issue by rounding the values to the nearest valid discrete HAQ-DI score. The ERG notes that this approach 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. An example would be that of small changes (lower than 0.0625), that would always be rounded down to zero. In order to avoid this problem, the AG in TA375 rounded up with a probability inversely proportional to the distance of the value to the closest valid HAQ-DI score, and rounded down otherwise. For example, a change of 0.4 would have a 0.8 probability of being rounded down to 0.375 and a probability of 0.2 of being rounded up to 0.5

The ERG are correct that HAQ-DI scores for each patient are rounded deterministically to the nearest 0.125 in the tofacitinib economic model; with changes in HAQ-DI scores between 0 and 0.0625 rounded down and changes between 0.0625 and 0.125 rounded up.

Unfortunately, it was not possible to provide the ERG with an updated version of the model within the given timeframe. Whilst probabilistic rounding has the potential to negate the risk that values might be rounded up more often that down (or vice versa), rounding is applied consistently across treatments irrespective of time, treatment modality and sequence to minimise the risk of introducing bias to estimates of HAQ-DI scores and subsequent cost-effectiveness results. Over a sample of 10,000 patients in the deterministic model, it is likely that values would tend towards the mean HAQ score, irrespective of the approach to rounding. Stability of model outputs is tested extensively in probabilistic sensitivity analysis and results did not significantly differ from the base case. We have included a simplified data set to test the assumption within this document.

Overall, the analysis demonstrates that when comparing the Pfizer implemented approach with the AG approach, 7,459 HAQ scores were identical, 1,243 scores were rounded down and 1,297 were rounded up. Although in 25% instances the HAQ-DI rounding differed between the methods, the direction was approximately evenly spread, which should reassure that overall the results of the economic analyses within this document can be viewed as robust.

Simple HAQ rounding impact analyses.xlsx

3 Results

For clarity, we have provided economic results including the original PAS ([redacted]) and the revised PAS ([redacted]), for:

1. The post ERG clarification company basecase for Estimate 1 and Estimate 2
2. The post ERG clarification company basecase for Estimate 2-corrected

The post ERG clarification company basecase model set up included:

- Probit network meta-analyses as set out by the ERG clarification request for cDMARD-IR and bDMARD-IR populations
- Adjusted odd ratio (OR) calculations for all treatments comparing to tofacitinib+MTX, including monotherapies (presented in table 1-2)
- Only Norton et al progression for all csDMARDs including palliative care

Please note, we ran model analyses using 20,000 patients to reduce uncertainty in the deterministic analyses, as we were unable to complete probabilistic analysis within the time constraints, as these analyses require substantial model run time. Please note, the results presented in the CS for the deterministic and probabilistic analyses didn't differ significantly.

3.1 *cDMARD-IR population (severe RA pathway)*

3.1.1 *combination therapy (cDMARD-IR)*

Table 3 Treatment sequences for moderate-to-severe cDMARD-IR – combi-therapy

Treatment sequences	MTX	ABT+MTX	ADA+MTX	CZP+MTX	ETNb+MTX	GOL+MTX	INFb+MTX	TOC+MTX	TOF+MTX
1	MTX	ABT+MTX	ADA+MTX	CZP+MTX	ETNb+MTX	GOL+MTX	INFb+MTX	TOC+MTX	TOF+MTX
2	PBT	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX
3		TOC+MTX	TOC+MTX	TOC+MTX	TOC+MTX	TOC+MTX	TOC+MTX	MTX	TOC+MTX
4		MTX	MTX	MTX	MTX	MTX	MTX	PBT	MTX
5		PBT	PBT	PBT	PBT	PBT	PBT		PBT

Abbreviations: TOF: tofacitinib; ABT: abatacept; TOC: tocilizumab; ADA: adalimumab; CTZ: certolizumab pegol ETNb: etanercept biosimilar; GOL: golimumab; IFXb: infliximab biosimilar; RTX: rituximab; MTX: methotrexate; PBT: palliative care

Table 4 cDMARD-IR ERG base-case results for combi-therapy based on Estimate 1
[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,132
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,422
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,530
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£340,761
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 5 cDMARD-IR ERG base-case results for combi-therapy based on Estimate 2

[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,487
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£55,608
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£315,766
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 6 cDMARD-IR ERG base-case results for combi-therapy based on corrected Estimate 2

[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,803
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£55,145
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£100,354
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 7 cDMARD-IR ERG base-case results for combi-therapy based on Estimate 1

[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,378
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£91,278
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£340,761
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 8 cDMARD-IR ERG base-case results for combi-therapy based on Estimate 2

[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,084
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£65,381
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,941,604
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 9 cDMARD-IR ERG base-case results for combi-therapy based on corrected Estimate 2

[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,063
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£78,401
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£149,782
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

3.1.2 *monotherapy (MTX-intolerant)*

Table 10 Treatment sequences for moderate-to-severe cDMARD-IR - monotherapy

Treatment sequences	SUL	TOC	TOF	ETNb	ADA
1	SUL	TOC	TOF	ETNb	ADA
2	PBT	ETNb	ETNb	ADA	ETNb
3		SUL	SUL	SUL	SUL
4		PBT	PBT	PBT	PBT
5					

Abbreviations: ADA, adalimumab; ETNb, etanercept biosimilar; PBT, palliative care; SUL, sulfasalazine; TOC, tocilizumab; TOF, tofacitinib.

Table 11 cDMARD-IR ERG base-case results for monotherapy based on Estimate 1

[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,196
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext.

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
						Dominated
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,332

Table 12 cDMARD-IR ERG base-case results for monotherapy based on Estimate 2 [redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,816
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,845
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,894

Table 13 cDMARD-IR ERG base-case results for monotherapy based on corrected Estimate 2 [redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,769
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,073

Table 14 cDMARD-IR ERG base-case results for monotherapy based on Estimate 1 [redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,450
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£60,878

Table 15 cDMARD-IR ERG base-case results for monotherapy based on Estimate 2 [redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,215
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,548

Table 16 cDMARD-IR ERG base-case results for monotherapy based on corrected Estimate 2

[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,120
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£58,038

3.2 *bDMARD-IR population*

3.2.1 *combination therapy (RTX tolerant) – alongside RTX*

Table 17 Treatment sequences for severe bDMARD-IR - combi-therapy alongside RTX

Treatment sequences	RTX+MTX	after RTX	before TOC	after TOC
1	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX
2	TOC+MTX	TOF+MTX	TOF+MTX	TOC+MTX
3	MTX	MTX	TOC+MTX	TOF+MTX
4	PBT	PBT	MTX	MTX
5			PBT	PBT

Abbreviations: RTX: rituximab; PBT, palliative care; MTX: methotrexate; TOC, tocilizumab; TOF, tofacitinib.

Table 18 bDMARD-IR (alongside RTX) ERG base-case results for combi-therapy based on Estimate 1

[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
after RTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
before TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,168
after TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 19 bDMARD-IR (alongside RTX) ERG base-case results for combi-therapy based on Estimate 2

[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
after RTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
before TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,077
after TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£188,090

Table 20 bDMARD-IR (alongside RTX) ERG base-case results for combi-therapy based on Estimate 1

[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
after RTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated

before TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,120
after TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 21 bDMARD-IR (alongside RTX) ERG base-case results for combi-therapy based on Estimate 2 [redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
after RTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
before TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,180
after TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£255,506

3.2.2 *combination therapy (RTX tolerant) – compared to RTX (vs RTX)*

Table 22 Treatment sequences for severe bDMARD-IR - combi-therapy compared to RTX

Treatment sequences	RTX+MTX	TOF+MTX	ETNb+MTX	GOL+MTX	TOC+MTX	ABT+MTX
1	RTX+MTX	TOF+MTX	ETNb+MTX	GOL+MTX	TOC+MTX	ABT+MTX
2	TOC+MTX	TOC+MTX	TOC+MTX	TOC+MTX	GOL+MTX	TOC+MTX
3	MTX	MTX	MTX	MTX	MTX	MTX
4	PBT	PBT	PBT	PBT	PBT	PBT
5						

Abbreviations: TOF: tofacitinib; ABT: abatacept; TOC: tocilizumab; ETNb: etanercept biosimilar; GOL: golimumab; MTX: methotrexate; PBT: palliative care

Table 23 bDMARD-IR (vs RTX) ERG base-case results for combi-therapy based on Estimate 1 [redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£112,714
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 24 bDMARD-IR (vs RTX) ERG base-case results for combi-therapy based on Estimate 2 [redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£127,687
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 25 bDMARD-IR (vs RTX) ERG base-case results for combi-therapy based on Estimate 1

[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
RTX+MTX	[redacted]					
TOF+MTX						Dominated
GOL+MTX						Dominated
TOC+MTX						Dominated
ETNb+MTX						£112,714
ABT+MTX						Dominated

Table 26 bDMARD-IR (vs RTX) ERG base-case results for combi-therapy based on Estimate 2

[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
RTX+MTX	[redacted]					
TOF+MTX						Dominated
GOL+MTX						Dominated
TOC+MTX						Dominated
ETNb+MTX						£127,687
ABT+MTX						Dominated

3.2.3 *combination therapy (RTX intolerant) - (RTX-IT)*

Table 27 Treatment sequences for severe bDMARD-IR RTX-IT - combi-therapy

Treatment sequences	TOF+MTX	ABT+MTX	ETNb+MTX	GOL+MTX	TOC+MTX
1	TOF+MTX	ABT+MTX	ETNb+MTX	GOL+MTX	TOC+MTX
2	TOC+MTX	TOC+MTX	TOC+MTX	TOC+MTX	GOL+MTX
3	MTX	MTX	MTX	MTX	MTX
4	PBT	PBT	PBT	PBT	PBT
5					

Table 28 bDMARD-IR (RTX-IT) ERG base-case results for combi-therapy based on Estimate 1

[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
TOF+MTX	[redacted]					
GOL+MTX						Dominated
TOC+MTX						Dominated
ETNb+MTX						£32,281
ABT+MTX						Dominated

Table 29 bDMARD-IR (RTX-IT) ERG base-case results for combi-therapy based on Estimate 2

[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
TOF+MTX	[redacted]					
GOL+MTX						Dominated

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,134
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 30 bDMARD-IR (RTX-IT) ERG base-case results for combi-therapy based on Estimate 1
[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,244
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 31 bDMARD-IR (RTX-IT) ERG base-case results for combi-therapy based on Estimate 2
[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,452
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

3.2.4 *monotherapy (MTX-intolerant) (MTX-IT)*

Table 32 Treatment sequences for severe bDMARD-IR MTX-IT - monotherapy

Treatment sequences	TOF	TOC	ETNb
1	TOF	TOC	ETNb
2	SUL	SUL	SUL
3	PBT	PBT	PBT
4			
5			

Abbreviations: ETNb, etanercept biosimilar; PBT, palliative care; SUL, sulfasalazine; TOC, tocilizumab; TOF, tofacitinib.

Table 33 bDMARD-IR (MTX-IT) ERG base-case results for monotherapy based on Estimate 1
[redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,597
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 34 bDMARD-IR (MTX-IT) ERG base-case results for monotherapy based on Estimate 2 [redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,120
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 35 bDMARD-IR (MTX-IT) ERG base-case results for monotherapy based on Estimate 1 [redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,879
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Table 36 bDMARD-IR (MTX-IT) ERG base-case results for monotherapy based on Estimate 2 [redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,029
TOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

3.3 *cDMARD-IR population (moderate RA)*

3.3.1 *combination therapy (severe model)*

Table 37 Treatment sequences for moderate cDMARD-IR – combi-therapy (severe model)

Treatment sequences	MTX	TOF+MTX
1	MTX	TOF+MTX
2	PBT	RTX+MTX
3		TOC+MTX
4		MTX
5		PBT

Abbreviations: RTX: rituximab; PBT, palliative care; MTX: methotrexate; TOC, tocilizumab; TOF, tofacitinib.

Table 38 cDMARD-IR moderate RA (severe model) ERG base-case results for combi-therapy based on Estimate 1 [redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,330

Table 39 cDMARD-IR moderate RA (severe model) ERG base-case results for combi-therapy based on Estimate 2 [redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,469

Table 40 cDMARD-IR moderate RA (severe model) ERG base-case results for combi-therapy based on corrected Estimate 2

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX						
TOF+MTX						£45,595

Table 41 cDMARD-IR moderate RA (severe model) ERG base-case results for combi-therapy based on Estimate 1

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX						
TOF+MTX						£43,791

Table 42 cDMARD-IR moderate RA (severe model) ERG base-case results for combi-therapy based on Estimate 2

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX						
TOF+MTX						£43,067

Table 43 cDMARD-IR moderate RA (severe model) ERG base-case results for combi-therapy based on corrected Estimate 2

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX						
TOF+MTX						£43,123

3.3.2 *monotherapy (severe model)*

Table 44 Treatment sequences for moderate cDMARD-IR – monotherapy (severe model)

Treatment sequences	SUL	TOF
1	SUL	TOF
2	PBT	ETNb
3		SUL
4		PBT
5		

Abbreviations: ETNb, etanercept biosimilar; PBT, palliative care; SUL, sulfasalazine; TOF, tofacitinib.

Table 45 cDMARD-IR moderate RA (severe model) ERG base-case results for monotherapy based on Estimate 1

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
SUL						
TOF						£49,709

Table 46 cDMARD-IR moderate RA (severe model) ERG base-case results for monotherapy based on Estimate 2

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,635

Table 47 cDMARD-IR moderate RA (severe model) ERG base-case results for monotherapy based on corrected Estimate 2 [redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,919

Table 48 cDMARD-IR moderate RA (severe model) ERG base-case results for monotherapy based on Estimate 1 [redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,137

Table 49 cDMARD-IR moderate RA (severe model) ERG base-case results for monotherapy based on Estimate 2 [redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,272

Table 50 cDMARD-IR moderate RA (severe model) ERG base-case results for monotherapy based on corrected Estimate 2 [redacted]

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,500

3.3.3 *combination therapy (moderate model)*

Table 51 Treatment sequences for moderate cDMARD-IR – combi-therapy (moderate model)

	Moderate sequence		Severe sequence
Treatment sequences	MTX	TOF+MTX	ETNb+MTX
1	MTX	TOF+MTX	ETNb+MTX
2	PBT	MTX	RTX+MTX
3		PBT	TOC+MTX
4			MTX
5			PBT

Abbreviations: RTX: rituximab; PBT, palliative care; MTX: methotrexate; TOC, tocilizumab; TOF, tofacitinib; ETNb, etanercept biosimilar

Table 52 cDMARD-IR moderate RA (moderate model) ERG base-case results for combi-therapy based on Estimate 1 [redacted]

Strategy	Cost	QALYs	Comparison	Inc. Cost	Inc QALY	ICER
Moderate RA pathway only (up to DAS 5.1)						

MTX	[redacted]	[redacted]				
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,134
moderate RA and severe RA pathway – lifetime model						
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,457

Table 53 cDMARD-IR moderate RA (moderate model) ERG base-case results for combi-therapy based on Estimate 2 [redacted]

Strategy	Cost	QALYs	Comparison	Inc. Cost	Inc QALY	ICER
Moderate RA pathway only (up to DAS 5.1)						
MTX	[redacted]	[redacted]				
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£19,934**
moderate RA and severe RA pathway – lifetime model						
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£52,178**

Table 54 cDMARD-IR moderate RA (moderate model) ERG base-case results for combi-therapy based on corrected Estimate 2 [redacted]

Strategy	Cost	QALYs	Comparison	Inc. Cost	Inc QALY	ICER
Moderate RA pathway only (up to DAS 5.1)						
MTX	[redacted]	[redacted]				
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£19,758**
moderate RA and severe RA pathway – lifetime model						
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£49,460**

Table 55 cDMARD-IR moderate RA (moderate model) ERG base-case results for combi-therapy based on Estimate 1 [redacted]

Strategy	Cost	QALYs	Comparison	Inc. Cost	Inc QALY	ICER
Moderate RA pathway only (up to DAS 5.1)						
MTX	[redacted]	[redacted]				
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£17,108**
moderate RA and severe RA pathway – lifetime model						
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£38,680**

Table 56 cDMARD-IR moderate RA (moderate model) ERG base-case results for combi-therapy based on Estimate 2 [redacted]

Strategy	Cost	QALYs	Comparison	Inc. Cost	Inc QALY	ICER
Moderate RA pathway only (up to DAS 5.1)						
MTX	[redacted]	[redacted]				

TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£17,823**
moderate RA and severe RA pathway – lifetime model						
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£42,574**

Table 57 cDMARD-IR moderate RA (moderate model) ERG base-case results for combi-therapy based on corrected Estimate 2 [redacted]

Strategy	Cost	QALYs	Comparison	Inc. Cost	Inc QALY	ICER
Moderate RA pathway only (up to DAS 5.1)						
MTX	[redacted]	[redacted]				
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£17,663**
moderate RA and severe RA pathway – lifetime model						
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£40,429**

3.3.4 *monotherapy (moderate model)*

	Moderate sequence		Severe sequence
Treatment sequences	**SUL**	**TOF**	**ETNb**
1	SUL	TOF	ETNb
2	PBT	SUL	ADA
3		PBT	SUL
4			PBT
5			

Abbreviations: ADA, adalimumab; ETNb, etanercept biosimilar; PBT, palliative care; SUL, sulfasalazine; TOF, tofacitinib.

Table 58 cDMARD-IR moderate RA (moderate model) ERG base-case results for monotherapy based on Estimate 1 [redacted]

Strategy	Cost	QALYs	Comparison	Inc. Cost	Inc QALY	ICER
Moderate RA pathway only (up to DAS 5.1)						
SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£19,222**
moderate RA and severe RA pathway – lifetime model						
SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£46,538**

Table 59 cDMARD-IR moderate RA (moderate model) ERG base-case results for monotherapy based on Estimate 2 [redacted]

Strategy	Cost	QALYs	Comparison	Inc. Cost	Inc QALY	ICER
Moderate RA pathway only (up to DAS 5.1)						
SUL	[redacted]	[redacted]				
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£19,871**

moderate RA and severe RA pathway – lifetime model						
SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£49,967**

Table 60 cDMARD-IR moderate RA (moderate model) ERG base-case results for monotherapy based on corrected Estimate 2 [redacted]

Strategy	Cost	QALYs	Comparison	Inc. Cost	Inc QALY	ICER
Moderate RA pathway only (up to DAS 5.1)						
SUL	[redacted]	[redacted]				
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£20,011**
moderate RA and severe RA pathway – lifetime model						
SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£48,160**

Table 61 cDMARD-IR moderate RA (moderate model) ERG base-case results for monotherapy based on Estimate 1 [redacted]

Strategy	Cost	QALYs	Comparison	Inc. Cost	Inc QALY	ICER
Moderate RA pathway only (up to DAS 5.1)						
SUL	[redacted]	[redacted]				
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£17,172**
moderate RA and severe RA pathway – lifetime model						
SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£38,764**

Table 62 cDMARD-IR moderate RA (moderate model) ERG base-case results for monotherapy based on Estimate 2 [redacted]

Strategy	Cost	QALYs	Comparison	Inc. Cost	Inc QALY	ICER
Moderate RA pathway only (up to DAS 5.1)						
SUL	[redacted]	[redacted]				
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£17,748**
moderate RA and severe RA pathway – lifetime model						
SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£41,549**

Table 63 cDMARD-IR moderate RA (moderate model) ERG base-case results for monotherapy based on corrected Estimate 2 [redacted]

Strategy	Cost	QALYs	Comparison	Inc. Cost	Inc QALY	ICER
Moderate RA pathway only (up to DAS 5.1)						
SUL	[redacted]	[redacted]				
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£17,872**
moderate RA and severe RA pathway – lifetime model						

SUL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,048

4 Summary of Estimate 2 error (as per correspondence from the 17th of July 2017)

4.1 *Brief summary of error*

In the absence of comparative 6 month data due to the early escape design, these two estimates are presented as the possible range of clinical efficacy for tofacitinib compared to placebo within the ORAL trials. As part of the patient level data analyses, Pfizer conducted several scenarios using non-responder imputations (NRI) with and without advancement penalty (AP).

During the patient level data analyses, a copy and paste error occurred in the calculation of Estimate 2 for ORAL Sync. For the placebo arm this effectively resulted in including all placebo-randomised patients who received tofacitinib from month 3 to 6. Therefore the efficacy values for placebo in Table 57 of CS are confounded by patients receiving active treatment with tofacitinib between the months 3 and 6. Additionally, the analysis was performed on the full data set of the Oral Sync trial, including bDMARD experienced patients, rather than exclusively on the cDMARD-IR population.

This simple copy and paste error at the patient level data analysis stage unfortunately carried through to the NMA and CS write up.

In our letter to NICE on the 17th July 2017 we presented the correct patient level data analysis values for ORAL Sync, the revised NMA using the corrected values, revised rankograms and economic analyses.

We concluded that correcting for the ORAL Sync Estimate 2 error did not change the cost-effectiveness conclusion as presented in the CS or by the ERG.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

Dear Jo,

The Evidence Review Group, School of Health and Related Research (ScHARR), and the technical team at NICE have looked at the submission received on 10 April 2017 from Pfizer. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm on 22 May 2017**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the checklist for confidential information available on NICE Docs.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact [Aminata Thiam, Technical Lead (Aminata.Thiam@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Clarification on Literature searching

1. In *Section 4.12.4* on *Safety overview*, the Company Submission (CS) reported that '*As of 31 March 2015, no new risks of safety signals were identified in the long-term safety database*'.

    i. Please confirm whether separate adverse events searches were undertaken for this section?

    ii. If adverse events searches were conducted, please provide search strategies to the various sources searched as this does not appear in Appendices 3, 4, 9, 11 and 13 of the CS submission.

2. In the CS *Appendix 8.3: Search strategy for indirect and mixed treatment comparisons*, the observational studies filter (e.g statements 89-100 of the original search in Medline) was applied in the original review (June 2010), 4th update (June 2016) and 5th update (December 2016) Medline and Embase searches. However, observational studies filters were not applied in the 1st (April 2011), 2nd (September 2012) and 3rd (November 2014) update searches. Therefore, observational or follow-up studies would not be retrieved for the period of June 2010 until October 2014. Please explain the reason for the not applying the filters in these updates and discuss the likely implications of the omission?

3. In the CS *Appendix 8.3. Search strategy for indirect and mixed treatment comparisons*, the search terms for the intervention tofacitinib was not in the original search and subsequent updates (1st-3rd) but only found in the 4th update (June 2016) and 5th update (December 2016). As date limits have been applied in the update searches, studies for tofacitinib would only be retrieved from October 2014 until December 2016. Please explain the reason for limiting the search for tofacitinib from October 2014 onwards and discuss the likely implications of the omission?

<u>Section A: Clarification on effectiveness data</u>

A1. **Priority question**: The "data cut" (CS page 228) for adverse event data, means that safety data are only provided up to March 2015, which is two years prior to the current appraisal. In addition, the CS provides incidence rates for patients with events rather than the number of events. Please provide an up-to-date analysis of safety data with the raw number of events and number of patient years of treatment. Additionally please provide odds ratios or a relative measure for tofacitinib versus the control arms. Please ensure data for the following adverse events are included in the updated safety analysis:

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

- Serious adverse events
- Serious infection events
- Pneumonia
- Bronchitis
- Herpes Zoster
- Interstitial lung disease
- Malignancies/ lymphoma
- Gastrointestinal perforations
- Hepatic enzymes elevations
- Drug-induced liver injury
- Cardiovascular risks
- Discontinuation due to AEs
- Mortality until the end of the trial

A2. **Priority question**: Please ensure the safety analysis includes data for all treatment arms in the two ongoing studies, ORAL Sequel and ORAL Strategy. Please also include safety data from the following trials not currently included in the pooled safety analysis in the CS:

- Trial NCT02147587. This is a completed (July 2015) Phase 2 trial which enrolled 112 patients and is not referred to in the CS but has safety data from subjects with rheumatoid arthritis receiving tofacitinib or placebo with background methotrexate.

- Trial NCT00687193. This is a completed (March 2013) Phase 2 trial which enrolled 112 patients and is referred to in the CS and has safety data from subjects with rheumatoid arthritis receiving tofacitinib monotherapy with a range of doses including 5mg and 10mg or placebo who have failed an adequate trial of therapy with at least 1 DMARD.

A3. **Priority question**: Page 204/205 of the CS states "*the ORAL Strategy trial (which includes tofacitinib monotherapy) is due to report the final data set soon; Pfizer will therefore be able to provide further comparative analysis at the end of April/early May, which will allow a more reliable direct comparison of both head-to-head trial data and an updated network meta-analysis (NMA) network*." Please provide these data and updated NMA taking into consideration requests regarding the NMA (see

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

questions A7-A9, A11-A19 and A21 listed in the section "Related to the network Meta-Analysis" below).

A4. Please confirm how many reviewers performed study selection, data extraction and quality assessment for the systematic reviews.

A5. Section 5.4.6.1 (page 303) estimates serious infections versus comparators. This analysis pools data across the trials from the comparators, which breaks randomisation. Odds ratio data from the Strand et al (2015) study are reportedly used to estimate relative occurrence of serious infection events versus comparators. However, odds ratios do not appear to be reported in this paper, only risk ratio and risk difference. Please clarify.

A6. Regarding the CS Table 210, Appendix 4, please confirm who exactly were blinded (i.e., patients, physicians, outcome assessors) in the double-blind trials.

Network Meta-Analysis

A7. **Priority question:**

i. Please provide the NMA results for EULAR in cDMARD-IR and TNFi-IR population with the following settings:

- Using a random effects probit model with an informative prior for the between-study variance (log normal with mean of -2.56 and variance of 1.74^2. The log normal is truncated so that the odds ratio in one study would not be ≥50 times than in another, and re-scaled to match the probit scale). The BUGS code for this prior is:
    - var~dlnorm(-2.56,0.33)I(,1)
    - sd <-sqrt(var)/1.81
    - tau <- pow(sd,-2)
- EULAR response for ORAL trials derived using DAS ESR with all trial data by applying non-responder imputation Estimate 2 in the CS Table 53. Use the individual EULAR results from trials in the NMA, i.e. not pooling individual patient-level data from ORAL trials.
- Excluding studies which only reported DAS (i.e. did not report EULAR) in the NMA.
- Not assuming intensified DMARD arm is equivalent to the central DMARD node in the LARA trial and including the SWEFOT trial.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

- Choosing PBO+cDMARD/cDMARD as the reference treatment (treatment 1) in the analyses.

Please present the results using both relative and absolute measures. Please also present the point estimate and 95% credible interval for the between-study standard deviation. In the results, please also provide how the baseline absolute probabilities were estimated.

ii. Please supply sensitivity analyses amending parts of this proposed NMA where you feel this is appropriate.

A8. **Priority question:** Please provide a sensitivity analysis for the requested NMA excluding patients with prior biologic use in ORAL trials and excluding studies which had a proportion of patients with prior biologic use.

A9. **Priority question:** The CS page 151 stated that EULAR response were derived using patient-level data for the ORAL trials. Please clarify why in Appendix 4 Table 206 the outcome for the ORAL trials was DAS not EULAR. Are the EULAR data for the pooled ORAL trials based on CRP or ESR measures?

A10. **Priority question:** Please clarify whether the results from the post-hoc subgroup analyses of the ORAL Standard, Scan, Sync and Solo trials, which excluded patients with prior biologic use, were used in the NMA.

A11. **Priority question:** Please clarify what treatment was chosen as the reference treatment (treatment 1) in each NMA (including the binomial model for EULAR, the probit model for EULAR, and HAQ). Please also clarify what values were used for the baseline meanA and precA in the WinBUGS code provided in Appendix 6, and where these values came from.

A12. **Priority question:** In the CS (pages 198 and 200), it was stated that vague priors are used for the treatment effect sizes relative to treatment 1 in the form of a normal distribution with mean of 1 and variance of 100^2. If a prior was used, please present the NMA results using a prior from a normal distribution with mean 0 and variance of 100^2.

A13. **Priority question:** Please clarify in the CS Table 69 and 71 whether the comparator is placebo or placebo +cDMARD when it was compared with intervention + cDMARD.

A14. **Priority question:** Please clarify the dose of tofacitinib in the CS Table 70 and 72.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

A15. **Priority question:** Please provide additional results for moderate EULAR response in the CS Tables 73 and 74.

A16. Please clarify why the number of patients in the ADA+MTX arm for pooled data for three ORAL trials (ORAL Scan, Standard and Sync) was 195 but the number of patients for that arm was 178 in the CS Table 25.

A17. Please clarify how the EULAR response were derived for the other included trials from DAS scores including whether DAS CRP or DAS ESR was used to convert to EULAR.

A18. Please clarify what studies included in the NMA had patients with prior bDMARD use, and what studies had a proportion of RhF+ patients. Please also indicate the proportions of prior bDMARD and proportion of RhF+ patients in these studies.

A19. Please provide the model fit statistics for the cDMARD-IR NMA probit model for EULAR outcome.

A20. Please clarify what the 95% credible interval is for the standard deviation using a random effects model probit model for EULAR in the CS Table 67.

A21. In the CS page 199, it was stated that “Change from baseline scores of continuous outcomes (HAQ-DI) were computed from mean baseline and endpoint scores where necessary.” Please clarify how the standard deviation of the change from baseline scores of HAQ-DI were computed.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** Please provide the file with the CODA to allow the ERG to run the PSA.

B2. **Priority question:** The company assumed an annual worsening in their HAQ score of 0.06 for patients on palliative care. It is claimed in the CS that this is in line with TA375. However, the AG in TA375 assumed that the HAQ progression on palliative care would be equivalent to that of non-biological therapy, which followed the trajectories of cDMARDs. Please provide results of the analyses including this assumption if possible and otherwise assess the direction of the relevant ICERs if this assumption had been included.

B3. **Priority question:** Please re-run analyses to provide fully incremental results based on the efficacy data from the requested NMA analyses.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

B4. **Priority question:** Please clarify why predicted HAQ changes are rounded to the nearest 0.125. This method will cause markedly different results if the predicted HAQ change between events was consistently 0.0620 compared with when it was 0.0630. Please amend the model if possible, or discuss the potential implications of this limitation.

B5. **Priority question:** Please clarify why the sequences used in all three populations are not in line with TA375. Please provide ICERs for the cDMARD-IR population using sequences similar to those used in TA375 (Tables 159 and 160 for MTX tolerant and intolerant respectively) and for the bDMARD-IR population with sequences where biologics are only followed by MTX therapy (once only) followed by PaC. For the moderate population, please provide ICERs for sequences similar to those in Table 161 and Table 162 of the TA375 report for MTX tolerant and intolerant respectively.

B6. **Priority question:** It is noted that the RTX tolerant (after RTX) analysis all extend the number of biological interventions in the sequence. Please provide incremental analyses for when TOF + MTX is assumed to replace TOC + MTX. Further, please provide the incremental analysis where TOF + MTX is assumed to go after TOC + MTX for comparison with the elongated sequence adding TOF + MTX.

B7. Please clarify why the annual cost of RTX reported in Table 122 (£10,163) is higher than that of other bDMARDs, when in TA375 it was the cheapest. The number of RTX doses seems to be calculated to be twice the correct quantity.

B8. Please clarify why the prior_bDMARD flag of the patients is not updated after going through the first biologic in the sequence. Please re-run analyses if appropriate.

B9. Please clarify whether the model assumes the same probability of moderate and good EULAR response for TOF in combination with MTX and as monotherapy. Please clarify also whether the multinomial logistic regression model used to estimate the probability of moderate and good EULAR response was based on all ORAL trials (as listed in Figure 3) or only Standard, Scan, Sync, and Step. Please provide the observed and predicted EULAR responses for ORAL Step and Solo.

B10. Please clarify why the SC formulations of ABA and TOC were not included as comparators.

B11. Please clarify why the average changes in HAQ score at month 6 used for moderate and good response (-0.321, -0.678 respectively), allegedly based on TA375, were different from the values used in TA375 (-0.317 and -0.672 respectively).

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

B12. Please clarify whether the population for the monotherapy analyses was sampled or defined based on the population in ORAL Solo. Similarly, clarify whether the population for the bDMARD-IR analyses was sampled or defined based on the population in ORAL Step.

B13. Please clarify why the probability of class membership for the HAQ progression latent classes was recalculated based on patient's age if the predictor is age at onset.

B14. Please provide details on the validation of the OLS regression described in page 263 for changes in DAS28 (e.g. R-squared, scatter plot).

B15. Please provide significance levels for the variables of the predictive model for HAQ score change in page 275. Clarify whether non-linear models were explored.

B16. Please provide patient numbers at risk for the long-term extension study by level of response at month 6 (Table 110).

B17. Please clarify why in the analyses, biosimilars are estimated to result in slightly different number of QALYs? If this is due to Monte Carlo sampling error, would it be more appropriate to remove the parent drug as this is dominated.

B18. Please clarify whether the number of patients and iterations used in the PSA was enough to provide stable results.

B19. Please provide tables with probabilities of EULAR response for different treatments, for the cDMARD-IR and the bDMARD-IR populations.

B20. Please provide tables with the average baseline characteristics of the three populations considered in the analyses: moderate cDMARD-IR, severe cDMARD-IR and severe bDMARD-IR.

Section C: Textual clarifications and additional points

C1. Please provide the SmPC for tofacitinib. The CS states that the SmPC is provided in Appendix 1. Appendix 1 states that the SmPC is provided in the reference pack. The "SPC" provided in the reference pack is the EPAR summary for Etanercept.

C2. Please confirm typo on page 221 of CS:

[redacted]

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

C3. Please clarify whether in section 5.7.1.1., page 321, in the second bullet point ETNb+MTX was wrongfully omitted from the list of treatments that are not dominated by TOF + MTX.

C4. In the CS Table 88 the DAS28-4(ESR) for ORAL Sync are reported as 9.1 and 2.7 for TOF vs PBO respectively. In the corresponding journal paper (Kremer et al 2013) these data are reported in Figure 3 as 8.5 and 2.6. Please clarify the discrepancy. Likewise, in CS Table 88 HAQ-DI (-0.46 and -0.21) and ACR20, % (52.7 and 31.2) are different to Figure 3 in the corresponding journal paper (Kremer et al 2013) (HAQ-DI, -0.44 and -0.16; ACR20 %, 52.1 and 30.8). Please clarify the discrepancy.

C5. Please specify whether the first comparator in the cDMARD-IR combination therapy is MTX as specified in Section 5.7.1 or DMC as specified in Table 126.

C6. Please clarify whether in section 5.7.2 the references to MTX are actually meant to be SSZ+HQC.

List of Pfizer clarification requests on the ID526 ERG clarification letter

Relevant text from ERG clarifications: excerpt from the introduction in ID526 ERG clarification letter: *The Evidence Review Group, School of Health and Related Research (ScHARR), and the technical team at NICE have looked at the submission received on 10 April 2017 from Pfizer. In general they felt that it is well presented and clear.*

Pfizer question: Can you please confirm that ScHARR is now the ERG for the ID526 technology assessment? Previous correspondence confirmed York as the ERG, e.g. during the decision problem meeting and also listed in Appendix A at invitation to submit.

Relevant text from ERG clarifications: A2. Priority question: Please ensure the safety analysis includes data for all treatment arms in the two ongoing studies, ORAL Sequel and ORAL Strategy. Please also include safety data from the following trials not currently included in the pooled safety analysis in the CS:

- Trial NCT02147587. This is a completed (July 2015) Phase 2 trial which enrolled 112 patients and is not referred to in the CS but has safety data from subjects with rheumatoid arthritis receiving tofacitinib or placebo with background methotrexate.

- Trial NCT00687193. This is a completed (March 2013) Phase 2 trial which enrolled 112 patients and is referred to in the CS and has safety data from subjects with rheumatoid arthritis receiving tofacitinib monotherapy with a range of doses including 5mg and 10mg or placebo who have failed an adequate trial of therapy with at least 1 DMARD.

Pfizer question: Can you please confirm the request on trial NCT00687193? This study was already included in the pooled analysis by Cohen et al (see Table 84 of the evidence submission) Furthermore, the patient numbers stated by the ERG (112) don't match the numbers in the trial (265 patients receiving tofactinib, total of 318 patients randomised).

Relevant text from ERG clarifications: A7. Priority question:

i. Please provide the NMA results for EULAR in cDMARD-IR and TNFi-IR population with the following settings:

   - Using a random effects probit model with an informative prior for the between-study variance (log normal with mean of -2.56 and variance of 1.74^2. The log normal is truncated so that the odds ratio in one study would not be ≥50 times than in another, and re-scaled to match the probit scale). The BUGS code for this prior is:
     - var~dlnorm(-2.56,0.33)I(,1)
     - sd <-sqrt(var)/1.81

    - tau <- pow(sd,-2)
- EULAR response for ORAL trials derived using DAS ESR with all trial data by applying non-responder imputation Estimate 2 in the CS Table 53. Use the individual EULAR results from trials in the NMA, i.e. not pooling individual patient-level data from ORAL trials.
- Excluding studies which only reported DAS (i.e. did not report EULAR) in the NMA.

Pfizer question:

With respect to bullet point 1; TA375 used weakly informative priors, without providing a rationale nor supporting it with clinical validation. The ERG are now providing informative priors; Could you please provide a supportive justification for the rationale and the choice of informative priors?

With respect to bullet point 3; the EULAR evidence networks for the NMA were derived from the published literature for non-tofactinib studies. Therefore it was only possible to produce a network if the non-tofactinib publications reported a EULAR response for at least one of the response categories. For the non-tofactinib studies there are therefore no studies in the network that can be excluded which only report DAS and do not present EULAR.

For the tofacitinib studies, patient level data analyses of DAS were used to derive the EULAR response. Excluding the tofactinib studies would no longer allow a connected network to be formed between tofactinib and comparators.

In light of this, please can you clarify this request?

Relevant text from ERG clarifications: B2. Priority question: The company assumed an annual worsening in their HAQ score of 0.06 for patients on palliative care. It is claimed in the CS that this is in line with TA375. However, the AG in TA375 assumed that the HAQ progression on palliative care would be equivalent to that of non-biological therapy, which followed the trajectories of cDMARDs. Please provide results of the analyses including this assumption if possible and otherwise assess the direction of the relevant ICERs if this assumption had been included.

Pfizer question: Could you please provide the excerpt and reference of the NICE TA375 document for palliative care HAQ progression you are referring to?

Relevant text from ERG clarifications: B6. Priority question: It is noted that the RTX tolerant (after RTX) analysis all extend the number of biological interventions in the sequence. Please provide incremental analyses for when TOF + MTX is assumed to replace TOC + MTX. Further, please provide the incremental analysis where TOF + MTX is assumed to go after TOC + MTX for comparison with the elongated sequence adding TOF + MTX.

Pfizer question: Could you please clarify the exact sequences requested for this population using the following table format?

RTX tolerant (after) RTX)			
RTX+MTX	**TOF+MTX**	**ABT+MTX**	**GOL+MTX**
RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX
TOC+MTX	TOF+MTX	ABT+MTX	GOL+MTX
DMC	TOC+MTX	TOC+MTX	TOC+MTX
DMC	DMC	DMC	DMC
LEF	DMC	DMC	DMC
PaC	LEF	LEF	LEF
-	PaC	PaC	PaC

Abbreviations: ABA, abatacept; ADA, adalimumab; cDMARD, conventional disease modifying anti-rheumatic drug; DMC, DMARD combination; GOL, golimumab; LEF, leflunomide; PaC, palliative care; RTX, rituximab TOC, tocilizumab; TOF, tofacitinib.

Relevant text from ERG clarifications: B16. Please provide patient numbers at risk for the long-term extension study by level of response at month 6 (Table 110).

Pfizer question: Please could you clarify whether you are asking for the patient numbers by EULAR response for each month presented?

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Single technology appraisal

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

Dear Jo,

The Evidence Review Group, School of Health and Related Research (ScHARR), and the technical team at NICE have looked at the submission received on 10 April 2017 from Pfizer. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by 5pm on 22 May 2017. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as [redacted] in turquoise, and all information submitted as [redacted] in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the checklist for confidential information available on NICE Docs.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact [Aminata Thiam, Technical Lead (Aminata.Thiam@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Yours sincerely

Helen Knight

Associate Director – Appraisals

Centre for Health Technology Evaluation

Encl. checklist for confidential information

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

Monday 22nd May 2017

Company response to ERG clarification questions (received 8th May 2017)

Dear Helen,

Thank you for the clarification questions and opportunity to provide further detail to aid the evaluation of our evidence submission.

We have received a high number of clarification questions from the Evidence Review Group (ERG) for the above appraisal and have outlined below a summary of our key comments that we believe should be considered by the ERG and the NICE Appraisal Committee (AC).

In the Company Submission (CS), the Pfizer base case proposed that tofacitinib is a cost-effective treatment option for patients with severe RA who have experienced an inadequate response to conventional disease modifying anti-rheumatic drugs (cDMARDs) when considered alongside currently available treatments recommended in TA375. Base case incremental cost effectiveness ratios (ICERs) for tofacitinib in combination with methotrexate (MTX) ranged from £23,676 (rapid HAQ progressors) to £41,617 (as per Norton et al.), and £25,807 to £56,231for tofacitinib monotherapy, which were consistent with the results presented in TA375. In addition, for patients with severe RA who have experienced an inadequate response to biologic DMARDs (bDMARDs), both tofacitinib in combination with MTX, and tofacitinib monotherapy were cost-effective when treatment with rituximab and/or MTX was inappropriate or contraindicated. Furthermore, as per TA415, tofacitinib in combination with MTX was also cost-effective after treatment with tocilizumab.

Results were explored under multiple scenario analyses and probabilistic sensitivity analyses, and both reinforced our conclusions in the CS.

The ERG requested Pfizer explore changes to the evidence network, and where relevant we have provided these:

- A random effects probit model with an informative prior
- EULAR response for ORAL trials derived using DAS ESR with all trial data by applying non-responder imputation Estimate 2.
- Use the individual EULAR results from trials in the NMA, i.e. not pooling individual patient-level data from ORAL trials.
- Including the SWEFOT trial

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

In addition, the ERG also requested changes to the economic model set up, which included:

- Norton et al., non-linear HAQ progression be used for post-biologic-therapy (PBT)
- Sequences as presented in the TA375 Assessment Groups (AGs) Technical Assessment Report (TAR) (as opposed to Pfizer's understand of those used in the TA375 economic model)

As a consequence of the ERG requests, the ICERs (as per Noprton et al.) for tofacitinib, both in combination with MTX and as monotherapy, and other biologics currently recommended by NICE (TA198, TA375, and TA415), decrease by approximately £8,000 across the relevant populations. However, conclusions on the cost-effectiveness of tofacitinib (in combination with MTX and monotherapy) compared to treatments currently recommended in TA199, TA375 and TA415 remain broadly consistent with those presented in the CS.

Given the unprecedented volume of questions posed by the ERG, and the time required to run the respective analyses and quality assure the outputs, we have not been able to fully explore the impact of the various options for correcting cross-over in the ORAL trials in terms of cost-effectiveness results, namely Estimate 1. NMA results using cross-over correction Estimate 1 are presented in Table 13; we believe that cost-effectiveness results from this approach, which is clinically more plausible, would positively impact the cost-effective estimates for tofacitinib in combination with MTX and as monotherapy compared to what we have presented in our response.

Please find below Pfizer's responses to the ERG's questions. Also, we have attached the amended Pfizer models, the CODA file used in the models, instructions on how to use this, and the Xeljanz SmPC, and alongside the signed Appendix H - checklist for confidential information.

Sincerely,

Angela Blake
Head of Health & Value, Pfizer UK

Additional instructions for using the CODA: To run any PSA, please insert the file path for the CODA into the 'CODApath' cell on the 'CODA' sheet. Then load the CODA and the PSA can be run.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Clarification on Literature searching

1. **In Section 4.12.4 on Safety overview, the Company Submission (CS) reported that 'As of 31 March 2015, no new risks of safety signals were identified in the long-term safety database'.**

    i. **Please confirm whether separate adverse events searches were undertaken for this section?**

Pfizer response: A separate search for adverse events was not undertaken; data on adverse events were identified as part of a broader search of efficacy, safety and health-related quality of life. The long-term safety database covered in section 4.12.4 of the CS refers to Pfizer's internal dataset for tofacitinib in rheumatoid arthritis.

    ii. **If adverse events searches were conducted, please provide search strategies to the various sources searched as this does not appear in Appendices 3, 4, 9, 11 and 13 of the CS submission.**

Pfizer response: Not applicable; see response to question 1i.

2. **In the CS Appendix 8.3: Search strategy for indirect and mixed treatment comparisons, the observational studies filter (e.g statements 89-100 of the original search in Medline) was applied in the original review (June 2010), 4th update (June 2016) and 5th update (December 2016) Medline and Embase searches. However, observational studies filters were not applied in the 1st (April 2011), 2nd (September 2012) and 3rd (November 2014) update searches. Therefore, observational or follow-up studies would not be retrieved for the period of June 2010 until October 2014. Please explain the reason for the not applying the filters in these updates and discuss the likely implications of the omission?**

Pfizer response: When the original scope of the project was defined in 2010, the study designs of interest were both randomised and non-randomised studies. However, for the initial updates, the focus of the project was to identify randomised clinical trials (RCTs) to provide additional data for input into the updated network meta-analysis (NMA). For purposes of expediency and efficiency, a non-randomised study filter was not added to update searches as only RCTs were required to be identified for the NMA evidence base. Pfizer's internal databases were searched to identify any non-randomised studies for tofacitinib, and Pfizer therefore judged the impact on the appraisal of omitting this filter in the update searches to be low. This is In line with previous Technology Appraisals (TAs) [TA415, TA375, TA195, etc] where only RCT evidence was considered for inclusion in the associated NMA.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

3. **In the CS Appendix 8.3. Search strategy for indirect and mixed treatment comparisons, the search terms for the intervention tofacitinib was not in the original search and subsequent updates (1st-3rd) but only found in the 4th update (June 2016) and 5th update (December 2016). As date limits have been applied in the update searches, studies for tofacitinib would only be retrieved from October 2014 until December 2016. Please explain the reason for limiting the search for tofacitinib from October 2014 onwards and discuss the likely implications of the omission?**

Pfizer response: The updated searches (June and December 2016) were date restricted for the interventions which were included in the original 2010 search and subsequent updates (1st–3rd). However, the search terms used to identify tofacitinib, baricitinib and biosimilars were not date restricted in the June 2016 update. For example, if one looks at the OVID Medline clinical search in Section 8.3.1.5 of the CS, the date restriction on line 116 is only applied to line 114 (which includes the original interventions [line 105]). The search terms for tofacitinib, baricitinib, and biosimilars were combined on line 115 and no date restriction is applied. In the December 2016 review, as all interventions of interest were already searched up to June 2016, a date restriction was applied to identify only the most recent evidence.

Section A: Clarification on effectiveness data

A1. Priority question: The "data cut" (CS page 228) for adverse event data, means that safety data are only provided up to March 2015, which is two years prior to the current appraisal. In addition, the CS provides incidence rates for patients with events rather than the number of events. Please provide an up-to-date analysis of safety data with the raw number of events and number of patient years of treatment. Additionally please provide odds ratios or a relative measure for tofacitinib versus the control arms. Please ensure data for the following adverse events are included in the updated safety analysis:

- **Serious adverse events**
- **Serious infection events**
- **Pneumonia**
- **Bronchitis**
- **Herpes Zoster**
- **Interstitial lung disease**
- **Malignancies/ lymphoma**
- **Gastrointestinal perforations**
- **Hepatic enzymes elevations**

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

- **Drug-induced liver injury**
- **Cardiovascular risks**
- **Discontinuation due to AEs**
- **Mortality until the end of the trial**

Pfizer response: In order to answer this question we have reviewed pooled data from patients with rheumatoid arthritis treated with tofacitinib in Phases I – III and the Long Term Extension study. Because of the timing of the ERG request the data sets created in January 2016 vary from the information provided in a January 2017 update as there was insufficient time to produce an additional set in response to the questions. Instead the answers to individual questions – other than Serious Adverse Events have been drawn from both data sets. Unfortunately we have been unable to update the incidence of Serious Adverse Events within the timelines provided as these are listed in a separate data base. The safety database has been reconciled with the adverse event database at regular intervals. Readily available data is presented in available it is presented in terms of the number of events and the number of affected patients and as incidence, defined according to a 100 year treatment period. Table 1 describes safety events from all patients treated with tofacitinib during Phases I-III and the Long Term Extension study thus odds ratios and comparisons have not been provided. At the time of this data cut in January 2016 6301 patients had received treatment with tofacitinib with a total of 21199.23 years of patient exposure.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 1 tofacitinib safety data listed by safety events (ORAL trials January 2016 data set analysis)

Event Term	Total number of events	Number of patients affected	Incidence per 100 patient exposure years
Serious Infection Events	XXX	XXX	XXX
Drug Induced Liver Injury (Cases meeting Hy's law)	X	X	XXXX
Gastrointestinal Perforation Events	XX	XX	XXXXX
Treatment discontinuations as a result of an Adverse Event	XXXX	XXXX	XXXXX
All-cause mortality	XXX	XXX	XXXXX
Herpes Zoster infection	XXX	XXX	XXXXX
Interstital Lung Disease	XX	XX	XXXXX
Malignancies			
All Cancers (other than non-melanomatous cancers of the skin)	XXX	XXX	XXXXX
Lymphoma	XX	XX	XXXX
Non-melanomatous cancers of the skin	XXX	XXX	XXXXX
Breast Cancer (Female patients only)	XX	XX	XXXXX
Lung Cancer	XX	XX	XXXXX
Melanoma	XX	XX	XXXX

This updated summary of selected safety events is consistent with that included in the previous submission and no new safety signals have been identified in this longer follow up period. Skin cancer (melanoma and non-melamomatous) remains the most commonly reported malignancy and the incidence of Herpes Zoster remains low. Overall the safety profile remains consistent with other DMARDs in rheumatoid arthritis as described in Cohen et al 2017.

Table 2 presents adverse events reported by patients treated with tofacitinib by dose to January 2017 by starting dose by Higher Level Term MeDRA, which was of greater relevance to EMA.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 2 MeDRA safety event profile as submitted to EMA (ORAL trials January 2017 data set analysis)

Higher Level Term	5 mg BD Number of affected patients (%)	10 mg BD Number of affected patients (%)	Overall Number of affected patients (%)
Pneumonia including necrotizing pneumonia	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]
All Cardiovascular Disorders -	[redacted]	[redacted]	[redacted]
Cardiac disorders by Higher Level Term			
Cardiac Arrythmias	[redacted]	[redacted]	[redacted]
Cardiac Disorder Signs and Symptoms	[redacted]	[redacted]	[redacted]
Cardiac Valve Disorders	[redacted]	[redacted]	[redacted]
Coronary Artery Disorders	[redacted]	[redacted]	[redacted]
Endocardial Disorders	[redacted]	[redacted]	[redacted]
Heart Failure	[redacted]	[redacted]	[redacted]
Myocardial Disorders	[redacted]	[redacted]	[redacted]
Pericardial Disorders	[redacted]	[redacted]	[redacted]

These data confirm the absence of any new safety signals arising during this prolonged follow up period.

A2. Priority question: Please ensure the safety analysis includes data for all treatment arms in the two ongoing studies, ORAL Sequel and ORAL Strategy. Please also include safety data from the following trials not currently included in the pooled safety analysis in the CS:

- **Trial NCT02147587. This is a completed (July 2015) Phase 2 trial which enrolled 112 patients and is not referred to in the CS but has safety data from subjects with rheumatoid arthritis receiving tofacitinib or placebo with background methotrexate.**

- **Trial NCT00687193. This is a completed (March 2013) Phase 2 trial which enrolled 112 patients and is referred to in the CS and has safety data from subjects with rheumatoid arthritis receiving tofacitinib monotherapy with a**

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

range of doses including 5mg and 10mg or placebo who have failed an adequate trial of therapy with at least 1 DMARD.

Note: A query was also raised by the ERG on a second study (NCT00687193) although the ERG subsequently clarified that there was no need to provide a response in relation to this study.

Pfizer response: NCT02147587 explored the safety and efficacy of Herpes Zoster vaccination in patients receiving either tofacitinib or placebo in combination with methotrexate. A total of 112 patients were enrolled. In total 21 subjects reported 39 Treatment Emergent Adverse Events in the placebo group compared with 16 subjects treated with tofacitinib who reported a total of 40 Treatment Emergent Adverse Events (Table 3). In summary there was no excess of Adverse Events amongst subjects randomised to receive tofacitinib.

Table 3 NCT02147587 - Overview of Treatment Emergent Adverse Events – all causalities

All Causalities	Placebo (number of subjects – 57)	Tofacitinib 5 mg BD (number of subjects – 55)
Number of Adverse Events	[redacted]	[redacted]
Subjects with Adverse Events	[redacted]	[redacted]
Subjects with Adverse Events leading to discontinuation	[redacted]	[redacted]
Subjects with Adverse Events leading to dose reduction or temporary discontinuation	[redacted]	[redacted]

Further details of the reported Adverse Events are included in the Table 4 below.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 4 additional MeDRA safety event profile as submitted to EMA (ORAL trials January 2017 data set analysis)

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

MeDRA coding	Placebo	Placebo	Tofacitinib 5 mg BD	Tofacitinib 5 mg BD
System Organ Class/Preferred Term	All causalities	Treatment-related	All causalities	Treatment-related
Number of Subjects with AEs	[redacted]	[redacted]	[redacted]	[redacted]
Blood and Lymphatic System Disorders	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Heparin-induced thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Leukopaenia	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropaenia	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac Disorders (palpitations)	[redacted]	[redacted]	[redacted]	[redacted]
Ear and Labyrinth disorders (cerumen impaction)	[redacted]	[redacted]	[redacted]	[redacted]
Eye Disorders (vision blurred/visual impairment)	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal Disorders	[redacted]		[redacted]	
Abdominal discomfort	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Dry Mouth	[redacted]	[redacted]	[redacted]	[redacted]
Gastroesophageal Reflux disease	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis/Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
General Disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia/nodule	[redacted]	[redacted]	[redacted]	[redacted]
Edema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary Disorders	[redacted]	[redacted]	[redacted]	[redacted]
Bile Duct Stone and Cholangitis	[redacted]	[redacted]	[redacted]	[redacted]
Immune System Disorders/Seasonal Allergy	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]
Candida Infection	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]	[redacted]	[redacted]
Herpes Zoster	[redacted]	[redacted]	[redacted]	[redacted]

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Disseminated Infectious mononucleosis	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory Tract Infection	[redacted]	[redacted]	[redacted]	[redacted]
Upper Respiratory Tract Infection	[redacted]	[redacted]	[redacted]	[redacted]
Urinary Tract Infection	[redacted]	[redacted]	[redacted]	[redacted]

Overall herpes zoster vaccination was well tolerated by both groups. A small excess of infections was reported in patients receiving tofacitinib when compared to placebo.

ORAL Strategy (NCT02187055) was a 1-year, double-blind, Phase 3b/4, controlled head-to-head trial in patients aged ≥18 years with moderate-to-severe RA despite methotrexate therapy who received tofacitinib 5 mg twice daily (BID) monotherapy, tofacitinib 5 mg BID plus methotrexate ('tofacitinib + MTX') or adalimumab 40 mg every other week plus methotrexate ('adalimumab + MTX'). Randomization completed on 28 December 2015. The study will be presented at the EULAR annual congress in June 2017, and the full manuscript has been submitted for publication. We herein share the following safety data as academic-in-confidence. A summary of treatment emergent AEs is provided in Table 5 below:

Table 5 ORAL Strategy safety summary

	Tofacitinib monotherapy (N=384)	**Tofacitinib + MTX (N=376)**	**Adalimumab + MTX (N=386)**
Total number of AEs, n*	[redacted]	[redacted]	[redacted]
Patients with AEs, n (%)	[redacted]	[redacted]	[redacted]
Patients with SAEs, n (%)	[redacted]	[redacted]	[redacted]
Patients discontinuing due to AEs, n (%)	[redacted]	[redacted]	[redacted]
Patients with severe AEs, n (%) (defined by the investigator)	[redacted]	[redacted]	[redacted]
Deaths†	[redacted]	[redacted]	[redacted]
AEs of special interest			

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

	Tofacitinib monotherapy (N=384)	Tofacitinib + MTX (N=376)	Adalimumab + MTX (N=386)
Serious infections, n (%)	[redacted]	[redacted]	[redacted]
Herpes zoster (serious and non-serious), n (%)	[redacted]	[redacted]	[redacted]
Herpes zoster (serious and non-serious) in patients who were vaccinated, n/N (%)	[redacted]	[redacted]	[redacted]
Opportunistic infections (excluding tuberculosis), n (%)	[redacted]	[redacted]	[redacted]
Tuberculosis, n (%)	[redacted]	[redacted]	[redacted]
Major adverse cardiovascular events (non-fatal), n (%)	[redacted]	[redacted]	[redacted]
Malignancy (excluding NMSC), n (%)	[redacted]	[redacted]	[redacted]
NMSC, n (%)	[redacted]	[redacted]	[redacted]

Overall, [redacted] of patients discontinued treatment due to AEs; rates were similar across all three treatment arms

A3. Priority question: Page 204/205 of the CS states "the ORAL Strategy trial (which includes tofacitinib monotherapy) is due to report the final data set soon; Pfizer will therefore be able to provide further comparative analysis at the end of April/early May, which will allow a more reliable direct comparison of both head-to-head trial data and an updated network meta-analysis (NMA) network." Please provide these data and updated NMA taking into consideration requests regarding the NMA (see questions A7-A9, A11-A19 and A21 listed in the section "Related to the network Meta-Analysis" below).

Pfizer response: The initial ORAL Strategy results have been analysed and QC'd for the relevant key outcomes, and a CSR is currently being drafted. The EULAR responses are presented in Table 6. However, at this early stage of data analysis for the trial, no further post-hoc subgroup analysis are currently possible to further inform this technology appraisal. Therefore, Table 6 presents the results for the full trial population, which includes patients with prior bDMARD use across the study arms. The percentage of participants with prior bDMARD use per treatment arm was [redacted], [redacted] and [redacted] for tofacitinib 5 mg BID, tofacitinib 5 mg BID + MTX and adalimumab 40mg + MTX, respectively. The EULAR results presented in Table 6 informed the ERG-requested NMA (A7).

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 6: DAS28-4 (ESR) EULAR response at each visit by treatment group (FAS)

Visit	Treatment	N	Observed DAS28-4 (ESR) EULAR response				
			No response	Missing	Moderate	Good	At least moderate (moderate and good)
Month 3	TOF 5 mg BID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TOF 5 mg BID + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ADA 40mg + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	TOF 5 mg BID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TOF 5 mg BID + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ADA 40mg + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; BID, twice daily; DAS28, disease activity score in 28 joints; EULAR, European League Against Rheumatism; ESR, erythrocyte sedimentation rate; MTX, methotrexate; TOF, tofacitinib.

A4. Please confirm how many reviewers performed study selection, data extraction and quality assessment for the systematic reviews.

Pfizer response: Two independent reviewers were involved at all the aforementioned stages and any differences were either resolved through discussion or referred to the project manager.

A5. Section 5.4.6.1 (page 303) estimates serious infections versus comparators. This analysis pools data across the trials from the comparators, which breaks randomisation. Odds ratio data from the Strand et al (2015) study are reportedly used to estimate relative occurrence of serious infection events versus comparators. However, odds ratios do not appear to be reported in this paper, only risk ratio and risk difference. Please clarify.

Pfizer response: The model uses serious infection (SI) rates to calculate the probability that a patient experiences an adverse event while on treatment. The baseline rate applied is 3.02 SIs per 100 patient-years with tofacitinib 5 mg BID, taken from Figure 2 in Strand et al, 2015

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

(1). The ERG are correct in stating that no odds ratios are reported; this was a mistake in the CS as we had previously retrieved odds ratios from another source. We then updated the analysis to use risk ratios reported by Strand et al, but neglected to update the terminology in the CS. We apologise for this error.

To calculate the SI rate for comparators, the risk ratio for each comparator vs placebo is divided by the risk ratio for tofacitinib vs placebo reported in Figure 3 in Strand et al. This gives an estimated risk ratio for the comparator vs tofacitinib, which is then applied to the 6-month probability of an SI with tofacitinib and transformed into an SI rate for the comparator.

A6. Regarding the CS Table 210, Appendix 4, please confirm who exactly were blinded (i.e., patients, physicians, outcome assessors) in the double-blind trials.

Pfizer response: An updated version of Table 210 with this information is provided in Table 43 of Appendix 1.

Network Meta-Analysis

A7. Priority question:

i. A7 request 1: Please provide the NMA results for EULAR in cDMARD-IR and TNFi-IR population with the following settings:

- **Using a random effects probit model with an informative prior for the between-study variance (log normal with mean of -2.56 and variance of 1.74^2. The log normal is truncated so that the odds ratio in one study would not be ≥50 times than in another, and re-scaled to match the probit scale). The BUGS code for this prior is:**
  - **var~dlnorm(-2.56,0.33)I(,1)**
  - **sd <-sqrt(var)/1.81**
  - **tau <- pow(sd,-2)**
- **EULAR response for ORAL trials derived using DAS ESR with all trial data by applying non-responder imputation Estimate 2 in the CS Table 53. Use the individual EULAR results from trials in the NMA, i.e. not pooling individual patient-level data from ORAL trials.**
- **Excluding studies which only reported DAS (i.e. did not report EULAR) in the NMA.**

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

- **Not assuming intensified DMARD arm is equivalent to the central DMARD node in the LARA trial and including the SWEFOT trial.**
- **Choosing PBO+cDMARD/cDMARD as the reference treatment (treatment 1) in the analyses.**

Please present the results using both relative and absolute measures. Please also present the point estimate and 95% credible interval for the between-study standard deviation. A7 request 2; in the results, please also provide how the baseline absolute probabilities were estimated.

Pfizer clarification request:

With respect to bullet point 1; TA375 used weakly informative priors, without providing a rationale nor supporting it with clinical validation. The ERG are now providing informative priors; Could you please provide a supportive justification for the rationale and the choice of informative priors?

With respect to bullet point 3; the EULAR evidence networks for the NMA were derived from the published literature for non-tofacitinib studies. Therefore, it was only possible to produce a network if the non-tofacitinib publications reported a EULAR response for at least one of the response categories. For the non-tofacitinib studies there are therefore no studies in the network that can be excluded which only report DAS and do not present EULAR.

For the tofacitinib studies, patient level data analyses of DAS were used to derive the EULAR response. Excluding the tofacitinib studies would no longer allow a connected network to be formed between tofacitinib and comparators.

ERG response:

*With respect to bullet point 1: a predictive distribution for the between-study variance in a general setting proposed by Turner et al (2012), log normal with mean -2.56, variance 1.74*1.74, was used as the informative prior (Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP; Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. Int J Epidemiol 2012;41:818–27. doi:10.1093/ije/dys041). This prior still has some probability for the heterogeneity being huge. The ERG doesn't believe that the odds ratio in one study could be 50 times or more than the odds ratio in another study, hence truncated the log normal prior to reflect this belief. Dividing by 1.81 is to transform the effect from the odds ratio scale to the probit scale.*

With respect to bullet point 3: In appendix 4 Table 206, there appeared to be seven non-tofacitinib studies, GO-FORTH (Tanaka 2012 - GOL vs PBO), RAPID 1 (Keystone 2008, Strand 2009 - CZP vs PBO), START (Westhovens 2006 - IFX vs PBO), ATTAIN (Genovese 2005 - ABT vs PBO), GO AFTER (Smolen 2009 - GOL vs PBO), SATORI (Nishimoto 2009 - TCZ vs MTX), TOWARD (Genovese 2008 - TCZ vs PBO), that only reported DAS (not EULAR). Can you please exclude these studies for the requested analysis.

Pfizer response to A7 request 1:

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

The ERG-requested NMA results for EULAR in cDMARD-IR are presented in Table 7 and Table 8. The NMA results for EULAR in bDMARD-IR are presented in Table 9–Table 10. The associated evidence networks are shown in Figure 1 and Figure 2, respectively.

Table 7: cDMARD-IR EULAR response (Estimate 2) – effects of interventions relative to placebo + cDMARD on the probit scale (random effects)

Treatment	Mean	SD	Median	95% CrI
ABT + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
ADA + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
CTZ 200mg Q2W SC + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
ETN + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
ETN HD203 25 mg BIW + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
ETN SB4 50mg QW SC + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
GOL + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
IFX + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
IFX CT-P13 3mg/kg Q8W + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
IFX SB2 + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
TCZ + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
TOF 5mg BID + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]
TCZ	[redacted]	[redacted]	[redacted]	[redacted]
ETN 25mg SC BIW	[redacted]	[redacted]	[redacted]	[redacted]
TOF 5 mg BID	[redacted]	[redacted]	[redacted]	[redacted]
Intensified cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
Between study SD	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; TCZ, tocilizumab; TOF, tofacitinib.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

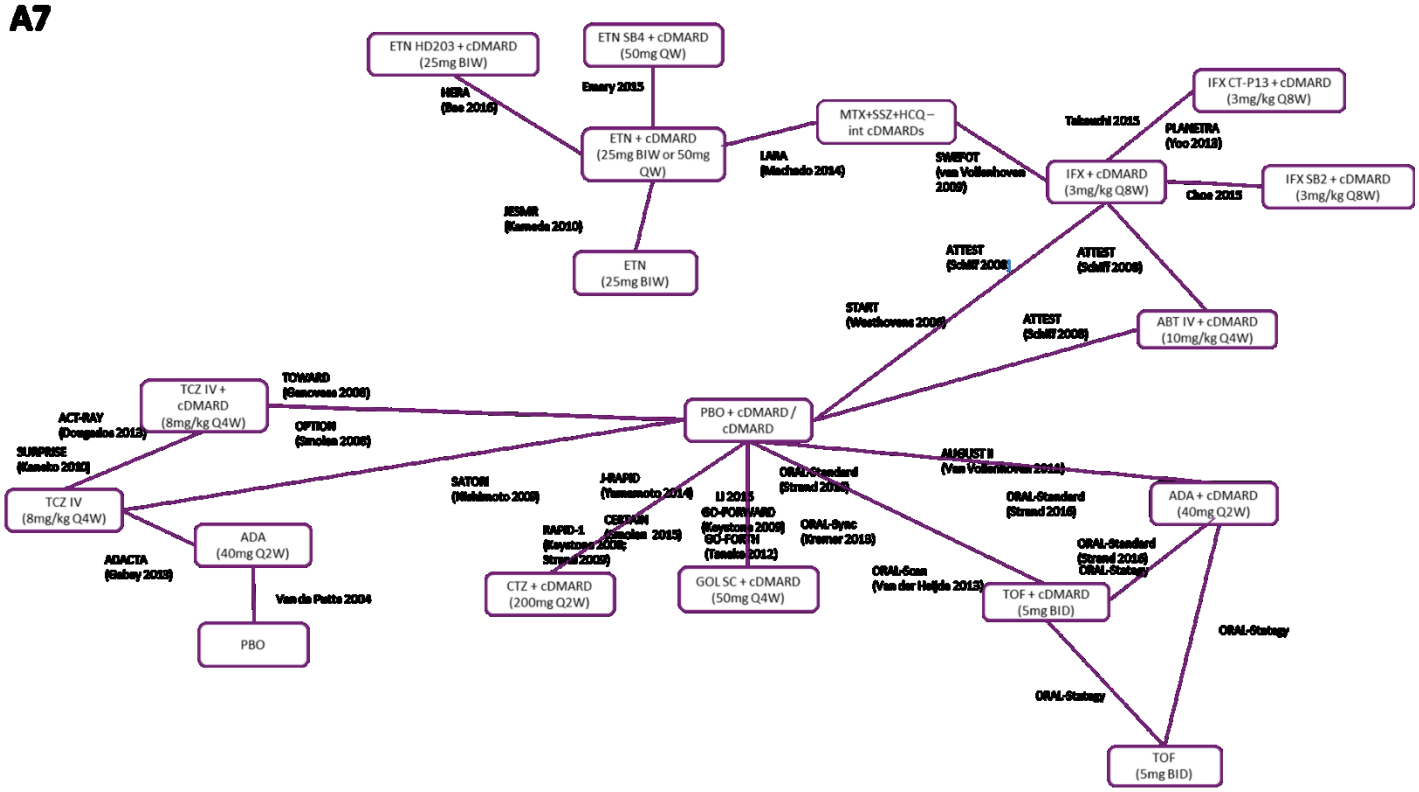
Table 8: cDMARD-IR EULAR response (Estimate 2) – probability of achieving a good response or at least a moderate response

Treatment	Good EULAR response					At least a moderate EULAR response				
	Mean	SD	Median	95% CrI		Mean	SD	Median	95% CrI	
				Lower	Upper				Lower	Upper
PBO + cDMARD	[redacted]									
ABT + cDMARD	[redacted]									
ADA + cDMARD	[redacted]									
CTZ 200mg Q2W SC + cDMARD	[redacted]									
ETN + cDMARD	[redacted]									
ETN HD203 25 mg BIW + cDMARD	[redacted]									
ETN SB4 50mg QW SC + cDMARD	[redacted]									
GOL + cDMARD	[redacted]									
IFX + cDMARD	[redacted]									
IFX CT-P13 3mg/kg Q8W + cDMARD	[redacted]									
IFX SB2 + cDMARD	[redacted]									
TCZ + cDMARD	[redacted]									
TOF 5mg BID + cDMARD	[redacted]									
PBO	[redacted]									
ADA	[redacted]									
TCZ	[redacted]									
ETN 25mg SC BIW	[redacted]									
TOF 5 mg BID	[redacted]									
intensified cDMARD	[redacted]									

Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; TCZ, tocilizumab; TOF, tofacitinib.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Figure 1: cDMARD-IR – evidence network for both EULAR moderate response and EULAR good response (as separate analyses)



Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 9: bDMARD-IR EULAR response (Estimate 2) – effects of interventions relative to placebo + cDMARD on the probit scale (random effects)

Treatment	Mean	SD	Median	95% CrI
ABT + cDMARD 10mg/kg IV Q4W	[redacted]	[redacted]	[redacted]	[redacted]
ETN + cDMARD 50mg SC QW	[redacted]	[redacted]	[redacted]	[redacted]
GOL + cDMARD 50mg SC Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Non TNFi+ cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
RTX + cDMARD 2x1000mg IV	[redacted]	[redacted]	[redacted]	[redacted]
TCZ + cDMARD 8mg/kg IV Q4W	[redacted]	[redacted]	[redacted]	[redacted]
TNFi + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
TOF + cDMARD 5mg BID	[redacted]	[redacted]	[redacted]	[redacted]
Between study SD	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; TCZ, tocilizumab; TOF, tofacitinib.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

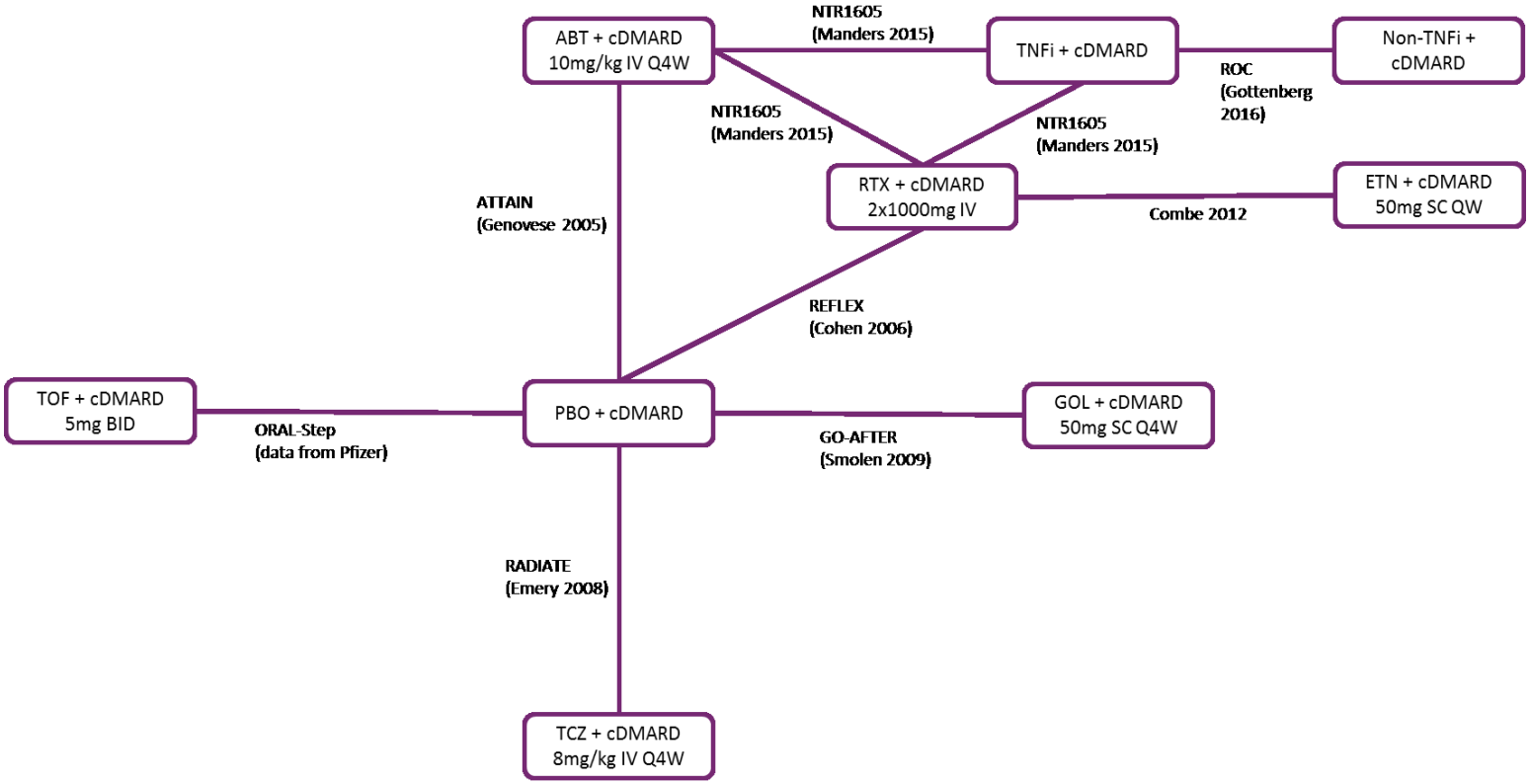
Table 10: bDMARD-IR EULAR response – probability of achieving a good response or at least a moderate response

Treatment	Good EULAR response					At least a moderate EULAR response				
	Mean	SD	Median	95% CrI		Mean	SD	Median	95% CrI	
				Lower	Upper				Lower	Upper
PBO + cDMARD	[redacted]									
ABT + cDMARD 10mg/kg IV Q4W	[redacted]									
ETN + cDMARD 50mg SC QW	[redacted]									
GOL + cDMARD 50mg SC Q4W	[redacted]									
Non TNFi+ cDMARD	[redacted]									
RTX + cDMARD 2x1000mg IV	[redacted]									
TCZ + cDMARD 8mg/kg IV Q4W	[redacted]									
TNFi + cDMARD	[redacted]									
TOF + cDMARD	[redacted]									

Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; TCZ, tocilizumab; TOF, tofacitinib.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Figure 2: bDMARD-IR – evidence network for both EULAR moderate response and EULAR good response (as separate analyses)



Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

With respect to bullet point 3:

Except for the tofacitinib ORAL trial studies, all other evidence was derived from publicly available resources. Pfizer elicited published data in line with the EULAR response criteria definition (Table 11), which is in line with previous technology assessments, namely TA375 and TA415.

Table 11: The EULAR response criteria

DAS28 at Month 6	Improvement in DAS28 from baseline		
	>1.2	≤1.2 and >0.6	≤0.6
≤3.2	Good	Moderate	No response
≤5.1 and >3.2	Moderate	Moderate	No response
>5.1	Moderate	No response	No response

Source: Fransen et al, 2009 (2).
Abbreviations: DAS28, disease activity score in 28 joints.

The seven non-tofactinib studies queried by the ERG as reporting only DAS response and not EULAR response were labelled as DAS in the evidence submission to reflect the reporting in the original papers. However, these original papers appear to have been using the term DAS when EULAR would have been more accurate. On the basis of both the review of the original publications, and their inclusion in previous technology appraisals in RA, it should be considered that all seven of the publications have EULAR data readily available, and do not need to be excluded from the analysis. As the EULAR response was not clearly presented in two source publications (ATTAIN [Genovese et al, 2005] and RAPID 1 [Keystone et al, 2008, Strand et al, 2009]), the values were obtained from TA375 and TA415, respectively. This was deemed appropriate to broaden the evidence base, especially as in both cases, NICE accepted the inclusion of these two studies. Table 12 presents an overview of the source publications, how EULAR was reported and the reference technology appraisal the publication was used in, providing precedence of the use of these studies in the evidence network.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 12: Overview of publications reporting EULAR response

Author	Reported as	Reference within paper	NICE reference TA
TOWARD, Genovese 2008	EULAR good/moderate response	Page 2973 of paper, Figure 3B	Part of TA375 – within ERG base-case (section 5.2.3.1 table 15 and section 5.3 table 19)
START, Westhovens 2006	DAS28 good or moderate response	Page 1081 of paper, Table 3	Part of TA375 – within ERG base-case (section 5.2.3.1 table 15 and section 5.3 table 19)
SATORI, Nishimoto 2009	DAS28 "good" response and "good or moderate" response	Page 15, 1st paragraph below Figure 2	Part of TA375 – within ERG base-case (section 5.2.3.1 table 15 and section 5.3 table 19)
GO-FORTH, Tanaka 2012	DAS28(ESR) "moderate" response and "good" response	Page 820, Table 2	Part of TA375 – within ERG base-case (section 5.2.3.1 table 15 and section 5.3 table 19)
RAPID 1, Keystone 2008, Strand 2009	EULAR "no" response and "good/moderate" response	Taken from TA375 ACD document, Table 18	Part of TA375 – within ERG scenario analysis (section 5.2.3.1 table 15 and section 5.3 table 19)
GO AFTER, Smolen 2009	DAS28 (EULAR) response	Page 214, Table 3	Part of TA415 – within company and ERG base-case (ACD document, table 42 on page 135 and page 35 of ERG report)
ATTAIN, Genovese 2005	EULAR "good" response and "good/moderate" response	Taken from TA415 ACD document: Table 42 (p135); Table 43 (p136).	Part of TA415 – within company and ERG base-case (ACD document, table 42 on page 135 and page 35 of ERG report)

No tofacitinib ORAL publication reported EULAR in the format required to meet the decision problem. Therefore, Pfizer used the patient level data to establish the EULAR responses from the ORAL trials as outlined in section 4.8 of the CS. For the ERG requested NMA settings, Pfizer has now used the individual ORAL trial EULAR responses. Also, please also refer to Pfizer's response to A9 of the ERG clarification request for further points on the derivation of EULAR responses from the tofactinib patient level data.

Pfizer response to A7 request 2: Baseline absolute probabilities were estimated by performing a random effect meta-analysis of the log odds of no response for the reference treatment (placebo + cDMARD/cDMARD). MeanA and precA were generated by transforming the log odds of no response for the reference treatment onto the probit scale (inverse of the cumulative distribution function of the standard normal distribution).

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

ii. Please supply sensitivity analyses amending parts of this proposed NMA where you feel this is appropriate.

In responding to the request from the ERG, Pfizer have incorporated the requested NMA changes into a new analysis, which include a revised NMA setting based on informative priors, ORAL trial cross-over correction Estimate 2 and the incorporation of the Swefot study into the network, with the results presented in A7i.

Pfizer would like to reiterate that design of the ORAL trials incorporated an early escape to minimise the exposure of patients to ineffective treatments, which has resulted in confounding of the month 6 data due to patients in the placebo arm switching over to receive tofactinib at month 3 if they did not have a 20% improvement in swollen and tender joint counts at month 3 (see Section 4.7.6.1 of the CS). Within the comparative evidence assessment a number of studies allowed patients' early escape based on interim assessment of response, however adjusting for these early escape designs within the NMA was not possible due to the imitated availability of published data.

To explore the uncertainty for the ORAL trials in month 6 EULAR response due to this confounding, Pfizer presented two estimates of relative treatment efficacy in the evidence submission (see Section 4.7.6.2 of the CS).

Briefly, Estimate 1 was used as the Pfizer base case, and utilised the non-responder imputation without an advancement penalty applied to tofactinib treated patients who did not meet the criteria of a 20% improvement in both tender and swollen joint counts at month 3. Estimate 2 was provided as a scenario analysis and used the non-responder imputation with advancement penalty applied to tofacitinib treated patients who did not meet the criteria of a 20% improvement of swollen tender and joint counts at month 3.

In Section 4.7.6.2 of the CS, Pfizer provided rationale for why we believe that Estimate 1 is the more appropriate base case. In summary, this highlighted that assumptions implicit in Estimate 2 are not consistent with the data. Specifically that tofacitinib treated patients who were deemed non-responders at month 3 would not go on to develop a response by month 6. Table 54 shows that in the pooled analysis of ORAL Scan, Sync and Standard, of the tofactinib treated patients who were deemed non-responders at [redacted] went on to subsequently develop a moderate EULAR response and [redacted] went on to develop a good EULAR response by month 6; a quarter of the non-responders at month 3.

Furthermore, clinical opinion sought regarding the matter indicated that in a population of patients who would have received MTX for ≥6 months in total and been on a stable dose of MTX for the at least 6 weeks prior to randomisation, it would be expected that less than 10% of the placebo-treated non-responders at Month 3 would develop a subsequent response at month 6 (Section 4.7.6.2 in evidence submission).

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 13 and Table 14 present results of the alternative analysis using the Estimate 1 for ORAL Standard, Sync and Scan whilst retaining all the other ERG requested changes as per A7i. The associated evidence network is presented in Figure 1. Due to the time constraints on running all requested ERG scenarios, the extended time for model runs and subsequent QC of input and outputs, Pfizer was not able to run Estimate 1 results within the economic analyses. However, the results presented in Table 13 and Table 14 suggest a greater proportion of participants attain a moderate or good EULAR response when considering Estimate 1, which will likely result in more positive cost-effective results than those presented here.

Table 13: cDMARD-IR EULAR response using Estimate 1 for ORAL Standard, Sync and Scan – effects of interventions relative to placebo + cDMARD on the probit scale (random effects)

Treatment	Mean	SD	Median	95% CrI
ABT + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
ADA + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
CTZ 200mg Q2W SC + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
ETN + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
ETN HD203 25 mg BIW + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
ETN SB4 50mg QW SC + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
GOL + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
IFX + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
IFX CT-P13 3mg/kg Q8W + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
IFX SB2 + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
TCZ + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
TOF 5mg BID + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]
TCZ	[redacted]	[redacted]	[redacted]	[redacted]
ETN 25mg SC BIW	[redacted]	[redacted]	[redacted]	[redacted]
TOF 5 mg BID	[redacted]	[redacted]	[redacted]	[redacted]
Intensified cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
Between study SD	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; TCZ, tocilizumab; TOF, tofacitinib.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 14: cDMARD-IR EULAR response using Estimate 1 for ORAL Standard, Sync and Scan – probability of achieving a good response or at least a moderate response

Treatment	Good EULAR response					At least a moderate EULAR response				
	Mean	SD	Median	95% CrI		Mean	SD	Median	95% CrI	
				Lower	Upper				Lower	Upper
PBO + cDMARD	[redacted]									
ABT + cDMARD	[redacted]									
ADA + cDMARD	[redacted]									
CTZ 200mg Q2W SC + cDMARD	[redacted]									
ETN + cDMARD	[redacted]									
ETN HD203 25 mg BIW + cDMARD	[redacted]									
ETN SB4 50mg QW SC + cDMARD	[redacted]									
GOL + cDMARD	[redacted]									
IFX + cDMARD	[redacted]									
IFX CT-P13 3mg/kg Q8W + cDMARD	[redacted]									
IFX SB2 + cDMARD	[redacted]									
TCZ + cDMARD	[redacted]									
TOF 5mg BID + cDMARD	[redacted]									
PBO	[redacted]									
ADA	[redacted]									
TCZ	[redacted]									
ETN 25mg SC BIW	[redacted]									

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Treatment	Good EULAR response					At least a moderate EULAR response				
	Mean	SD	Median	95% CrI		Mean	SD	Median	95% CrI	
				Lower	Upper				Lower	Upper
TOF 5 mg BID	[redacted]									
intensified cDMARD	[redacted]									

Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; TCZ, tocilizumab; TOF, tofacitinib.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

A8. Priority question: Please provide a sensitivity analysis for the requested NMA excluding patients with prior biologic use in ORAL trials and excluding studies which had a proportion of patients with prior biologic use.

Pfizer response: The requested sensitivity analysis is presented in Table 15. The associated evidence network is presented in A7. The main impact of exclusion of patients with prior bDMARD use is that CTZ becomes less effective than in the base case response to B7; variations for other treatments are minimal. Please be aware that as outlined in A3, it was not possible to exclude patients with prior biologics use from the ORAL Strategy trial for this analysis.

Table 15: cDMARD-IR EULAR response (Estimate 2) excluding prior biologic patients/trials – effects of interventions relative to placebo + cDMARD on the probit scale (random effects)

Treatment	Mean	SD	Median	95% CrI
ABT + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
ADA + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
CTZ 200mg Q2W SC + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
ETN + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
ETN HD203 25 mg BIW + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
ETN SB4 50mg QW SC + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
GOL + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
IFX + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
IFX CT-P13 3mg/kg Q8W + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
IFX SB2 + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
TCZ + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
TOF 5mg BID + cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]
TCZ	[redacted]	[redacted]	[redacted]	[redacted]
ETN 25mg SC BIW	[redacted]	[redacted]	[redacted]	[redacted]
TOF 5 mg BID	[redacted]	[redacted]	[redacted]	[redacted]
Intensified cDMARD	[redacted]	[redacted]	[redacted]	[redacted]
Between study SD	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; TCZ, tocilizumab; TOF, tofacitinib.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 16: cDMARD-IR EULAR response (Estimate 2) excluding prior biologic patients/trials – probability of achieving a good response or at least a moderate response

Treatment	Good EULAR response					At least a moderate EULAR response				
	Mean	SD	Median	95% CrI		Mean	SD	Median	95% CrI	
				Lower	Upper				Lower	Upper
PBO + cDMARD	[redacted]									
ABT + cDMARD	[redacted]									
ADA + cDMARD	[redacted]									
CTZ 200mg Q2W SC + cDMARD	[redacted]									
ETN + cDMARD	[redacted]									
ETN HD203 25 mg BIW + cDMARD	[redacted]									
ETN SB4 50mg QW SC + cDMARD	[redacted]									
GOL + cDMARD	[redacted]									
IFX + cDMARD	[redacted]									
IFX CT-P13 3mg/kg Q8W + cDMARD	[redacted]									
IFX SB2 + cDMARD	[redacted]									
TCZ + cDMARD	[redacted]									
TOF 5mg BID + cDMARD	[redacted]									
PBO	[redacted]									
ADA	[redacted]									
TCZ	[redacted]									
ETN 25mg SC BIW	[redacted]									

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Treatment	Good EULAR response					At least a moderate EULAR response				
	Mean	SD	Median	95% CrI		Mean	SD	Median	95% CrI	
				Lower	Upper				Lower	Upper
TOF 5 mg BID	[redacted]									
intensified cDMARD	[redacted]									

Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; CrI, credible interval; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; TCZ, tocilizumab; TOF, tofacitinib.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

A9. Priority question: The CS page 151 stated that EULAR response were derived using patient-level data for the ORAL trials. Please clarify why in Appendix 4 Table 206 the outcome for the ORAL trials was DAS not EULAR. Are the EULAR data for the pooled ORAL trials based on CRP or ESR measures?

Pfizer response: In the ORAL trials, EULAR was not reported. Pfizer used ORAL trial patient level data (PLD) to derive the EULAR responses based on the DAS28-4(ESR) measure. As such, the outcome was reported as DAS in Table 206 of the CS in order to remain faithful to the original reporting.

A10. Priority question: Please clarify whether the results from the post-hoc subgroup analyses of the ORAL Standard, Scan, Sync and Solo trials, which excluded patients with prior biologic use, were used in the NMA.

Pfizer response: Pfizer would like to confirm that, as outlined in CS section 4.8, the patient level data analyses for the cDMARD/MTX-IR patient population all ORAL Standard, Scan, Sync and Solo trials patients who received prior biologics were excluded. With that, ORAL Standard, Scan, Sync and Solo trials informed the cDAMRD-IR NMAs. For the bDMARD-IR NMA only ORAL Step efficacy data was used.

A11. Priority question: Please clarify what treatment was chosen as the reference treatment (treatment 1) in each NMA (including the binomial model for EULAR, the probit model for EULAR, and HAQ). Please also clarify what values were used for the baseline meanA and precA in the WinBUGS code provided in Appendix 6, and where these values came from.

Pfizer response: The reference treatment used across all the NMAs was placebo + cDMARD/cDMARD. Absolute treatment effects were not presented for the analyses presented in the original CS. The WinBUGSs code presented included code for generating the absolute treatment effects but they were not generated.

For question A7, absolute responses were requested. These were generated by performing a random effect meta-analysis of the log odds of no response for the reference treatment (placebo + cDMARD/cDMARD). MeanA and precA (Table 17) were generated by transforming the log odds of no response for the reference treatment to a probability and then onto the probit scale (inverse of the cumulative distribution function of the standard normal distribution).

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 17: Summary of meanA and precA values used in the ERG response analyses

	cDMARD NMAs	bDMARD NMAs
meanA	[redacted]	[redacted]
precA	[redacted]	[redacted]

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug; NMA, network meta-analysis.

A12. Priority question: In the CS (pages 198 and 200), it was stated that vague priors are used for the treatment effect sizes relative to treatment 1 in the form of a normal distribution with mean of 1 and variance of 100^2. If a prior was used, please present the NMA results using a prior from a normal distribution with mean 0 and variance of 100^2.

Pfizer response: This was an error in the CS. All analyses used a vague prior for the treatment effect sizes relative to treatment 1 in the form of a normal distribution with mean of 0 and variance of 100^2 (as per the NICE Decision Support Unit [DSU] Technical Support Document [TSD] 2). An update of the results is therefore not required.

A13. Priority question: Please clarify in the CS Table 69 and 71 whether the comparator is placebo or placebo +cDMARD when it was compared with intervention + cDMARD.

Pfizer response: In the networks, placebo + cDMARD and cDMARD were considered equivalent. Therefore, all results are compared with the treatment node 'placebo + cDMARD or cDMARD'.

A14. Priority question: Please clarify the dose of tofacitinib in the CS Table 70 and 72.

Pfizer response: Pfizer would like to confirm that the tofacitinib dose table 70 and 72 of the CS are referring to is 5mg BID. For further clarification, Pfizer would like to reiterate that the CS was based on tofacitinib licenced dose of 5mg throughout the dossier, including the comparative and cost effectiveness analysis. A tofacitinib dose of 10 mg BID (unlicensed) was included in the main Phase III clinical trials for comparison and has been included in the clinical section of dossier for completeness only.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

A15. Priority question: Please provide additional results for moderate EULAR response in the CS Tables 73 and 74.

Pfizer response: EULAR moderate response was listed as an outcome for bDMARD-IR in error in the submission network diagram. As a probit model was used for this outcome only good EULAR and at least a moderate EULAR response were collected as per the NICE TSD2 code.

A16. Please clarify why the number of patients in the ADA+MTX arm for pooled data for three ORAL trials (ORAL Scan, Standard and Sync) was 195 but the number of patients for that arm was 178 in the CS Table 25.

Pfizer response: Table 25 in the CS presents the data as recorded in the ORAL Standard CSR, which presents results for patients with an observed DAS score at month 6. As outlined in section 4.8 of the CS, the PLD analysis imputes missing values using the last observation carried forward method for EULAR response, where a patients DAS score was missing but they had not left the trial. This led to differences in patient numbers.

A17. Please clarify how the EULAR response were derived for the other included trials from DAS scores including whether DAS CRP or DAS ESR was used to convert to EULAR.

Pfizer response:

As outlined in section 4.8 of the CS, Pfizer used ORAL trial patient level data (PLD) to derive the EULAR responses. The PLD analyses utilised individual's DAS28-4 (ESR) values at baseline and at Month 6 to calculate the EULAR response, based on the EULAR response criteria algorithm (Table 18).

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 18: The EULAR response criteria

DAS28 at Month 6	Improvement in DAS28 from baseline		
	>1.2	≤1.2 and >0.6	≤0.6
≤3.2	Good	Moderate	No response
≤5.1 and >3.2	Moderate	Moderate	No response
>5.1	Moderate	No response	No response

Source: Fransen et al, 2009 (2).
Abbreviations: DAS28, disease activity score in 28 joints.

Missing data for reasons other than crossover were treated in accordance with the trial protocols for ORAL studies and the following corrections have been applied:

- LOCF was applied to account for missing observations.
- Patients who had no baseline DAS score were assumed to be a non-responder.
- Patients who dropped out of the trial prior to Month 6 were imputed as a non-responder.

The analyses were carried out for all ORAL trial treatments.

A18. Please clarify what studies included in the NMA had patients with prior bDMARD use, and what studies had a proportion of RhF+ patients. Please also indicate the proportions of prior bDMARD and proportion of RhF+ patients in these studies.

Pfizer response: The proportion of RhF+ patients was originally presented in Table 204 for cDMARD-IR and in table 205 for bDMARD-IR of the CS. An updated version of the patient baseline characteristics table including prior bDMARD use is provided in Table 44 of Appendix 1. Also, as outlined in section 4.10.2 and listed in table 61 of the CS, the OPTION, J-RAPID and RAPID-1 trials were included in the base-case network, and a sensitivity analysis of excluding these studies was performed to estimate the impact of these studies within the NMA. The impact on the binomial model was discussed in the sensitivity analyses section (4.10.5.5) of the CS, and it was concluded that results were largely insensitive to prior-bDMARD usage, unless multiple potential effect modifiers (section 4.10.3.2 of CS) were considered simulataniously, such as exclusion of Asian studies, prior bDMARD usage, milder disease and near naïve treatment RA (SWEFOT), which would have a substantial impact on the network feasibility.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

A19. Please provide the model fit statistics for the cDMARD-IR NMA probit model for EULAR outcome.

Pfizer response: Model fit statistics are provided in

.

Table 19 Model fit statistics for the cDMARD-IR NMA probit model for EULAR

	Number of data points	DIC	Posterior residual deviance	Average residual deviance	Standard deviation (95% CI)
EULAR probit model-CDMARD IR					
Fixed effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Random effects		[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: cDMARD, conventional disease-modifying anti-rheumatic drug; CI, confidence interval; DIC, deviance information criterion; EULAR, European League Against Rheumatism; IR, inadequate response; NMA, network meta-analysis.

A20. Please clarify what the 95% credible interval is for the standard deviation using a random effects model probit model for EULAR in the CS Table 67.

Pfizer response: The standard deviation (95% CI) was [redacted].

A21. In the CS page 199, it was stated that "Change from baseline scores of continuous outcomes (HAQ-DI) were computed from mean baseline and endpoint scores where necessary." Please clarify how the standard deviation of the change from baseline scores of HAQ-DI were computed.

Pfizer response: The standard deviation of the change from baseline score was imputed using a correlation coefficient as outlined within the Cochrane handbook. A correlation coefficient of 0.5 was applied (conservative estimate).

$$\mathbf{SD_{E,change}} = \sqrt{\mathbf{SD^2_{E,baseline}} + \mathbf{SD^2_{E,final}} - (\mathbf{2\ x\ Corr\ x\ SD_{E,baseline}\ x\ SD_{E,final}})}$$

<u>Section B: Clarification on cost-effectiveness data</u>

B1. Priority question: Please provide the file with the CODA to allow the ERG to run the PSA.

Pfizer response: We have provided this as a separate file alongside the submission of responses.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

B2. Priority question: The company assumed an annual worsening in their HAQ score of 0.06 for patients on palliative care. It is claimed in the CS that this is in line with TA375. However, the AG in TA375 assumed that the HAQ progression on palliative care would be equivalent to that of non-biological therapy, which followed the trajectories of cDMARDs. Please provide results of the analyses including this assumption if possible and otherwise assess the direction of the relevant ICERs if this assumption had been included.

Pfizer clarification request: *Could you please provide the excerpt and reference of the NICE TA375 document for palliative care HAQ progression you are referring to?*

ERGs response*: In (Stevenson 2016) from the company's reference pack, in the subsection "Health Assessment Questionnaire trajectory following initial response" of the "Independent economic assessment" section (page 251) it is specified that palliative care equated to non-biologic therapy (NBT), which falls into the category of cDMARDs and that the annual 0.06 increase in HAQ for palliative care was only used in sensitivity analyses.*

Pfizer response: Thank you for the additional clarification. This appears to be a misunderstanding on Pfizer's part. We set up our model base case for this submission in what we thought was aligned to the TA375 economic model for the ID526 submission and which was not in line with the Assessment Group Technical Assessment Report (TAR). We have now made the ERG requested changes.
Table 20 presents the results of the revised cDMARD-IR base-case analysis using:

- The ERGs preferred sequences
- The base-case ERG NMA
- Corrected change in HAQ scores (see B11)
- Norton progression for LEF and PBT
- Baseline age used to predict class membership in the Norton HAQ progression analysis (B13)
- A model where the prior_bdmard flag updates after the first biologic or JAK inhibitor

Table 20–Table 24 present the results without each of these last four points, respectively, in order to assess the impact on results. There was minimal variation in the ICERs across these analyses, with the exception of the analyses using linear PBT progression and without the prior_bdmards flag updating.

Table 20: cDMARD-IR ERG base-case results

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]		

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,764
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£55,322
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£183,478
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TCZ, tocilizumab; TOF, tofacitinib.

Table 21: ERG base case without changes to HAQ change at month 6

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]		
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,736
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,315
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£120,939
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TCZ, tocilizumab; TOF, tofacitinib.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 22: ERG base case without corrections to Norton class prediction

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]		
TCZ +MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,719
INF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£55,413
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£180,647
ETN+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£214,624
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TCZ, tocilizumab; TOF, tofacitinib.

Table 23: ERG base case with linear PBT progression

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TCZ +MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,766
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,757

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£63,568
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TCZ, tocilizumab; TOF, tofacitinib.

Table 24: ERG base case without the prior_bdmards flag updating

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]		
TCZ +MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,277
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,008
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£114,497
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TCZ, tocilizumab; TOF, tofacitinib.

B3. Priority question: Please re-run analyses to provide fully incremental results based on the efficacy data from the requested NMA analyses.

Pfizer response:

cDMARD-IR population

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 25: cDMARD-IR population using Estimate 2 of efficacy and rapid progression

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]		
TCZ +MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,320
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,131
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£103,577
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Moderate results in the severe RA model

Table 26: Results for the moderate population using the ERG basecase NMA (Estimate 2)

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]		
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,827

Abbreviations: ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

Table 27 Results for the moderate population using the ERG basecase NMA (Estimate 2) and Rapid Progression

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
MTX	[redacted]	[redacted]	[redacted]	[redacted]		
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,640

Abbreviations: ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

Moderate results in the moderate RA model

Table 28 Results for the moderate population using the ERG base case NMA (Estimate 2)

Strategy	Cost	QALYs	Comparison	Inc. Cost	Inc QALY	ICER
Moderate RA pathway only						

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

MTX	[redacted]	[redacted]				
TOF+MTX	[redacted]	[redacted]	vs. MTX	[redacted]	[redacted]	£18,907
moderate RA and severe RA pathway – lifetime model						
MTX	[redacted]	[redacted]				
TOF+MTX	[redacted]	[redacted]	vs MTX	[redacted]	[redacted]	£49,704

Abbreviations: ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life years; TOF, tofacitinib.

bDMARD-IR population

Table 29: bDMARD-IR population after RTX (as per table 33) using the ERG base case bDMARD-IR NMA (Estimate 2)

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
TOF_insTOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
RTX+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
TOF_aftRTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,782
TOF_aftTOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£72,510

Abbreviations: ADA, adalimumab; ABA, abatacept; bDMARD, biologic disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab; TCZ, tocilizumab; TOF, tofacitinib.

Table 30: bDMARD-IR population, RTX intolerant using the ERG base case bDMARD-IR NMA (Estimate 2)

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]		
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
TCZ +MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,628
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ADA, adalimumab; ABA, abatacept; bDMARD, biologic disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab; TCZ, tocilizumab; TOF, tofacitinib.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 31: bDMARD-IR population, alongside RTX using the ERG base case bDMARD-IR NMA (Estimate 2)

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline	ICER
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£104,917
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ADA, adalimumab; ABA, abatacept; bDMARD, biologic disease modifying anti-rheumatic drug; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; RTX, rituximab; TOC, tocilizumab; TOF, tofacitinib.

B4. Priority question: Please clarify why predicted HAQ changes are rounded to the nearest 0.125. This method will cause markedly different results if the predicted HAQ change between events was consistently 0.0620 compared with when it was 0.0630. Please amend the model if possible, or discuss the potential implications of this limitation.

Pfizer response: HAQ scores are rounded to the nearest 0.125 as this reflects the way the HAQ-DI questionnaire is scored. There are 25 possible HAQ-DI scores, ranging from 0 to 3 in increments of 0.125 (3). Thus, by rounding HAQ scores, we present an analysis that will more closely model clinical reality. This matches the analysis performed by the assessment group in TA375, which also forced HAQ scores to be multiples of 0.125 (4).

The implications of this are that HAQ changes at Month 6 observed in the model may be larger or smaller than those sampled. We do not expect this to provide an advantage to wither MTX, tofacitinib, or biologics, This approach may provide a small advantage to drugs modelled using Norton progression, as until the average change in HAQ is greater than 0.0625, they will experience no progression.

B5. Priority question: Please clarify why the sequences used in all three populations are not in line with TA375. Please provide ICERs for the cDMARD-IR population using sequences similar to those used in TA375 (Tables 159 and 160 for MTX tolerant and intolerant respectively) and for the bDMARD-IR population with sequences where biologics are only followed by MTX therapy (once only) followed by PaC. For the moderate population, please provide ICERs for sequences similar to those in Table 161 and Table 162 of the TA375 report for MTX tolerant and intolerant respectively.

The ERG also added for clarity the sequences requested in clarification question B5 in Table 32–Table 34.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Pfizer response: Thank you for the additional clarification. This appears to be a misunderstanding on Pfizer part. In preparation for the ID526 submission Pfizer utilized what we thought to be the sequences used in the TA375 economic model set up and not as per Assessment Group report. We have now made the requested change. The results of the revised economic analyses are presented in B2 and B3.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 32: Treatment sequences for moderate-to-severe cDMARD-IR

Treatment sequence	Combination therapy									Monotherapy				
	MTX	ABT+MTX	ADA+MTX	CZP+MTX	GOL+MTX	TCZ +MTX	TOF+MTX	ETNb+MTX	INFb+MTX	SSZ	TCZ	TOF	ETN	ADA
1	MTX	ABT+ MTX	ADA+ MTX	CZP+ MTX	GOL+ MTX	TCZ + MTX	TOF+ MTX	ETNb+ MTX	INF+ MTX	SSZ	TCZ	TOF	ETN	ADA
2	PaC	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	PaC	ETN	ETN	ADA	ETN
3		TCZ + MTX	TCZ + MTX	TCZ + MTX	TCZ + MTX	MTX	TCZ + MTX	TCZ + MTX	TCZ + MTX		SSZ	SSZ	SSZ	SSZ
4		MTX	MTX	MTX	MTX	PaC	MTX	MTX	MTX		PaC	PaC	PaC	PaC
5		PaC	PaC	PaC	PaC		PaC	PaC	PaC					

Abbreviations: ABA, abatacept; ADA, adalimumab; cDMARD, conventional disease modifying anti-rheumatic drug; CZP, certolizumab pegol; DMC, DMARD combination; ETN, etanercept; GOL, golimumab; INF, infliximab; PaC, palliative care; RTX, rituximab TCZ, tocilizumab; TOF, tofacitinib.
‡This will reflect a combination of potential therapies, including monotherapy and combination therapy.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 33: Treatment sequences for bDMARD-IR

Treatment sequence	RTX tolerant (with RTX)				RTX intolerant				RTX tolerant (after) RTX			
	RTX+MTX	**TOF+MTX instead of** TCZ **+ MTX**	**TOF+MTX after RTX + MTX**	**TOF+MTX after** TCZ **+ MTX**	**TOF+MTX**	**ABT+MTX**	TCZ **+MTX**	**GOL+MTX**	**RTX+MTX**	**TOF+MTX instead of** TCZ **+ MTX**	**TOF+MTX after RTX + MTX**	**TOF+MTX after** TCZ **+ MTX**
1	RTX+MTX	TOF+MTX	ABT+MTX	GOL+MTX	TOF+MTX	ABT+MTX	TCZ +MTX	GOL+MTX	RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX
2	TCZ +MTX	TCZ +MTX	TCZ +MTX	TCZ +MTX	TCZ +MTX	TCZ +MTX	GOL+MTX	TCZ +MTX	TCZ +MTX	TOF+MTX	TOF+MTX	TCZ +MTX
3	MTX	MTX	MTX	MTX	MTX	MTX	MTX	MTX	MTX	MTX	TCZ +MTX	TOF+MTX
4	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC	PaC*	PaC*	MTX	MTX
5											PaC*	PaC*

Abbreviations: ABA, abatacept; ADA, adalimumab; cDMARD, conventional disease modifying anti-rheumatic drug; DMC, DMARD combination; GOL, golimumab; LEF, leflunomide; PaC, palliative care; RTX, rituximab TCZ, tocilizumab; TOF, tofacitinib.
‡This will reflect a combination of potential therapies, including monotherapy and combination therapy.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 34: Treatment sequences for moderate cDMARD-IR

Treatment sequence†	Moderate sequence						Severe sequence
	Combination TA375 sequence		Combination alternate sequence		Monotherapy		
	MTX	TOF+MTX	MTX	TOF+MTX	SSZ	TOF	ETN+MTX
1	MTX	TOF+MTX	MTX	TOF+MTX	SSZ	TOF	ETN+MTX
2	DMC	RTX+MTX	PaC	MTX	PaC	ADA	RTX+MTX
3	PaC	TCZ +MTX		PaC		PaC	TCZ +MTX
4		MTX					DMC
5		DMC					PaC
6		PaC					

Abbreviations: cDMARD, conventional disease modifying anti-rheumatic drug; PaC, palliative care; TOF, tofacitinib.
†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. ‡This will reflect a combination of potential therapies, including monotherapy and combination therapy. ¶Combination therapy will still be possible with cDMARD but will not include MTX.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

B6. Priority question: It is noted that the RTX tolerant (after RTX) analysis all extend the number of biological interventions in the sequence. Please provide incremental analyses for when TOF + MTX is assumed to replace TCZ + MTX. Further, please provide the incremental analysis where TOF + MTX is assumed to go after TCZ + MTX for comparison with the elongated sequence adding TOF + MTX.

Pfizer clarification request: Could you please clarify the exact sequences requested for this population using the following table format?

RTX tolerant (after) RTX)			
RTX+MTX	**TOF+MTX**	**ABT+MTX**	**GOL+MTX**
RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX
TCZ +MTX	TOF+MTX	ABT+MTX	GOL+MTX
DMC	TCZ +MTX	TCZ +MTX	TCZ +MTX
DMC	DMC	DMC	DMC
LEF	DMC	DMC	DMC
PaC	LEF	LEF	LEF
-	PaC	PaC	PaC

Abbreviations: ABA, abatacept; ADA, adalimumab; cDMARD, conventional disease modifying anti-rheumatic drug; DMC, DMARD combination; GOL, golimumab; LEF, leflunomide; PaC, palliative care; RTX, rituximab TCZ, tocilizumab; TOF, tofacitinib.

ERG's response:

RTX tolerant (after) RTX			
RTX+MTX	**TOF+MTX instead of TCZ + MTX**	**TOF+MTX after RTX + MTX**	**TOF+MTX after TCZ + MTX**
RTX+MTX	RTX+MTX	RTX+MTX	RTX+MTX
TCZ +MTX	TOF+MTX	TOF+MTX	TCZ +MTX
MTX	MTX	TCZ +MTX	TOF+MTX

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

PaC*	PaC*	MTX	MTX
		PaC*	PaC*

Abbreviations: ABA, abatacept; ADA, adalimumab; cDMARD, conventional disease modifying anti-rheumatic drug; MTX, methotrexate; PaC, palliative care; RTX, rituximab TCZ, tocilizumab; TOF, tofacitinib.

*Please note the previous comment on the non-linear trajectory of patients on PaC

Pfizer response: Thank you for the additional clarification. To coherently present the revised base-case results for each population outlined in the NICE decision problem, the results of the requested analysis are presented in B3.

B7. Please clarify why the annual cost of RTX reported in Table 122 (£10,163) is higher than that of other bDMARDs, when in TA375 it was the cheapest. The number of RTX doses seems to be calculated to be twice the correct quantity.

Pfizer response: This is a mistake in the model. However, this mistake is purely cosmetic as these are not the values used in the calculation of costs for RTX and so there is no impact on results. RTX dosing is modelled as an event, with costs calculated in the VBA in the 'costs' module.

B8. Please clarify why the prior_bDMARD flag of the patients is not updated after going through the first biologic in the sequence. Please re-run analyses if appropriate.

Pfizer response: Please also see response to B2. As requested the flag is now updated after the first biologic in the sequence and for simplicity also after tofacitinib.

B9. Please clarify whether the model assumes the same probability of moderate and good EULAR response for TOF in combination with MTX and as monotherapy. Please clarify also whether the multinomial logistic regression model used to estimate the probability of moderate and good EULAR response was based on all ORAL trials (as listed in Figure 3) or only Standard, Scan, Sync, and Step. Please provide the observed and predicted EULAR responses for ORAL Step and Solo.

Pfizer response: The model assumes the same probabilities of response for tofacitinib with and without MTX. Response rates with tofacitinib in ORAL Solo were high and Table 35 shows that the predictive model presents a conservative estimate of the response rates. This model was fit using data from ORAL Scan, Sync and Standard only and does not use ORAL Step or Solo.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 35: Observed and predicted response rates for ORAL Step and ORAL Solo

Trial	Predicted response rate	Actual response rate	Predicted moderate	Actual moderate	Predicted good	Actual good
Step	38.6%	38.4%	48.1%	40.0%	13.3%	21.6%
Solo	28.7%	22.1%	56.3%	55.6%	15.0%	22.1%

B10. Please clarify why the SC formulations of ABA and TCZ were not included as comparators.

Pfizer response: The systematic review did not identify any tocilizumab SC studies that would meet the NCE decision problem and thus allow inclusion into the NMA. However, the cost of TCZ SC presented in MIMS is £913.12 for four 162 mg/0.9 ml prefilled syringes. The recommended dose for TCZ-SC is 162 mg once weekly, which gives an annual cost for TCZ SC of £12,010.96 including cost of administration. The average annual cost of TCZ IV is estimated to be £11,388.00. And therefore, for simplicity if assuming equivalence in efficacy, TCZ IV would dominate TCZ SC, when accounting for the cost differential between formulations.

Similarly, for abatacept (ABT), the systematic review did not identify any ABT SC studies that would meet the NCE decision problem and thus allow inclusion into the NMA. In MIMS the costs for ABT SC is £1,209.60 for four 125 mg pre-filled syringes or pens. The recommended dose is 125 mg once weekly, giving an annual cost of £15,865.20 including administration costs. This compares to an average annual cost for £13,863.20 for ABT IV. With assuming the same efficacy between formulations, ABT IV would dominate ABT SC in the cost-effectiveness analyses.

B11. Please clarify why the average changes in HAQ score at month 6 used for moderate and good response (-0.321, -0.678 respectively), allegedly based on TA375, were different from the values used in TA375 (-0.317 and -0.672 respectively).

Pfizer response: Please also see response to B2 (Table 21).

This appears to be a mistake in the model. We have now assessed the effect of changing these inputs and it does not appear to be significant, as the change in ICER values across treatments vs MTX is marginal (up to £500). All additional analyses have been performed using the updated values.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

B12. Please clarify whether the population for the monotherapy analyses was sampled or defined based on the population in ORAL Solo. Similarly, clarify whether the population for the bDMARD-IR analyses was sampled or defined based on the population in ORAL Step.

Pfizer response: The monotherapy analysis was based on a population sampled from all second-line trials. The bDMARD-IR analysis was based on a population sampled from ORAL Step.

B13. Please clarify why the probability of class membership for the HAQ progression latent classes was recalculated based on patient's age if the predictor is age at onset.

Pfizer response: Please also see response to B2.

This is a mistake in the analysis. We have now updated the model to use age at baseline/age at onset, though the effect on ICERs appears to be negligible as none of the ICERs vs MTX change by more than £100.

B14. Please provide details on the validation of the OLS regression described in page 263 for changes in DAS28 (e.g. R-squared, scatter plot).

Pfizer response: Results for the regression model for DAS28 are presented in Table 36. Scatter plots for fitted values and residuals vs DAS28 (change from baseline) are shown in Figure 3 and Figure 4, respectively. A scatter plot for residuals vs HAQ (change from baseline) is shown in Figure 5.

Table 36: Validation results of the OLS regression model for predicting change in DAS28

Source	SS	df	MS	Number of obs = [redacted]
Model	[redacted]	[redacted]	[redacted]	[redacted]
				[redacted]
Residual	[redacted]	[redacted]	[redacted]	[redacted]
				[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OLS, ordinary least squares.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Figure 3: Fitted values vs DAS28 (change from baseline)

Abbreviations: DAS28, disease activity in 28 joints; ESR, erythrocyte sedimentation rate; OLS, ordinary least squares.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Figure 4: Residuals vs DAS28 (change from baseline)

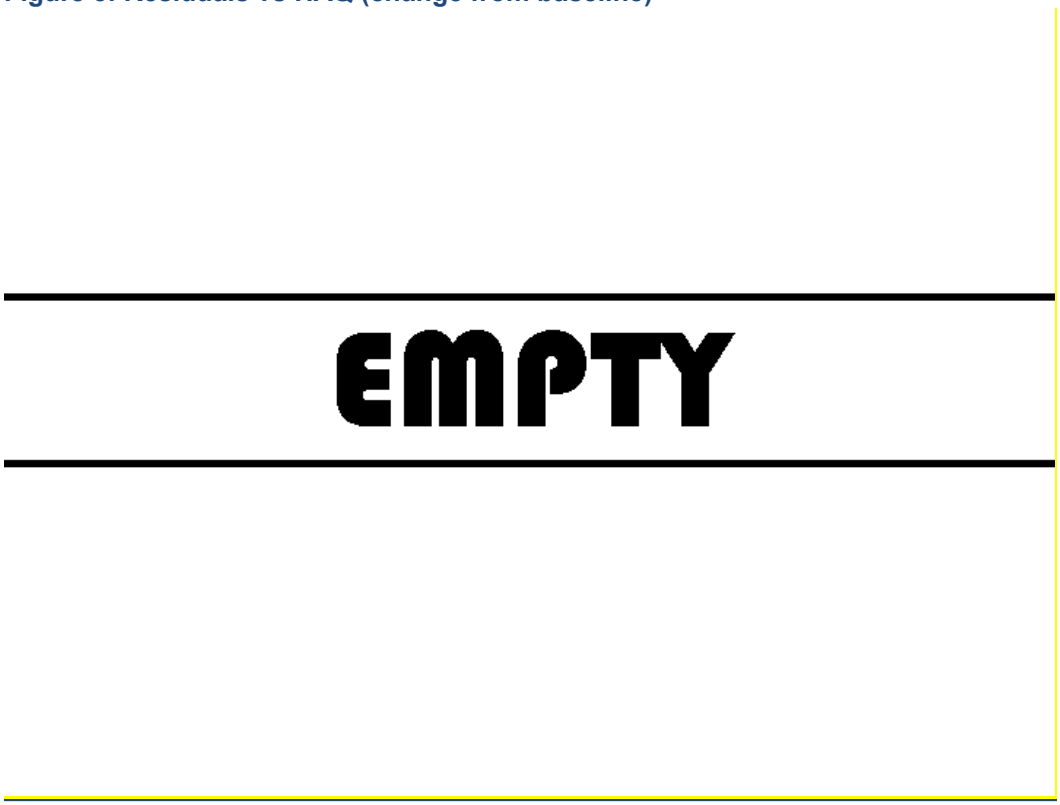
EMPTY

Abbreviations: DAS28, disease activity in 28 joints; ESR, erythrocyte sedimentation rate; OLS, ordinary least squares.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Figure 5: Residuals vs HAQ (change from baseline)



Abbreviations: HAQ, Health Assessment Questionnaire disability index; OLS, ordinary least squares.

B15. Please provide significance levels for the variables of the predictive model for HAQ score change in page 275. Clarify whether non-linear models were explored.

Pfizer response:

[redacted]Table 37[redacted]Table 38[redacted]

Table 37: Results of the regression model for predicting change in HAQ-DI

Source	SS	df	MS	Number of obs = [redacted]
Model	[redacted]	[redacted]	[redacted]	[redacted]
				[redacted]

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Residual	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HAQ-DI, Health Assessment Questionnaire disability index.

Table 38: Predictive model of change in HAQ score at Month 6

Variable	Coefficient	SE	t	P>t	95% CI
[redacted]					

B16. Please provide patient numbers at risk for the long-term extension study by level of response at month 6 (Table 110).

Pfizer clarification request: *Please could you clarify whether you are asking for the patient numbers by EULAR response for each month presented?*

ERGs response: *Yes, please, could we have numbers at risk for moderate and good response for each time point presented in Table 110?*

Pfizer response: Patient numbers by HAQ-DI response are presented in Table 39.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Table 39: Change in HAQ-DI by level of response (patient numbers)

Month	Moderate responders	Good responders
0	[redacted]	[redacted]
3	[redacted]	[redacted]
6	[redacted]	[redacted]
9	[redacted]	[redacted]
12	[redacted]	[redacted]
15	[redacted]	[redacted]
18	[redacted]	[redacted]
21	[redacted]	[redacted]
24	[redacted]	[redacted]
27	[redacted]	[redacted]
30	[redacted]	[redacted]
33	[redacted]	[redacted]
36	[redacted]	[redacted]
39	[redacted]	[redacted]
42	[redacted]	[redacted]
45	[redacted]	[redacted]
48	[redacted]	[redacted]
51	[redacted]	[redacted]
54	[redacted]	[redacted]
57	[redacted]	[redacted]
60	[redacted]	[redacted]
63	[redacted]	[redacted]
66	[redacted]	[redacted]
69	[redacted]	[redacted]
72	[redacted]	[redacted]
75	[redacted]	[redacted]
78	[redacted]	[redacted]
81	[redacted]	[redacted]
84	[redacted]	[redacted]
87	[redacted]	[redacted]

Abbreviations: HAQ-DI, Health Assessment Questionnaire disability index.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

B17. Please clarify why in the analyses, biosimilars are estimated to result in slightly different number of QALYs? If this is due to Monte Carlo sampling error, would it be more appropriate to remove the parent drug as this is dominated.

Pfizer response: This is down to sampling error. For the ease of cost-effectiveness analysis the parent drug has been removed in the revised analysis.

B18. Please clarify whether the number of patients and iterations used in the PSA was enough to provide stable results.

Pfizer response: The PSA uses 1,000 simulations, each using 100 patients. The results of the PSA were considered to be stable enough, as they produce similar results (Table 40) to the base-case analysis (Table 20). Figure 6 presents the ICER for TOF vs MTX by the number of simulations up to 3,000 simulations. It shows that after 1,000 simulations there is little variation in the average ICER.

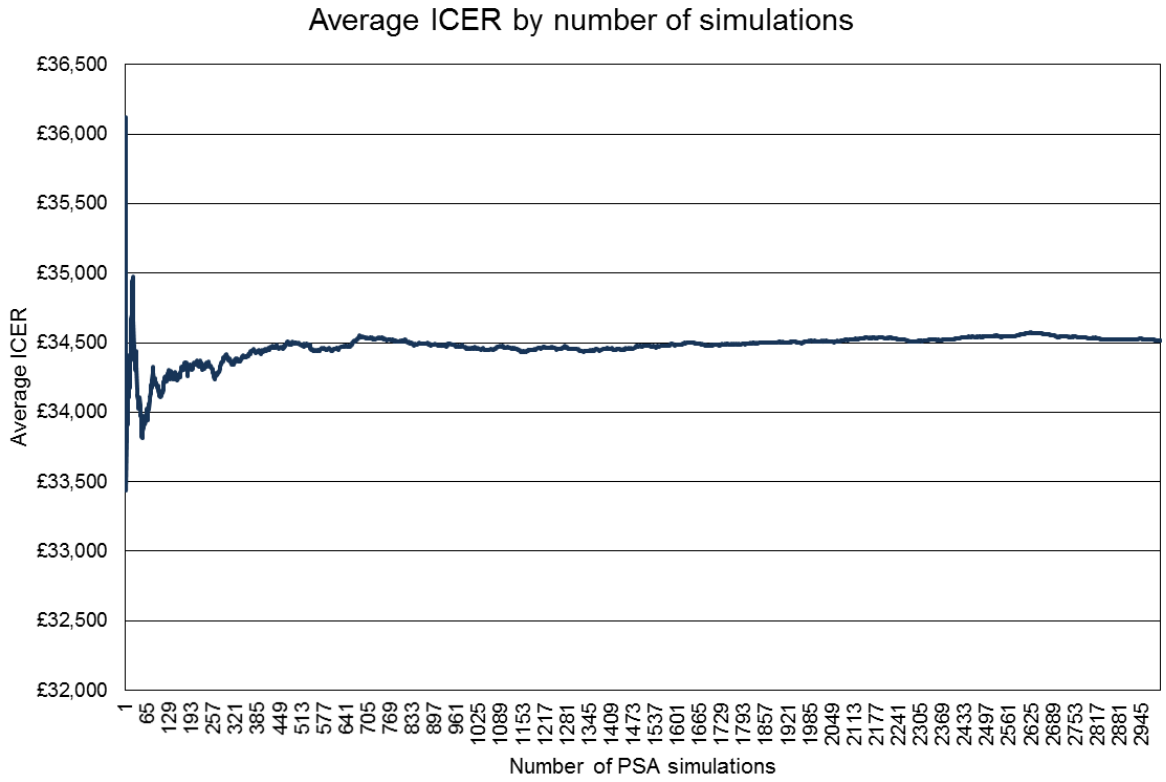
Table 40: Updated base-case PSA results using A7 response NMA

Strategy	Cost	QALYs	Inc. Cost	Inc QALY	ICER vs baseline
MTX	[redacted]	[redacted]			
TOC+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£34,024
INFb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£33,967
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£35,072
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£36,988
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£34,208
CZP+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£34,974
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£35,442
ABT+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£41,985

Abbreviations: ADA, adalimumab; ABA, abatacept; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; MTX, methotrexate; QALYs, quality-adjusted life years; TOC, tocilizumab; TOF, tofacitinib.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Figure 6 ICER value by number of simulations



Abbreviations: ICER, incremental cost-effectiveness ratio.

19. Please provide tables with probabilities of EULAR response for different treatments, for the cDMARD-IR and the bDMARD-IR populations.

Pfizer response: These values are provided in Table 41. These values are presented for the base-case NMAs for each population in the CS. These values can also be found in the model, on the Efficacy_2 sheet and will update based on the NMA being used.

Table 41: Probability of EULAR response by treatment and population

	Moderate to severe cDMARD-IR		Moderate cDMARD-IR		Severe bDMARD-IR	
Therapy	**At least moderate**	**Good**	**At least moderate**	**Good**	**At least moderate**	**Good**
Tofacitinib + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abatacept + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

	Moderate to severe cDMARD-IR		Moderate cDMARD-IR		Severe bDMARD-IR	
Therapy	**At least moderate**	**Good**	**At least moderate**	**Good**	**At least moderate**	**Good**
Golimumab + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rituximab + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept Biosimilar + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab biosimilar + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ciclosporin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sulfasalazine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DMARD combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept Biosimilar Mono	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-biologic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug; IR, inadequate response; MTX, methotrexate.

B20. Please provide tables with the average baseline characteristics of the three populations considered in the analyses: moderate cDMARD-IR, severe cDMARD-IR and severe bDMARD-IR.

Pfizer response: These are provided in Table 42.

Table 42: Population characteristics

	Moderate cDMARD-IR	Moderate to severe cDMARD-IR	Severe bDMARD-IR
Age	[redacted]	[redacted]	[redacted]

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

	Moderate cDMARD-IR	Moderate to severe cDMARD-IR	Severe bDMARD-IR
Gender (Female = 1)	XXX	XXX	XXX
Weight	XXXX	XXXX	XXXX
HAQ	XXXX	XXXX	XXXX
DAS28	XXXX	XXXX	XXXX
Prior cDMARDs	XXXX	XXXX	XXXXXXX
Prior bDMARDs	XXX	XXX	XXXX
Anti-CCP positive	XXX	XXX	XXX
Disease duration (years)	XXX	XXX	XXXX
Hemoglobin	XXXX	XXXX	XXXX
CRP	XXX	XXXX	XXXX
ESR	XXXX	XXXX	XXXX
Total cholesterol	XXXXX	XXXXX	XXXXX
CDAI	XXXX	XXXX	XXXX
Number of previous DMARDs	XXX	XXX	XXX

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; CCP, cyclic citrullinated peptide; CDAI, clinical disease activity index; cDMARD, conventional disease-modifying anti-rheumatic drug; CRP, c-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; IR, inadequate response.

Section C: Textual clarifications and additional points

C1. Please provide the SmPC for tofacitinib. The CS states that the SmPC is provided in Appendix 1. Appendix 1 states that the SmPC is provided in the reference pack. The "SPC" provided in the reference pack is the EPAR summary for Etanercept.

Pfizer response: We apologise for the omission. The SmPC has been provided along with this response.

C2. Please confirm typo on page 221 of CS: These trials report opposite relative treatment effects as the Fleischmann 2012a results are less favourable for tocilizumab in comparison with the ORAL solo trial.

Pfizer response: The sentence should read '…are less favourable for tofacitinib in comparison with the ORAL solo trial." In addition, the sentence prior to this sentence should also refer to tofacitinib rather than tocilizumab.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

C3. Please clarify whether in section 5.7.1.1., page 321, in the second bullet point ETNb+MTX was wrongfully omitted from the list of treatments that are not dominated by TOF + MTX.

Pfizer response: The list of treatments that were not dominated by tofacitinib + MTX should include tocilizumab + MTX and etanercept biosimilar + MTX. Infliximab biosimilar + MTX was erroneously included in this list as it was extendedly dominated by tofacitinib + MTX.

C4. In the CS Table 88 the DAS28-4(ESR) for ORAL Sync are reported as 9.1 and 2.7 for TOF vs PBO respectively. In the corresponding journal paper (Kremer et al 2013) these data are reported in Figure 3 as 8.5 and 2.6. Please clarify the discrepancy. Likewise, in CS Table 88 HAQ-DI (-0.46 and -0.21) and ACR20, % (52.7 and 31.2) are different to Figure 3 in the corresponding journal paper (Kremer et al 2013) (HAQ-DI, -0.44 and -0.16; ACR20 %, 52.1 and 30.8). Please clarify the discrepancy.

Pfizer response: The values presented in Table 88 can be found in the supplement to Kremer et al, 2013 (supplementary Figure 2, page 32). These data were chosen over those presented in the main text as they were more consistent with how these data were presented in the other ORAL trials and with the primary values presented in the associated CSR (Pfizer Inc. CSR A3921046 2012; see Table 16 – ACR20, Table 17 – HAQ-DI and Table 18 DAS28-4[ESR]).

C5. Please specify whether the first comparator in the cDMARD-IR combination therapy is MTX as specified in Section 5.7.1 or DMC as specified in Table 126.

Pfizer response: Yes, the first comparator should read DMC.

C6. Please clarify whether in section 5.7.2 the references to MTX are actually meant to be SSZ+HQC.

Pfizer response: Yes, this should read SSZ+HQC rather than MTX.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

References

1. Strand V, Ahadieh S, French J, Geier J, Krishnaswami S, Menon S, et al. Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. Arthritis Res Ther. 2015;17:362.
2. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. Rheum Dis Clin North Am. 2009;35(4):745-57, vii-viii.
3. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: Dimensions and Practical Applications. Health Qual Life Outcomes. 2003;1:20-.
4. TA375 Assessment Group Report - Estimated cost per QALY ratios for bDMARD strategies following the correction of identified errors. (May 2015).
5. Dougados M, Kissel K, Conaghan PG, Mola EM, Schett G, Gerli R, et al. Clinical, radiographic and immunogenic effects after 1 year of tocilizumab-based treatment strategies in rheumatoid arthritis: the ACT-RAY study. Annals of the Rheumatic Diseases. 2014;73(5):803-9.
6. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. The Lancet.381(9877):1541-50.
7. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti–tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: The ARMADA trial. Arthritis & Rheumatism. 2003;48(1):35-45.
8. Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Annals of the Rheumatic Diseases. 2008;67(8):1096-103.
9. van Vollenhoven RF, Kinnman N, Vincent E, Wax S, Bathon J. Atacicept in patients with rheumatoid arthritis and an inadequate response to methotrexate: Results of a phase II, randomized, placebo-controlled trial. Arthritis & Rheumatism. 2011;63(7):1782-92.
10. Smolen JS, Emery P, Ferraccioli GF, Samborski W, Berenbaum F, Davies OR, et al. Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomised, placebo-controlled trial. Annals of the Rheumatic Diseases. 2015;74(5):843-50.
11. Miyasaka N, The CSI. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Modern Rheumatology. 2008;18(3):252-62.
12. Choe J-Y, Prodanovic N, Niebrzydowski J, Staykov I, Dokoupilova E, Baranauskaite A, et al. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

severe rheumatoid arthritis despite methotrexate therapy. Annals of the Rheumatic Diseases. 2015.

13. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti–tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: A randomized, placebo-controlled, 52-week trial. Arthritis & Rheumatism. 2004;50(5):1400-11.

14. Emery P, Vencovský J, Sylwestrzak A, Leszczyński P, Porawska W, Baranauskaite A, et al. A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. Annals of the Rheumatic Diseases. 2015.

15. Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum. 2012;64(3):617-29.

16. Tanaka Y, Harigai M, Takeuchi T, Yamanaka H, Ishiguro N, Yamamoto K, et al. Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study. Annals of the Rheumatic Diseases. 2012;71(6):817-24.

17. Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumour necrosis factor α given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Annals of the Rheumatic Diseases. 2009;68(6):789-96.

18. Bingham CO, Weinblatt M, Han C, Gathany TA, Kim L, Lo KH, et al. The effect of intravenous golimumab on health-related quality of life in rheumatoid arthritis: 24-week results of the phase III GO-FURTHER trial. The Journal of Rheumatology. 2014;41(6):1067-76.

19. Bae S-C, Kim J, Choe J-Y, Park W, Lee S-H, Park Y-B, et al. A phase III, multicentre, randomised, double-blind, active-controlled, parallel-group trial comparing safety and efficacy of HD203, with innovator etanercept, in combination with methotrexate, in patients with rheumatoid arthritis: the HERA study. Annals of the Rheumatic Diseases. 2016.

20. Kameda H, Ueki Y, Saito K, Nagaoka S, Hidaka T, Atsumi T, et al. Etanercept (ETN) with methotrexate (MTX) is better than ETN monotherapy in patients with active rheumatoid arthritis despite MTX therapy: a randomized trial. Modern Rheumatology. 2010;20(6):531-8.

21. Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. Mod Rheumatol. 2014;24(5):715-24.

22. Kim H-Y, Lee S-K, Song YW, Yoo D-H, Koh E-M, Yoo B, et al. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

rheumatoid arthritis patients treated with methotrexate. APLAR Journal of Rheumatology. 2007;10(1):9-16.

23. Kremer JM, Cohen S, Wilkinson BE, Connell CA, French JL, Gomez-Reino J, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. Arthritis Rheum. 2012;64(4):970-81.

24. Machado DA, Guzman RM, Xavier RM, Simon JA, Mele L, Pedersen R, et al. Open-label observation of addition of etanercept versus a conventional disease-modifying antirheumatic drug in subjects with active rheumatoid arthritis despite methotrexate therapy in the Latin American region. Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases. 2014;20(1):25-33.

25. Li Z, Zhang F, Kay J, Fei K, Han C, Zhuang Y, et al. Efficacy and safety results from a Phase 3, randomized, placebo-controlled trial of subcutaneous golimumab in Chinese patients with active rheumatoid arthritis despite methotrexate therapy. International Journal of Rheumatic Diseases. 2015.

26. Kremer JM, Blanco R, Brzosko M, Burgos-Vargas R, Halland A-M, Vernon E, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: Results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis & Rheumatism. 2011;63(3):609-21.

27. Fleischmann RM, Halland A-M, Brzosko M, Burgos-Vargas R, Mela C, Vernon E, et al. Tocilizumab Inhibits Structural Joint Damage and Improves Physical Function in Patients with Rheumatoid Arthritis and Inadequate Responses to Methotrexate: LITHE Study 2-year Results. The Journal of Rheumatology. 2013;40(2):113-26.

28. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. The Lancet. 2008;371(9617):987-97.

29. van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum. 2013;65(3):559-70.

30. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med. 2012;367(6):495-507.

31. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367(6):508-19.

32. Strand V, van Vollenhoven RF, Lee EB, Fleischmann R, Zwillich SH, Gruben D, et al. Tofacitinib or adalimumab versus placebo: patient-reported outcomes from a phase 3 study of active rheumatoid arthritis. Rheumatology. 2016;55(6):1031-41.

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

33. Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2013;159(4):253-61.

34. Yoo DH, Hrycaj P, Miranda P, Ramiterre E, Piotrowski M, Shevchuk S, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: The PLANETRA study. Annals of the Rheumatic Diseases. 2013;72(10):1613-20.

35. Keystone E, Heijde DVD, Mason D, Landewé R, Vollenhoven RV, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: Findings of a fifty-two–week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis & Rheumatism. 2008;58(11):3319-29.

36. Strand V, Mease P, Burmester GR, Nikaï E, Coteur G, van Vollenhoven R, et al. Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. Arthritis Research & Therapy. 2009;11(6):R170-R.

37. Smolen J, Landewé RB, Mease P, Brzezicki J, Mason D, Luijtens K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Annals of the Rheumatic Diseases. 2009;68(6):797-804.

38. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Modern Rheumatology. 2009;19(1):12-9.

39. Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: A large, randomized, placebo-controlled trial. Arthritis & Rheumatism. 2006;54(4):1075-86.

40. van Vollenhoven RF, Ernestam S, Geborek P, Petersson IF, Coster L, Waltbrand E, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet. 2009;374(9688):459-66.

41. Kaneko Y, Atsumi T, Tanaka Y, Inoo M, Kobayashi-Haraoka H, Amano K, et al. Comparison of adding tocilizumab to methotrexate with switching to tocilizumab in patients with rheumatoid arthritis with inadequate response to methotrexate: 52-week results from a prospective, randomised, controlled study (SURPRISE study). Annals of the Rheumatic Diseases. 2016;75(11):1917-23.

42. Takeuchi T, Yamanaka H, Tanaka Y, Sakurai T, Saito K, Ohtsubo H, et al. Evaluation of the pharmacokinetic equivalence and 54-week efficacy and safety of CT-P13 and

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

innovator infliximab in Japanese patients with rheumatoid arthritis. Modern Rheumatology. 2015;25(6):817-24.

43. Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: The tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis & Rheumatism. 2008;58(10):2968-80.

44. van de Putte LBA, Atkins C, Malaise M, Sany J, Russell A, van Riel PLCM, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Annals of the Rheumatic Diseases. 2004;63(5):508-16.

45. Dougados M, Kissel K, Sheeran T, Tak PP, Conaghan PG, Mola EM, et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Annals of the Rheumatic Diseases. 2013;72(1):43-50.

46. Weinblatt ME, Bingham CO, Mendelsohn AM, Kim L, Mack M, Lu J, et al. Intravenous golimumab is effective in patients with active rheumatoid arthritis despite methotrexate therapy with responses as early as week 2: results of the phase 3, randomised, multicentre, double-blind, placebo-controlled GO-FURTHER trial. Annals of the Rheumatic Diseases. 2013;72(3):381-9.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Appendix 1: Additional data

Table 43: Quality assessment of clinical studies in NMA for the cDMARD-IR population

Study name Author, Year	Was randomisation adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between groups?	Was the trial blinded?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Was an ITT analysis used?
ACT-RAY Dougados 2014 (5)	Not clear Randomisation method NR	Not clear Allocation method NR	Yes	Yes Double-blind (patients, care provider, investigator, and outcomes assessor)	No	No	Yes ITT
ADACTA Gabay 2013 (6)	Yes IVRS	Yes IVRS	Yes	Yes Double-blind (patients and investigator)	No	No	Yes mITT
ARMADA Weinblatt 2003 (7)	Not clear Randomisation method NR	Not clear Allocation method NR	Yes	Yes Double-blind (unclear)	No	No	Not clear Analysis population NR
ATTEST Schiff 2008 (8)	Not clear Randomisation method NR	Not clear Allocation method NR	Yes	Yes Double-blind (patients, care provider, investigator, and outcomes assessor)	No	No	Yes mITT
AUGUST II Van Vollenhoven 2011 (9)	Yes Central randomisation using permuted blocks	Yes IVRS	Yes	Yes Double-blind (patients and investigator)	No	Yes DAS28 reported in methods, no results presented	Yes ITT

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Study name Author, Year	Was randomisation adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between groups?	Was the trial blinded?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Was an ITT analysis used?
CERTAIN Smolen 2015 (10)	Yes IVRS	Yes IVRS	Yes	Yes Double-blind (patients, care provider, investigator, and outcomes assessor)	No	No	Yes ITT
CHANGE Miyasaka 2008 (11)	Not clear Randomisation method NR	Not clear Allocation method NR	Yes	Yes Double-blind (unclear)	No	No	Yes ITT
Choe 2015 (12)	Yes IVRS	Yes IVRS	Yes	Yes Double-blind (patients, care provider, investigator, and outcomes assessor)	No	No	Yes mITT
DE019 Keystone 2004 (13)	Not clear Randomisation method NR	Not clear Allocation method NR	Yes	Yes Double-blind (patients and outcomes assessor)	No	No	Yes mITT
Emery 2015 (14)	Yes IVRS	Yes IVRS	Yes	Yes Double-blind (patients, care provider, investigator, and outcomes assessor)	No	No	Yes ITT
Fleischmann 2012a (15)	Not clear Randomisation method NR	Not clear Allocation method NR	Yes	Yes Double-blind (patients, care provider, investigator, and outcomes assessor)	No	No	Yes mITT

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Study name Author, Year	Was randomisation adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between groups?	Was the trial blinded?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Was an ITT analysis used?
GO-FORTH Tanaka 2012 (16)	Not clear Randomisation method NR	Not clear Allocation method NR	Yes	Yes Double-blind (patients and outcomes assessor)	No	No	Yes mITT
GO-FORWARD Keystone 2009 (17)	Yes IVRS	Yes IVRS	Yes	Yes Double-blind (patients, care provider, and investigator)	No	No	Yes ITT
GO-FURTHER Bingham 2014 (18)	Yes IVRS	Yes IVRS	Yes	Yes Double-blind (patients, care provider, investigator, and outcomes assessor)	No	No	Yes ITT
HERA Bae 2016 (19)	Yes IWRS	Yes IWRS	Yes	Yes Double-blind (patients, care provider, investigator, and outcomes assessor)	No	No	Yes mITT
JESMR Kameda 2010 (20)	Not clear Stratified randomisation on the website; method NR	Not clear Allocation method NR	Yes	No Open-label	Yes 6.5% from ETN + MTX; 20.3% from ETN	No	Yes mITT

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Study name Author, Year	Was randomisation adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between groups?	Was the trial blinded?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Was an ITT analysis used?
J-RAPID Yamamoto 2014 (21)	Yes Block randomisation using SAS RANUNI function	Yes Centralised allocation	Yes	Yes Double-blind (patients, care provider, investigator, and outcomes assessor)	No	No	Yes ITT
Kim 2007 (22)	Not clear Randomisation method NR	Not clear Allocation method NR	Yes	Yes Double-blind (unclear)	No	No	Yes ITT
Kremer 2012 (23)	Not clear Randomisation method NR	Not clear Allocation method NR	Yes	Yes Double-blind (patients, care provider, investigator, and outcomes assessor)	No	No	Yes mITT
LARA Machado 2014 (24)	Yes eClinical Enrollment System	Not clear Allocation method NR	Yes	No Open-label	No	No	Yes mITT
Li 2015 (25)	Not clear Randomisation method NR	Not clear Allocation method NR	Yes	Yes Double-blind (patients, care provider, investigator, and outcomes assessor)	No	No	Yes ITT

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Study name Author, Year	Was randomisation adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between groups?	Was the trial blinded?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Was an ITT analysis used?
LITHE Kremer 2011 (26); Fleischmann 2013 (27)	Not clear Randomisation method NR	Not clear Allocation method NR	Yes	Yes Double-blind (patients and investigator)	No	No	Yes mITT
OPTION Smolen 2008 (28)	Yes Central randomisation using list provided by sponsor	Yes IVRS	Yes	Yes Double-blind (patients and investigator)	No	No	Yes mITT
ORAL-Scan Van der Heijde 2013 (29)	Yes IVRS	Yes IVRS	Yes	Yes Double-blind (patients, care provider, investigator, and outcomes assessor)	No	No	Yes mITT
ORAL-Solo Fleischmann 2012b (30)	Yes Automated web-based or telephone-based system	Yes Automated web-based or telephone-based system	Yes	Yes Double-blind (patients, care provider, investigator, and outcomes assessor)	Yes 13.9% from PBO; 4.5% from TOF	No	Yes ITT

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Study name Author, Year	Was randomisation adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between groups?	Was the trial blinded?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Was an ITT analysis used?
ORAL-Standard Van Vollenhoven 2012 (31); Strand 2016 (32)	Yes IVRS	Yes IVRS	Yes	Yes Double-blind (patients, care provider, investigator, and outcomes assessor)	No	No	Yes mITT
ORAL-Sync Kremer 2013 (33)	Yes Automated web-based or telephone-based system	Not clear Allocation method NR	Yes	Yes Double-blind (patients, care provider, investigator, and outcomes assessor)	No	No	Yes mITT
PLANETRA Yoo 2013 (34)	Not clear Randomisation method NR	Not clear Allocation method NR	Yes	Yes Double-blind (patients and investigator)	No	No	Yes ITT
RAPID 1 Keystone 2008 (35); Strand 2009 (36)	Not clear Randomisation method NR	Not clear Allocation method NR	Yes	Yes Double-blind (patients and outcomes assessor)	No	No	Yes ITT
RAPID 2 Smolen 2009 (37)	Not clear Randomisation method NR	Not clear Allocation method NR	Yes	Yes Double-blind (patients and outcomes assessor)	Yes 86.6% from PBO; 29.3% from CZP	No	Yes ITT

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Study name Author, Year	Was randomisation adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between groups?	Was the trial blinded?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Was an ITT analysis used?
SATORI Nishimoto 2009 (38)	Not clear Central randomisation, method NR	Not clear Allocation method NR	Yes	Yes Double-blind (patients, care provider, investigator, and outcomes assessor)	Yes 48.4% from PBO; 11.5% from TCZ	No	Yes ITT
START Westhovens 2006 (39)	Not clear Randomisation method NR	Not clear Allocation method NR	Yes	Yes Double-blind (patients, investigators, and other study personnel, except for pharmacists)	No	No	Yes ITT
SWEFOT van Vollenhoven, 2009 (40)	Yes Computer-generated random list	Yes Centralised randomisation with telephonic assignment	Yes	No Open-label	Yes 31.5% from SFZ + HCQ + MTX; 17.9% from IFX + MTX	No	Yes ITT
SURPRISE Kaneko 2016 (41)	Not clear Central randomisation, method NR	Not clear Allocation method NR	Yes	No Open-label	No	No	Yes mITT
Takeuchi 2015 (42)	Not clear Randomisation method NR	Not clear Allocation method NR	Yes	Yes Double-blind (unclear)	No	No	Yes mITT

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Study name Author, Year	Was randomisation adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between groups?	Was the trial blinded?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Was an ITT analysis used?
TOWARD Genovese 2008 (43)	Not clear Randomisation method NR	Not clear Allocation method NR	Yes	Yes Double-blind (patients and investigator)	No	No	Yes mITT
Van de Putte 2004 (44)	Yes Randomised in blocks of 5, with computer-generated randomisation list	Not clear '…blinding was achieved by the packaging procedure…', allocation method NR	No	Yes Double-blind (unclear)	Yes 27.2% from ADA; 56.4% from PBO	No	Yes mITT

Abbreviations: ADA, adalimumab; CTZ, certolizumab; ETN, etanercept; FAS, full analysis set; HCQ, hydroxychloroquine; IFX, infliximab; ITT, intention to treat; IVRS, interactive voice response system; mITT, modified intention to treat; MTX, methotrexate; NR, not reported; PBO, placebo; PPS, per protocol set; SFZ, sulfasalazine; TCZ, tocilizumab; TOF, tofacitinib.

Table 44: Patients baseline characteristics among studies included in the network meta-analysis for the cDMARD-IR population (n=37)

Study	Interventions	Concomitant cDMARDs (other than MTX)	No. of patients	Mean age (yrs)	Female (%)	Mean disease duration (yrs)	SJC	TJC	ESR (mm/hr)	CRP (mg/L)	RF +ve no. (%)	Patients with prior bDMARDs (%)	Mean (SD) DAS28: BL score	Mean HAQ: BL score
ACT-RAY Dougados 2013 (45); Dougados 2014 (5)	TCZ 8mg/kg Q4W + MTX	None	277	53	81.9	8.2	14.4	25.8	39.9	NR	NR	NR	ESR; 6.3 (1.0)	1.4
	TCZ 8mg/kg Q4W	None	276	53.6	78.6	8.3	15.3	26.6	39.6	NR	NR	NR	ESR; 6.3 (1.0)	1.4

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Study	Interventions	Concomitant cDMARDs (other than MTX)	No. of patients	Mean age (yrs)	Female (%)	Mean disease duration (yrs)	SJC	TJC	ESR (mm/hr)	CRP (mg/L)	RF +ve no. (%)	Patients with prior bDMARDs (%)	Mean (SD) DAS28: BL score	Mean HAQ: BL score
ADACTA Gabay 2013 (6)	TCZ 8mg/kg	None	163	54.4	79	7.3	11.3	15.9	50.5	26	NR	NR	ESR; 6.7 (0.9)	1.6
	ADA 40mg	None	162	53.3	82	6.3	12.4	16.5	45.5	25	NR	NR	ESR; 6.8 (0.9)	1.7
ARMADA Weinblatt 2003 (7)	ADA 40mg Q2W + MTX	None	67	57	75	12	17.3	28	NR	21	NR	NR	NR	1.5
	PBO + MTX	None	62	56	82	11	16.9	28.7	NR	31	NR	NR	NR	1.6
ATTEST Schiff 2008 (8)	ABT 10mg/kg Q4W + MTX	None	156	49	83	8	21.3	31.6	49.4	31	87	NR	ESR; 6.9 (1.0)	1.8
	IFX 3mg/kg Q8W + MTX	None	165	49	87	8	20.1	30.3	47	27	77	NR	ESR; 6.8 (1.0)	1.7
	PBO + MTX	None	110	49	82	7	20.3	31.7	47.8	33	85	NR	ESR; 6.8 (1.0)	1.8
AUGUST II Van Vollenhoven 2011 (9)	ADA 40mg Q2W + MTX	None	79	53.0	81.0	8.8	16.2	27.8	41.7	16.6	81.0	NR	CRP; 5.8 (1.0)	1.6
	PBO + MTX	None	76	54.0	84.0	8.4	16.4	24.3	39.3	16.5	83.0	NR	CRP; 5.8 (1.0)	1.7
CERTAIN Smolen 2015 (10)	CTZ 200mg Q2W SC + cDMARDs	Mono or combi: MTX, 84.4% Others SFZ or HCQ	96	53.6	84.4	4.5	3.4	3.7	32.0	6.0	74.0	NR	ESR; 4.5 (0.4)	1.1
	PBO + cDMARDs	Mono or combi: MTX, 80.6% Others SFZ or HCQ	98	54.0	76.5	4.7	3.2	3.9	30.5	8.0	67.3	NR	ESR; 4.5 (0.3)	1.0
CHANGE	ADA 40mg Q2W SC	None	91	56.9	79.1	9.9	19.1	24.4	NR	6.48 mg/dL	89.0	NR	NR	1.6

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Study	Interventions	Concomitant cDMARDs (other than MTX)	No. of patients	Mean age (yrs)	Female (%)	Mean disease duration (yrs)	SJC	TJC	ESR (mm/hr)	CRP (mg/L)	RF +ve no. (%)	Patients with prior bDMARDs (%)	Mean (SD) DAS28: BL score	Mean HAQ: BL score
Miyasaka 2008 (11)	PBO	None	87	53.4	77.0	8.4	19.3	23.7	NR	5.86 mg/dL	86.2	NR	NR	1.4
Choe 2015 (12)	IFX 3mg/kg Q8W IV + MTX	None	293	52.6	80.1	6.6	14.9	24	46.7	13.7	71	NR	ESR; 6.5 (0.8)	1.5
	IFX SB2 3mg/kg Q8W IV + MTX	None	291	51.6	80.5	6.3	14.6	23.6	44.5	12.5	73.9	NR	ESR; 6.5 (0.8)	1.5
DE019 Keystone 2004 (13)	ADA 40mg Q2W + MTX	None	207	56	76	11	19.3	27.3	NR	18	82	NR	NR	1.4
	PBO + MTX	None	200	56	73	11	19	28.1	NR	18	90	NR	NR	1.4
Emery 2015 (14)	ETN 50mg QW SC + MTX	None	297	51.6	85.2	6.2	15.0	23.6	46.4	1.3 mg/dL	77.8	NR	ESR; 6.5 (0.8)	1.5
	ETN SB4 50mg QW SC + MTX	None	299	52.1	83.3	6.0	15.4	23.5	46.5	1.5 mg/dL	79.3	NR	ESR; 6.5 (0.9)	1.5
Fleischmann 2012a (15)	TOF 5mg BID	None	49	54	87.8	8.1	17.4	27.1	47.4	24.5	77.5	4.1	ESR: 6.6 CRP: 5.6	1.4
	ADA 40mg Q2W	None	53	54	84.9	7.7	14.9	24.1	44.8	20.1	74.6	7.5	ESR; 6.6 CRP; 5.6	1.4
	PBO	None	59	53	88.1	10.8	16.9	25.9	46.2	23.5	74.5	8.5	ESR: 6.6 CRP: 5.6	1.5
GO-FORTH Tanaka 2012 (16)	GOL 50mg Q4W SC + MTX	None	86	50.4	84.9	8.8	11.8	13.1	NR	1.9 mg/dL	NR	NR	5.5 (1.2)	1
	PBO + MTX	None	88	51.1	83.0	8.7	11.4	13.2	NR	2.2 mg/dL	NR	NR	5.6 (1.0)	1

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Study	Interventions	Concomitant cDMARDs (other than MTX)	No. of patients	Mean age (yrs)	Female (%)	Mean disease duration (yrs)	SJC	TJC	ESR (mm/hr)	CRP (mg/L)	RF +ve no. (%)	Patients with prior bDMARDs (%)	Mean (SD) DAS28: BL score	Mean HAQ: BL score
GO-FORWARD Keystone 2009 (17)	GOL 50mg Q4W + MTX	None	89	52 M	81	4.5 M	13 M	26 M	NR	10 M	81	NR	ESR: 6.2 (range: 5.4 to 6.9) CRP: 5.1 (range: 4.1 to 5.6)	Median: 1.4
	PBO + MTX	None	133	52 M	82	6.5 M	12 M	21 M	NR	8 M	81	NR	ESR: 6.1 (range: 5.3 to 6.6) CRP: 4.9 (range: 4.2 to 5.5)	Median: 1.4
GO-FURTHER (46)	GOL 2mg/kg Q8W IV + MTX	None	395	51.9	82.5	6.9	15.0	26.4	NR	2.8 mg/dL	NR	NR	CRP; 6 (0.8)	1.6
	PBO + MTX	None	197	51.4	79.7	7.0	14.8	25.9	NR	2.2 mg/dL	NR	NR	CRP; 5.9 (0.9)	1.6
HERA Bae 2016 (19)	ETN 25mg BIW SC + MTX	None	118	51.3	85.6	8.1	12.2	17.5	54.0	1.6 mg/dL	91.5	NR	NR; 6.2 (0.8)	1.1
	ETN HD203 25mg BIW SC + MTX	None	115	51.0	87.8	7.2	12.5	17.4	53.2	2.1 mg/dL	81.7	NR	NR; 6.1 (0.8)	1.1
JESMR Kameda 2010 (20)	ETN 25mg BIW SC + MTX	None	75	56.5	80.0	8.1	12.6	14.9	59.5	3.0 mg/dL	86.7	NR	NR; 6.1 (95% CI: 5.8 to 6.2)	1.2
	ETN 25mg BIW SC	None	71	58.1	87.3	10.6	12.5	15.0	59.7	2.5 mg/dL	91.5	NR	NR; 6 (95% CI: 5.9 to 6.4)	1.3
J-RAPID Yamamoto 2014 (21)	CTZ 200mg Q2W SC + MTX	None	82	50.6	84.1	5.6	16.6	19.0	46.3	1.4 mg/dL	86.6	13.4	ESR; 6.2 (0.8)	1.1
	PBO + MTX	None	77	51.9	85.7	5.8	17.4	19.6	47.6	1.6 mg/dL	85.7	19.5	ESR; 6.5 (0.9)	1.2

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Study	Interventions	Concomitant cDMARDs (other than MTX)	No. of patients	Mean age (yrs)	Female (%)	Mean disease duration (yrs)	SJC	TJC	ESR (mm/hr)	CRP (mg/L)	RF +ve no. (%)	Patients with prior bDMARDs (%)	Mean (SD) DAS28: BL score	Mean HAQ: BL score
Kremer 2012 (23)	TOF 5mg BID + MTX	None	71	52	80.3	9	14.1	21.5	NR	18	82.8	2	ESR: 6.1 CRP: 5.2	1.4
	PBO + MTX	None	69	53	81.2	9.2	15.7	21.6	NR	18.9	83	5.6	ESR: 6.1 CRP: 5.3	1.2
Kim 2007 (22)	ADA 40mg Q2W SC + MTX	None	65	48.5	95.4	6.8	12.2	19.2	NR	2.2 mg/dL	76.9	NR	NR	1.4
	PBO + MTX	None	63	49.8	85.7	6.9	12.8	20.3	NR	2.7 mg/dL	82.5	NR	NR	1.3
LARA Machado 2014 (24)	ETN 50mg QW SC + MTX	None	281	48.4	88.3	7.9	18.2	25.1	43.2	20.7	86.1	NR	ESR; 6.6 (0.7)	1.6
	cDMARD + MTX	None	142	48.6	90.1	9.0	19.3	26.2	42.8	20.8	83.8	NR	ESR; 6.7 (0.7)	1.6
Li 2015 (25)	GOL 50mg Q4W + MTX	None	132	47.7	83.3	7.6	10.7	22.9	55.8	16.8	87.1	NR	CRP; 5.4 (1.1)	1.3
	PBO + MTX	None	132	46.7	78.8	8.0	11.8	22.5	52.8	19.4	92.4	NR	CRP; 5.5 (1.1)	1.2
LITHE Kremer 2011 (26); Fleischmann 2013 (27)	TCZ 8mg/kg Q4W + MTX	None	398	53.4	82	9.3	17.3	29.3	46.4	23	NR	10.8	NR; 6.6 (1.0)	1.5
	PBO + MTX	None	393	51.3	83	9	16.6	27.9	46.5	22	NR	11.5	NR; 6.5 (1.0)	1.5
OPTION Smolen 2008 (28)	TCZ 8mg/kg Q4W + MTX	None	205	51	NR	8	19.5	31.9	51.2	26	83	5	ESR; 6.8 (0.9)	1.6
	PBO + MTX	None	204	51	NR	8	20.7	32.8	49.7	24	71	9	ESR; 6.8 (0.9)	1.5

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Study	Interventions	Concomitant cDMARDs (other than MTX)	No. of patients	Mean age (yrs)	Female (%)	Mean disease duration (yrs)	SJC	TJC	ESR (mm/hr)	CRP (mg/L)	RF +ve no. (%)	Patients with prior bDMARDs (%)	Mean (SD) DAS28: BL score	Mean HAQ: BL score
ORAL-Scan Van der Heijde 2013 (29)	TOF 5mg BID + MTX	None	321	53.7	83.8	8.9	14.1	24.1	50.1	15.5	75.2	Prior TNFi : 19.3 Prior non-TNFi: 5.3	ESR; 6.3 CRP; 5.2	1.4
	PBO + MTX	None	154	PBO f/b TOF 5 mg: 53.2; PBO f/b TOF 10 mg: 52.1	PBO f/b TOF 5 mg: 80.2; PBO f/b TOF 10 mg: 91.1	PBO f/b TOF 5 mg: 8.8; PBO f/b TOF 10 mg: 9.5	PBO f/b TOF 5 mg: 14; PBO f/b TOF 10 mg: 14.5	PBO f/b TOF 5 mg: 23.3; PBO f/b TOF 10 mg: 22.6	PBO f/b TOF 5 mg: 47.8; PBO f/b TOF 10 mg: 54.4	PBO f/b TOF 5 mg: 12.2; PBO f/b TOF 10 mg: 15.3	PBO f/b TOF 5 mg: 79.7; PBO f/b TOF 10 mg: 75.3	PBO f/b TOF 5 mg Prior TNFi : 9.9 Prior non-TNFi: 3.7 PBO f/b TOF 10 mg Prior TNFi : 8.9 Prior non-TNFi: 2.5	PBO f/b TOF 5 mg, ESR, 6.2; CRP, 5.1; PBO f/b TOF 10 mg, ESR, 6.2; CRP, 5.1	PBO f/b TOF 5 mg: 1.4 PBO f/b TOF 10 mg: 1.2
ORAL-Solo Fleischmann 2012b (30)	TOF 5mg BID	None	243	52.2	85.2	8.0	16.3	29.4	53.1	22.9	76.8	Prior TNFi : 14 Prior non-TNFi: 4.9	ESR: 6.7 CRP: 5.6	1.5
	PBO	None	122	49.7	86.1	7.7	17.3	28.9	50.9	17.8	68.0	Prior TNFi : 19.7 Prior non-TNFi: 8.2	ESR: 6.6 CRP: 5.5	1.5
ORAL-Standard Van Vollenhoven	TOF 5mg BID + MTX	None	204	53	85	7.6	16.7	28.5	48.6	15	66.8	Prior TNFi : 5.9 Prior non-TNFi: 1	ESR: 6.5 (0.9) CRP: 5.4 (0.9)	1.5

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Study	Interventions	Concomitant cDMARDs (other than MTX)	No. of patients	Mean age (yrs)	Female (%)	Mean disease duration (yrs)	SJC	TJC	ESR (mm/hr)	CRP (mg/L)	RF +ve no. (%)	Patients with prior bDMARDs (%)	Mean (SD) DAS28: BL score	Mean HAQ: BL score
2012 (31); Strand 2016 (32)	ADA + MTX	None	204	52.5	79	8.1	16.4	26.7	48.5	18	68.2	Prior TNFi : 7.8 Prior non-TNFi: 1.5	ESR: 6.4 (0.9) CRP: 5.3 (0.9)	1.5
	PBO + MTX	None	108	PBO f/b TOF 5 mg: 55.5 PBO f/b TOF 10 mg: 51.9	PBO f/b TOF 5 mg: 76.8 PBO f/b TOF 10 mg: 75	PBO f/b TOF 5 mg: 6.9 PBO f/b TOF 10 mg: 9	PBO f/b TOF 5 mg: 16.9 PBO f/b TOF 10 mg: 16.4	PBO f/b TOF 5 mg: 26.6 PBO f/b TOF 10 mg: 28.1	PBO f/b TOF 5 mg: 52.7 PBO f/b TOF 10 mg: 42.9	PBO f/b TOF 5 mg: 20.3 PBO f/b TOF 10 mg: 11.6	PBO f/b TOF 5 mg: 71.4 PBO f/b TOF 10 mg: 60.8	PBO f/b TOF 5 mg Prior TNFi : 7.1 Prior non-TNFi: 7.1 PBO f/b TOF 10 mg Prior TNFi : 9.6 Prior non-TNFi: 3.8	PBO f/b TOF 5 mg: ESR, 6.6; CRP, 5.6 PBO f/b TOF 10 mg: ESR, 6.3; CRP, 5.3	1.4
Oral-Sync Kremer 2013 (33)	TOF 5mg BID + cDMARDs	MTX, 79.4% Others NR	315	52.7	83.8	8.1	14.5	25.0	50.5	168.4 nmol/L	73.9	Prior TNFi : 7.3 Prior non-TNFi: 2.2	ESR: 6.2 (1.0)	1.4

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Study	Interventions	Concomitant cDMARDs (other than MTX)	No. of patients	Mean age (yrs)	Female (%)	Mean disease duration (yrs)	SJC	TJC	ESR (mm/hr)	CRP (mg/L)	RF +ve no. (%)	Patients with prior bDMARDs (%)	Mean (SD) DAS28: BL score	Mean HAQ: BL score
	PBO + cDMARDs	MTX, ~80% Others NR	159	PBO f/b TOF 5 mg: 50.8; PBO f/b TOF 10 mg: 53.3	PBO f/b TOF 5 mg: 79.7; PBO f/b TOF 10 mg: 75	PBO f/b TOF 5 mg: 9.5; PBO f/b TOF 10 mg: 10.2	PBO f/b TOF 5 mg: 14.6; PBO f/b TOF 10 mg: 13.9	PBO f/b TOF 5 mg: 27.2; PBO f/b TOF 10 mg: 21.9	PBO f/b TOF 5 mg: 51; PBO f/b TOF 10 mg: 49.3	PBO f/b TOF 5 mg: 160.8 nmol/L; PBO f/b TOF 10 mg: 157.5 nmol/L	PBO f/b TOF 5 mg: 73.1; PBO f/b TOF 10 mg: 72.2	PBO f/b TOF 5 mg Prior TNFi : 6.3 Prior non-TNFi: 7.6 PBO f/b TOF 10 mg Prior TNFi : 6.3 Prior non-TNFi: 0	ESR: PBO f/b TOF 5 mg: 6.4 (1.0); PBO f/b TOF 10 mg: 6.1 (1.0)	PBO f/b TOF 5 mg: 1.5 PBO f/b TOF 10 mg: 1.2
PLANETRA Yoo 2013 (34)	IFX 3mg/kg Q8W + MTX	None	304	50.0 M	84.2	NR	15.2	24.0	48.5	1.9 mg/dL	NR	NR	CRP; 5.8 (0.9)	1.6
	IFX CT-P13 3mg/kg Q8W + MTX	None	302	50.0 M	81.1	NR	16.2	25.6	46.6	1.9 mg/dL	NR	NR	CRP; 5.9 (0.8)	1.6
RAPID 1 Keystone 2008 (35); Strand 2009 (36)	CTZ 200mg Q2W + MTX	None	393	51	82	6	9.9 M	12.4 M	43.5 M	16 M	80	NR	ESR; (range): 6.9 (4.3-8.9)	1.7
	PBO + MTX	None	199	52	84	6	9.7 M	13 M	45 M	16 M	83	NR	ESR; (range): 7 (4.9-8.7)	1.7
RAPID 2 Smolen 2009 (37)	CTZ 200mg Q2W + MTX	None	246	52.2	83.7	6.1	20.5	30.1	43.7	14.2	77.5	1.6	ESR; 6.8 (0.8)	1.6
	PBO + MTX	None	127	51.5	84.3	5.6	21.9	30.4	40.8	13.5	78.2	1.6	ESR; 6.8 (0.8)	1.6
SATORI	TCZ 8mg/kg Q4W IV	None	61	52.6	90.2	8.5	12.4††	13.8‡‡	51.9	30.0	NR	NR	NR; 6.1 (0.9)	NR

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Study	Interventions	Concomitant cDMARDs (other than MTX)	No. of patients	Mean age (yrs)	Female (%)	Mean disease duration (yrs)	SJC	TJC	ESR (mm/hr)	CRP (mg/L)	RF +ve no. (%)	Patients with prior bDMARDs (%)	Mean (SD) DAS28: BL score	Mean HAQ: BL score
Nishimoto 2009 (38)	MTX	None	64	50.8	75.0	8.7	12.7††	14.2‡‡	51.9	32.0	NR	NR	NR; 6.2 (0.9)	NR
START Westhovens 2006 (39)	IFX 3mg/kg Q8W + MTX	≥1 other, 29%	360	53	80	8	15	22	NR	16	83	NR	NR; 5.1	Median: 1.5
	PBO + MTX	≥1 other, 30%	363	42	83	8	15	22	NR	12	81	NR	NR; 5.1	Median: 1.5
SURPRISE Kaneko 2016 (41)	TCZ 8mg/kg Q4W IV + MTX	None	115	55.8	87.0	3.6	7.6	9.6	40.8	1.2 mg/dL	NR	NR	ESR; 5.1 (1.1)	1
	TCZ 8mg/kg Q4W IV	None	111	56.3	86.5	3.8	9.9	10.1	44.7	1.8 mg/dL	NR	NR	ESR; 5.3 (1.2)	1
SWEFOT van Vollenhoven, 2009 (40)	SFZ + HCQ + MTX	None	130	52.9	78	6.3 months	NR	NR	NR	NR	85	NR	NR; 4.7	1.3
	IFX + MTX	None	128	51.1	76	6.2 months	NR	NR	NR	NR	88	NR	NR; 4.9	1.2
Takeuchi 2015 (42)	IFX 3mg/kg Q8W + MTX	None	51	53.8	80.4	8.0	12.8	17.8	54.6	2.3 mg/dL	88.2	NR	ESR: 6.1 (0.8) CRP: 5.3 (0.9)	1.03
	IFX CT-P13 3mg/kg Q8W + MTX	None	50	54.5	80.0	7.1	12.1	14.7	55.9	2.1 mg/dL	86.0	NR	ESR: 5.9 (1.1) CRP: 5.2 (1.0)	1.12
TOWARD Genovese 2008 (43)	TCZ 8mg/kg IV + cDMARDs	MTX, 75.8% CQ/HCQ, 20.6% SFZ, 13.1% LEF, 12.1%	803	53	81	9.8	19.7	30.1	48.2	2.6 mg/dL	NR	NR	ESR; 6.7 (1.0)	1.5

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom
+44 (0)300 323 0140

Study	Interventions	Concomitant cDMARDs (other than MTX)	No. of patients	Mean age (yrs)	Female (%)	Mean disease duration (yrs)	SJC	TJC	ESR (mm/hr)	CRP (mg/L)	RF +ve no. (%)	Patients with prior bDMARDs (%)	Mean (SD) DAS28: BL score	Mean HAQ: BL score
	PBO + cDMARDs	MTX, 73.9% CQ/HCQ, 19.8% SFZ, 14.3% LEF, 15.5%	413	54	84	9.8	18.7	29.1	49.2	2.6 mg/dL	NR	NR	ESR; 6.6 (1.0)	1.5
Van de Putte 2004 (44)	ADA 40mg Q2W	None	113	53	80	11	20.5	33.7	55.8	52.6	80	NR	NR; 7.1 (0.8)	1.8
	PBO	None	110	54	77	12	19.8	35.5	56.1	57	82	NR	NR; 7.1 (0.8)	1.8

Abbreviations: ABT, abatacept; ADA, adalimumab; BID, twice daily; BIW, twice weekly; BL, baseline; CI, confidence interval; CQ, chloroquine; CTZ, certolizumab pegol; cDMARD, conventional disease modifying anti-rheumatic drug; CRP, C-reactive protein; DAS, Disease activity score; ESR, erythrocyte sedimentation rate; ETN, etanercept; GOL, golimumab; HAQ-DI, Health assessment questionnaire – disability index; HCQ, hydroxychloroquine; IFX, infliximab; IV, intravenous; LEF, leflunomide; MTX, methotrexate; NR, not reported; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily; QW, once weekly; SC, subcutaneous; SD, standard deviation; SFZ, sulfasalazine; SLB, sarilumab; TNFi: tumour necrosis factor inhibitor; TCZ, tocilizumab; TOF, tofacitinib.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: National Rheumatoid Arthritis Society

Your position in the organisation: [redacted]

Brief description of the organisation: We provide services for people with RA and children, young people and adults with JIA across the UK, support their families and carers and also work with the Health Professionals who treat these diseases.

(For example: who funds the organisation? How many members does the organisation have?)

We have approx 5,500 members including health professional members. We have a wide range of income streams with the majority of our funding coming from grant-giving trusts and foundations, events and legacy income. We have a maximum cap, which we impose, of 15% of annual income coming from projects funded by pharmaceutical industry, although to date such funding has never reached as much as 15%.

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Being diagnosed with an incurable, painful disease like RA can be extremely distressing as it is life-changing and as you can be diagnosed at any age post 16, it can have a major impact on your future life plans, dreams and aspirations, although being diagnosed today has significantly better potential

outcomes than when I was diagnosed over 35 years ago when treatments and the way the disease was treated were quite different. RA impacts on every area of life and both physical and emotional wellbeing. Health beliefs, how you come to diagnosis (how long it takes to be diagnosed), the network of support you have and how aggressive the disease is will all impact on how you come to terms with your diagnosis and cope day to day. It can be very distressing for a partner of someone with RA to witness their loved-one in severe pain and suffering the debilitating effects of fatigue and so this disease does very much impact on the whole family. As ¾ of people are diagnosed when of working age, anxiety over job-loss due to their disease is a significant factor and whilst we are making steps towards seeing work as a health outcome, we are far from a situation where rheumatology teams pay enough attention to how worried patients may be about their job. By the time you get a diagnosis, you may well have had quite a bit of time off work which may be causing anxiety - we know from the HQIP early RA audit that the majority of people have a relatively high Disease Activity Score at diagnosis – so many may already be at risk of losing their job. For young people who are not yet in a permanent relationship, it can be very hard to come to terms with the fact that they have a long-term condition which they may have to disclose to a potential partner at some point. We know from our own research that RA can make people with RA feel less desirable, much less confident and worried that they will not be able to find a partner. For older people diagnosed as they approach retirement for example, dreams of being able to travel and look after grand-children can suddenly seem unachievable. Diagnosed in mid-years with young children to care for can also be incredibly challenging. Imagine not being able to pick up your baby and change its nappy. For whilst much has been done in terms of new and innovative therapies coming into rheumatology and the way in which we now treat the disease, there remains a lot of pain and distress at all stages of this disease.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is,

what would patients or carers like treatment to achieve?) re most important? If possible, please explain why.

People simply want their life back. They want a reduction in pain, want to prevent permanent disability, want reduction in fatigue, and above all want to maintain independence and ability to work, if of working age, and carry out all the normal activities of daily living. Side effects of some drugs can be quite debilitating, however, by comparison to methotrexate for example, side effects from biologics are generally fewer in our experience. In my own experience and also listening to many thousands of people over the last 15.5 years running NRAS, one of the most important things people want is to be able to maintain their independence. Pain and fatigue are the two most common symptoms and therefore the most major barriers to being able to live independently and without having to rely heavily on others for a myriad of things.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

One of the key issues associated with current care is the variability of access to best, evidence-based care and access to all the relevant members of a consultant-led multi-disciplinary team. This has been demonstrated in the past by the Kings Fund and National Audit Office reports into services for people with RA and most recently by the 3-year audit results from the HQIP audit into early RA. People do experience different levels of care and not all, by any means, have access to research studies for example. In the early stages of their disease, people don't know what good looks like or what they should be able to ask for or expect and they are also vulnerable at that time as a consequence. This is where we come in – our goal is to be there at the start of everyone's journey and whenever they need us along the way. We try to emphasise the importance of supported self-management early on as the more you know about the disease and the more you can do to help yourself in a positive way, the better your outcomes are likely to be. Unfortunately, whilst

there is a lot of rhetoric about self-management for people with LTCs, we still live in a very medical management model where investment in patient education, support and self-management by commissioners is far too low. That's one of the reasons it is essential that health professionals sign-post patients to organisations who can help and support like NRAS. Access to treatment where there are specific eligibility criteria – ref the biologics and biosimilars – is better than pre-NICE, however, with the introduction of biosimilars, the market has changed and there is a lot of confusion at the moment with local procurement deals ensuring that what is available in one area, may not be the same as the next. Even with all the new treatments available, the heterogeneity of this disease means that there remains unmet need. Even with cheaper drugs available and many people thinking that therefore more people will be able to get the treatment they need, this is not the case unless NICE change the eligibility criteria which currently apply.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

The key driver of RA is inflammation which can result quite quickly in bone erosion leading ultimately to joint destruction and potential disability. For the

first time since the introduction of the biologics, JAKs offer a completely new class of innovative therapy that could, as I understand it from our Chief Medical Advisor be positioned post DMARD failure or post first TNF failure. This is fantastic because it really adds to the therapeutic options available to clinicians and patients. Also the fact that this is an oral therapy means that there are no costs associated with infusions based therapies or those delivered via sub-cut route. All those costs associated with home care delivery companies also disappear. It's really very exciting especially for patients like me who have refractory disease and who have been through all the biologics available. Should my current biologic fail to keep my disease under control, this new class of drug gives me an option to palliative steroid therapy.

Patients are very likely to prefer an oral (biologic) drug to having a regular infusion or having to inject themselves.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

I think that what I have said in the above statement summarises why patients would be likely to prefer an oral drug over injecting themselves or having to attend hospital (and take time off work) for infusion therapy. Although this may seem a minor point, many people with little fridge space, also may prefer not to have to keep their medicine refrigerated. The potential cost savings by not having to bring people into day case care for infusions or have home healthcare companies delivering drugs must also surely be welcome in a cash-strapped NHS.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. I am not aware of any but should also point out that few patients will be aware of the arrival of these new JAK inhibitors.

6. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

I am not aware of any.

Please list any concerns patients or carers have about current NHS treatments in England.

Current biologics have to be infused or injected. People of working age, and ¾ of people are diagnosed with RA when of working age – (and we also need to bear in mind that age of retirement is extending quite considerably) generally find it problematic to take time off work to visit the hospital for infusions. Often there is more waiting around than they would like and what might have been expected to take half a day can extend into the best part of a whole day. People who self-inject can also find this difficult sometimes and those with major hand deformity or pain have to get someone else to inject for them and

family members don't always find this easy. Also if you are living alone and can't self-inject, you may have to get one of the home delivery company nurses to attend or go the hospital. All additional inconveniences. Having said that, many people like myself, have no difficulty injecting themselves.

Please list any concerns patients or carers have about the treatment being appraised.

Not aware of any

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Not aware of any

7. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

People who are really needly phobic or would have great difficulty in injecting themselves due to hand function limitations and for whom an oral preparation would be therefore preferable.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Not that I am aware of

8. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

The drug is not in use in the NHS currently and therefore this question is superfluous

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

The clinical trials have been very positive

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not available in the NHS in the UK

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

There is a wealth of research on this subject and we carry out our own social research – relevant reports/surveys listed below:

- Family Matters NRAS 2012
- I want to work NRAS 2007
- RA Fatigue Survey and Report 2014
- The Mapping Project, Sue Oliver and Ailsa Bosworth, 2009
- Scotland Work survey, NRAS 2010
- Who Cares Report, Scotand NRAS 2015
- Emotions, Relationships and Sexuality Survey & Report, NRAS 2013
- RA and physiotherapy NRAS 2011
- Wales State of Play Report, BSR and NRAS, 2016

9. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular

protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

None that I am aware of

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

No

10. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

This is a truly innovative drug as it represents the introduction of a new class of medicine which targets the inside of cells involved in the immune system rather than blocking receptors on the outside of cells as per all the other biologic and biosimilar drugs. It is a small molecule drug.

Are there any other issues that you would like the Appraisal Committee to consider?

11. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- This is a new class of therapy not previously available
- It is truly innovative
- Patients are likely to be more prepared to take an oral medicine than inject themselves or be infused
- It has the potential to save a lot of costs due to the fact that it is oral
- It can be used in different places in the current pathway, ie. post dmard failure and post TNF failure
-

Appendix G - professional organisation submissiontemplate

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Society for Rheumatology
Are you (tick all that apply):

- ✓a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Secondary care; out-patient clinics. Is there significant geographical variation in current practice? No. Are there differences of opinion between professionals as to what current practice should be? No. What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages? Methotrexate (oral or subcutaneous), anti-TNFα blockers, anti-IL6-R blockers, rituximab.
Advantages: efficacy proven, toxicity profile established, long term benefit vs harm, cost: for methotrexate minimal, for biologic agents price falling as more biosimilars become available.
Disadvantages: small proportion of patients have toxicity and a small proportion primary inefficacy. Biologics – parenteral administration.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? No. Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology? Benefit: primary or secondary failures on methotrexate or methotrexate with biologic, or biologic failure

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Specialist rheumatology clinics in secondary care that cater specifically for RA patients. Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)? No.

If the technology is already available, is there variation in how it is being used in the NHS? Patient access schemes are being offered by the manufacturer. Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.
NICE, SIGN, BSR and EULAR on treating early (NICE and SIGN), as well as established RA (BSR)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available,will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

NICE recommends initial early sustained use of triple therapy (methotrexate, sulphasalazine, and hydroxychloroqine) – the technology has only been compared to methorexate or other dmard failures rather than triple therapy failures.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation. It will be potentially easier to use than biologic agents. Noted is that most patients adapt quickly to self-administered parenteral therapy.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes? Practical implications of use: may necessitate more frequency drug monitoring for toxicity.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
Rules of start/stop therapy.
Generalisability of evidence: RA patients have considerable numbers of comorbidities. Most trial patients will be pre-selected and the impact of the technology on course and treatments of comorbidities is not clear
Conduct of clinical trials: Most trials will have been undertaken for limited time periods in a life long disorder. Most important outcomes are: disease activity and functional capacity as measured by HAQ.
Adverse reactions: Increased incidence of cardiovascular events and raised lipids may be of concern in the long term sustained use of the drug.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Additional evidence source: nil

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Cost may mean that home delivery to avoid VAT .

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

No issues.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation:

[redacted]

UK Clinical Pharmacy Association / RPUK

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **Yes**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? **YES – Member, Pharmacist**
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The management of RA is predominately covered by NICE Clinical Guidance CG79. Progression of the disease requires rapid intervention to prevent irreversible joint damage, and multiple therapy options are available and outlined in NICE TA375. TA375 covers the use of several biologic immune modulators covering very different pharmacological pathways; namely: TNFα, IL-6 and CTLA-4, but makes no recommendations regarding the choice of therapy, other than that choice should be guided according to cost effectiveness. This consequently leads to significant differences in local treatment pathways.

Tofacitinib introduces a novel treatment option by inhibiting Janus Kinase intracellularly, rather than reducing extracellular signalling mechanisms effected by cytokines.

There is insufficient evidence to show if there are any diagnostic tests, genetic phenotyping, biomarkers or other forms of assessment which may identify which specific treatment an individual patient may respond well to. Therefore a patient may or may not respond adequately to a particular therapy – and it is useful to have a large armoury of therapies with different pharmacological actions in order to continue research into various sub-types of rheumatoid patients.

As a small molecule, it is unlikely that patients receiving tofacitinib would develop neutralising antibodies to the drug as occurs in some patients receiving treatment with the parenteral biologics (although the clinical significance of these is still unclear). This may potentially result in patients achieving remission from the disease for longer periods, although there is no long-term data at present to support this hypothesis.

It is very important to distinguish between two methods of use of tofacitinib: that of using it alone as monotherapy; and using tofacitinib in combination with methotrexate. The clinical effectiveness, and the incidence of adverse reactions, is significantly different between the two treatment regimens – and thus the cost-effectiveness in comparison with current treatments needs to be considered separately. Additionally, any cost evaluation should include the ongoing hidden costs associated with any required clinical monitoring.

There appears to be little published data comparing the efficacy of tofacitinib monotherapy against standard therapy with biologics. Therefore caution is advised before recommending the use of this instead of biologics with demonstrated monotherapy efficacy (for example tocilizumab). The study published by Fleischmann in 2012 showed no significant change in DAS28 score with Tofacitinib 5mg BD compared to placebo after 3 months.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

Compared against standard TNF biologic with Methotrexate, tofacitinib plus methotrexate has a similar, non-significant difference odds of achieving ACR50 outcome.

The optimal role of tofacitinib the management of RA has not yet been established. On this basis, tofacitinib in combination with methotrexate should be reserved for patients showing an inadequate response to TNF-inhibition and other biologic therapies with demonstrated efficacy unless alternatives are either contraindicated or not tolerated.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In contrast with currently used parenteral biologics, tofacitinib should not be used in patients with severe hepatic impairment. Patients with moderate hepatic impairment or with severe renal impairment should have their dose adjusted. Additionally doses should also be reduced when co-prescribed with CYP3A4 and CYP2C19 inhibitors.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Secondary care clinics specialising in musculoskeletal/rheumatology.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Not applicable. No JAK-inhibitor is currently approved by NICE.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

NICE CG79; NICE QS33.
SIGN Guidance 123.
These are appropriate, and a sound basis for the evaluation of patient and therapy effectiveness.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Tofacitinib is an orally active immunomodulator therapy for the treatment of RA. Currently, there are no oral therapies approved for use by NICE, and patients must be treated using parenteral drugs. Therefore, this may offer significant benefit to patients averse to injections, or who are physically unable to self-inject. In addition, there are no cold-storage requirements for this medication, which will significantly reduce the burden to patients and reduce the risk of wasted or ineffective pharmaceuticals.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

In line with the requirements for parenteral biologics, patients should be assessed for initial clinical severity prior to commencing therapy with tofacitinib, and also for ongoing response. Taking the protocol from van der Heijde (2013) clinical effectiveness should be assessed after 3 months of therapy.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Most clinical trials focus on the evaluation of clinical effectiveness defined by an ACR20 response. This is a low-threshold, and is achieved by a significant number of patients on placebo. Studies measuring outcomes based upon DAS28 should be given more weight.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Adverse reactions to this class of medications are significant, and broadly similar to biologic immunomodulators such as TNF-inhibitors which are currently employed. Specifically, an increased risk of serious infections is relatively common.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

The incidence of serious adverse events in trials using tofacitinib monotherapy is lower when compared to standard biologic therapy combined with methotrexate.

However, the combination of tofacitinib with methotrexate was associated with a higher incidence of serious adverse events compared with abatacept or adalimumab or certolizumab when co-administered with a DMARD. Tofacitinib & methotrexate co-administration also resulted in a higher incidence of adverse drug reactions leading to trial withdrawal when compared against standard-dose etanercept or abatacept plus methotrexate.

In addition, I note section 4.4 of the SPC which states :
"XELJANZ should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis, patients with concomitant use of corticosteroids and/or nonsteroidal anti-inflammatory drugs)."

The concomitant use of steroids in patient with RA is not uncommon, and this clinical risk evaluation will need to be regularly reviewed as further data is collected.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Most of the data quoted within this submission is drawn from:

Singh JA, Hossain A, Tanjong Ghogomu E, Kotb A, Christensen R, Mudano AS, et al. Biologics or tofacitinib for rheumatoid arthritis in incomplete responders to methotrexate or other traditional disease-modifying anti-rheumatic drugs: a systematic review and network meta-analysis. In: Cochrane Database of Systematic Reviews [Internet]. John Wiley & Sons, Ltd; 2016 [cited 2017 May 9]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD012183/abstract

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

I do not consider that it would be necessary to implement any additional education and/or training for any member of the NHS team.

The relative high-cost of this therapy will restrict its use to secondary care, with probable supply via third-party contractors, in order to reduce the liability for VAT. This may restrict the options available to patients on how to obtain continuing supplies; and although technically there is no reason why a prescription could not be dispensed at any community pharmacy, it may be that commercial restrictions imposed by the manufacturer limit the supply routes available (which, it could be argued, is contrary to the spirit of the NHS founding principles).

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Nothing noted.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Rajan Madhok**
2. Name of organisation	**British Society of Rheumatology /Greater Glasgow Health Board and Clyde**

3. Job title or position	**Consultant Physician and Rheumatologist**
4. Are you (please tick all that apply):	x☐ an employee or representative of a healthcare professional organisation that represents clinicians? x☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
The aim of treatment for this condition	
5. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To achieve low disease activity or remission using pre- defined criteria established by International Consensus. The tool most frequently used is the Disease Activity Score (DAS) To halt /reduce radiographic progression as assessed on hand and foot xrays To prevent /improve disability assessed by using the Health Assessment questionnaire
6. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Low disease activity or remission using the DAS Improvement (reduction) in HAQ score by at least 0.3 which is the lowest change to detect meaningful clinical improvement

x cm, or a reduction in disease activity by a certain amount.)	
7. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There have been major advances in the management of RA – few patients achieve remission but this is complex area
What is the expected place of the technology in current practice?	
8. How is the condition currently treated in the NHS?	Managed in secondary care at specialist clinics
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes : NICE SIGN ; BSR and EULAR
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	The pathway is well defined no major regional variations in care. I am based in Scotland

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	It would change care in a small minority of patients
9. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	No major difference this would be an additional option
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care – out patient
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None

10. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
11. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not clear from currently available data in public domain
The use of the technology	

12. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No significant difference may reduce need for sub-cutaneous injections
13. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
14. Do you consider that the use of the technology will result in any substantial health-	

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
15. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	

16. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
17. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
18. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
19. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA375	
20. How do data on real-world experience compare with the trial data?	
Equality	

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your statement.

-
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**James Galloway**
2. Name of organisation	**King's College London / King's College Hospital NHS Foundation Trust**
3. Job title or position	**Senior Lecturer / Honorary Consultant Rheumatologist**

4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
The aim of treatment for this condition	
5. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	For people with active rheumatoid arthritis despite treatment with methotrexate: • Improve quality of life • Prevent disability • Reduce pain and fatigue
6. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinical significant treatment response in rheumatoid arthritis is defined as: - Reduction in disease activity measured by the Disease Activity Score (clinically important difference = reduction >1.2) - Reduction in disability measured by the Health Assessment Questionnaire (clinically important difference = improvement >0.22) Other outcomes relevant include: - Prevention of radiographic progression of disease
7. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. 1. Many patients remain in a state of severe persistent active rheumatoid, reliant upon agents such as corticosteroids (with substantial toxicity burden). One specific issue relates to the current treatment options for severe disease: biologic therapies. Whilst biologic therapies can be enormously effective, we know that the median drug survival (time a patient remains on therapy before loss of disease control occurs) is between 3-4 years. We are now facing a

	growing number of patients in routine practice who had long standing rheumatoid, and commenced their first biologic >15 years ago. These patients have now exhausted all existing biologic treatment options. 2. Despite the wide range of existing therapies, fewer than a third of patients achieve acceptable responses (e.g. disease remission as defined by DAS score). This statement is based clinical trial data as well as local experience (at KCH only 30% of 1200 patients with rheumatoid arthritis are in remission), data from the National Early Inflammatory Arthritis Audit (commissioned by HQIP) and data from established observational studies in the UK (e.g. the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis). 3. All biologic therapies require parenteral administration (infusion or injection) as they are protein based products. Challenges related to this include: drug immunogenicity (may explain limited drug survival noted above), needle phobia. 4. Tofacitinib targets a biological pathway that represents a significant advance in therapeutics, increasing the opportunity for personalised medicine in the future. Whilst there are effective therapies in existence, we know many patients fail to achieve adequate disease control. The burden of rheumatoid arthritis upon individuals and society remains substantial. Developing alternative strategies to manage the disease is essential to reduce this burden. The care of people with rheumatoid is moving towards a more personalised approach; as we learn why individuals respond differently to the available treatment strategies, we will be able to select the right drug first time. An ability to target the Janus kinase pathway is a step change in the therapeutic armamentarium.
What is the expected place of the technology in current practice?	
8. How is the condition currently treated in the NHS?	First line therapy: oral immunosuppression with one or combination of Methotrexate, Leflunomide, Sulfasalazine, Hydroxychloroquine If disease control is not achieved with these agents and disease (defined as DAS score remaining >5.1), biologic therapy is initiated - Biologic options are: anti-TNF (5 drugs available), B cell depletion, CTLA-4, anti-IL-6

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE CG79, alongside NICE TA375 & TA126 In addition, many local guidelines exist to supplement the above NICE documents.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The current pathway for biologic treatment is clearly defined in the NICE TA documents. Patients with severely active rheumatoid despite 6 months of combination DMARD therapy should be escalated to biologic therapy. The first line biologic choice is an anti-TNF (although the specific drug varies regionally, usually based upon local cost agreements). Area where opinion differs: - Which is the optimal biologic in patients who have failed more than one biologic? - Which is the optimal biologic in patients not on background DMARD (monotherapy)?
• What impact would the technology have on the current pathway of care?	1. Provide additional treatment option for patients failing initial DMARD therapy 2. Add alternative monotherapy strategy 3. Add option for patients failing existing biologic options Whilst to the onlooker it may be perceived that there are already many effective options for rheumatoid arthritis, it is crucial to be aware that only a minority of patients achieve disease remission with each individual therapy. Looking to the future, we need to continue to grow our therapeutic armamentarium, and learn how to stratify patients into the best drug for everyone. JAK inhibitors have clearly demonstrated therapeutic success in clinical trials. Making them available to clinical teams in the UK will have a significant positive benefit to the people we care for with rheumatoid.
9. Will the technology be used (or is it already used) in the	Yes. Tofacitinib would represent an additional option in the clinical pathway.

same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The major advances include: 1) Availability of a targeted DMARD (of equivalent efficacy to biologic agents) which is <u>available orally</u> (and hence no risk of immunogenicity). 2) Ability to target the JAK pathway (no existing therapies target this mechanism). It has long been recognised that rheumatoid is characterised by the upregulation of many cytokines. A common downstream effect of many of these cytokines is activation of the JAK pathway.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care rheumatology clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional facilities / equipment needed. Rheumatologists are familiar with the principles of prescribing targeted immunotherapy.
10. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. The clinical trial data from the ORAL trials provide robust evidence for drug efficacy. Real-world evidence for effectiveness is growing, but until use in Europe increases and registry / post-marketing data emerge in large quantity it is not possible to draw much information from real-world sources.

• Do you expect the technology to increase length of life more than current care?	No. Current evidence suggests that with modern therapy, life expectancy is not reduced in rheumatoid (this contrasts with historic data).
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. 1. For patients with severe disease currently on DMARDs, there is robust trial evidence (as presented by the ORAL trials) that tofacitinib improves HRQoL outcomes compared to continuing DMARDs alone. The magnitude of benefit is equivalent to that observed with anti-TNF therapy. 2. In patients who have failed to respond to anti-TNF therapy, the magnitude of improvement was numerically smaller than for patients who were biologic naïve, however the benefits were still clinically meaningful, well exceeding the accepted minimum clinically important differences. It is very difficult to compare across treatment strategies in biologic treatment failure populations given the heterogeneity of patients in this category.
11. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Efficacy: Not major signals to date suggest differential performance across subgroups (e.g. seropositive/seronegative). Efficacy greater in people on background methotrexate, but monotherapy data also impressive. Safety: Infection risk signal has received a lot of attention. Overall safety analyses show comparability to other biologic options. TB risk exists (which rheumatologists are familiar with from using other biologics, and realistically has little impact on UK population now we have robust screening strategies). Shingles risk does appear greater than other therapeutics. The question regards safety must be balanced with the likely benefit of the drug. When weighing an increased risk of shingles (rate estimates ~4% - i.e. 96% remain unaffected), this is balanced against having active rheumatoid arthritis. Acknowledging the impact of rheumatoid arthritis on health and quality of life, I think the risk/benefit balance falls on the side treatment.
The use of the technology	

12. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Easier. • Oral formulation (in comparison to available alternatives for equivalent stage in disease. • No injection site reactions • No home care delivery costs • No contracts with pharmacy and external companies for delivery • Substantial administrative burden reduction • Shorter half-life drugs – easier to interrupt therapy (e.g. around surgery) Monitoring will be equivalent to existing options.
13. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Anticipate NICE technology appraisal to provide recommendations Starting: Severe active rheumatoid despite DMARD or biologics Stopping: Failure to respond by 3 months / adverse events
14. Do you consider that the use of the technology will result in any substantial health-related benefits that are	No.

unlikely to be included in the quality-adjusted life year (QALY) calculation?	
15. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Adding a further treatment option will reduce the burden of rheumatoid arthritis upon individuals and society by controlling inflammation more effectively, resulting in increased HRQoL and reduced disability (including work disability).
• Is the technology a 'step-change' in the management of the condition?	Yes. Reiteration of points already mentioned: (1) oral targeted therapy (2) novel therapeutic mode of action
• Does the use of the technology address any particular unmet need of the patient population?	Yes.
16. How do any side effects or adverse effects of the technology affect the	Relevant side effects: 1. Shingles: The incidence of shingles is higher in patients on tofacitinib compared to existing biologics. This could adversely impact on HRQoL. However, in absolute terms, the incidence of shingles is low (approximately 4% across the ORAL trials), and the risk must be weighed against benefits: severe active rheumatoid has a more substantial adverse impact of HRQoL than shingles.

management of the condition and the patient's quality of life?	2. Increased rate of serious infections: The rate of serious infections with tofacitinib exceeded the observed rate for placebo. However, the rate is comparable to that observed in patients on other anti-rheumatic therapies of similar efficacy. Again, the risk must be weighed against the benefit; the negative impact of active rheumatoid arthritis on all aspects of HRQoL is significant.
Sources of evidence	
17. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. The ORAL trials have tested tofacitinib across the range of clinical settings: treatment naïve, DMARD failure, biologic failure. In view of cost, in the NHS it seems likely that the DMARD and biologic failure groups will be most likely to be the groups we consider this therapeutic option for.
• If not, how could the results be extrapolated to the UK setting?	Not relevant.
• What, in your view, are the most important outcomes, and were they measured in the trials?	1. Disease activity improvement (measured by improved in DAS28 response) 2. Prevention of disability (measured by the Health Assessment Questionnaire) 3. Prevention of radiographic damage (measured by serial radiographs)
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not relevant
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No. Long term extension studies are ongoing.

18. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
19. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA375	No.
20. How do data on real-world experience compare with the trial data?	Data available provide reassuring comparisons. However, it should be noted that real world data is scarce in European populations.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not to my knowledge.

21b. Consider whether these issues are different from issues with current care and why.	Not applicable.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your statement.

- Efficacy data for tofacitinib is convincing across populations studied in ORAL trials (inc. DMARD and biologic failure groups)
- Mode of action is novel, which is key strength of agent
- Oral availability is important advantage
- Risks identified in trials are comparable to other equivalent targeted therapies, and outweighed by the treatment benefits
- Real-world data will be needed to ensure long-term effectiveness/safety and to improve personalised medicine in future

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Tofacitinib for treating moderate to severe rheumatoid arthritis [ID526]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Jennie Jones
Name of your nominating organisation: National Rheumatoid Arthritis Society
Do you know if your nominating organisation has submitted a statement?

X Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

X Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

X Yes ☐ No

- a carer of a patient with the condition?

☐ Yes X No

- a patient organisation employee or volunteer?

X Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes X No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: No

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

RA has had a devastating impact on my life and life expectations. It has affected my family, my working life and prospects and my emotional well being. When initially diagnosed, my disease was aggressive and getting worse through a number of years while drugs were tried and found not to be effective in controlling my disease. I had to stop my full time work as the travel and hours involved couldn't be sustained with the pain, chronic fatigue and unreliability of my body. It has taken years to get to a steady state of remission and Humira has helped me get a life back (although not as it was before RA). Psychologically getting to a point of acceptance that this disease is here to stay is very difficult. My Mother also had the disease and I cared for her until she passed away, so I am also aware that the effectiveness of drugs and sensitivity to side effects etc can change over time, so no one knows what the future holds. I just have to live as well as possible today. It is particularly hard on your family who have to witness your pain, accommodate your lack of energy and help you when you cannot manage to do even basic tasks. Loss of independence and having to ask for help I have found very hard, even when it is offered freely and with much love.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

Achieving a target of remission or as close to it as possible with reduced inflammations, pain and less chronic fatigue, in the least possible time to avoid loss of work and independence.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer

and why?

The quality of care available in the NHS is inconsistent and I had to move hospitals to avoid poor practice. The rationing of Biologic drugs combined with the fact that it usually takes at least 3 months to determine whether a DMARD is working meant for me that my life was on a total downward spiral physically and emotionally for a few years before I got treatments that made a significant difference (steroids work, but they are not sustainable long term without side effects). I have used Methatrexate, Prednisolone, Hydroxychloroquine and Sulphasalazine and Humira. It should be noted that even using a biologic is not without problem as normal infections mean the drug has to be stopped and then a period of inflammations etc are likely again until the RA settles down.

The Humira has been the only thing that really works for me, but injecting is not ideal and arranging deliveries, etc takes significant time. Methatrexate I find very unpleasant to take orally with bad effects on my stomach even now.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

This disease specific treatment should deliver another option for reducing pain and inflammation at any stage of the disease, hopefully with fewer side

effects. I am likely to be living with this disease for the rest of my life, and I am aware drugs can become less effective, other illness or side effects may mean changes in medication has to happen in response. The more effective alternatives, the better for every patient

Please explain any advantages that you think this treatment has over other NHS treatments in England.

Oral dose rather than infusion/injection will be a benefit to many patients who may have difficulty getting to hospital appointments or injecting themselves due to disease/disability in their hands.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

Not aware

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Limiting access to Biologic drugs via strict rationing criteria means many patients endure life changing levels of pain and inflammation and still do not qualify for that therapy. All aspects of their lives are affected – family, work,

relationships and emotional well being. This is a great loss to society as a whole, and devastating for those individuals who have to live with this disease for the rest of their lives.

Please list any concerns you have about the treatment being appraised.

None known

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None known

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

This drug should benefit patients at all stages of their disease pathway as a first line or alternative treatment.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

Not known

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes X No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are

there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

X Yes ☐ No

If yes, please provide references to the relevant studies.

National Rheumatoid Association

- Family Matters NRAS 2012
- I want to work NRAS 2007
- RA Fatigue Survey and Report 2014
- The Mapping Project, Sue Oliver and Ailsa Bosworth, 2009
- Scotland Work survey, NRAS 2010
- Who Cares Report, Scotand NRAS 2015
- Emotions, Relationships and Sexuality Survey & Report, NRAS 2013
- RA and physiotherapy NRAS 2011
- Wales State of Play Report, BSR and NRAS, 2015

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

No

9. Other issues

Do you consider the treatment to be innovative?

X Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Disease specific delivered orally

Is there anything else that you would like the Appraisal Committee to

consider?

No

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- This is a new class of therapy not previously available
- It is truly innovative – a targeted drug attacking the disease directly
- Patients are likely to be more prepared to take an oral medicine than inject themselves or be infused
- It has the potential to save a lot of costs due to the fact that it is oral
- It can be used in different places in the current pathway, i.e. post Dmard failure and post TNF failure and adds to the armoury of drugs that may be needed to meet changing requirements during a lifetime of living with this disease.

Tofacitinib for Treating Moderate to Severe Active Rheumatoid Arthritis after the Failure of Disease-Modifying Anti-Rheumatoid Drugs: A Single Technology Appraisal

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Lesley Uttley, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Iñigo Bermejo, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Marrissa Martyn-St James, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Shijie Ren, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Ruth Wong, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK David L Scott, Department of Rheumatology, King's College Hospital NHS Foundation Trust, London, UK Adam Young, Department of Rheumatology, West Hertfordshire Hospital NHS Trust, Hertfordshire, UK Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
Corresponding Author	Lesley Uttley, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
Date completed	Date completed 28 June 2017

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 19/04/17.

Declared competing interests of the authors

David Scott has no conflicts of interest relating to Tofacitinib. However, his department has received a peer-reviewed grant from Pfizer within the last 12 months to undertake academic research on polypharmacy in arthritis. The department has also received free etanercept from Pfizer to use in an NIHR-funded programme grant in rheumatoid arthritis. Also he has undertaken work for the following companies in rheumatology and related areas in the last 3 years:

1. Eli Lilly And Co. Autumn 2014: Advisory Board Baricitinib, summer 2015: Educational meeting on rheumatoid arthritis
2. Roche Products Ltd. Summer 2014: Advisory Board Biologics in Arthritis
3. Napp Pharmaceuticals. Summer 2014: Advisory Board Biosimilars in Arthritis
4. Baxalta. Autumn 2015: Advisory Board Biosimilars in Arthritis
5. Novartis. Spring 2016: Advisory Board Assessment of Multiple Sclerosis

He was paid between £1000 and £3300 for these various activities.

David Scott and Matt Stevenson declare that they have written a commentary on JAK inhibitors for The Lancet (http://dx.doi.org/10.1016/S0140-6736(17)31659-8)

None of the other authors have any conflicts of interest to declare.

Acknowledgements

We would like to thank Paul Tappenden, ScHARR, for providing comments on the draft report and Andrea Shippam, Programme Manager, ScHARR, for providing administrative support and in preparing and formatting the report.

Rider on responsibility for report

This report was commissioned by the NIHR HTA Programme. The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Uttley L, Bermejo I, Martyn-St James M, Ren S, Wong R, Scott DL, Young A, Stevenson M. Tofacitinib for Treating Moderate to Severe Active Rheumatoid Arthritis After the Failure of Disease-Modifying Anti-Rheumatic Drugs: A Single Technology Appraisal. School of Health and Related Research (ScHARR), 2017.

Contributions of authors

Lesley Uttley acted as project lead, reviewed and critiqued the clinical effectiveness data reported within the company's submission. Marrissa Martyn-St James summarised and critiqued the clinical effectiveness data. Inigo Bermejo and Matt Stevenson summarised and critiqued the health economic analysis submitted by the company. Shijie Ren critiqued the company's network meta-analysis. Ruth Wong critiqued the company's search strategy. David Scott and Adam Young provided clinical advice to the team. All authors were involved in drafting and commenting on the final report.

CONTENTS

List of Tables

List of Figures

ABBREVIATIONS

ABT	Abatacept
AC	Appraisal Committee
ACR	American College of Rheumatology
ACR20	20% improvement in the ACR score
ACR50	50% improvement in the ACR score
ACR70	70% improvement in the ACR score
ADA	Adalimumab
AE	Adverse event
AG	Assessment Group
AiC	Academic in confidence
AIC	Akaike Information Criterion
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the curve
BD	Twice per day
bDMARD	Biologic disease-modifying anti-rheumatic drug
BIC	Bayesian Information Criterion
BIW	Twice weekly
BNF	British National Formulary
BSR	British Society for Rheumatology
BSRBR	British Society for Rheumatology Biologics Register
CADTH	Canadian Agency for Drugs and Technologies in Health
cDMARD	Conventional disease-modifying anti-rheumatic drug
CDAI	Clinical Disease Activity Index
CG	Clinical Guideline
CI	Confidence interval
CIC	Commercial in confidence
CODA	Convergence diagnostic and output analysis
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
CTZ	Certolizumab pegol
DAS28	Disease Activity Score 28

DAS-CRP	Disease Activity Score C-reactive protein
DES	Discrete event simulation
DMARD	Disease-modifying anti-rheumatic drug
DMC	cDMARD combination
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5 Dimensions
ERAS	Early RA Study
ERG	Evidence Review Group
ESR	Erythrocyte Sedimentation Rate
ETN	Etanercept
ETN-b	Etanercept biosimilar
EULAR	European League Against Rheumatism
GOL	Golimumab
HAQ-DI	Health Assessment Questionnaire disability index
HAS	Haute Autorité de Santé
HCQ	Hydroxychloroquine
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
IFX	Infliximab
IFX-b	Infliximab biosimilar
IR	Incidence rate
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention to treat
IV	Intravenous
JAK	Janus kinase
LDL	Low-density lipoprotein
MD-HAQ	Multidimensional HAQ
MeDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention to treat
MTA	Multiple Technology Appraisal
mTSS	Modified Total Sharp Score
MTX	Methotrexate
MTX-IR	Methotrexate inadequate responders

NBT	Non-biologic treatment
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NOAR	Norfolk Arthritis Register
NR	Not reported
NRI	Non-responder imputation
NSAIDs	Non-steroidal anti-inflammatory drugs
OCS	Oral corticosteroid
ONS	Office for National Statistics
OR	Odds ratio
PALL	Palliative care
PAS	Patient Access Scheme
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)
PBO	Placebo
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QD	Once daily
QW	Once weekly
Q2W	Every two weeks
Q4W	Every four weeks
Q8W	Every eight weeks
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RF	Rheumatoid factor
RRR	Relative risk ratio
RTX	Rituximab
SAE	Serious adverse event
SC	Subcutaneous injection
SD	Standard deviation
SDAI	Simplified Disease Activity Index
SE	Standard error
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics

STA	Single Technology Appraisal
SSZ	Sulfasalazine
SW28	Swelling 28 joints
TA	Technology Appraisal
TCZ	Tocilizumab
TEN28	Tenderness to the touch 28 joints
TNFi	Tumour necrosis factors alpha inhibitor
TOF	Tofacitinib
TSD	Technical Support Document

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The Evidence Review Group (ERG) considers the company's description of the underlying health problem in the company's submission (CS) to be appropriate and relevant to the decision problem set out in the final National Institute for Health and Care Excellence (NICE) scope. The decision problem assesses tofacitinib for treating moderate-to-severe active rheumatoid arthritis (RA) after the failure of disease-modifying anti-rheumatic drugs (DMARDs).

1.2 Summary of clinical effectiveness evidence submitted by the company

The key clinical effectiveness evidence in the CS for tofacitinib was based primarily on four randomised controlled trials (RCTs). Three RCTs investigated tofacitinib in combination with methotrexate and one RCT investigated tofacitinib monotherapy. The study population in the four RCTs relates to patients who were methotrexate or DMARD inadequate responders. All four RCTs compared tofacitinib with placebo plus cDMARD, one RCT also included adalimumab as a comparator (ORAL Standard).

For the primary endpoint of 20% improvement in the American College of Rheumatology score (ACR20), in three RCTs of tofacitinib 5 mg, twice per day (BD) plus methotrexate (ORAL Standard, ORAL Scan and ORAL Sync) at six months, and one RCT for tofacitinib monotherapy (ORAL Solo) at three months, tofacitinib was statistically significantly superior to placebo plus cDMARD ($p \leq 0.001$). Also for the European League Against Rheumatism (EULAR) response endpoint, a significantly greater proportion of patients had a good or moderate EULAR response (based on change from baseline in Disease Activity Score 28 [DAS28 score]) versus placebo was reported for ORAL Standard, ORAL Scan and ORAL Sync at six months and for ORAL Solo at three months ($p \leq 0.001$). All four trials demonstrated a significant change from baseline in the Health Assessment Questionnaire disability index (HAQ-DI) at 3 months compared to placebo ($p \leq 0.001$). The clinical efficacy results demonstrated tofacitinib in combination with methotrexate to be superior to placebo across a number of other relevant endpoints in three trials (ORAL Standard, Scan and Sync), including the proportion of patients achieving low disease activity at 3 and 6 months, and the proportion of patients achieving disease remission at 3 months using the Disease Activity Score 28 outcome (DAS28).

The ERG notes that the RCT of tofacitinib monotherapy (ORAL Solo) was not statistically superior to placebo for the primary outcome of the proportion of patients with disease remission according to DAS28 at 3 months but demonstrated a significantly greater proportion of patients for low disease activity at 3 months versus placebo. As all patients in this trial crossed over from placebo to receive tofacitinib at 3 months, there are no placebo-controlled results for 6 months for any of the other relevant endpoints in ORAL Solo. Another recently completed head-to-head RCT including tofacitinib

monotherapy versus tofacitinib plus methotrexate or adalimumab plus methotrexate (ORAL Strategy) was presented but only as a preliminary result for the primary endpoint of 50% improvement in the American College of Rheumatology (ACR50) in the CS. This RCT found tofacitinib monotherapy to have inferior efficacy to adalimumab plus methotrexate and tofacitinib plus methotrexate at 6 months whilst tofacitinib plus methotrexate was found to be non-inferior to adalimumab plus methotrexate using ACR50 at 6 months.

A revised summary of safety data for tofacitinib provided by the company following an ERG request showed that the highest incidence rates of adverse events (AEs) were for serious infection events and herpes zoster. Additional data provided by the company indicated bronchitis, pneumonia and all cardiac disorders occurred most commonly in the tofacitinib treatment arms.

Network meta-analyses (NMA) were performed to assess the relative efficacy of tofacitinib compared with the comparators in patients who were inadequate responders (IR) to conventional DMARDs (cDMARD-IR) or to biologic DMARDs (bDMARD–IR) patients with moderate-to-severe RA for EULAR response and change in the Health Assessment Questionnaire disability index (HAQ-DI) at 6 months. For the base case NMA cDMARD-IR population, the odds of achieving a EULAR response were all statistically higher for tofacitinib in combination with methotrexate (tofacitinib plus cDMARD) compared to cDMARD at 6 months. No statistically significant differences were found for tofacitinib plus cDMARD versus bDMARDs plus cDMARD, except for tocilizumab plus cDMARD, which was statistically superior in attaining at least a good EULAR response.

Whilst the odds of all EULAR responses were higher in tofacitinib monotherapy compared to cDMARD, only the effect for a good response was statistically significant. No statistically significant differences were found in tofacitinib versus bDMARDs. Both tofacitinib plus cDMARD and tofacitinib monotherapy were associated with significant reduction in HAQ-DI compared with cDMARD at 6 months.

For the base case NMA bDMARD-IR population, the odds of all EULAR responses were all statistically higher in tofacitinib plus cDMARD compared with cDMARD at 6 months. No statistically significant differences were found for tofacitinib plus cDMARD versus abatacept plus cDMARD. Tofacitinib plus cDMARD was statistically superior compared to golimumab plus cDMARD in attaining both at least a moderate and a good EULAR response; but statistically inferior versus rituximab plus cDMARD, tocilizumab plus cDMARD, non-tumour necrosis factors alpha inhibitors (non-TNFi) plus cDMARD and TNFi plus cDMARD. Tofacitinib in combination with cDMARD was associated with a significant reduction in HAQ-DI compared with cDMARD at 6 months.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG considers the searches for clinical effectiveness evidence reported in the CS to be adequate, and believes the included RCTs of tofacitinib to be relevant to the decision problem. It is noted that one recently published RCT (ORAL Strategy) was stated to be "ongoing" in the CS but full results should have been included in the CS as this trial has recently been published and contains data relevant for this decision problem. Following a request from the ERG, the company provided an updated NMA of clinical effectiveness that included data from ORAL Strategy.

The eligibility criteria applied in the selection of evidence for clinical effectiveness were considered by the ERG to be reasonable and consistent with the decision problem outlined in the final NICE scope. The quality of the included RCTs was assessed using well-established and recognised criteria. Primary endpoints and selected analyses for clinical efficacy were appropriate.

The ERG considers that the company's safety overview lacks transparency due to pooling both combination and monotherapy trials to produce incidence rates; the lack of consistent comparison to the control arms; the lack of NMA of adverse events versus comparators; and the failure to search for and provide a complete, comprehensive and up-to-date overview of all AEs including serious adverse events (SAEs). Clinical advice received by the ERG indicates that a more informative AE profile would describe the relative occurrence of all adverse events versus the control arm. Clinical advice received by the ERG also stresses the importance of monitoring the occurrence of AEs for new classes of drugs, and in turn, the importance of searching and including up-to-date evidence to inform the AE profile for the current assessment of tofacitinib. Whilst the CS did not provide a NMA of adverse events versus comparators, the company did reference a paper that conducted a NMA showing that the incidence of herpes zoster was significantly higher for tofacitinib versus bDMARD comparators.

The ERG believes that the results presented in NMA of clinical effectiveness should be treated with caution, as the ordered categorical EULAR data were dichotomised in the cDMARD-IR population, which ignores the natural ordering and correlations between the EULAR response categories. A fixed effects model was used in all the analyses in the bDMARD-IR population, and EULAR response (moderate response and good response) in the cDMARD-IR population. Heterogeneity is expected and this approach underestimates uncertainty in the treatment effects. For tofacitinib trials with early escape, the results from non-responder imputation without advancement penalty (non-responder imputation only applied for the placebo arm, not the tofacitinib arm) were used in the base case NMAs. This imputation approach potentially overestimates the relative treatment effect of tofacitinib in these trials. Depending on the non-responder imputation approach applied to the tofacitinib trials with early escape, the conclusion for the efficacy ranking of tofacitinib among the bDMARDs varies markedly.

1.4 Summary of cost effectiveness submitted evidence by the company

The manufacturer supplied a *de novo* discrete event simulation (DES) model constructed in Microsoft Excel®. The model simulates patients' disease progressions through the sequences of treatments being compared. For each line of treatment, patients may achieve good, moderate or no EULAR response, which is assessed at 6 months after treatment initiation. The EULAR response rates for tofacitinib as a monotherapy or in combination with methotrexate (MTX) are estimated using a regression model calculated based on tofacitinib trial data. The EULAR response rates for the comparators are calculated by applying odd ratios (ORs) based on the company's NMA. Patients who achieve moderate or good EULAR response are assumed to have an improvement in Health Assessment Questionnaire (HAQ) score and remain on treatment until loss of efficacy (as assessed by a clinician), the incidence of AEs or death. Time to treatment discontinuation for responders is estimated using survival curves fitted to the tofacitinib trial data using the characteristics of each patient as predictive covariates. Patients who fail to achieve a moderate or good EULAR response discontinue treatment at 6 months and start the next treatment in the sequence. HAQ-DI is assumed to be constant whilst on bDMARDs or tofacitinib. Contrastingly, for patients on cDMARDs and palliative care, HAQ-DI progression is assumed to be non-linear based on latent HAQ-DI trajectory classes. Patients are assumed to suffer a rebound in HAQ-DI equal to that achieved on treatment initiation over the six months before treatment discontinuation, and start on the next treatment in the sequence. The mortality rate is assumed to be affected by the HAQ-DI score of a patient at baseline. The model estimates the costs and quality-adjusted life years (QALYs) over a lifetime horizon. EuroQol 5 Dimensions (EQ-5D) values are calculated based on a mapping algorithm from HAQ-DI scores and patient characteristics. Hospitalisation costs and resource use estimates were based on HAQ-DI score bands as in NICE technology appraisal (TA) 375, with unit costs taken from the British National Formulary (BNF) and NHS Reference Costs 2015/16.

The analyses presented in the CS relate to six different populations of rheumatoid arthritis patients: (i) patients with severe RA who have had an inadequate response to cDMARDs (cDMARD-IR) that can tolerate MTX; (ii) cDMARD-IR patients with severe RA for whom MTX is contraindicated or not tolerated; (iii) patients who have had an inadequate response to a bDMARD (bDMARD-IR), for whom rituximab (RTX) is an option; (iv) patients who are bDMARD-IR and RTX ineligible; (v) patients who are bDMARD-IR for whom MTX is contraindicated or not tolerated; and, (vi) patients with moderate RA who are cDMARD-IR. Severe RA was define as a DAS28 > 5.1, whilst moderate RA was defined as a DAS28 > 3.2 and ≤ 5.1. Baseline characteristics of patients are based on the relevant clinical tofacitinib trials.

In the analyses presented by the company for cDMARD-IR patients with severe RA who could tolerate MTX, tofacitinib + MTX dominated or extendedly dominated most of its bDMARD comparators; the incremental cost-effectiveness ratios (ICERs) of those which were not dominated against tofacitinib +

MTX were higher than £80,000 per QALY gained. In cDMARD-IR patients with severe RA for whom MTX was contraindicated or not tolerated, tofacitinib is less effective and less expensive than the recommended bDMARDs (etanercept, adalimumab and tocilizumab) but the cost saved per QALY lost (southwest quadrant) is higher than £50,000. In bDMARD-IR patients with severe RA for whom rituximab was an option, rituximab + MTX dominated tofacitinib + MTX. [redacted] On the other hand, in bDMARD-IR patients with severe RA for whom RTX was not an option, tofacitinib + MTX dominated all the comparators included in the analysis (four recommended comparators were missing). In bDMARD-IR patients with severe RA for whom MTX was contraindicated or not tolerated, the ICER for tofacitinib compared with tocilizumab was estimated to be £25,932 per QALY gained. However, tocilizumab monotherapy is not recommended by NICE in this population and none of the comparators recommended by NICE were included in the analysis. In cDMARD-IR patients with moderate RA, the ICER for tofacitinib + MTX compared with a sequence of cDMARD treatments was estimated to be £51,693 per QALY gained and the ICER for tofacitinib monotherapy compared with a different sequence of cDMARDs was estimated to be £51,370 per QALY.

The company presented additional analyses during the clarification round amending the NMA and incorporating the following corrections requested by the ERG: (i) modified sequences in line with TA375; (ii) using non-linear latent class HAQ-DI trajectories for palliative care, (iii) amended changes in HAQ-DI scores upon moderate or good EULAR response, (iv) use of age at onset instead of age as predictor of class membership for the latent class mixture model, (v) and, the activation of the flag that establishes a patient as bDMARD-IR after going through their first bDMARD or JAK inhibitor. The analyses undertaken with the revised model resulted in slightly different ICERs but did not modify the conclusions of the analyses included in the CS.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The company's model was based on the model developed by the Assessment Group (AG) in NICE TA375 with some minor deviations. The ERG believes that the conceptual model was appropriate and suffered only from minor implementation errors, most of which were resolved during the clarification process.

However, the analyses presented by the company included a number of limitations. First, relevant comparators recommended by NICE were missing from the company's analyses: adalimumab, etanercept, infliximab and certolizumab pegol with concomitant MTX in bDMARD-IR RTX-ineligible patients with severe RA and all relevant comparators in bDMARD-IR MTX-intolerant patients with severe RA. Second, the sequences used in the company's original analyses were not appropriate for a

number of reasons: (i) the inclusion of multiple consecutive lines of the same treatment; (ii) the inclusion of bDMARD treatments in points in the pathway not recommended by NICE; and, (iii) the inclusion of three or four post-biologic treatments before palliative care. Thirdly, the company assumed equal efficacy for tofacitinib as monotherapy and in combination with MTX in terms of the probabilities of achieving moderate and good EULAR responses. However, the results of the NMA show that these probabilities are lower for tofacitinib monotherapy compared with tofacitinib with concomitant MTX. Fourth, the company used the results for placebo from the NMA to estimate the efficacy sulfasalazine for the analysis for the cDMARD-IR MTX-intolerant population. The ERG believes this to lead to an underestimation of the efficacy of sulfasalazine. Finally, the company rounded modified 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. The ERG notes that this approach might lead to inaccurate estimations of HAQ-DI scores, as values might be rounded up more often than they are rounded down or *vice versa.* The company corrected the first two issues in the revised model submitted with the clarification responses but did not present a full set of analyses relating to their revised base case.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The ERG considers the data on clinical effectiveness in the CS to be well-reported and the included trials are of good quality.

The model used appears conceptually appropriate with very few implementation errors, most of which were rectified during the clarification process. The ERG considers that the DES approach taken by the company, which was based on the model used in TA375, was deemed appropriate to represent the disease. The ERG considers the company's analysis of patients with moderate RA that can progress to severe RA and then start with a sequence of bDMARDs to reflect the treatment pathway of these patients better than other previous analyses.

The ERG also notes that the amendments, corrections and different assumptions tested by the ERG do not significantly impact the broad conclusions of the analyses presented in the CS.

1.6.2 Weaknesses and areas of uncertainty

Whilst full data were not available for inclusion into the CS, the ERG believes that the recently published ORAL Strategy trial is also relevant to the decision problem because it has head-to-head evidence at 6 months, demonstrating than tofacitinib monotherapy was statistically inferior to both adalimumab plus MTX and tofacitinib plus MTX using the primary endpoint of ACR50.

The company focuses its safety profile on whether the AEs were comparable across the tofacitinib treatment arms and whether any new or unexpected safety events have occurred. The ERG considers that a more informative analysis would present all AEs, including SAEs, versus the comparator arm. Additionally the company did not conduct targeted up-to-date literature searches to retrieve evidence for AEs associated with tofacitinib treatment for this appraisal meaning that some relevant analyses of adverse event data for tofacitinib are not included. Pooled analyses of AE data across trials of both tofacitinib monotherapy and tofacitinib in combination with methotrexate are unlikely to provide an accurate reflection of the incidence of adverse event rates from these two treatment regimens, which are noted in sources not referenced in the CS, to be different.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook exploratory analyses based on the company's revised model. The ERG presented two full sets of analyses: one based on the company's preferred NMA and the other based on the NMA undertaken for the clarification response, which the company denoted 'ERG preferred'. As this is not the ERG's preferred analysis we have renamed this the 'clarification NMA'. All analyses presented in this report have not taken any commercial-in-confidence PASs into consideration.

For cDMARD-IR patients with severe RA who can tolerate MTX, based on the company's NMA, tofacitinib + MTX dominated all of its bDMARD comparators except etanercept biosimilar + MTX. Based on the clarification NMA, tofacitinib + MTX dominated ADA+MTX but was extendedly dominated in the full incremental analysis. For cDMARD-IR patients with severe RA for whom MTX was contraindicated or not tolerated, tofacitinib and tocilizumab monotherapy extendedly dominated ADA and ETN biosimilar regardless of the NMA used. The ICER of tocilizumab compared with tofacitinib was £51,488 and £50,430 per QALY gained using the company's NMA and using the clarification NMA, having removed the constraint that TOF monotherapy had the same efficacy as TOF+MTX, respectively.

In the bDMARD-IR patients with severe RA for whom rituximab was an option, rituximab + MTX dominated tofacitinib + MTX regardless of the NMA used. [redacted] Replacing tocilizumab + MTX with tofacitinib + MTX after rituximab + MTX was estimated to result in £67,852 and £90,846 per QALY lost using the company's and the clarification NMA respectively. The ERG notes, however, that the confidential PAS of TCZ was not included in these analyses. In the bDMARD-IR patients with severe RA for whom RTX was not an option, tofacitinib + MTX dominated golimumab+MTX regardless of the NMA used, and dominated abatacept + MTX also when using the

company's NMA. The ICER of etanercept biosimilar and tocilizumab with MTX compared with tofacitinib + MTX was higher than £30,000 per QALY gained regardless of the NMA used.

Finally, in patients with moderate RA who where cDMARD-IR, the ICER of tofacitinib + MTX compared with MTX was £47,594 and £50,708 per QALY gained using the company's and the clarification NMA respectively.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The Evidence Review Group (ERG) considers the company's description of the underlying health problem in the company's submission (CS)[1] to be appropriate, mostly up-to-date and relevant to the decision problem set out in the final National Institute for Health and Care Excellence (NICE) scope[2]. The ERG provides a brief summary of the underlying health problem in the subsequent sections. Epidemiological numbers provided by the ERG may differ from those presented in the CS but do not affect the broad messages.

Clinical features of rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by: progressive, irreversible, joint damage; impaired joint function; pain and tenderness caused by swelling of the synovial lining of joints.[3] The condition is associated with increasing disability and reduced quality of life.[3] The primary symptoms are pain; morning stiffness; swelling; tenderness; loss of movement; redness of the peripheral joints; and fatigue.[4, 5] RA is associated with substantial costs both directly (associated with drug acquisition and hospitalisation) and indirectly due to reduced productivity.[6] RA has long been reported as being associated with increased mortality,[7, 8] particularly due to cardiovascular events.[9]

Epidemiology

NICE estimates that there are 400,000 people in the UK with RA,[10] based on a prevalence of 0.8% reported by Symmons *et al*.[11] The incidence of RA is greater in females (3.6 per 100,000 per year) than in males (1.5 per 100,000 per year).[12] For both genders, the peak age of incidence in the UK is in the eighth decade of life, but all ages can develop the disease.[12]

Aetiology

There is no identified specific cause for RA, but there seem to be a variety of contributing factors such as genetic and environmental influences. Genetic factors have a substantial contribution to RA. The heritability of RA is estimated to be between 53 and 65%[13] and family history of RA has a corresponding risk ratio of 1.6 compared with the general population.[14] Many genes associated with RA susceptibility are concerned with immune regulation. Infectious agents have been suspected but no consistent relationship with an infective agent has been proven. Similarly, sex hormones have been suspected due to the higher prevalence of RA in women and a tendency for the disease to improve during pregnancy. However, a precise relationship has not been identified. There is no proof of any causal link with lifestyle factors such as diet, smoking, or occupation.

Management of rheumatoid arthritis

Traditionally, patients have been treated with conventional disease-modifying anti-rheumatic drugs (cDMARDs) which include methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), leflunomide (LEF), and gold injections as well as corticosteroids, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). However, more recently, a group of biologic immunosuppressant drugs have been developed that specifically modify the disease process by blocking key protein messenger molecules (such as cytokines) or cells (such as B-lymphocytes).[10] Such drugs have been labelled as biologic disease-modifying anti-rheumatic drugs (bDMARDs): certolizumab pegol (CTZ); adalimumab (ADA); etanercept (ETN); golimumab (GOL); and infliximab (IFX) are tumour necrosis factor (TNF) inhibitors (or antagonists) (TNFi). Of the remaining bDMARDs, tocilizumab (TCZ) is a cytokine interleukin-6 inhibitor; abatacept (ABT) is a selective modulator of the T lymphocyte activation pathway; and rituximab (RTX) is a monoclonal antibody against the CD20 protein. For patients who have exhausted all NICE recommended treatments, palliative care (PALL) is the final treatment option.

Assessment of response to therapy

The initial response criteria for RA were produced in 1987 by the American College of Rheumatology[15] (ACR). NICE Clinical Guideline (CG) 79 provides a summary of the ACR criteria, namely that patients must have at least four of seven criteria: (i) morning stiffness lasting at least 1 hour; (ii) swelling in three or more joints; (iii) swelling in hand joints; (iv) symmetric joint swelling; (v) erosions or decalcification on X-ray of hand; (vi) rheumatoid nodules; (vii) and abnormal serum rheumatoid factor. For the first four criteria, these must have been present for a period of at least six weeks. However, in NICE CG 79 the Guideline Development Group preferred a clinical diagnosis of RA rather than the ACR criteria because 'an early persistent synovitis where other pathologies have been ruled out needs to treated as if it is RA to try to prevent damage to joints. Identification of persistent synovitis and appropriate early management is more important than whether the disease satisfies classification criteria', referencing recommendations from the European League Against Rheumatism (EULAR).[16]

In 2010, the ACR and EULAR jointly published RA Classification Criteria, which focussed on the features at earlier stages of disease that are associated with persistent and/or erosive disease, rather than defining the disease by its late stage features.[17] The classification criteria allocates scores to: characteristics of: joint involvement; serology; acute-phase reactants; and duration of symptoms, to produce a score between 0 and 10 inclusive. Those patients scoring six or greater and with obvious clinical synovitis being defined as having "definite RA" in the absence of an alternative diagnosis that better explains the synovitis.

Two classifications have dominated the measurement of improvement in RA symptoms: ACR responses[18] and EULAR responses.[19]

The initial ACR response 'ACR20', required: a 20% improvement in tender joint counts; a 20% improvement in swollen joint counts; and a 20% improvement in at least three of the following five 'core set items': physician global assessment; patient global assessment; patient pain; self-reported disability (using a validated instrument), and; erythrocyte sedimentation rate (ESR) / C-reactive protein (CRP).

ACR response has been widely adopted in randomised controlled trials (RCTs) although studies have shown that the value of the measure can vary between trials due to the timing of the response.[20] Since the inception of the ACR20, two further response criteria (ACR50 and ACR70) have become widely used. These are similar to ACR20 and differ only in the level of percentage improvements required in order for a patient to be classified as a responder. These are nested responses, thus patients who achieve ACR70 will also achieve ACR20 and ACR50.

In the UK, monitoring the progression of RA is often undertaken using the disease activity score of 28 joints (DAS28) in terms of swelling (SW28) and of tenderness to the touch (TEN28). The DAS28 score incorporates measures of the ESR and a subjective assessment on a scale of 0-100 made by the patient regarding disease activity in the previous week.

The equation for calculating DAS28 is as follows:[21]

$$DAS28 = 0.56 * TEN28^{0.5} + 28 * SW28^{0.5} + 0.70 * \ln(ESR) + 0.014 * \text{subjective assessment}$$

The DAS28 can be used to classify both the disease activity of the patient and the level of improvement estimated within the patient.

A second version of DAS28, using C-reactive protein (CRP) rather than ESR exists. Clinical advice to the ERG was that ESR and CRP measurements are similar, but not identical, with ESR being slightly higher. However, as the majority of studies have used DAS28 ESR, this is the metric used by the company in assessing comparative effectiveness between interventions.

The EULAR response criteria uses the individual change in DAS28 and the absolute DAS28 score to classify a EULAR response as: good; moderate; or none.[19] The EULAR response criteria and the ACR20 improvement criteria were found to have reasonable agreement in the same set of clinical trials, although van Gestel *et al.* state that the EULAR response criteria showed better construct and discriminant validity than ACR20.[22] EULAR response has been reported less frequently in RCTs than ACR responses,[23] although EULAR is much more closely aligned to the treatment continuation rules stipulated by NICE for treatment in England. These rules require either a moderate or good EULAR response or a DAS28 improvement of more than 1.2 to continue treatment, with the latter criterion

applying to RTX. The relationship between change in DAS28 and the absolute DAS28 score and EULAR response is shown in Table 1.

Table 1: Determining EULAR response based on DAS28[22]

	Improvement in DAS 28		
DAS28 at endpoint	>1.2	>0.6 and ≤1.2	≤0.6
≤ 3.2	Good	Moderate	None
>3.2 and ≤5.1	Moderate	Moderate	None
>5.1	Moderate	None	None

Patients with a DAS28 ≤3.2 are regarded as having inactive disease, those with a DAS28 > 3.2 and ≤ 5.1 are regarded as having moderate disease and >5.1 as having very active disease.[21] Within NICE Technology Appraisal (TA) 375, patients with a DAS28 > 3.2 and ≤ 5.1 were considered as having moderate-to-severe disease whilst those with a DAS28 > 5.1 were denoted as having severe diseas.[24]

A widely used measure of patient disability is the Health Assessment Questionnaire (HAQ). The HAQ-DI score is a patient completed disability assessment which has established reliability and validity.[25] HAQ-DI scores range from zero to three, with higher scores indicating greater disability The HAQ-DI is a discrete scale with step values of 0.125, resulting in the HAQ-DI scale containing 25 points. The HAQ-DI has been used in many published RCTs in RA.[23]

2.2 Critique of company's overview of current service provision

The company's overview of current service provision is concise but appropriate and relevant to the decision problem set out in the final NICE scope. The ERG provides a summary of current service provision below.

Clinical guidelines

For people with newly diagnosed RA, NICE CG79[10] recommends a combination of cDMARDs (including MTX and at least one other cDMARD plus short-term glucocorticoids) as first-line treatment, ideally beginning within 3 months of the onset of persistent symptoms. Where combination therapies are not appropriate, for example, where there are comorbidities or pregnancy, cDMARD monotherapy is recommended. Where cDMARD monotherapy is used, emphasis should be made on increasing the dose quickly to obtain best disease control. For the purposes of this assessment, the term "intensive cDMARDs" has been used to denote that this involves treatment with multiple cDMARDs simultaneously.

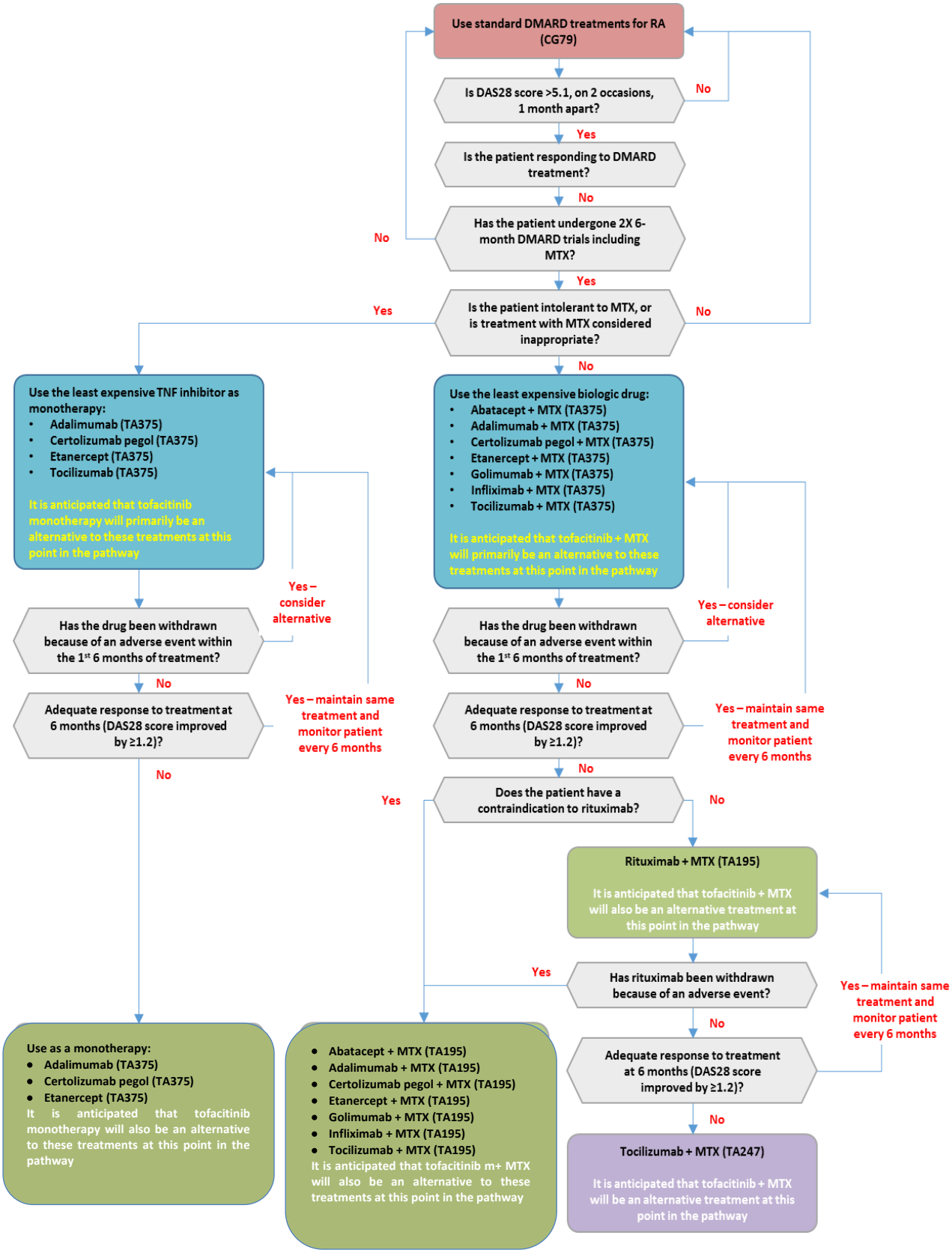
NICE guidance (TA375)[24] recommends the use of ABT, ADA, CTZ, ETN, GOL, IFX, and TCZ in combination with MTX in people with RA after the failure to respond to intensive cDMARDs treatment

and who have severe active RA (defined as a DAS28 score > 5.1). For people who meet these criteria but cannot take MTX because it is contraindicated or because of intolerance, TA375[24] recommends the following bDMARDs as monotherapy options: ADA; CTZ; ETN; or TCZ.

After the failure of the first TNF-inhibitor, TA195[26] recommends RTX in combination with MTX for the treatment of severe active RA. If RTX is contraindicated or withdrawn because of an adverse event (AE), TA195 recommends ABT, ADA, ETN, or IFX in combination with MTX. If MTX is contraindicated, or withdrawn because of an AE, TA195 recommends ADA or ETN as monotherapy. TA247[27] recommends TCZ, and TA415[28] recommends CTZ as alternatives to TNF-inhibitors in the same circumstances as TA195, that is, after the failure of a TNF-inhibitor in patients with severe active RA, in combination with MTX when RTX is contraindicated or withdrawn and as monotherapy if MTX is contraindicated or withdrawn. In addition, TA247 recommends TCZ in combination with MTX in patients in whom TNF-inhibitors and RTX have not worked.

The summary of the NICE recommended treatment pathway for RA presented in the CS and amended by the ERG is presented in Figure 1.

Figure 1: Treatment pathway presented in the CS (Figure 2) modified by the ERG



NICE criteria for continuing treatment

NICE TA375[24] states that for patients to continue treatment with their first bDMARD treatment they must maintain at least a moderate EULAR response. TA195,[26] which for all bDMARDs excluding RTX was updated in TA375[24], states that bDMARD treatment after the failure of a TNFi should be continued only if there is an adequate response (defined as an improvement in the DAS28 score of ≥ 1.2 points) at initiation of treatment and as long as this adequate response is maintained. If the criterion of having at least a moderate EULAR response at six months has not been met, then treatment should be stopped and the next intervention in the sequence should be initiated.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

3.1 Population

Tofacitinib is licensed in the UK for the treatment of moderate-to-severe active RA in adult patients (aged over 16 years). The target population in the company's decision problem matches the populations described in the final NICE scope which are:

1. Tofacitinib in combination with methotrexate for patients whose disease has responded inadequately to at least one conventional DMARD (second-line patients) or biologic DMARD (third-line patients).
2. Tofacitinib as monotherapy in case of intolerance to methotrexate or when treatment with methotrexate is inappropriate.

The study population presented in the company submission (CS) for tofacitinib is largely appropriate. The company highlight that the proportion of patients in the included trials with moderate RA is 8.2% (323 out of 3,954) therefore, the study population is mostly comprised of people with severe disease. The CS estimates that around 15% of the 441,000 people diagnosed with RA in England have severe disease RA. Severe RA is defined in the CS as having a Disease Activity Score 28 (DAS28) of greater than 5.1 whilst moderate disease is defined as DAS28 3.2 – 5.1, which the ERG note to be appropriate and established cut-offs.

In a submission to NICE, a representative of the British Society for Rheumatology (BSR) highlighted some limitations of the generalisability of evidence from RA study populations including:

- RA patients in clinical practice have considerable numbers of comorbidities. Most trial patients will be pre-selected and the impact of the technology on the course and treatment of comorbidities is not clear.
- Most trials will have been undertaken for limited time periods in a lifelong disorder.
- With regards to adverse reactions, increased incidence of cardiovascular events and raised lipids may be of concern in the long-term sustained use of the drug.

3.2 Intervention

Tofacitinib citrate (Xeljanz™) is an oral Janus kinase (JAK) inhibitor marketed by Pfizer. Janus kinases are enzymes that transduce intracellular signals from cell surface receptors for a number of cytokines and growth factors. Tofacitinib preferentially inhibits JAK1 and JAK3 leading to an attenuation of signalling of interleukins (IL-2, -4, -6, -7, -9, -15, -21) and type I and type II interferons, which will result in modulation of the immune and inflammatory response. The intervention is not a biological DMARD, and is described by the company as a *targeted synthetic* disease-modifying anti-rheumatic

drug (tsDMARD). Tofacitinib is available as a 5mg film-coated tablet to be taken by mouth twice a day (BD).

Tofacitinib received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on the 26th January 2017 for the treatment of RA. Prior to this approval, the CHMP had adopted a negative opinion for granting marketing authorisation to tofacitinib in 2013 (25th April) which was confirmed on the 22nd July 2013 on the basis of: (1) Serious and unresolved incidence of infection; (2) Uncertainties in the overall safety profile in relation to incidence and severity of infections, malignancies, lymphoma, gastrointestinal perforations, hepatic enzymes elevations/drug-induced liver injury and lipids and cardiovascular risks; (3) Unresolved safety concerns are not offset by the benefits of the treatment. [29]

Tofacitinib was added to the EMA's list of medicines under additional monitoring in April 2017.

Laboratory tests are required for patients undergoing treatment with tofacitinib to monitor:

- neutrophils at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter
- lipid parameters after 8 weeks following initiation of therapy
- lymphocytes (at baseline and every 3 months thereafter)
- haemoglobin (at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter).

The ERG's clinical advisors state that these tests would ordinarily be provided in clinical practice for this patient population.

The Summary of Product Characteristics (SmPC)[30] reports the following contraindications for treatment with tofacitinib:

- patients who are allergic or hypersensitive to ingredients of the medicine
- severe hepatic impairment
- paediatric population
- pregnant and breast-feeding
- patients with active infections, including localised infections, tuberculosis (TB), serious infections such as sepsis, or opportunistic infection.

A number of additional points regarding tofacitinib are emphasised in the SmPC including:

- A higher rate of infections in patients aged 65 and older and diabetic populations.
- A caution that data in the elderly population of 75 years and over are limited.
- A higher rate of herpes zoster (shingles) in Japanese and Korean patients.

The SmPC also notes that the risks and benefits should be considered prior to initiating tofacitinib in patients:

- with recurrent infections or a history of a serious or an opportunistic infection
- who have resided or travelled in areas of endemic mycoses, or; who have underlying conditions that may predispose them to infection
- who have been exposed to TB or have travelled in areas of endemic TB
- with current or a history of malignancy (other than a successfully treated non-melanoma skin cancer (NMSC)) due to the possibility for tofacitinib to affect host defences against malignancies
- with a history of chronic lung disease as they may be more prone to infections
- at increased risk of gastrointestinal perforation
- with elevated liver enzymes- alanine aminotransferase (ALT) or aspartate aminotransferase (AST)
- in combination with other bDMARDs because of the possibility of increased immunosuppression and increased risk of infection.

A higher incidence of AEs is noted in the SmPC for combination therapy of tofacitinib with methotrexate versus tofacitinib monotherapy.

The list price for tofacitinib is £690.03 per pack (56 x 5 mg tablets). The discount price with Patient Access Scheme (PAS) applied is [redacted] per pack. The cost-effectiveness results presented by the company are based on the PAS price.

3.3 Comparators

The comparators to tofacitinib (TOF) considered in the decision problem in the CS are documented in Table 2.

Table 2: Comparators to tofacitinib considered in the CS

Generic name (Abbreviation) [Trade name]	Licensed Dose for RA
Most commonly used conventional DMARDs	
Methotrexate (MTX)	Oral or SI: 7.5 mg QW, up to 20/25 mg QW.
Sulfasalazine (SSZ)	Oral: 500 mg QD, increased by 500 mg every week, to 2–3 g QD
Hydroxychloroquine (HCQ)*	Oral: 200 mg to 400 mg QD, reduced to Q2W or Q3.
Leflunomide (LEF)*	Oral: 10 mg once daily increased to 20 mg as necessary.
Ciclosporin*	Oral: 2.5 mg/kg QD in 2 doses, up to 4 mg/kg QD after 6 weeks.
Biological DMARDS (Tumour Necrosis Factor-αlpha-inhibitors)	
Adalimumab (ADA) [HUMIRA]	SC: 40 mg Q2W, increased if necessary to 40mg QW.
Etanercept (ETN) [ENBREL]	SC: 25 mg BIW, alternatively 50mg QW.
Infliximab (IFX) [REMICADE]	IV: 3 mg/kg, then after 2 weeks, then after 4 weeks, then Q8W.
Golimumab (GOL) [SIMPONI]	SC: 50 mg Q4W for (< 100kg); 100 mg Q4W for 3–4 doses (>100kg).
Certolizumab pegol (CTZ) [CIMZIA]	SC: 400 mg Q2W for 3 doses, then 200 mg Q2W.
Biological DMARDS (Anti-B-cell therapy)	
Rituximab (RTX) [MABTHERA]	IV: 1 g, Q2W, then every 9 months
Abatacept (ABT) [ORENCIA]	IV or SI: 500 mg (< 60 kg) / 750 mg (60–100kg) / 1 g (101+ kg) Q2W for 3 doses, then 500 mg / 750 mg / 1 g Q4W.
Biological DMARDS (Anti-IL-6 therapy)	
Tocilizumab (TCZ) [ACTEMRA]	IV or SI: 8 mg/kg Q4W (maximum per dose 800 mg)
Biological DMARDS (Biosimilars)	
Etanercept (ETNb) [BENEPALI]	SC: 25 mg BIW, alternatively 50 mg QW.
Infliximab (IFXb) [INFLECTRA]	IV: 3 mg/kg, then after 2 weeks, then after 4 weeks, then Q8W.

IV: Intravenous infusion: SC: Subcutaneous injection; QD: once a day; BD: twice per day; BIW: Twice weekly; QW: once weekly; Q2W: every two weeks; Q4W: every four weeks; Q8W: every eight weeks
* These interventions were considered explicitly in the modelling presented in the CS but were omitted after the clarification process.

The comparators in the CS are largely in line with the final scope issued by NICE. Tofacitinib 5 mg BD is compared in a network meta-analysis and economic model with:

- combination therapy with cDMARDs (including methotrexate and at least once other cDMARD)
- bDMARDs in combination with cDMARD
- bDMARDs as monotherapy.

Other potentially relevant comparators such as anakinra [KINERET]; baricitinib [OLUMIANT] sarilumab [KEVZARA] and sirukimab, were excluded in the CS as they are either currently unlicensed, unapproved or yet to be assessed by NICE. Baricitinib is currently under assessment by NICE (ID979) for treating moderate-to-severe RA and, like tofacitinib, is an orally administered JAK inhibitor (4mg once per day).

3.4 Outcomes

The outcome measures in the final scope issued by NICE and those considered in the CS are outlined in Table 3:

Table 3: Outcome measures from the NICE scope considered in the CS

Outcomes as per NICE Scope	Outcomes as defined and measured in the CS
Disease activity	Disease Activity Score (DAS28) American College of Rheumatology (ACR)20; ACR50; ACR70
Physical function	Health Assessment Questionnaire-Disability Index (HAQ-DI)
Joint damage, pain	Visual analogue scale (VAS): Patient's assessment of arthritis pain (PAAP)
Mortality	Death within 30 days of last dose of study drug in pooled safety analysis
Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale
Radiological progression	Sharp-van der Heidje scale modified Total Score (mTSS)
Extra-articular manifestations of disease	Not provided
Adverse effects of treatment	Pooled incidence rates of 19 trials' intervention arms without comparator
Health-related quality of life.	EuroQol 5-dimension questionnaire (EQ-5D)

3.5 Other relevant factors

Adherence

Adherence to treatment is not measured in the CS however, some potential benefits towards adherence are alluded to. The company states (see CS, page 49) that the mode of administration may be important in adherence to RA treatment and that patients with RA have reported a preference for oral administration over other routes including subcutaneous injection. They cite a paper[31] which contains one reference to oral therapy (methotrexate) from a study that actually reported lower adherence than either intravenous (IV) infliximab or self-administered subcutaneous (SC) etanercept. Whilst the CS

does correctly reference a study[32] which reported that RA patients prefer the oral route of administration to other routes, patient preference does not necessarily equate with increased adherence. Clinical advice to the ERG was that whilst it may be easier for patients to take oral medication, self-administration in itself may be a contributing factor towards non-adherence, whereas the involvement of a third person can sometimes aid adherence. The CS states some valid potential patient groups where an oral therapy presents a useful alternative to clinicians such as those with impaired hand function who may have problems with self-injection.

Ongoing trials of tofacitinib in RA

Ongoing primary research identified from searching clinicaltrials.gov and relevant to the decision problem is documented in Table 4. Nine ongoing studies were noted to be relevant to the long-term safety and efficacy of tofacitinib and plan completion between April 2016 and December 2021.

Table 4: Ongoing trials relevant for tofacitinib in RA

Trial no. Sponsor	Aim	Planned enrolment	Planned completion
NCT02157012 Shinshu University	Phase 4 single arm study to examine the safety and effectiveness after tofacitinib treatment in RA patients	100	April 2016
NCT03073109 Pfizer	Study of patient-reported outcomes in RA patients treated with tofacitinib or bDMARDs	320	Mar 2018
NCT00413699 Pfizer	Phase 3 study of long-term effectiveness and safety of tofacitinib in RA subjects after participating in another "qualifying" study of tofacitinib (ORAL Sequel)	4500	Dec 2018
NCT02831855 Pfizer	Phase 4 study of methotrexate withdrawal on tofacitinib modified release formulation (11mg QD) versus tofacitinib (11mg QD) plus continued methotrexate treatment	580	Mar 2019
NCT03016884 HaEmek Medical Center, Israel	Phase 4 study evaluating the safety, tolerability, and immunogenicity of Zostavax vaccine in the RA population prior to initiation of biologic/tofacitinib therapy for RA	250	May 2019
NCT02092467 Pfizer	Phase 3b/4 post-marketing safety study of tofacitinib compared with ADA and ETN for major cardiovascular adverse events, malignancies, hepatic events, infections, and efficacy parameters.	4400	Aug 2019
NCT02984020 Pfizer	Korean post-marketing surveillance study for the safety and efficacy of Xeljanz during the post-marketing period as required by the Korean Ministry Of Food And Drug Safety.	3000	Jan 2020
NCT01932372 Pfizer	Special investigation of tofacitinib 5mg in clinical practice of occurrence of adverse reactions/ factors that may potentially affect safety and efficacy and long-term safety vs other bDMARDs	6000	Mar 2021
NCT03011281 Hanyang University	Prospective study to evaluate the effectiveness and safety of tofacitinib in clinical practice in Korean RA patients	378	Dec 2021

Source: Clinicaltrials.gov

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

This chapter presents a review of the clinical effectiveness evidence provided in the CS for tofacitinib for treating moderate-to-severe RA. The clinical evidence provided in the CS comprised a systematic review of tofacitinib RCTs, and a network meta-analysis (NMA) of cDMARD and bDMARD comparators. The safety profile contained a pooled analysis of AEs from the ORAL tofacitinib trial programme.

4.1.1 Searches

The company performed one clinical effectiveness literature search to identify all clinical and safety studies of tofacitinib and its comparators (see Table 5).

Original searches were performed in June 2010. Several electronic bibliographic databases were searched including: MEDLINE [via Ovid], MEDLINE in Process [via Ovid], EMBASE [via Ovid], Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, the Health Technology Assessment database, the Database of Abstracts and Reviews of Effects [via Wiley]), the EULAR website, ACR website and the BSR website. Five update searches were subsequently performed between April 2011 and December 2016 using the same sources, which cover the period from 2005 to 2016.

The company searched several clinical trials registries in the update review of clinical effectiveness data (clinicaltrials.gov, UK Clinical Trials Gateway and WHO International Clinical Trials Registry). The company also carried out supplementary searches by scanning bibliographies of included studies, reviews, meta-analyses and also performed hand searching for HTA submissions via HTA agency websites (NICE, the Scottish Medicines Consortium (SMC), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Australian Pharmaceutical Benefits Advisory Committee (PBAC) and Haute Autorité de Santé (HAS)) (see page 68 of the CS).

The company reported the full literature search strategies for both the original and review update searches (see CS, Appendix 3). The ERG considers that the search strategies are sufficiently comprehensive to retrieve important citations relating to eligible studies with clinical effectiveness data.

In the safety overview of the CS (Section 4.12.4), the company reported that no new risks of safety signals were identified in the long-term safety database. However the CS reports that a "data cut" was imposed on the safety data such that only trials included in the published pooled analysis,[33] which included trial data up to March 2015, were included in the safety overview. The company's clarification response[34] (question 1) confirmed that a separate search for AEs was not undertaken and that data on

AEs were identified as part of a broader search of efficacy, safety and health-related quality of life (HRQoL).

The ERG reviewed the search strategy for indirect and mixed treatment comparisons conducted in the CS (Appendix 8.3) and found that:

(i) the observational studies filter was not applied consistently in the searches and,
(ii) date limits were applied in the original review (June 2010), the 4th update (June 2016) and the 5th update (December 2016) for the MEDLINE and EMBASE searches, but not in the 1st update (April 2011), the 2nd update (September 2012) or the 3rd update (November 2014).

The ERG sought clarification with the company regarding this inconsistency. The company's clarification response[34] (question 2) judged the impact of omitting this filter in the update searches on the appraisal to be low and in line with previous Technology Appraisals (TAs) [TA415, TA375, TA195, etc.] where only RCT evidence was considered for inclusion in the associated NMA. The ERG carried out a short AE search for tofacitinib combined with an adverse events filter in Medline on 27th April 2017 (see Appendix 1). Further details of this search are discussed in Section 4.4. Whilst the ERG considers that the company's literature searches were sufficient and comprehensive to retrieve relevant and up-to-date data for clinical effectiveness, the searches for safety data were not sufficient to identify all up-to-date relevant adverse event data for tofacitinib.

4.1.2 Inclusion criteria

The inclusion and exclusion criteria for the systematic review search strategy are listed collectively (i.e., not listed separately by inclusion and exclusion) in the CS (see Table 5) and are in accordance with the decision problem in the final NICE scope.

Table 5: Inclusion and exclusion criteria in systematic review search strategy (reproduced from Table 60 of the CS)

Clinical effectiveness	Inclusion/exclusion criteria	
	cDMARD-IR	**bDMARD-IR**
Population	Adult patients (≥18 years of age) meeting ACR classification criteria for RA who have had an inadequate response to at least one cDMARD or MTX	Adult patients (≥18 years) with RA (as defined by the ACR criteria) who have had an IR to at least one bDMARD
Interventions/comparators[†]	Only licensed doses of each treatment were included • TNF-α-inhibitors: o Adalimumab o Etanercept o Infliximab o Golimumab o Certolizumab • JAK-inhibitors: o Tofacitinib o Baricitinib • Anti-B-cell therapy: o Rituximab o Co-stimulatory inhibitor molecules o Abatacept • Anti-IL-6 therapy: o Tocilizumab o Sarukinumab (sic) o Sirulimumab (sic) • Anti-IL-1 therapy: o Anakinra Biosimilars	
Outcomes	**Efficacy:** • EULAR response • Patient assessment of functional ability (Health Assessment Questionnaire [HAQ], Arthritis Impact Measurement Scales [AIMS], McMaster Toronto Arthritis [MACTAR]) • Radiographic progression (as measured by a valid scoring system e.g. Larsen/Sharp/modified Sharp score). • ACR 20/50/70 response rate to treatment (defined as a 20%/50%/70% improvement in tender and swollen joint counts and the same level of improvement in three of the five following variables: patient and physician global assessments, pain Health Assessment Questionnaire, and acute phase reactants). • C-reactive protein (CRP) levels • Changes in either DAS or DAS28 score.	

Clinical effectiveness	Inclusion/exclusion criteria	
	cDMARD-IR	**bDMARD-IR**
	• Achieving 'low disease activity' (defined as DAS28 <3.2) or 'remission' (defined as DAS28 < 2.6). • Patient's assessment of pain (VAS or Likert scale). • Patient/physician assessment of disease activity (VAS or Likert scale) • Morning stiffness, number of flares **Safety:** • Incidence of adverse events, including allergic reactions, and infections • Incidence of serious adverse events • Treatment withdrawal (and reason for withdrawal, e.g. lack of efficacy, adverse events, serious adverse events) **Health-related quality of life:** As measured by EQ-5D or other instruments	
Trial design	RCTs, no restriction on phase	
Language restrictions	No restriction. English abstracts of foreign language papers were considered	
Date of publication	Original review: no restriction April 2011 update: post-June 2010 September 2012 update: post-April 2011 November 2014 update: post-September 2012 June 2016 update: post-November 2014 December 2016 update: post-June 2016	No restriction

Abbreviations: ACR = American College of Rheumatology; DAS = disease activity score; c/bDMARD = conventional/biological disease modifying anti-rheumatic drug; EULAR = European League Against Rheumatism; HAQ-DI = health assessment questionnaire – disability index; IL = interleukin; JAK = Janus kinase; MTX = methotrexate; NICE = National Institute for Health and Care Excellence; QoL = quality of life; RA = rheumatoid arthritis; RCT = randomised controlled trial; SJC = swollen joint count; SR = systematic review; TJC = tender joint count; TNF-α = tumour necrosis factor-alpha; VAS = visual analogue scale.
Footnote: †Interventions were considered alone or in combination with other conventional/biological DMARDs. There were no restrictions with regard to drug dose or formulation, mode of delivery, or duration of treatment.

Further exclusion criteria were then applied in the CS to identify studies for inclusion into the NMA as follows:

- outcomes were restricted to EULAR (moderate, good, or at least a moderate response) and change in HAQ-DI from baseline;
- study follow-up restricted to 20–30 weeks;
- disease duration >3 years;
- comparator treatments only at licensed doses (baricitinib, sirukimab, and sarilumab excluded as currently unlicensed or not yet assessed by NICE).

The study selection process described in the CS (page 166) reported that studies identified for the systematic review were assessed by 'a reviewer', which is not considered as best practice in systematic reviews. A second reviewer was employed to resolve any uncertainties identified by the first reviewer. Reference lists of systematic reviews and included studies were not checked for RCTs meeting the inclusion criteria. In response to a request for clarification by the ERG (see clarification response,[34] question A4), the company responded that two independent reviewers "were involved" in study selection.

In addition to the tofacitinib RCTs that met the decision problem, the CS also included two other tofacitinib RCTs from the ORAL trial programme: ORAL Step[35] (Pfizer Clinical Study Report (CSR), 2012[36]) and ORAL Start[37] (Pfizer CSR, 2015[38]). ORAL Step evaluated tofacitinib in patients with moderate-to-severe RA who were TNFi-IR. The CS reported that this was less relevant to the decision question, given the second-line positioning of tofacitinib within the current decision problem. ORAL Start evaluated tofacitinib monotherapy in adults who were MTX naïve (approximately 39% of patients had received treatment with non-MTX cDMARDs); the majority of the study population therefore were outside of the licenced population for tofacitinib. The ERG agrees that the trial populations in ORAL Step and ORAL Start are less relevant to the target population in the decision problem.

Two further tofacitinib RCTs, ORAL Sequel and ORAL Strategy were described in the CS (Section 4.14 of the CS). The CS reported that ORAL Sequel (NCT00413699) evaluated the long-term safety and efficacy of tofacitinib in an open-label extension study of patients who had previously participated in randomised Phase I, Phase II, or Phase III tofacitinib trials. Section 4.11 of the CS included some data from long-term extension studies for DAS28(ESR) and HAQ-DI up to Month 75. ORAL Sequel is reported in the CS as ongoing with the next data cut off as being expected in September 2017. The ERG notes that patients with treatment-related SAEs were excluded from participation in this trial. Exclusion of patients discontinuing therapy during the initial RCT phase due to toxicity or inefficacy automatically provides a population enriched with responders and resistant to toxicity for the LTE study. This usually gives the appearance of proportionately more responders and greater safety.[39]

The CS reported ORAL Strategy (NCT02187055)[40] as an "ongoing" one-year Phase 3b/4 RCT evaluating tofacitinib 5 mg BID with or without MTX and adalimumab 40 mg SC Q2W with MTX. Adults (N=1080) who have moderate-to-severe active RA and an inadequate response to MTX were randomised to treatment groups. The primary outcome was ACR50 response rates at Month 6. Preliminary efficacy results for the primary endpoint for this non-inferiority trial were provided in Section 4.12.2.1 of the CS. Secondary outcomes were ACR20, ACR70, change from baseline in Simple Disease Activity Index (SDAI), DAS 28-4(ESR), and HAQ-DI over time. This trial was completed in December 2016 and results have recently been published.[41] In this trial, tofacitinib plus MTX was found

to be non-inferior to adalimumab plus MTX. However, tofacitinib monotherapy failed to demonstrate non-inferiority against tofacitinib plus MTX and adalimumab plus MTX for the primary endpoint of ACR50 response rate. The ERG requested effectiveness data for the ORAL Strategy trial and an updated NMA considering these data (see clarification response,[34] question A3). The company's clarification response provided DAS28(ESR) EULAR response data for the full trial population but stated [redacted].

As the results have been published in a peer reviewed publication the ERG note that ORAL Strategy cannot be considered an ongoing trial and consider that further relevant data for this patient population could have been included in the CS.

The CS also reported a study "A3921041" (NCT00661661) which was completed in December 2013. This was an open-label, long-term extension study to assess safety, but only included Japanese patients. Clinical advice received by the ERG states that data there may be differences between UK and Japanese clinical populations in terms of tolerance and dosage of cDMARD treatment therefore the ERG considers that data from this trial may not be fully applicable to the decision problem.

4.1.3 Critique of data extraction

The CS reported that data were extracted from eligible publications into a predefined table by 'a reviewer', which is not considered as best practice in undertaking systematic reviews. In response to a request for clarification by the ERG (see clarification response,[34] question A4), the company responded that two independent reviewers "were involved" in data extraction and quality assessment.

Data extracted from the four included tofacitinib RCTs reported in the CS, and reported below, were checked by the ERG against published trial papers, and were found to be accurate.

4.1.4 Quality assessment

Quality assessment of the four included tofacitinib RCTs is presented in Section 4.6 and Appendix 4 of the CS. The items assessed were taken from the NICE Single Technology Appraisal: User guide for company evidence submission template.[42] These are appropriate criteria for assessing the risk of bias in RCTs. Table 6 presents the company's quality assessment of the tofacitinib trials. It is considered good practice for two reviewers either to independently perform quality assessment or to check assessed items, but this was not reported in the CS. The ERG checked the company's quality assessment against the publications of the RCTs relevant to the decision problem, ORAL Standard (van Vollenhoven *et al.*[43]), ORAL Scan (van der Heijde *et al.*[44], ORAL Sync (Kremer *et al.*[45]) and ORAL Solo (Fleischmann *et al*.[46]). Where quality criteria were not clear from the publications, the CSRs provided by the company were then consulted.

Table 6: Quality assessment of the tofacitinib RCTs relevant to the decision problem (adapted from Table 20 of the CS)

Trial acronym and trial number	ORAL Standard NCT00853385	ORAL Scan NCT00847613	ORAL Sync NCT00856544	ORAL Solo NCT00814307
Was randomisation carried out appropriately?	Yes[43]	Yes[44]	Yes[45]	Yes[47]
Was the concealment of treatment allocation adequate?	Yes[43]	Yes[44]	Yes[45]	Yes[47]
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes[43]	Yes[44]	Yes[45]	Yes[46]
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes[43]	Yes[44]	Yes[45]	Yes[46]
Were there any unexpected imbalances in drop-outs between groups?	No[43]	No[44]	No[45]	No[46]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No[43]	No[44]	No[45]	No[46]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Intention-to-treat analysis was considered unsuitable for the Month 6 assessment in clinical trials due to the advancement of patients receiving placebo to active treatment at Month 3 (CS Section 4.13.2.2). However, for clinical trials, where the primary endpoint was at Month 3, were not impacted by this issue. (CS page 102)			

Details of the generation of random sequences and the concealment of treatment allocation were not provided in one of the published trial papers (ORAL Standard[43]) but were provided in Section 9.4.3 of the CSR for this trial.[47] The ERG considers the company's quality assessment to be broadly accurate. In three of the RCTs (ORAL Standard[43], ORAL Scan[44], and ORAL Sync[45]), randomisation and concealment of allocation was accomplished using an interactive voice recognition system. However, one RCT (ORAL Solo[46]) used a private automated web-based or telephone-based system called "Impala" for randomisation and allocation. The ERG notes that this was the only trial that reported that groups were not comparable at baseline for [redacted] (see Section 4.2.1).

All four RCTs reported some blinding of participants, clinicians and outcome assessors (see Section 4.3). There were no unexpected imbalances in dropouts between treatment groups in any of the four trials. There was no evidence that any of the four RCTs measured more outcomes than they reported.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Included trials for tofacitinib

Four tofacitinib RCTs were identified in the CS as being relevant to the decision problem (ORAL Standard, ORAL Scan, ORAL Sync and ORAL Solo). MTX plus placebo was the comparator in ORAL Scan and ORAL Sync; placebo without MTX was the comparator in ORAL Solo; and an active treatment (adalimumab) and placebo were the comparators in ORAL Standard. In addition to treatment groups receiving the licenced dose of tofacitinib at 5 mg BID, all four RCTs also included treatment groups receiving tofacitinib 10 mg BID. The tofacitinib 10 mg BID treatment groups from all four of the tofacitinib RCTs are not considered further in the clinical effectiveness section of this ERG report as they relate to an unlicensed dose.

The population in ORAL Standard and ORAL Scan related to adults with active moderate-to-severe RA who were cDMARD experienced and MTX-IR. The population in ORAL Sync and ORAL Solo was adults with active moderate-to-severe RA who were DMARD-IR (cDMARD including MTX or bDMARD).

Details of the four RCTs (ORAL Standard, ORAL Scan, ORAL Sync and ORAL Solo) included in the CS are shown in Table 7 (adapted from CS, Table 12). ORAL Solo had a 24-week randomised period, ORAL Standard and ORAL Sync had a 52-week randomised period and ORAL Scan had a 104-week randomised period. In ORAL Standard, ORAL Scan and ORAL Sync, patients receiving placebo advanced to tofacitinib 5 mg at Month 3 if trial response criteria were not met (defined as a 20% reduction in the number of tender and swollen joints).

Table 7: Characteristics of included tofacitinib RCTs (adapted from Table 12 of the CS)

Trial acronym and trial number	Population	Intervention, N randomised	Comparators, N randomised	Primary outcome(s)
ORAL Standard NCT00853385	cDMARD experienced and MTX-IR adult patients with active moderate-to-severe RA	Tofacitinib 5mg, oral, BID (with background MTX), N=204	Adalimumab 40mg, SC injection, Q2W (with background MTX), N=204 Placebo to tofacitinib 5mg, oral, BID (with background MTX)† N=56	ACR20 response rate at Month 6 (NRI) HAQ-DI score at Month 3 DAS28(ESR) <2.6 at Month 6 (NRI) (Table 21 of CS)
ORAL Scan NCT00847613	cDMARD experienced and MTX-IR adult patients with active moderate-to-severe RA who are	Tofacitinib 5mg, oral, BID (with background MTX), N=321	Placebo to tofacitinib 5mg, oral, BID (with background MTX)†, N=81	ACR20 response rate at Month 6 (NRI) mTSS score at Month 6 (LE) HAQ-DI score at Month 3 DAS28(ESR) <2.6 at Month 6 (NRI) (Table 27 of CS)
ORAL Sync NCT00856544	DMARD-IR (cDMARD including MTX or bDMARD) adult patients with active moderate-to-severe RA	Tofacitinib 5mg, oral, BID (with background cDMARD), N=315	Placebo to tofacitinib 5mg, oral, BID (with background cDMARDs)†, N=79	ACR20 response rate at Month 6 (NRI) HAQ-DI score at Month 3 DAS28(ESR) <2.6 at Month 6 (NRI) (Table 34 of CS)
ORAL Solo NCT00814307	DMARD-IR (cDMARD including MTX or bDMARD) adult patients with active moderate-to-severe RA	Tofacitinib 5mg, oral, BID, N=243	Placebo to tofacitinib 5mg, oral, BID‡, N=61	ACR20 response rate at Month 3 (NRI) HAQ-DI score at Month 3 (Table 40 of CS)

Abbreviations: ACR = American College of Rheumatology; ADA = adalimumab; bDMARD = biologic disease-modifying anti-rheumatic drug; BID = twice daily; cDMARD = conventional disease-modifying anti-rheumatic drug; IR = inadequate response; LE = linear extrapolation; mTSS = van der Heijde modified total sharp score; MTX = methotrexate; NRI = non-responder imputation; ORAL = Oral Rheumatoid Arthritis Phase 3 Trials; Q2W = twice weekly; RA = rheumatoid arthritis; SC = subcutaneous; TNFi = tumour necrosis factor inhibitor; TOF = tofacitinib.

Footnote: †Patients receiving placebo advanced to TOF 5 mg at Month 3 if trial response criteria were not met (defined as 20% reduction in number of tender and swollen joints) or Month 6 regardless of response. ‡All patients receiving placebo advanced to a TOF 5 mg at Month 3

In all four placebo-controlled trials, data for the placebo comparator group is presented in the CS as a "combined placebo group" because patients crossed over to receive either 5 mg (licensed dose) or 10 mg of tofacitinib but results are not provided for the licenced 5 mg dose separately. An early escape design allowed that, at Month 3, placebo non-responders advanced to either 5 mg or 10 mg tofacitinib and at Month 6, all patients receiving placebo advanced to either 5mg or 10mg tofacitinib "*in order to minimise the time patients spent on inactive treatment*" (CS, page 89). Additionally in the ORAL Standard, Scan and Sync trials an "advancement penalty" was applied whereby patients who did not meet the response criteria at Month 3 were considered to be non-responders for the remainder of the

trial. This non-responder imputation (NRI) was also applied to the analysis of patients deemed to be non-responders in the tofacitinib treatment groups at Month 3.

Table 8 reports the number of non-responders in ORAL Standard, ORAL Scan, and ORAL Sync at three months (adapted from Table 51 of the CS) who crossed over to receive tofacitinib. In the combined placebo group, [redacted] of patients in ORAL Standard, 49% (n/N= 79/160) of patients in ORAL Scan and 49% (n/N= 78/159) of patients on ORAL Sync were considered non-responders compared with [redacted], 26.2% and 25.2% respectively of patients receiving tofacitinib 5mg BID and [redacted] receiving adalimumab in ORAL Standard. The CS reported that for ORAL Solo, a study design was used that allowed for three months of treatment in the placebo arm before advancing all placebo patients to tofacitinib.

Table 8: Summary of Month 3 non-responders in ORAL Standard, ORAL Scan, and ORAL Sync (adapted from Table 51 of the CS)

Treatment sequence	Month three non-responders n/N (%)		
	ORAL Standard	ORAL Scan	ORAL Sync
Tofacitinib 5 mg BID	[redacted]	84/321 (26.2%)	80/318 (25.2%)
Placebo to tofacitinib 5mg BID	[redacted]	42/81 (51.9%)	38/79 (48.1%)
Placebo to tofacitinib 10mg BID	[redacted]	37/79 (46.8%)	40/80 (50%)
Adalimumab	[redacted]	-	

Abbreviations: BID = twice daily

Details of the four included tofacitinib RCTs

Eligibility criteria for the four included tofacitinib RCTs are shown in Table 9. All four RCTs (ORAL Standard, ORAL Scan, ORAL Sync and ORAL Solo) required a diagnosis of RA according to ACR (1987) revised criteria.[15] ORAL Standard, ORAL Scan, and ORAL Solo included patients with moderate-to-severe, active RA, as defined by the presence of at least 6/68 tender joints and at least 6/66 swollen joints. In ORAL Sync, active RA was defined as the presence of at least 4/68 tender joints and at least 4/66 swollen joints. Further details of eligibility criteria were provided in Appendix 5 of the CS.

Table 9: Eligibility criteria for the tofacitinib RCTs (reproduced from Table 14 of the CS)

Trial acronym and trial number	ORAL Standard NCT00853385	ORAL Scan NCT00847613	ORAL Sync NCT00856544	ORAL Solo NCT00814307
Inclusion criteria	• Adults aged ≥18 years with a diagnosis of active RA†, consistent with the ACR 1987 Revised Criteria[15] • Ongoing treatment with MTX for ≥4 months with stable dosing (7.5–25 mg/week) ≥6 weeks before receiving the study drug; doses <15 mg were allowed in the case of intolerance or toxicity from higher doses • An inadequate response to MTX (defined as sufficient residual disease activity to meet entry criteria) ORAL Scan only • Evidence of ≥3 distinct joint erosions on posteroanterior hand and wrist radiographs or anteroposterior foot radiographs as determined by the investigator, or, if radiographic evidence of joint erosions was unavailable, IgM RF+ or antibodies to CCP	• Adults aged ≥18 years with a diagnosis of active RA†, consistent with the ACR 1987 Revised Criteria[15] • Ongoing treatment with MTX for ≥4 months with stable dosing (7.5–25 mg/week) ≥6 weeks before receiving the study drug; doses <15 mg were allowed in the case of intolerance or toxicity from higher doses • An inadequate response to MTX (defined as sufficient residual disease activity to meet entry criteria) ORAL Scan only • Evidence of ≥3 distinct joint erosions on posteroanterior hand and wrist radiographs or anteroposterior foot radiographs as determined by the investigator, or, if radiographic evidence of joint erosions was unavailable, IgM RF+ or antibodies to CCP	• Adults aged ≥18 years with a diagnosis of active RA‡, consistent with the ACR 1987 Revised Criteria[15] • Ongoing treatment with ≥1 cDMARD therapy – patients receiving MTX required ≥4 months of treatment, with stable dosing (≤25 mg/week) ≥6 weeks before receiving the study drug • An inadequate response to ≥1 cDMARD or bDMARD ([redacted]	• Adults aged ≥18 years and had received a diagnosis of active RA†, consistent with the ACR 1987 Revised Criteria[15] • Discontinued all DMARDs except stable doses of anti-malarial agents • An inadequate response to ≥1 cDMARD or bDMARD (lack of efficacy or occurrence of toxicity)

Exclusion criteria	• Haemoglobin <9.0 gm/dL • Haematocrit <30% • White blood cell count <3.0x109/L • Absolute neutrophil count <1.2x109/L • Platelet count <100x109/L • eGFR rate ≤40 ml/min • AST or ALT levels >1.5 x Upper limit of normal • A history of another autoimmune rheumatic disease except Sjögren's syndrome • Infection that required hospitalisation or parenteral antimicrobial therapy within 6 months of randomisation • Infection requiring antimicrobial therapy within 2 weeks of randomisation • Recurrent or disseminated herpes zoster infection • Recent, current, or chronic infection, including HBV, HCV or HIV • Current infection or evidence of active or inadequately treated infection with Mycobacterium tuberculosis • History of lymphoproliferative disorder or malignancy except for adequately treated non-metastatic basal/squamous cell cancer of the skin or cervical carcinoma in situ • Prior treatment with lymphocyte-depleting therapies or alkylating agents ORAL Standard only • Prior treatment with ADA • Lack of response to prior anti-TNF biologic treatment • Current treatment with other anti-rheumatic agents, including biologic agents

Abbreviations: ACR = American College of Rheumatology; ADA = adalimumab; ALT = alanine aminotransferase; AST = aspartate aminotransferase; bDMARD = biologic disease-modifying anti-rheumatic drug; CCP = cyclic citrullinated peptide; cDMARD = conventional disease-modifying anti-rheumatic drug; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; ESR = erythrocyte sedimentation rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MTX = methotrexate; ORAL = Oral Rheumatoid Arthritis Phase 3 Trials; RA = rheumatoid arthritis; RF = rheumatoid factor; TNF = tumour necrosis factor.

Footnote: †Active disease was defined as the presence of ≥6 tender or painful joints (of 68 joints examined) and ≥6 swollen joints (of 66 joints examined) and either an ESR ≥28 mm/hr (Westergren method) or a CRP level >7 mg/L. ‡Active disease was defined as the presence of ≥4 tender or painful joints (68 joints examined) and ≥4 swollen joints (of 66 joints examined) and either an ESR ≥28 mm/hr or a CRP level >66.7 nmol/L

In ORAL Standard, patients received tofacitinib 5 mg BD, adalimumab 40 mg SC Q2W or placebo plus methotrexate. In ORAL Scan, patients received tofacitinib 5 mg BD or placebo plus methotrexate. In ORAL Sync, patients received tofacitinib 5 mg BD or placebo in combination with cDMARDs, and in ORAL Solo, patients received tofacitinib 5 mg BD or placebo.

In ORAL Standard and ORAL Scan, patients continued background arthritis therapy, which was required to include MTX supplemented with folic acid and could also include NSAIDs, selective COX-2 inhibitors, opioids, acetaminophen (<2.6 g per day), and/or low dose oral corticosteroid (OCS) (≤10 mg prednisone or equivalent per day) at a stable dose throughout the trial. In ORAL Sync, patients continued on their stable background arthritis therapy, which may include a cDMARD and could also include NSAIDs, selective COX-2 inhibitors, opioids, acetaminophen (<2.6 g per day), and/or low dose OCS (≤10 mg prednisone or equivalent per day) at a stable dose. In ORAL Solo patients were required to remain on NSAIDs, selective COX-2 inhibitors, opioids, acetaminophen (<2.6 g per day), and/or low dose OCS (≤10 mg prednisone or equivalent per day) at a stable dose (see CS, Table 13). Patients in ORAL Solo were also allowed to remain on antimalarial medication at stable doses during the study (see CS, Table 13).

ORAL Standard was conducted at 115 study centres across 21 countries. Patients were included from three centres in the UK. ORAL Scan was conducted at 111 study centres across 15 countries. No UK centres were included. ORAL Sync was conducted at 114 centres across. Patients were included from three centres in the UK. ORAL Solo was conducted at 94 study centres across 15 countries. No UK centres were included.

Baseline characteristics of the four tofacitinib RCTs are shown in Table 10. The proportion of white patients included in the four trials ranges between 46 and 72 per cent. The number of included patients described as Asian (Japanese and Korean) was [redacted], and [redacted] for ORAL Standard, ORAL Scan, ORAL Sync and ORAL Solo, respectively (see CS, Tables 16 to 19). Baseline characteristics within trials were balanced across trial arms however, in ORAL Solo [redacted]

Table 10: **Baseline characteristics of participants of ORAL Standard (adapted from Table 16 of the CS)**

ORAL Standard		**Placebo to tofacitinib 5mg BID (N=56)**	**Placebo to tofacitinib 10mg BID (N=52)**	**Tofacitinib 5mg BID (N=204)**	**Adalimumab 40mg SC Q2W (N=204)**
Gender, n (%)	Female, n (%)	43 (76.8)	39 (75.0)	174 (85.3)	162 (79.4)
	Male, n (%)	13 (22.3)	13 (25.0)	30 (14.7)	42 (20.6)
Race, n (%)	White	40 (71.4)	35 (67.3)	151 (74.0)	148 (72.5)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region of origin, %	Europe	51.8	44.2	53.9	53.9
	North America	28.6	28.8	24.5	25.5
	Latin America	3.6	5.8	3.9	2.9
	Rest of the world	16.1	21.1	17.6	17.6
Age, years (SD)		55.5 (13.7)	51.9 (13.7)	53.0 (11.9)	52.5 (11.7)
Mean duration of RA, years (range)		6.9 [redacted]	9.0 [redacted]	7.6 [redacted]	8.1 [redacted]
Rheumatoid factor	n	[redacted]	[redacted]	[redacted]	[redacted]
	Positive, n (%)	[redacted] (71.4)	[redacted] (60.8)	[redacted] (66.8)	[redacted] (68.2)
Anti-CCP	n	[redacted]	[redacted]	[redacted]	[redacted]
	Positive, n (%)	[redacted] (76.4)	[redacted] (62.0)	[redacted] (71.3)	[redacted] (74.8)
Tender and swollen joints	n	[redacted]	[redacted]	[redacted]	[redacted]
	Tender joints, mean (SD)	26.6 [redacted]	28.1 [redacted]	28.5 [redacted]	26.7 [redacted]
	Swollen joints, mean (SD)	16.9 [redacted]	16.4 [redacted]	16.7 [redacted]	16.4 [redacted]
DAS28(ESR)	n	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
DAS28-3(CRP)	n	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI score	n	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Prior therapy, n (%)	TNF inhibitor	4 (7.1)	5 (9.6)	12 (5.9)	16 (7.8)
	Non-TNF inhibitor bDMARD	4 (7.1)	2 (3.8)	2 (1.0)	3 (1.5)
	Non-MTX cDMARD	30 (53.6)	29 (55.8)	109 (53.4)	114 (55.9)
Concomitant therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Lipid-lowering medication	1 (1.8)	3 (5.8)	8 (3.9)	10 (4.9)

ORAL Standard	Placebo to tofacitinib 5mg BID (N=56)	Placebo to tofacitinib 10mg BID (N=52)	Tofacitinib 5mg BID (N=204)	Adalimumab 40mg SC Q2W (N=204)
Abbreviations: ADA = adalimumab; bDMARD = biologic disease-modifying anti-rheumatic drug; CCS = corticosteroid; CCP = cyclic citrullinated peptide; cDMARD = conventional disease-modifying anti-rheumatic drug; CRP = C-reactive protein; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire-disability index; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug; ORAL = Oral Rheumatoid Arthritis Phase 3 Trials; RA = rheumatoid arthritis; SD = standard deviation; TNF = tumour necrosis factor; TOF = tofacitinib. **Footnote**: †In the ORAL trial programme Asian refers to Japanese and Korean patients.				

Table 11: Baseline characteristics of participants of ORAL Scan (adapted from Table 17 of the CS)

ORAL Scan		Placebo to tofacitinib5mg BID (N=81)	Placebo to tofacitinib10mg BID (N=79)	Tofacitinib 5mg BID (N=321)
Gender, n (%)	Female, n (%)	65 (80.2)	72 (91.1)	269 (83.8)
	Male, n (%)	16 (19.8)	7 (8.9)	52 (16.2)
Race, n (%)	White	36 (44.4)	36 (45.6)	152 (47.4)
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Age, years (SD)		53.2 (11.5)	52.1 (11.8)	53.7 (11.6)
Mean duration of RA, years (range)		8.8 (0.6–30.8)	9.5 (0.4–43.5)	8.9 (0.3–43.0)
Rheumatoid factor	n	[redacted]	[redacted]	[redacted]
	Positive, n (%)	[redacted] (79.7)	[redacted] (75.3)	[redacted] (75.2)
Anti-CCP	n	[redacted]	[redacted]	[redacted]
	Positive, n (%)	[redacted] (84.0)	[redacted] (82.3)	[redacted] (85.9)
Tender and swollen joints	n	[redacted]	[redacted]	[redacted]
	Tender joints, mean (SD)	23.3 ([redacted])	22.6 ([redacted])	24.1 ([redacted])
	Swollen joints, mean (SD)	14.0 ([redacted])	14.5 ([redacted])	14.1 ([redacted])
Total mTSS	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	35.0 [redacted]	30.1 [redacted]	31.1 [redacted]
DAS28(ESR)	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	6.25 [redacted]	6.29 [redacted]	6.34 [redacted]
DAS28-3(CRP)	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	5.14 [redacted]	5.18 [redacted]	5.22 [redacted]
HAQ-DI score	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	1.40 [redacted]	1.23 [redacted]	1.41 [redacted]
Prior therapy, n (%)	TNF inhibitor	[redacted] (9.9)	[redacted] (8.9)	[redacted] (19.3)
	Non-TNF inhibitor bDMARD	[redacted] (3.7)	[redacted] (2.5)	[redacted] (5.3)
	Non-MTX cDMARD	[redacted] (76.5)	[redacted] (58.2)	[redacted] (60.1)
Concomitant therapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: bDMARD = biologic disease-modifying anti-rheumatic drug; CCP = cyclic citrullinated peptide; CCS = corticosteroid; cDMARD = conventional disease-modifying anti-rheumatic drug; CRP = C-reactive protein; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire-disability index; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug; ORAL = Oral Rheumatoid Arthritis Phase 3 Trials; RA = rheumatoid arthritis; SD = standard deviation; mTSS = van der Heijde modified total sharp score; TNF = tumour necrosis factor; TOF = tofacitinib.
Footnote: [†]In the ORAL trial programme Asian refers to Japanese and Korean patients.

Table 12: **Baseline characteristics of participants of ORAL Sync (adapted from Table 18 of the CS)**

ORAL Sync		Placebo to TOF 5mg (N=79)	Placebo to TOF 10mg (N=80)	TOF 5 mg (N=315)
Gender, n (%)	Female, n (%)	[redacted] (79.7)	[redacted] (75.0)	[redacted] (83.8)
	Male, n (%)	[redacted] (79.7)	[redacted] (25.0)	[redacted] (16.2)
Race, n (%)	White	[redacted] (60.8)	[redacted] (55.0)	[redacted] (54.9)
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Region of origin, %	Europe	31.7	28.8	28.9
	North America	22.8	18.8	16
	Latin America	13.9	13.8	14.2
	Rest of world	31.7	38.8	40.9
Age, years (SD)		50.8 (11.2)		52.7 (11.7)
Mean duration of RA	Years (range)	9.5 (0.3–39.3)	10.2 (0.3–49.0)	8.1 (0.2–39.9)
Rheumatoid factor	n	[redacted]	[redacted]	[redacted]
	Positive, n (%)	[redacted] (73.1)	[redacted] (72.2)	[redacted] (73.9)
Anti-CCP	n	[redacted]	[redacted]	[redacted]
	Positive, n (%)	[redacted]	[redacted]	[redacted]
Tender and swollen joints	n	[redacted]	[redacted]	[redacted]
	Tender joints, mean (SD)	27.2 (16.8)	21.9 (13.0)	25.0 (15.3)
	Swollen joints, mean (SD)	14.6 (9.7)	13.9 (8.6)	14.5 (10.3)
DAS28(ESR)	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	6.44 [redacted])	6.14 [redacted]	6.27 [redacted]
DAS28-3(CRP)	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
HAQ-DI score	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	1.45 (0.64)	1.24 (0.66)	1.44 (0.69)
Prior therapy	TNF inhibitor, n (%)	[redacted] (6.3)	[redacted] (6.3)	[redacted] (7.3)
	Non-TNF inhibitor bDMARD, n (%)	[redacted](7.6)	0	[redacted](2.2)
	MTX, n (%)	[redacted] (83.5)	[redacted] (82.5)	[redacted] (86.7)
	Non-MTX cDMARD, %	55 (69.6)	62 (77.5)	232 (73.7)
	Failed DMARDs, mean	1.3	1.4	1.4
Concomitant therapy = n (%)	MTX	61(77.2)	64 (80.0)	250 (79.4)
	1 cDMARD	[redacted] (73.4)	[redacted] (62.5)	[redacted] (66.7)
	≥2 cDMARDs	[redacted] (25.3)	[redacted] (37.5)	[redacted] (33.3)
	NSAIDs	[redacted] (72.2)	[redacted] (63.8)	[redacted] (75.9)
	Systemic CCS	[redacted] (59.5)	[redacted] (58.8)	[redacted] (61.9)
	Lipid-lowering medication	[redacted]	[redacted]	[redacted]

Abbreviations: bDMARD = biologic disease-modifying anti-rheumatic drug; CCP = cyclic citrullinated peptide; CCS = corticosteroid; cDMARD = conventional disease-modifying anti-rheumatic drug; CRP = C-reactive protein; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire-disability index; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug; ORAL = Oral Rheumatoid Arthritis Phase 3 Trials; RA = rheumatoid arthritis; SD = standard deviation; TNF = tumour necrosis factor; TOF = tofacitinib.
Footnote: [†]In the ORAL trial programme Asian refers to Japanese and Korean patients.

Table 13: Baseline characteristics of participants of ORAL Solo (adapted from Table 19 of the CS)

ORAL Solo		Placebo to tofacitinib 5mg BID (N=61)	Placebo to tofacitinib 10mg BID (N=61)	Tofacitinib 5mg BID (N=243)
Gender, n (%)	Female, n (%)	[redacted]	[redacted]	207 (85.2)
	Male, n (%)	[redacted]	[redacted]	36 (14.8)
Race, n (%)	White	46 (75.4)	42 (68.9)	153 (63.0)
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Age, years (SD)		50.7 (12.8)	48.8 (11.9)	52.2 (11.5)
Mean duration of RA, years (range)		7.3 (0.3–28.0)	8.1 (0.1–28.0)	8.0 (0.2–42.3)
Rheumatoid factor	n	[redacted]	[redacted]	[redacted]
	Positive, n (%)	[redacted]	[redacted]	[redacted]
Anti-CCP	n	[redacted]	[redacted]	[redacted]
	Positive, n (%)	[redacted]	[redacted]	[redacted]
Tender and swollen joints	n	[redacted]	[redacted]	[redacted]
	Tender joints, mean (SD)	[redacted]	[redacted]	29.4 [redacted]
	Swollen joints, mean (SD)	[redacted]	[redacted]	16.3 [redacted]
DAS28(ESR)	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	6.71 [redacted]
DAS28-3(CRP)	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	5.68 [redacted]
HAQ-DI score	N	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	1.53 [redacted]
Prior therapy, n (%)	TNF inhibitor	[redacted]	[redacted]	[redacted] (14.0)
	Non-TNF inhibitor bDMARD	[redacted]	[redacted]	[redacted] (4.9)
	MTX	[redacted]	[redacted]	[redacted] (86.0)
	Non-MTX cDMARD	[redacted]	[redacted]	[redacted]
	Failed DMARDs, mean	[redacted]	[redacted]	1.70
Concomitant therapy, n (%)	NSAIDs	[redacted]	[redacted]	[redacted]
	Systemic CCS	[redacted]	[redacted]	[redacted]
	Lipid-lowering medication	[redacted]	[redacted]	[redacted] (11.5)
	Anti-malarial	[redacted]	[redacted]	[redacted] (18.5)

Abbreviations: bDMARD = biologic disease-modifying anti-rheumatic drug; CCP = cyclic citrullinated peptide; CCS = corticosteroid; cDMARD = conventional disease-modifying anti-rheumatic drug; CRP = C-reactive protein; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire-disability index; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug; ORAL = Oral Rheumatoid Arthritis Phase 3 Trials; RA = rheumatoid arthritis; SD = standard deviation; TNF = tumour necrosis factor; TOF = tofacitinib.

ORAL Solo	Placebo to tofacitinib 5mg BID (N=61)	Placebo to tofacitinib 10mg BID (N=61)	Tofacitinib 5mg BID (N=243)
Footnote: †In the ORAL trial programme Asian refers to Japanese and Korean patients			

All four RCTs employed modified intention-to-treat (mITT) analyses for effectiveness measures, comprising all randomised patients who received at least one dose of the study drug. All randomised patients in ORAL Standard (n=717) were included in the mITT analyses. Within ORAL Scan, 797/800 (99.6%) patients were included in the mITT analyses. Within ORAL Sync, 792/795 (99.6%) patients were included in the mITT analyses. Within ORAL Solo, 610/611 (99.8%) patients were included in the mITT analyses. All four RCTs are analysed with non-responder imputation and missing data are accounted for using last observation carried forward (LOCF) (see CS, pages 154-159).

4.2.2 Efficacy results for tofacitinib

ACR response data

ACR20 response data for the four included tofacitinib RCTs (ORAL Standard, Scan, Sync and Solo) are reported in Table 15, Table 16, Table 17 and Table 18 respectively. The primary outcome for ORAL Standard, ORAL Scan and ORAL Sync was the proportion of patients achieving an ACR20 response at six months. The primary outcome for ORAL Solo was the proportion of patients achieving an ACR20 response at three months. For ACR20, all four RCTs found a statistically significant advantage for tofacitinib 5mg BID compared with the combined placebo group: ORAL Standard, 51.1% vs 28.3% (p<0.001); ORAL Scan, 5.15% vs 25.3% (p<0.001); ORAL Sync 52.7% vs 31.2% (p<0.001); ORAL Solo 59.8% vs 26.7% (p<0.001) (see Table 15, Table 16, Table 17, and Table 18).

ACR50 responses for tofacitinib versus placebo were ORAL Standard, [redacted]% vs [redacted]% (p[redacted]); ORAL Scan, 32.4% vs 8.4% (p<0.001); ORAL Sync, [redacted]% vs [redacted]% ($p\leq$ [redacted]) ORAL Solo, 31.1% vs 12.5% (p<0.001) (data taken from the CS, Tables 23, 29, 36 and 41).

ACR70 responses for tofacitinib versus placebo were ORAL Standard, [redacted]% vs [redacted]% (p[redacted]); ORAL Scan, 14.6% vs 1.3% (p<0.001); ORAL Sync, [redacted]% vs [redacted]% (p[redacted]); ORAL Solo, 15.4% vs 5.8% (p<0.001) (data taken from the CS, Tables 23, 29, 36 and 41).

For ORAL Standard, the CS (page 106) reported that in terms of comparison between tofacitinib and adalimumab:

"[redacted]

[redacted]"

For the recently completed, head-to-head trial, ORAL Strategy, the CS (page 251) reported the preliminary primary endpoint data (ACR50 response) for tofacitinib plus MTX vs adalimumab plus MTX vs tofacitinib monotherapy. Table 14 shows that tofacitinib plus MTX, but not tofacitinib monotherapy, was non-inferior to adalimumab plus MTX. Data were provided in the CS as academic in confidence but have subsequently been published in an open access peer reviewed publication.[41]

Table 14: ORAL Strategy ACR50 response rates at Month 6 including non-inferiority results (adapted from Table 89 of the CS)

Outcome		**TOF 5 mg Monotherapy (N=384)**	**TOF 5 mg + MTX (N=376)**	**ADA 40 mg + MTX (N=386)**
ACR50 response rate at Month 6, n (%)		147 (38.28)	173 (46.01)	169 (43.78)
Differences in ACR50 response rate				
Comparing with ADA 40 mg + MTX	Absolute difference (TOF – ADA), %	-5.50	2.23	-
	98.34% CI*	-13.98, 2.98	-6.40, 10.86	-
	Non-inferiority criteria met?	No	Yes	-
	p-value†	0.0512	<0.0001	-
Comparing with TOF 5 mg + MTX	Absolute difference (TOF mono – TOF+MTX), %	-7.73	-	-
	98.34% CI*	-16.29, 0.83	-	-
	Non-inferiority criteria met?	No	-	-
	p-value†	0.2101	-	-

Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; MTX, methotrexate; TOF, tofacitinib.
†p-values are from non-inferiority hypothesis testing. The p-values are multiplicity-adjusted and should be compared with 0.05.
* Non-inferiority between groups was shown if the lower bound of the 98·34% CI of the difference between comparators was larger than –13·0%

In the corresponding journal publication (Fleischman *et al.,* 2017)[41] the authors claim that the results suggest that in patients with an inadequate response to MTX, the addition of tofacitinib or adalimumab is equally efficacious and more likely to be effective than switching to tofacitinib monotherapy. The paper further asserts, "[t]*he present analysis suggests that adding tofacitinib 5 mg BID to MTX is as effective as adding adalimumab, a TNFi, to MTX*". The ERG notes that non-inferiority trials do not

provide evidence that interventions are therapeutically equal, which is instead the purpose of an equivalence trial. Non-inferiority trials aim to determine whether one treatment is not statistically worse than another. In this case, non-inferiority was only demonstrated for tofacitinib combination therapy but tofacitinib monotherapy was found to be statistically inferior in the relevant patient population for the current decision problem.

EULAR response data

The CS estimated EULAR response criteria from DAS28 scores as a good or moderate EULAR response (described in the CS as an improvement in DAS28 from baseline) for ORAL Standard, ORAL Scan and ORAL Sync at six months and for ORAL Solo at three months. For this outcome, the responses for tofacitinib 5mg BID compared with the combined placebo group were ORAL Standard, [redacted]% vs [redacted]% (*p*[redacted]); ORAL Scan, vs [redacted]% [redacted]% (*p*[redacted]); ORAL Sync vs [redacted]% [redacted]% (*p*[redacted]); ORAL Solo [redacted]% vs [redacted]% (*p*[redacted]) (see CS, Tables 25, 31, 38 and 43).

Change from baseline in HAQ-DI scores

Mean change from baseline in HAQ-DI scores for the four included tofacitinib RCTs are shown in Table 15, Table 16, Table 17 and Table 18. The primary outcome for ORAL Standard, ORAL Scan, ORAL Sync and ORAL Solo was the mean change from baseline in HAQ-DI score at three months. For this outcome, ORAL Standard, ORAL Sync and ORAL Solo found a statistically significant advantage for tofacitinib 5mg BID compared with the combined placebo group: ORAL Standard, –0.55 vs –0.24 ($p<0.001$); ORAL Sync–0.46 vs –0.21 ($p<0.001$); ORAL Solo–0.50 vs–0.19 ($p<0.001$) (CS Tables 21, 27, 34 and 40). For ORAL Scan, the HAQ-DI scores for tofacitinib 5 mg BD versus placebo were not statistically significant (*p*-value not declared).

Mean change from baseline in HAQ-DI scores to six months for tofacitinib 5mg BID compared with the combined placebo group were: ORAL Standard, [redacted] vs [redacted] (*p*[redacted]); ORAL Scan, [redacted] vs [redacted] (*p*[redacted]); ORAL Sync, [redacted] vs [redacted] (*p*[redacted]); ORAL Solo,–0.50 vs –0.19 ($p<0.001$) (see CS, Tables 24, 30, 37 and 40).

DAS28(ESR) <2.6 and ≤3.2 response

DAS28(ESR) <2.6 response data for the four included tofacitinib RCTs are shown in Table 15, Table 16, Table 17 and Table 18. The primary outcome for ORAL Standard, ORAL Scan and ORAL Sync was the proportion of patients achieving a DAS28(ESR) <2.6 response at six months. The primary outcome for ORAL Solo was the proportion of patients achieving a DAS28(ESR) <2.6 response at three months. The proportions of patients achieving a response for tofacitinib 5mg BID compared with the combined placebo group were: ORAL Standard, 1.1% vs 6.2% (*p*[redacted]); ORAL Scan, 1.6% vs 7.2%

(statistical significance was not declared); ORAL Sync 2.7% vs 9.1% (p=0.0038); ORAL Solo 4.4% vs 5.6% (p=0.62) (CS Tables 25, 31, 34 and 40).

The proportions of patients achieving a DAS28(ESR) ≤3.2 response for tofacitinib 5mg BID compared with the combined placebo group were: ORAL Standard, [redacted]% vs [redacted]% (p[redacted]); ORAL Scan, [redacted]% vs [redacted]% (p[redacted]); ORAL Sync [redacted]% vs [redacted]% (p[redacted]); ORAL Solo 12.5% vs 5.3% (p<0.001) (see CS, Tables 25, 27, 38 and 43).

Table 15: Summary of primary efficacy results for ORAL Standard (adapted from CS Table 21)

Outcome		**Placebo to tofacitinib 5mg or 10mg BID**	**Tofacitinib 5mg BID**	**Adalimumab 40mg SC Q2W**
ACR20 response rate at Month 6 (NRI with advancement penalty)	n	106	196	199
	Response rate, n (%)	30 (28.3)	101 (51.5)	94 (47.2)
	Difference from placebo, %	-	[redacted]	[redacted]
	95% CI for difference	-	[redacted]	[redacted]
	p-value†	-	<0.001	<0.001
HAQ-DI score at Month 3	n	98	188	190
	LS mean change from baseline	–0.24	–0.55	–0.49
	LS mean difference from placebo	-	[redacted]	[redacted]
	95% CI for difference	-	[redacted]	[redacted]
	p-value†	-	<0.001	<0.001
DAS28(ESR) <2.6 at Month 6 (NRI with advancement penalty)	n	92	177	178
	Response rate, n (%)	1 (1.1)	11 (6.2)	12 (6.7)
	Difference from placebo, %	-	[redacted]	[redacted]
	95% CI for difference	-	[redacted]	[redacted]
	p-value†	-	[redacted]	[redacted]

Abbreviations: ACR = American College of Rheumatology; ADA = adalimumab; CI = confidence interval; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; FAS = full analysis set; HAQ-DI = Health Assessment Questionnaire-disability index; LS = least squares; NRI = non-responder imputation; Q2W = twice weekly; SC = subcutaneous; TOF = tofacitinib.
Footnote: †p-value is subject to the step-down approach

Table 15 shows that both tofacitinib and adalimumab were significantly superior to placebo for the ACR20 and DAS28(ESR) outcomes at 6 months and HAQ-DI at 3 months.

Table 16: Summary of primary efficacy results for ORAL Scan (adapted from CS Table 27)

Outcome		Placebo to tofacitinib 5mg or 10mg BID	Tofacitinib 5mg BID
ACR20 response rate at Month 6 (NRI with advancement penalty)	n	[redacted]	[redacted]
	Response rate, n (%)	[redacted] (25.3)	[redacted] (51.5)
	Difference from placebo, %	-	[redacted]
	95% CI for difference	-	[redacted]
	p-value†	-	<0.001
HAQ-DI score at Month 3	n	[redacted]	[redacted]
	LS mean change from baseline	–0.15	–0.40
	LS mean difference from placebo	-	[redacted]
	95% CI for difference	-	[redacted]
	p-value†	-	Not declared‡
DAS28(ESR) <2.6 at Month 6 (NRI with advancement penalty)	n	[redacted]	[redacted]
	Response rate, n (%)	[redacted] (1.6)	[redacted] (7.2)
	Difference from placebo, %	-	[redacted]
	95% CI for difference	-	[redacted]
	p-value†	-	Not declared‡
mTSS score at Month 6 (LE)	n	[redacted]	[redacted]
	LS mean change from baseline	0.47	0.12
	LS mean difference from placebo	-	[redacted]
	95% CI for difference	-	[redacted]
	p-value†	-	0.0792

Abbreviations: ACR = American College of Rheumatology; ADA = adalimumab; CI = confidence interval; DAS28 = Disease Activity Score in 28 joints; FAS = full analysis set; HAQ-DI = Health Assessment Questionnaire-disability index; LE = linear extrapolation; LS = least squares; NRI = non-responder imputation; mTSS = van der Heijde modified total sharp score; TOF = tofacitinib.
Footnote:†p-value is subject to the step-down approach. ‡Due to the step-down procedure applied to primary efficacy outcomes, significance was not declared for the HAQ-DI score or DAS28(ESR) <2.6 for TOF 5 mg. Nominal p-values (TOF 5 mg vs placebo) for these outcomes were <0.001 and 0.0034, respectively

Table 15 shows that both tofacitinib and adalimumab were significantly superior to placebo for the ACR20 and DAS28(ESR) outcomes at 6 months and HAQ-DI at 3 months.

Table 16 shows that ACR20 was the only outcome where tofacitinib 5 mg BD was declared to be significantly superior to placebo. The CS attributes the results to the use of the step-down approach to analysis for the HAQ-DI and DAS28(ESR) outcomes. The ERG notes that in ORAL Scan, a primary endpoint of mTSS score at Month 6 was also not statistically significant.

Table 17: Summary of primary efficacy results for ORAL Sync (adapted from CS Table 34)

Outcome		Placebo to tofacitinib 5mg or 10mg BID	Tofacitinib 5mg BID
ACR20 response rate at Month 6 (NRI with advancement penalty)	n	157	311
	Response rate, n (%)	49 (31.2)	164 (52.7)
	Difference from placebo, %	-	21.5
	95% CI for difference	-	12.4, 30.7
	p-value†	-	<0.001
HAQ-DI score at Month 3	N	147	292
	LS mean change from baseline	–0.21	–0.46
	LS mean difference from placebo	-	–0.26
	95% CI for difference	-	–0.35, –0.16
	p-value†	-	<0.001
DAS28(ESR) <2.6 at Month 6 (NRI with advancement penalty)	n‡	148	263
	Response rate, n (%)	4 (2.7)	24 (9.1)
	Difference from placebo, %	-	6.4
	95% CI for difference	-	2.1, 10.8
	p-value†	-	0.0038

Abbreviations: ACR = American College of Rheumatology; ADA = adalimumab; CI = confidence interval; DAS28 = Disease Activity Score in 28 joints; FAS = full analysis set; HAQ-DI = Health Assessment Questionnaire-disability index; LS = least squares; NRI = non-responder imputation; TOF = tofacitinib.

Footnote: †p-value is subject to the step-down approach. ‡The numbers are different for DAS28(ESR) <2.6 because ESR was measured locally and some study sites were not able to collect these data

Table 17 shows that tofacitinib was significantly superior to placebo for ACR20 and DAS28(ESR) at 6 months and HAQ-DI at 3 months.

Table 18: Summary of primary efficacy results for ORAL Solo (adapted from CS Table 40)

Outcome		Placebo to tofacitinib 5mg or 10mg BID	Tofacitinib 5mg BID
ACR20 response rate at Month 3 (NRI with advancement penalty)	n	[redacted]	[redacted]
	Response rate, n (%)	[redacted] (26.7)	[redacted] (59.8)
	Difference from placebo, %	-	[redacted]
	95% CI for difference	-	[redacted]
	p-value†	-	<0.001
HAQ-DI score at Month 3	n	[redacted]	[redacted]
	LS mean change from baseline	–0.19	–0.50
	LS mean difference from placebo	-	[redacted]
	95% CI for difference	-	[redacted]
	p-value†	-	<0.001
DAS28(ESR) <2.6 at Month 3 (NRI with advancement penalty)	n	114	232
	Response rate, n (%)	[redacted] (4.4)	[redacted] (5.6)
	Difference from placebo, %	-	[redacted]
	95% CI for difference	-	[redacted]
	p-value†	-	0.62

Abbreviations: ACR = American College of Rheumatology; ADA = adalimumab; CI = confidence interval; DAS28 = Disease Activity Score in 28 joints; FAS = full analysis set; HAQ-DI = Health Assessment Questionnaire-disability index; LS = least squares; NRI = non-responder imputation; TOF = tofacitinib.
Footnote: †p-value is subject to the step-down approach

Table 18 shows that tofacitinib was statistically superior to placebo for the ACR20 and HAQ-DI outcomes at 3 months. However, for the DAS28(ESR) at 3 months outcome, tofacitinib 5 mg BD is not significantly different from placebo.

Health related quality of life, fatigue and pain

Mean change from baseline in EQ-5D, FACIT-F and pain (VAS) scores, which are relevant outcomes for the decision problem, for the four included tofacitinib RCTs are shown in Table 19, Table 20, Table 21 and Table 22.

Mean change from baseline in EQ-5D scores for tofacitinib 5mg BID compared with combined placebo group were: ORAL Standard, [redacted] vs [redacted] (*p*[redacted]); ORAL Scan, [redacted] vs [redacted] (*p*[redacted]); ORAL Sync, [redacted] vs [redacted] (*p*[redacted]); ORAL Solo, [redacted] vs [redacted] (*p*[redacted]).

Mean change from baseline in FACIT-F scores for tofacitinib 5mg BID compared with combined placebo group were: ORAL Standard, [redacted] vs [redacted] (*p*[redacted]); ORAL Scan, [redacted] vs [redacted] (*p*[redacted]); ORAL Sync, [redacted] vs [redacted] (*p*[redacted]); ORAL Solo, [redacted] vs [redacted] (*p*[redacted]).

Mean change from baseline in pain (VAS) scores for tofacitinib 5mg BID compared with combined placebo group were: ORAL Standard, [redacted] vs [redacted] (p[redacted]); ORAL Scan, -26.36 vs -15.70 (p<0.001); ORAL Sync, [redacted] vs [redacted] (p[redacted]); ORAL Solo, [redacted] vs [redacted] (p[redacted]).

Table 19: Summary of EQ-5D, FACIT-F and pain (VAS) scores ORAL Standard (adapted from CS Table 26)

Outcome	Placebo to tofacitinib 5mg or 10mg BID	Tofacitinib 5mg BID	Adalimumab 40mg SC Q2W
Change from baseline in EQ-5D score, LS mean (SE) [n] Month 6	[redacted]	[redacted]	[redacted]
Change from baseline in FACIT-F score, LS mean (SE) [n] Month 6	[redacted]	[redacted]	[redacted]
Change from baseline in pain (VAS) score, LS mean (SE) [n] Month 6	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D = EuroQol five-dimension questionnaire; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; LS = least squares; Q2W – twice weekly; SC = subcutaneous = SE = standard error
Footnote: †p-value <0.001 for comparison with placebo. ‡p-value ≤0.05 for comparison with placebo

Table 20: Summary of EQ-5D, FACIT-F and pain (VAS) scores ORAL Scan (adapted from CS Table 33)

Outcome	Placebo to tofacitinib 5mg or 10mg BID	Tofacitinib 5mg BID
Change from baseline in EQ-5D score, LS mean (SE) [n] Month 6	[redacted]	[redacted]
Change from baseline in FACIT-F score, LS mean (SE) [n] Month 6	[redacted]	[redacted]
Change from baseline in pain (VAS) score, LS mean (SE) [n] Month 6	-15.70 (2.44) [62]	-26.36 (1.42) [202]†

Abbreviations: EQ-5D = EuroQol five-dimension questionnaire; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; LS = least squares; SE = standard error
Footnote: †p-value <0.001 for comparison with placebo.

Table 21: Summary of EQ-5D, FACIT-F and pain (VAS) scores ORAL Sync (adapted from CS Table 39)

Outcome	Placebo to tofacitinib 5mg or 10mg BID	Tofacitinib 5mg BID
Change from baseline in EQ-5D score, LS mean (SE) [n] Month 6	[redacted]	[redacted]
Change from baseline in FACIT-F score, LS mean (SE) [n] Month 6	[redacted]	[redacted]
Change from baseline in pain (VAS) score, LS mean (SE) [n] Month 6	[redacted]	[redacted]

Abbreviations: EQ-5D = EuroQol five-dimension questionnaire; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; LS = least squares; SE = standard error
Footnote: †*p*-value <0.001 for comparison with placebo.

Table 22: Summary of EQ-5D, FACIT-F and pain (VAS) scores ORAL Solo (adapted from CS Table 44)

Outcome	Placebo to tofacitinib 5mg or 10mg BID	Tofacitinib 5mg BID
Change from baseline in EQ-5D score, LS mean (SE) [n] Month 3	[redacted]	[redacted]
Change from baseline in FACIT-F score, LS mean (SE) [n] Month 3	[redacted]	[redacted]
Change from baseline in pain (VAS) score, LS mean (SE) [n] Month 3	[redacted]	[redacted]

Abbreviations: EQ-5D = EuroQol five-dimension questionnaire; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; LS = least squares; SE = standard error
Footnote: †*p*-value <0.001 for comparison with placebo.

4.2.3 Safety

The CS provided incidence rates for AEs using pooled trial data from the tofacitinib 5 mg and 10 mg treatment arms from 19 tofacitinib trials. The CS concluded that the safety profile for tofacitinib was acceptable based on comparable AE data across the tofacitinib 5 mg and 10 mg treatment arms; the types and rates of AEs remaining stable over time, and the apparent absence of new risks or safety signals. However, without estimating incidence rates of AEs for the non-tofacitinib study arms there is no clear comparison to tofacitinib for the incidence of AEs, which is compounded by a lack of NMA versus comparators for relevant adverse events. Data reporting the raw number of patients affected were provided for safety events of special interest (see CS, page 232) which included serious infection events (n/N: 527/6,194), malignancies excluding NMSC (n/N: 173/6,194), NMSC (n/N: 118/6,194) and gastrointestinal perforations (n/N: 22/6,194). Not all AEs that were highlighted as being of special interest in the EPAR 2015[29] such as interstitial lung disease and hepatic safety were reported. The company provided a rationale for not conducting an NMA for safety (see CS, page 166) stating that

"*data for specific AEs tend not to be reported consistently across studies*". However, the CS acknowledged an increased risk of herpes zoster with tofacitinib compared with bDMARD comparators. [48] As reported earlier, in Section 4.1.1, the CS presented adverse event data for tofacitinib only up to March 2015 which is two years prior to the current appraisal (April 2017). Incidence rates for tofacitinib-treated patients were calculated using the number of patients with events rather than the total number of events or the number of new cases using the formula: patient with events/100 patient-years (see CS, Tables 86 and 87). The ERG notes that adverse events that occur more than once may be unlikely to be adequately represented using this formula.

The ERG requested from the company up-to-date safety data with the raw number of events and number of patient years of treatment for particular safety events (see clarification response,[34] question A1). Additionally the ERG requested odds ratio (OR) or a relative measure for tofacitinib versus the control arms. In response, the company provided two data sets to address the ERG's particular requests for safety data: one entitled "ORAL trials January 2016 data set analysis" (Table 23) and one that was assessed by the Medical Dictionary for Regulatory Activities (MeDRA) in January 2017 entitled "ORAL trials MeDRA data set analysis" (Table 24). The company stated that at the point of this data cut in January 2016, 6301 patients had received tofacitinib treatment with a total of 21199.23 years of patient exposure. The company state that they were unable to provide data for Serious Adverse Events within the timelines as these are listed in a separate database. Additionally the company do not provide safety data versus the control arm or the requested ORs. In addition, requested data for hepatic enzymes elevation were not provided.

Mortality in the CS is always provided only within the last 30 days of study drug. The ERG's clinical advisors highlighted that whilst the half-life of this class of drugs is short and mortality within RA trials is relatively rare, the adverse events associated with drugs that lower immune response are important to monitor as they can lead to severe problems that may not be captured within the course of the trial. The ERG therefore also requested the company to provide mortality data for the study duration. In response the company provided all-cause mortality data in the ORAL trials January 2016 data set.

Table 23: ORAL trials January 2016 data set analysis: tofacitinib safety data (replicated from clarification response, question A1[34])

Event Term	Total number of events	Number of patients affected	Incidence per 100 patient exposure years
Serious Infection Events	[redacted]	[redacted]	[redacted]
Drug Induced Liver Injury (Cases meeting Hy's law†)	[redacted]	[redacted]	[redacted]
Gastrointestinal Perforation Events	[redacted]	[redacted]	[redacted]
Treatment discontinuations as a result of an Adverse Event	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]
Herpes Zoster infection	[redacted]	[redacted]	[redacted]
Interstitial Lung Disease	[redacted]	[redacted]	[redacted]
Malignancies			
All Cancers (other than non-melanomatous cancers of the skin)	[redacted]	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]	[redacted]
Non-melanomatous cancers of the skin	[redacted]	[redacted]	[redacted]
Breast Cancer (Female patients only)	[redacted]	[redacted]	[redacted]
Lung Cancer	[redacted]	[redacted]	[redacted]
Melanoma	[redacted]	[redacted]	[redacted]

Footnote: †prognostic indicator that a pure drug-induced liver injury (DILI) leading to jaundice, without a hepatic transplant, has a case fatality rate of 10% to 50%.

According to the data presented in the company response, the most commonly recorded AE was herpes zoster infection, with an estimated incidence rate per 100 patient years of [redacted]) (Table 23). However, the ERG's own search for AEs in Medline retrieved a study by Winthrop *et al*., (2014) who reviewed the tofacitinib RA development programme from the Phase II, III and long-term extension studies. They found that the incidence rate of herpes zoster was higher at 4.3 per 100 patient years and substantially higher within Asia (7.7 per 100 patient years). Clinical advice received by the ERG suggested that increased risk of herpes zoster is elevated about 2-fold in RA generally and the experts considered an increased risk by treatment as therefore more worrying as some instances can be serious, particularly in the elderly. Neither the CS nor the company's response to the clarification letter not provides incidence rates for the comparators arms, instead an analysis is presented which shows that the rate of herpes zoster is relatively stable over time (measured at 6-monthly intervals over 54 months). However, the

Winthrop *et al*., (2014) study estimates a lower incidence for adalimumab (2.8 per 100 patient years) and for placebo (1.5 per 100 patient years) using the data from the tofacitinib trial programme. Moreover, the CS does not include any NMA for AEs versus any of the comparators but states (page 67) that "*with the exception of the rates for herpes zoster, the incidence of most AEs were generally comparable with that of biologics of RA*." They reference a study by Curtis *et al.,* (2016)[48] who conducted an NMA of the "real-world" comparative risk of herpes virus infections from tofacitinib, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab and abatacept. They found that the rate of herpes zoster with tofacitinib was approximately double that observed in patients using bDMARDs. As the company does not provide an NMA versus bDMARD comparators or references to substantiate the claim that their safety profile, other than herpes zoster, is comparable to bDMARDs, this assertion cannot be verified by the ERG.

As well as herpes zoster, the revised summary of tofacitinib safety data (Table 23) provided by the company showed that the highest incidence rates (IR) of adverse events with tofacitinib included treatment discontinuation as a result of an adverse event ([redacted] per 100 patient exposure years) and serious infection events (SIEs) (IR=[redacted]). The company's analysis of risk factors for SIEs (CS, pages 234 to 235) reported that hazard ratios were higher for: baseline glucocorticoid dose; higher age; presence of chronic obstructive pulmonary disease (COPD); higher HAQ-DI score; higher body mass index; prior confirmed post-baseline lymphopenia (<500 cells/mL); diabetes; female gender; line of therapy (3rd vs 2nd line); geographical region (Asia, Europe and Latin America, each vs US/Canada); and time-varying tofacitinib dose (referent to 5 mg twice daily). Additional data provided by the company indicated that bronchitis, pneumonia and all cardiac disorders to occur most commonly in tofacitinib treatment arms.

Table 24: ORAL trials MeDRA data set analysis: tofacitinib 5mg and 10mg BID (adapted from clarification response, question A1[34])

Higher Level Term	5 mg BID Number of affected patients (%)	10 mg BID Number of affected patients (%)	Overall Number of affected patients (%)
Pneumonia including necrotizing pneumonia	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]
All Cardiovascular Disorders -	[redacted]	[redacted]	[redacted]
Cardiac disorders by Higher Level Term			
Cardiac Arrhythmias	[redacted]	[redacted]	[redacted]
Cardiac Disorder Signs and Symptoms	[redacted]	[redacted]	[redacted]
Cardiac Valve Disorders	[redacted]	[redacted]	[redacted]
Coronary Artery Disorders	[redacted]	[redacted]	[redacted]
Endocardial Disorders	[redacted]	[redacted]	[redacted]
Heart Failure	[redacted]	[redacted]	[redacted]
Myocardial Disorders	[redacted]	[redacted]	[redacted]
Pericardial Disorders	[redacted]	[redacted]	[redacted]

Abbreviation: BID = twice daily

The ERG requested the company to include trial NCT021475587 in the updated safety data as this trial was not referred to in the CS but collected safety data from subjects with RA receiving tofacitinib or placebo with background methotrexate (see clarification response,[34] question A2) and was completed in July 2015. The company responded that trial NCT02147587 explored the safety and efficacy of herpes zoster vaccination in patients receiving either tofacitinib or placebo in combination with methotrexate and supplied data for treatment emergent AEs, which are presented in Table 25. The company also provided additional MeDRA safety data for this trial (see clarification response[34], question A2). Herpes Zoster was reported in [redacted] of patients treated with tofacitinib 5mg BID and no cases were reported with placebo.

Table 25: NCT02147587 Overview of treatment emergent adverse events (all causalities) (adapted from clarification response[34])

All Causalities	Placebo (n=57)	Tofacitinib 5 mg BD (n=55)
Number of Adverse Events	[redacted]	[redacted]
Subjects with Adverse Events	[redacted]	[redacted]
Subjects with Adverse Events leading to discontinuation	[redacted]	[redacted]
Subjects with Adverse Events leading to dose reduction or temporary discontinuation	[redacted]	[redacted]

The ERG also requested the company to ensure the revised safety analysis included data for the "ongoing" ORAL Strategy RCT [NCT02187055][41] as it was stated to have concluded in December 2016 and it was not included in the pooled safety analysis in the CS. The company responded that ORAL Strategy (NCT02187055) was a 1-year, double-blind, Phase 3b/4, controlled head-to-head trial in patients aged ≥18 years with moderate-to-severe RA despite methotrexate therapy who received tofacitinib 5 mg BID monotherapy, tofacitinib 5 mg BID plus methotrexate or adalimumab 40 mg 2QW plus methotrexate. A summary of AEs supplied in the company's response to clarification for ORAL Strategy is presented in Table 26.

Table 26: ORAL Strategy safety summary (adapted from clarification response[34])

	Tofacitinib 5mg BID (N=384)	Tofacitinib + MTX (N=376)	Adalimumab + MTX (N=386)
Total number of AEs, n*	[redacted]	[redacted]	[redacted]
Patients with AEs, n (%)	[redacted]	[redacted]	[redacted]
Patients with SAEs, n (%)	[redacted]	[redacted]	[redacted]
Patients discontinuing due to AEs, n (%)	[redacted]	[redacted]	[redacted]
Patients with severe AEs, n (%) (defined by the investigator)	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]
Serious infections, n (%)			
Herpes zoster (serious and non-serious), n (%)	[redacted]	[redacted]	[redacted]
Herpes zoster (serious and non-serious) in patients who were vaccinated, n/N (%)	[redacted]	[redacted]	[redacted]
Opportunistic infections (excluding tuberculosis), n (%)	[redacted]	[redacted]	[redacted]
Tuberculosis, n (%)	[redacted]	[redacted]	[redacted]
Major adverse cardiovascular events (non-fatal), n (%)	[redacted]	[redacted]	[redacted]
Malignancy (excluding NMSC), n (%)	[redacted]	[redacted]	[redacted]
NMSC, n (%)	[redacted]	[redacted]	[redacted]

Abbreviations: AE = adverse event; BID = twice daily; NMSC = Non-melanoma skin cancer

In addition to the fragmented safety data provided by the company, the ERG notes that pooling safety data across all trials and providing incidence rates may be inappropriate to fully document the potentially different safety profiles of tofacitinib combination therapy with methotrexate versus tofacitinib monotherapy. The EPAR (2017)[49] highlighted "*a higher incidence of adverse events for the combination of Xeljanz with MTX, compared with Xeljanz as monotherapy*" and that "*combination of tofacitinib with methotrexate increased the risk of ALT elevation compared with tofacitinib monotherapy*". Moreover, differences in AEs between these two treatment regimens can be seen in the evidence provided by the company. For example, the proportion of patients experiencing more than 1 treatment-related AE at 3 months in the ORAL Solo (monotherapy) trial was [redacted] for tofacitinib 5 mg

whilst the proportion of patients experiencing ≥1 treatment-related AE at 3 months in the ORAL Standard, Scan and Sync (tofacitinib plus methotrexate) trials was [redacted] respectively (see CS, Appendix 2). The ERG has tabulated selected AE data deemed as related to the study drug for the tofacitinib treatment arms (data from both 5 mg and 10 mg arms) for the four key ORAL trials. As can be observed in Table 27, the three-tofacitinib combination trials have higher incidences of the selected treatment-related AEs than the monotherapy trial (ORAL Solo).

Table 27: Tofacitinib-related adverse event (data extracted from Appendix 2 of the CS)

Number experiencing event/ Number of patients in tofacitinib (5 mg and 10 mg) treatment arms				
	ORAL Standard	ORAL Scan	ORAL Sync	ORAL Solo
Treatment related SAEs between 0-6 months	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation due to AEs between 0-6 months	40/405 (9.9%)	53/637 (8.3%)	40/633 (6.3%)	14/488 (2.9%)
Deaths attributed to study treatment	1	5	3	0

Interestingly the recently published journal paper for the ORAL Strategy trial[41] describes this same issue (which is not drawn in the CS) when the authors state that "*concomitant csDMARDS augment the risk of herpes zoster with tofacitinib*." They cite an abstract from a study funded by Pfizer which found that "*concomitant use of nonbiologic DMARDs or GCs appears to increase the risk and overall IR per 100* [patient years] *of HZ from 0.56 to 4.82 with 5 mg BID*".[50] This study, published in 2015, is not referenced in the CS.

The ERG considers that a higher toxicity profile of tofacitinib plus methotrexate cannot be fully characterised in a pooled analysis with associated incidence rates from both dosing regimens, as combining the monotherapy and combination therapy trials potentially dilutes the apparent incidence of treatment-related adverse events that occur in tofacitinib combination therapy.

4.3 Critique of trials identified and included in the network-meta-analysis

4.3.1 Included trials for the network meta-analysis

NMAs were performed separately for the cDMARD-IR and bDMARD-IR population. Trials other than the tofacitinib RCTs (ORAL Standard, ORAL Scan, ORAL Sync and ORAL Solo) that were included in the NMA are listed in Table 28 (cDMARD-IR population) and Table 29 (bDMARD-IR population) below.

Quality assessments of the included trials (other than ORAL Standard, ORAL Scan, ORAL Sync and ORAL SOLO) were presented in Appendix 4 of the CS. Appropriate quality assessment items were used, however, it was unclear for the double-blind trials in Appendix 4 of the CS, who exactly was blinded (i.e., patients, physicians, outcome assessors). In response to a request for clarification from the ERG regarding who was blinded in the double-blind trials (see clarification response,[34] question A6), the company stated:

> *"patients and investigators were blind in six trials (ADACTA[51], AUGUST II[52], LITHE[53, 54], OPTION[55], PLANETRA [56], Van de Putte 2004[57]); patients and outcome assessors were blind in four trials (DE019, RAPID 1, RAPID 2, GO-FORTH); patients, care providers, and investigators were blind in one trial (GO-FORWARD); patients, care providers, investigators, and outcome assessors were blind in 11 trials (ACT-RAY, ATTEST, CERTAIN, Choe 2015, Emery 2015, Fleischmann 2012, GO-FURTHER, HERA, J-RAPID, Kremer 2012, Li 2015, SATORI); and patients, investigators, and other study personnel, except for pharmacists were blind in one trial (START)."*

It was not reported who was blinded in three of the "double-blind" trials (CHANGE[58], Kim 2007[59] and TOWARD[60]).

Trials in the analysis of the cDMARD-IR population were largely the same as those in the NMA undertaken by the independent Assessment Group (AG) in TA375. However, there were some exceptions, which have been grouped into the following categories: (i) trials in the CS that were not included in TA375, and; (ii) trials included in TA375 but excluded from the CS. A similar comparison could not be made for the bDMARD-IR population, as this was not the focus of TA375.

Trials included the CS not in TA375 NMA

In total, 10 trials were included the CS that were not included in the base case analysis of TA375. HERA[61] was published after the search date for TA375. Fleishmann 2012,[62] GO-AFTER,[63] Kremer 2012[64] and RADIATE[65], were excluded from TA375 as participants in these trials had received prior biologic therapy. J-RAPID[66] was excluded as separate 6-month data were not reported for those with concomitant cDMARDs and monotherapy. Four trials were only included in TA375 sensitivity analyses as trial participants had received prior biologics (LITHE,[53, 54] OPTION,[67] RAPID 1,[68, 69] RAPID 2[70]).

Trials in TA375 NMA not in the CS base case

In total, 19 trials were included in TA375 that were excluded from the base case analysis in the CS. Seven trials were undertaken in methotrexate-naïve populations (BeST,[71] Durez *et al*., 2007,[72] ERA,[73] GO-BEFORE,[74] HIT HARD,[75] OPTIMA,[76] PREMIER,[77]), and so would not be relevant to the NICE scope for tofacitinib. Of the remaining 12 trials, two were excluded by the CS: one because the outcomes of interest were not reported (ETN[78]) and one because disease duration was less than three years (SWEFOT[79]) however this trial was included in a sensitivity analysis. Possible reasons for exclusion identified by the ERG for all 12 studies are presented in Table 30.

Table 28: Summary of trials included in the NMAs for the cDMARD-IR population (adapted from CS Table 61 and Appendix 4 Table 202)

Trial acronym and author (year)	Design	Treatment groups (n)	Timepoint in NMA	Primary analyses from CS Table 61				In CS NMA Fig No.
				EULAR Moderate	EULAR Good	EULAR at least moderate	HAQ-DI	
ACT-RAY Dougados 2013[80]; Dougados 2014[81]	DB	TCZ 8mg/kg Q4W + MTX (n=277) TCZ 8mg/kg Q4W (n=276)	24 weeks	Yes	Yes	Yes	Yes	Fig 32 EULAR moderate and good Fig 33 EULAR at least moderate Fig 34 HAQ-DI
ADACTA Gabay 2013[51]	DB	TCZ 8mg/kg (n=163) ADA 40mg (n=162)	24 weeks	Yes	Yes	Yes	Yes	Fig 32 EULAR moderate and good Fig 33 EULAR at least moderate Fig 34 HAQ-DI
ARMADA Weinblatt 2003[82]	DB	ADA 40mg Q2W + MTX (n=67) PBO + MTX (n=62)	24 weeks	No	No	No	Yes	Fig 34 HAQ-DI
ATTEST Schiff 2008[83]	DB	ABT 10mg/kg Q4W + MTX (n=156) IFX 3mg/kg Q8W + MTX (n=165) PBO + MTX (n=110)	197 days	Yes	Yes	Yes	No	Fig 32 EULAR moderate and good Fig 33 EULAR at least moderate
AUGUST II Van Vollenhoven 2011[52]	DB	ADA 40mg Q2W + MTX (n=79) PBO + MTX (n=76)	26 weeks	No	No	Yes	No	Fig 33 EULAR at least moderate
CERTAIN Smolen 2015[84]	DB	CTZ 200mg Q2W SC + cDMARDs (n=96) PBO + cDMARDs (n=98)	24 weeks	Yes	Yes	Yes	No	Fig 32 EULAR moderate and good Fig 33 EULAR at least moderate Fig 34 HAQ-DI
CHANGE Miyasaka 2008[58]	DB	ADA 40mg Q2W SC (n=91) PBO (n=87)	24 weeks	No	No	No	Yes	Fig 34 HAQ-DI

Trial acronym and author (year)	Design	Treatment groups (n)	Timepoint in NMA	Primary analyses from CS Table 61				In CS NMA Fig No.
				EULAR Moderate	EULAR Good	EULAR at least moderate	HAQ-DI	
Choe 2015[85]	DB	IFX 3mg/kg Q8W IV + MTX (n=293) IFX SB2 3mg/kg Q8W IV + MTX (n=291)	30 weeks	Yes	Yes	Yes	No	Fig 32 EULAR moderate and good Fig 33 EULAR at least moderate
DE019 Keystone 2004[86]	DB	ADA 40mg Q2W + MTX (n=207) PBO + MTX (n=200)	24 weeks	No	No	No	Yes	Fig 34 HAQ-DI
Emery 2015[87]	DB	ETN 50mg QW SC + MTX (n=297) ETN SB4 50mg QW SC + MTX (n=299)	24 weeks	Yes	Yes	Yes	Yes	Fig 32 EULAR moderate and good Fig 33 EULAR at least moderate
Fleischmann 2012[62]	DB	TOF 5mg BID (n=49) ADA 40mg Q2W (n=53) PBO (n=59)	6 months	Yes	Yes	Yes	Yes	Fig 32 EULAR moderate and good Fig 33 EULAR at least moderate Fig 34 HAQ-DI
GO-FORTH Tanaka 2012[88]	DB	GOL 50mg Q4W SC + MTX (n=86) PBO + MTX (n=88)	24 weeks	Yes	Yes	Yes	Yes	Fig 32 EULAR moderate and good Fig 33 EULAR at least moderate Fig 34 HAQ-DI
GO-FORWARD Keystone 2009[89]	DB	GOL 50mg Q4W + MTX (n=89) PBO + MTX (n=133)	24 weeks	No	No	Yes †	No	Fig 33 EULAR at least moderate Fig 34 HAQ-DI
GO-FURTHER Bingham 2014[90]	DB	GOL 2mg/kg Q8W IV + MTX (n=395) PBO + MTX (n=197)	NR	No	No	No	Yes	Fig 34 HAQ-DI

Trial acronym and author (year)	Design	Treatment groups (n)	Timepoint in NMA	Primary analyses from CS Table 61				In CS NMA Fig No.
				EULAR Moderate	EULAR Good	EULAR at least moderate	HAQ-DI	
HERA Bae 2016[61]	DB	ETN 25mg BIW SC + MTX (n=118) ETN HD203 25mg BIW SC + MTX (n=115)	24 weeks	Yes	Yes	Yes	Yes	Fig 32 EULAR moderate and good Fig 33 EULAR at least moderate Fig 34 HAQ-DI
JESMR Kameda 2010[73]	OL	CTZ 200mg Q2W SC + MTX (n=82) PBO + MTX (n=77)	24 weeks	Yes	Yes	Yes	Yes	EULAR IFG 33 Fig 34 HAQ-DI
J-RAPID Yamamoto 2014[66]	DB	ETN 25mg BIW SC + MTX (n=75) ETN 25mg BIW SC (n=71)	24 weeks	No	No	Yes	Yes	Fig 32 EULAR moderate and good Fig 33 EULAR at least moderate Fig 34 HAQ-DI
Kim 2007[59]	DB	ADA 40mg Q2W SC + MTX (n=65) PBO + MTX (n=63)	NR	No	No	No	Yes	Fig 34 HAQ-DI
Kremer 2012[64]	DB	TOF 5mg BID + MTX (n=71) PBO + MTX (n=69)	24 weeks	No	No	No	Yes	Fig 34 HAQ-DI
LARA Machado 2014[91]	OL	ETN 50mg QW SC + MTX (n=281) cDMARD + MTX (n=142)	24 weeks	Yes	Yes	Yes	Yes	Fig 32 EULAR moderate and good Fig 33 EULAR at least moderate Fig 34 HAQ-DI
Li 2015[92]	DB	GOL 50mg Q4W + MTX (n=132) PBO + MTX (n=132)	24 weeks	No	No	Yes	Yes	Fig 33 EULAR at least moderate Fig 34 HAQ-DI
LITHE Kremer 2011[53]; Fleischmann 2013[54]	DB	TCZ 8mg/kg Q4W + MTX (n=398) PBO + MTX (n=393)	24 weeks	No	No	No	Yes	Fig 34 HAQ-DI

Trial acronym and author (year)	Design	Treatment groups (n)	Timepoint in NMA	Primary analyses from CS Table 61				In CS NMA Fig No.
				EULAR Moderate	EULAR Good	EULAR at least moderate	HAQ-DI	
OPTION Smolen 2008[67]	DB	TCZ 8mg/kg Q4W + MTX (n=205) PBO + MTX (n=204)	24 weeks	Yes	Yes	Yes	Yes	Fig 32 EULAR moderate and good Fig 33 EULAR at least moderate Fig 34 HAQ-DI
PLANETRA Yoo 2013[56]	DB	IFX 3mg/kg Q8W + MTX (n=304) IFX CT-P13 3mg/kg Q8W + MTX (n=302)	30 weeks	Yes	Yes	Yes	No	Fig 32 EULAR moderate and good Fig 33 EULAR at least moderate
RAPID 1 Keystone 2008[68]; Strand 2009[69]	DB	CTZ 200mg Q2W + MTX (n=393) PBO + MTX (n=199)	24 weeks	No	No	Yes	Yes[†]	Fig 32 EULAR moderate and good
RAPID 2 Smolen 2009[70]	DB	CTZ 200mg Q2W + MTX (n=246) PBO + MTX (n=127)	24 weeks	No	No	No	Yes	Fig 34 HAQ-DI
SATORI Nishimoto 2009[93]	DB	TCZ 8mg/kg Q4W IV (n=61) MTX (n=64)	24 weeks	Yes	Yes	Yes	Yes	Fig 32 EULAR moderate and good Fig 33 EULAR at least moderate Fig 34 HAQ-DI
START Westhovens 2006[94]	DB	IFX 3mg/kg Q8W + MTX (n=360) PBO + MTX (n=363)	22 weeks	No	No	Yes	No	Fig 33 EULAR at least moderate
SURPRISE Kaneko 2016[95]	OL	TCZ 8mg/kg Q4W IV + MTX (n=115) TCZ 8mg/kg Q4W IV (n=111)	24 weeks	No	No	Yes	Yes	Fig 33 EULAR at least moderate Fig 34 HAQ-DI
Takeuchi 2015[96]	DB	IFX 3mg/kg Q8W + MTX (n=51) IFX CT-P13 3mg/kg Q8W + MTX (n=50)	30 weeks	No	No	Yes	No	Fig 33 EULAR at least moderate

Trial acronym and author (year)	Design	Treatment groups (n)	Timepoint in NMA	Primary analyses from CS Table 61				In CS NMA Fig No.
				EULAR Moderate	EULAR Good	EULAR at least moderate	HAQ-DI	
TOWARD Genovese 2008[60]	DB	TCZ 8mg/kg IV + cDMARDs (n=803) PBO + cDMARDs (n=413)	24 weeks	No	No	Yes	No	Fig 33 EULAR at least moderate
Van de Putte 2004[57]	DB	ADA 40mg Q2W (n=113) PBO (n=110)	26 weeks	Yes	Yes	Yes	Yes	Fig 32 EULAR moderate and good Fig 33 EULAR at least moderate Fig 34 HAQ-DI

Abbreviations: ABT, abatacept; bDMARD, biologic disease-modifying anti-rheumatic drug; BRC, baricitinib; CFB, change from baseline; CI, confidence interval; DB = double-blind; GOL, golimumab; HAQ-DI, Health Assessment Questionnaire – Disability Index; IQR, interquartile range; IV, intravenous; NMA = network meta-analysis; NR, not reported; OL = open-label; PBO, placebo; Q4W, every four weeks; Q8W, every eight weeks QD, once daily; RTX, rituximab; SC, subcutaneous; SD, standard deviation; SE, standard error; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor. Q2W, twice weekly

Footnote: † possible typographic error

Table 29: Summary of trials included in the NMAs for the bDMARD-IR population (adapted from CS Table 61 and Appendix 4 Table 203)

Trial acronym and author (year)	Design	Treatment groups (n)	Timepoint in NMA	Primary analyses from CS Table 61				In CS NMA
				EULAR Moderate	EULAR Good	EULAR at least moderate	HAQ-DI	
ATTAIN Genovese 2005[97]	DB	ABT ~10 mg/kg on days 1, 15, and 29 & every 28 days + cDMARDs (n=258) PBO + cDMARDs (n=133)	6 months	Yes	Yes	Yes	No	EULAR moderate and good EULAR at least moderate
Combe 2012[98]	OL	ETN 50 mg QW + MTX (n=10) RTX 1000 mg IV on day 1 and day 15 + MTX (n=10)	24 weeks	Yes	Yes	Yes	No	EULAR moderate and good EULAR at least moderate
GO-AFTER Smolen 2009[63]	DB	GOL 50 mg Q4W (n=153) GOL 100 mg Q4W (n=153) PBO Q4W (n=155)	24 weeks	No	No	Yes	Yes	EULAR at least moderate HAQ-DI
Manders 2015 NTR1605[99]	OL	ABT 10mg/kg IV Q4W (n=43) RTX 2x1000mg IV weeks 0 & 2; & 6 months later (n=46) TNFi† (N=50: ADA n=21; ETN n=19; IFX n=5; GOL n=3; CTZ n=2)	6 months	Yes	Yes	Yes	Yes	EULAR moderate and good EULAR at least moderate HAQ-DI
ORAL-Step Burmester 2013[100]	DB	TOF 5 mg BID + MTX (n=133) TOF 10 mg BID + MTX (n=134) PBO + MTX (n=132)	NR	Yes	Yes	Yes	Yes	EULAR moderate and good EULAR at least moderate Fig 37 HAQ-DI
RADIATE Emery 2008[65]	DB	TCZ 4 mg/kg Q4W + MTX (n=163) TCZ 8 mg/kg Q4W + MTX (n=175) PBO + MTX (n=160)	24 weeks	No	No	Yes	No	EULAR at least moderate

Trial acronym and author (year)	Design	Treatment groups (n)	Timepoint in NMA	Primary analyses from CS Table 61				In CS NMA
				EULAR Moderate	EULAR Good	EULAR at least moderate	HAQ-DI	
REFLEX Cohen 2006[101]	DB	RTX (n=1000 mg on days 1 & 15) + MTX (n=311) PBO + MTX (n=209)	24 weeks	Yes	Yes	Yes	Yes	EULAR moderate and good EULAR at least moderate HAQ-DI
ROC Gottenberg 2016[102]	OL	Non-TNF (n=150) ABT, RTX, or TCZ TNFi (n=150) ADA, CTZ, ETN, IFX, or GOL	24 weeks	Yes	Yes	Yes	Yes	EULAR moderate and good EULAR at least moderate HAQ-DI

Abbreviations: ABT, abatacept; bDMARD, biologic disease-modifying anti-rheumatic drug; BRC, baricitinib; CFB, change from baseline; CI, confidence interval; DB = double-blind; GOL, golimumab; HAQ-DI, Health Assessment Questionnaire – Disability Index; IFX = infliximab, IQR, interquartile range; IV, intravenous; NMA = network meta-analysis; NR, not reported; OL = open-label; PBO, placebo; Q4W, every four weeks; QD, once daily; RTX, rituximab; SC, subcutaneous; SD, standard deviation; SE, standard error; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor. Q2W, twice weekly

Footnote: [†]possible reporting error in CS Table 61

Table 30: Trials included in TA375 excluded or not included by the CS with possible reasons for exclusion identified by the ERG

Trial	Reported in the CS	Reason for exclusion in the CS	Possible reason for exclusion from CS identified by the ERG	ERG notes
AIM[103]	No	-	Disease duration less than 3 years	Disease duration of ≥1 year
AMPLE[104]	No	-	Not time point of interest	Data only at 12 months
ATTRACT[105]	No	-	Not outcome of interest	ACR50/70
CREATE IIb	No	-	Not time point of interest	Weeks 2 and 4
De Filippis 2006[106]	No	-	Disease duration	<2 years
ETN Study 30988[74]	Yes	Data for outcomes of interest (HAQ-DI and EULAR responses) not reported	Disease duration less than 3 years	DAS28 for week 24 in Table 3
Moreland 1999[107]	No	-	Not licenced treatment	ETN 10mg and 25mg groups combined in outcomes
RACAT[108]	No	-	Not time point of interest	Week 48
SAMURAI[109]	No	-	Disease duration less than 3 years	Disease duration of ≥6 months and <5 years
STAR[110]	No	-	Not outcome of interest	ACR 20/50/70 and AEs
SWEFOT[79]	Yes	Early RA	-	-
Weinblatt 1999[111]	No	-	Not outcome of interest	HAQ-DI reported as median values at wk24

Abbreviations: ACR = American College of Rheumatology, DI = Disability Index, ETN = , etanercept, EULAR = European League Against Rheumatism, HAQ-DI = Health Assessment Questionnaire, RA = rheumatoid arthritis

4.3.2 Critique of the indirect comparison and/or multiple treatment comparison

NMAs were performed separately for the cDMARD-IR and bDMARD-IR population using a Bayesian approach for EULAR response at Month 6 and change from baseline HAQ-DI score at Month 6. For the continuous outcome, HAQ-DI, an identity-link function model was used in the NMA. For the ordered categorical EULAR response, a binomial likelihood with logit link-function model was used for the cDMARD-IR population by dichotomising the data, and a multinomial likelihood with probit link function model was used for bDMARD-IR population. The choice of the link function was based on the performance of convergence of the Markov chain Monte Carlo (MCMC). The choice between the fixed effect and random effects model was based on the deviance information criterion (DIC). Table 31 provides a summary of the model used for each outcome measure in the two populations.

Table 31: The model used for each analysis in the CS

Population	Outcome	Model
cDMARD-IR	EULAR response (moderate)	binomial logit (fixed effect)
	EULAR response (good)	binomial logit (fixed effect)
	EULAR response (at least moderate)	binomial logit (random effects)
	HAQ-DI	identity (random effects)
bDMARD-IR	EULAR response	multinomial probit (fixed effect)
	HAQ-DI	identity (fixed effect)

The ERG disagrees with the approach of using two different models for EULAR response in the two populations based on the performance of the convergence of the MCMC. When data are sparse, poor convergence may be caused by the use of a reference/vague prior. The choice of the likelihood function/link function should be based on the data generating process. A multinomial likelihood with probit link function is preferred to a binomial likelihood with logit link function for the ordered categorical EULAR data because it accounts for natural ordering and correlations between the EULAR categories. This is important to the decision problem when EULAR results are used to populate the economic model.

When data are sparse, comparing DIC of a fixed effect model with DIC of a random effects model using a reference/vague prior for the between-study standard deviation may not be appropriate since the reference/vague prior may lead to implausible posterior uncertainty for the results. The choice between the fixed effect and random effects model should be determined by the objective of the analysis and the conduct of the included studies. The fixed effect model was used for a moderate EULAR response and a good response, but the random effects model was used for at least a moderate response in the

cDMARD-IR population. It may not be reasonable to believe that heterogeneity exists in at least a moderate EULAR response network but not in a moderate response or a good response network.

In response to a request for clarification (question A11), the company clarified that placebo + cDMARD/cDMARD was used as the reference treatment across all the NMAs. To incorporate etanercept into the cDMARD-IR networks, the intensified cDMARD arm in the LARA[91] study was assumed to be the same as the cDMARD node. The ERG notes that this may not be an appropriate assumption to make, because this would overestimate the treatment effect of cDMARD.

For tofacitinib (TOF) trials with early escape, two non-responder imputation (NRI) approaches were applied. Estimate 1 of treatment effect was calculated by applying NRI to Month 3 non-responders from the placebo arm (termed NRI without advancement penalty). Estimate 2 of treatment effect was calculated by applying NRI to Month 3 placebo non-responders as well as the Month 3 TOF non-responders (termed NRI with advancement penalty). The primary analysis for the ORAL Standard, Scan and Sync trials was based on NRI with advancement penalty (Estimate 2).

Estimate 1 was used in the base case NMA for the ORAL Standard, Scan and Sync trials with the justification that, using the data combined from these three trials, [redacted] of non-responders treated with TOF at Month 3 subsequently developed a response to treatment at Month 6. The company estimated that less than 10% of the Month 3 placebo-treated non-responders would have subsequently developed a EULAR response by Month 6 (CS page 156). Estimate 1 was also used in the base case NMA for the ORAL Solo and Step trials with the reason that it is expected that few patients would go on to develop any subsequent response to treatment beyond that already seen by Month 3 (CS page 158) in the absence of any form of active DMARD treatment. The ERG believes that Estimate 1 overestimates the relative treatment effect of TOF and Estimate 2 underestimates the treatment effect of TOF.

In response to a request for clarification (question A12), the company stated that there was an error in the CS regarding the prior used for the treatment effect relative to the reference treatment. The vague prior used for the relative treatment effect was a normal distribution with mean 0 and variance 100^2. In RE models, a uniform [0, 5] prior was used for the between-study standard deviation. The ERG notes that when data are sparse, this uniform prior would lead to implausible posterior uncertainty in the results.

The I^2 statistic was used to assess the heterogeneity for the pairwise treatment comparisons. [redacted] The ERG notes that this suggests that a random effects model may be more appropriate for these two outcomes. However, the

fixed effect model was still used for a moderate EULAR response, and a good EULAR response. Statistical assessments of heterogeneity were not feasible in the bDMARD-IR population because single studies contributed to each direct comparison.

Inconsistency was checked using the Bucher method,[112] [redacted] The company provided no comments regarding the consistency between direct and indirect evidence.

[redacted]

[redacted]

[redacted]

[redacted]

Because a probit model was used in the bDMARD-IR population for EULAR response, it was not clear how the OR was calculated in this case. In response to a request for clarification from the ERG (question A11), the company stated that the WinBUGS code presented included code for generating the absolute treatment effects but these were not generated. Hence, it was still unclear how ORs were calculated from the probit model.

The base case NMA results in the CS should be interpreted with caution since Estimate 2 (NRI without advancement penalty) was used for calculating the relative treatment effect of TOF in the ORAL trials, which overestimated the relative treatment effect of TOF in these trials. A fixed effect model was used for moderate EULAR response, good EULAR response in the cDMARD-IR population and all the outcomes in the bDMARD-IR population, which underestimated treatment uncertainty. Two different models were used for EULAR response in the two populations.

Six sensitivity analyses were performed in the CS, which included:

1. Exclusion of predominantly Asian populations trials/lower dose MTX
2. Exclusion of trials that included patients with prior bDMARD exposure
3. Exclusion of trials with milder disease
4. Separating intensified cDMARDs from central node
5. Alternative modelling approach (probit) for cDMARD-IR
6. Alternative modelling approach (probit) for cDMARD-IR, using Estimate 2

The company concluded that results were sensitive to the trials included in the base case network, but less influenced by the modelling approach.

The ERG requested the company to perform additional analysis for EULAR response in both populations (clarification question A7) with the following settings:

- Using a random effects probit model with an informative prior for the between-study variance (log normal with mean of -2.56 and variance of 1.74^2, proposed by Turner *et al.,* (2012).[113] The log normal is truncated so that the OR in one study would not be ≥50 times than in another, and re-scaled to match the probit scale).
- EULAR response for ORAL trials derived using DAS ESR with all trial data by applying non-responder imputation Estimate 2 in the CS Table 53. Use the individual EULAR results from trials in the NMA, i.e. not pooling individual patient-level data from ORAL trials.
- Excluding studies which only reported DAS (i.e. did not report EULAR) from the NMA.

- Not assuming intensified DMARD arm is equivalent to the central DMARD node in the LARA trial and including the SWEFOT trial.
- Choosing PBO plus cDMARD/cDMARD as the reference treatment (treatment 1) in the analyses.

The ERG also requested a sensitivity analysis for the requested NMA as above by excluding patients with prior biologic use in the ORAL trials and excluding studies that enrolled a proportion of patients with prior bDMARD use (clarification question A8). In additional to the two analyses the ERG has requested, the company also provided the results using the settings suggested by the ERG as above but applying Estimate 1 (NRI without advancement penalty) to the ORAL trial [redacted] to [redacted] show the EULAR results from the additional analyses conducted by the company (clarification question A7 and A8). All the results were interventions relative to cDMARD on the probit scale, with larger negative numbers being associated with better health outcomes.

Using Estimate 2 (NRI with advancement penalty), which is consistent with the primary analysis of the ORAL Standard, Scan and Sync trials, the effect of TOF plus cDMARD was the smallest among the bDMARDs in the cDMARD-IR population (Figure 2). Using Estimate 1 (NRI without advancement penalty), the effect of TOF + cDMARD compared to cDMARD was smaller than that of TCZ, CTZ, GOL, ETN and ETN's biosimilars in combination with cDMARD, but larger than ABT, IFX and IFX's biosimilars in combination with cDMARD in the cDMARD-IR population (Figure 2).

For TOF as monotherapy, the effect of TOF compared with cDMARD was the smallest among the active treatments using Estimate 2, but had a larger effect than intensified cDMARD and ETN using Estimate 1 in the cDMARD-IR population (Figure 3).

The analyses including patients with and without prior biologics use provide very similar results for the cDMARD-IR population, except that the treatment effect of TCZ plus cDMARD versus cDMARD reduced noticeably using the studies without prior biologics and the effect of ADA monotherapy became statistically significant (

Figure 5 and Figure 6).

The effect of TOF plus cDMARD compared with cDMARD was bigger than GOL plus cDMARD, but smaller than non-TNFi, ETN, TNFi, RTX, TCZ and ABT in combination with cDMARD in the bDMARD-IR population using Estimate 2 (Figure 4). None of the treatment effects versus cDMARD were statistically significant, but the ERG suspects that a vague prior was used because the estimated between-study standard deviation was reported to have mean 1.21 with 95% credible interval (0.02, 4.52) which does not reflect the prior that the ERG has suggested. The company did not provide the results using Estimate 1.

The absolute treatment effects, including at least a moderate and at least a good EULAR response for both populations, are presented in Appendix 2.

Figure 2: EULAR response for treatments in combination with cDMARD in the additional analyses requested by the ERG – cDMARD-IR population on the probit scale

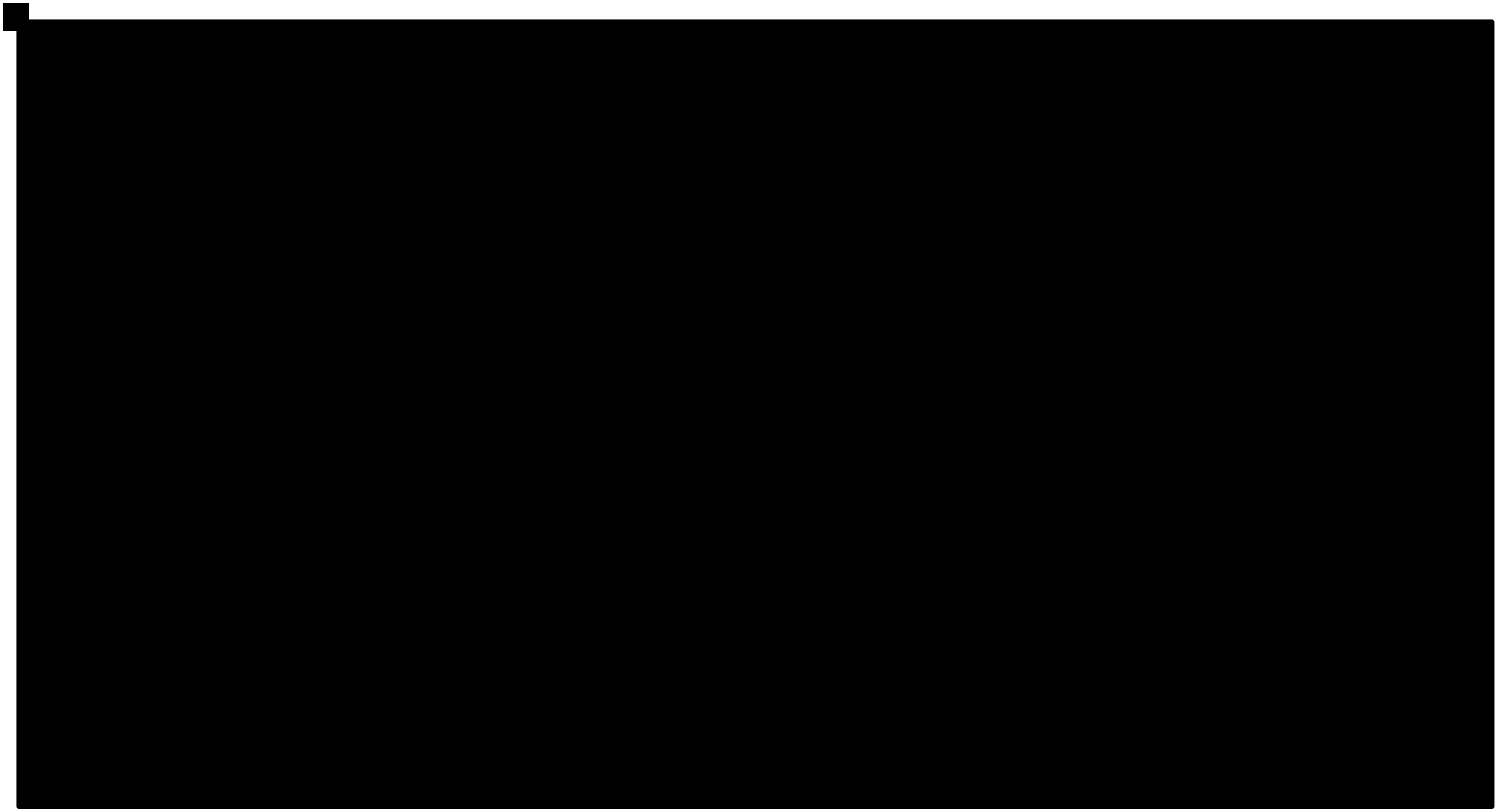


Figure 3: EULAR response for treatments as monotherapy with cDMARD in the additional analyses requested by the ERG – cDMARD-IR population

Figure 4: EULAR response for treatments in combination with cDMARD in the additional analyses requested by the ERG – bDMARD-IR population on the probit scale using Estimate 2 for the ORAL trials

Figure 5: EULAR response for treatments in combination with cDMARD in the additional analyses requested by the ERG (including patients with and without prior biologics) – cDMARD-IR population on the probit scale using Estimate 2 for the ORAL trials

Figure 6: EULAR response for treatments as monotherapy with cDMARD in the additional analyses requested by the ERG (including patients with and without prior biologics) – cDMARD-IR population on the probit scale using Estimate 2 for the ORAL trials

4.4 Additional work on clinical effectiveness undertaken by the ERG

The ERG searched and reviewed records of completed and ongoing trials of tofacitinib (presented earlier in Table 4). This search identified a trial which had examined safety of tofacitinib regarding herpes zoster vaccination which was completed but not included in the CS. AE data for this trial were subsequently requested and disclosed as part of the clarification process.

Clinical advice to the ERG highlighted the importance of monitoring AEs for new classes of drugs using ongoing observational registers. As the company did not conduct a targeted search for AEs, they are unlikely to capture all reports of relevant AE literature in tofacitinib other than those occurring within their clinical trial programme. The ERG conducted a specific search in MEDLINE of AEs for tofacitinib, from March 2015 to April 2017 (see Appendix 1), which retrieved 152 citations. The ERG screened the titles and abstracts for potentially relevant citations relating to AEs with tofacitinib. Whilst no relevant primary studies were identified from this limited search, some review papers examining the safety profile of tofacitinib were identified. One NMA of ten tofacitinib trials[114] examined the relative safety of both 5 mg and 10 mg doses of tofacitinib using 'withdrawals due to an adverse event' as an

outcome. A fixed effects model showed the OR to be in favour of tofacitinib monotherapy versus tofacitinib 5 mg plus methotrexate (OR 0.42, Credible Interval [Cr.I]: 0.20 – 0.84) and to be in favour of methotrexate versus tofacitinib 5 mg BD plus methotrexate (OR 0.57, Cr.I: 0.35 – 0.88) for this selected outcome of AE data. This again highlights a potentially different rate of AEs for tofacitinib plus methotrexate versus tofacitinib monotherapy, which is not drawn out by the safety analysis presented in the CS. A review of clinical studies examining patient outcomes with tofacitinib reported by Boyce *et al*., (2016)[115] echoed the sentiments of clinical advice to the ERG as they speculated that it may require years of additional clinical studies and post marketing surveillance to fully characterise the benefit-to-risk ratio of tofacitinib in a larger and diverse patient population.

The descriptions of the number of reviewers who "were involved" in study selection, data extraction and quality assessment were vague in both the CS and the company's response to clarification. Therefore, the ERG double-checked the rationale for study selection in the systematic review and NMA, corresponding data extraction and quality assessment from either the original papers or the corresponding CSRs to verify their accuracy. Where studies were included in TA375 but not included in the CS, without justification, original papers were consulted to assess possible reasons for exclusion by the company (presented earlier in Table 30).

4.5 Conclusions of the clinical effectiveness section

The ERG considers that the company's search strategy is sufficiently comprehensive to retrieve important citations relating to clinical effectiveness but not sufficient to retrieve up-to-date and comprehensive evidence for the safety of tofacitinib.

The four RCTs (ORAL Standard, Scan, Sync and Solo) were relevant to the decision problem outlined in the final NICE scope and were good quality, adequately powered, multi-centre international trials, two of which included UK centres (ORAL Standard and Sync). A primary outcome of ACR20 for three trials at 6 months showed tofacitinib 5 mg BD plus methotrexate to be statistically superior to placebo plus cDMARD ($p \leq 0.001$). Other significant results ($p \leq 0.001$) were demonstrated across these trials for tofacitinib plus methotrexate versus placebo for ACR50, ACR70, and treatment response using EULAR criteria and HAQ-DI at both 3 and 6 months with the following exceptions:

(i) the proportion achieving disease remission using DAS28(ESR) with tofacitinib plus methotrexate in ORAL Scan at 6 months when using the stepdown statistical approach;
(ii) the change in baseline HAQ-DI in ORAL Scan at 6 months when using the step-down statistical approach.

A primary endpoint of radiographic progression using the mTSS in ORAL Scan was not significant at either 6 or 12 months (p=0.0792). Further statistically significant benefits for tofacitinib in combination

with methotrexate (at 6 months) and for tofacitinib monotherapy (at 3 months) over placebo were observed using the EQ-5D, FACIT-F and pain assessed VAS outcomes ($p \leq 0.001$).

ACR20 at 3 months was significant for tofacitinib monotherapy versus placebo at 3 months in one trial (ORAL Solo) but not significant for the primary endpoint of the proportion achieving remission using DAS28(ESR) at 3 months. As all patients crossed over from placebo to receive tofacitinib at 3 months in ORAL Solo, there are no placebo-controlled results at 6 months for the other relevant endpoints. The ERG consider that the recently completed head-to-head trial, ORAL Strategy, has data relevant to the decision problem. The ORAL Strategy trial showed tofacitinib combination therapy with methotrexate to be non-inferior to adalimumab plus methotrexate but tofacitinib monotherapy was statistically inferior to both tofacitinib plus methotrexate and adalimumab plus methotrexate for the primary endpoint of ACR50 at 6 months.

Safety data for tofacitinib were presented in the CS from a pooled analysis of tofacitinib trial data up to March 2015 which was two years prior to the current appraisal. Whilst the company were able to provide some up-to-date safety data following a request, the ERG note that a full and transparent safety profile of tofacitinib versus comparators, which contains comprehensive data for all AEs including SAEs, was not provided. The company stated that they were "*unable to update the incidence of Serious Adverse Events within the timelines provided as these are listed in a separate data base*". One of the most common AEs for tofacitinib was herpes zoster, which was also noted from a published NMA to be significantly higher than bDMARD comparators. [48] Incidence rates in the company's safety set were highest for serious infection events, bronchitis, pneumonia and all cardiac disorders. The ERG considers that pooling trials to produce incidence rates of AEs with tofacitinib may dilute the appearance of adverse events for tofacitinib plus cDMARD, which are noted by several sources[41, 49, 50, 114] to be higher than for tofacitinib monotherapy, which are not referenced or discussed in the CS. Moreover, the company's reliance on AE data from their own trial programme without performing targeted searches for relevant safety literature for tofacitinib means that relevant studies regarding safety, such as NMAs versus other bDMARDs, are missed.

The ERG believes that the results presented in NMA should be treated with caution, as the ordered categorical EULAR data were dichotomised in the cDMARD-IR population, which ignores the natural ordering and correlations between the EULAR response categories. A fixed effect model was used in all the analyses in the bDMARD-IR population and EULAR response (moderate response and good response) in the cDMARD-IR population. Heterogeneity is expected and this approach underestimates uncertainty in the treatment effect. For tofacitinib trials with early escape, the results from non-responder imputation without advancement penalty (non-responder imputation only applied for the placebo arm, not the tofacitinib arm) were used in the base case NMAs. This imputation approach

potentially overestimates the relative treatment effect of tofacitinib in these trials. Depending on the non-responder imputation approach applied to the tofacitinib trials with early escape, the conclusion for the treatment ranking of tofacitinib among the bDMARDs varies markedly.

5 COST EFFECTIVENESS

This chapter presents a review of the cost-effectiveness evidence provided in the CS for TOF, with or without MTX, for treating moderate-to-severe, or severe RA. For brevity, the moderate-to-severe RA group is hereafter referred to as moderate RA. The cost-effectiveness evidence comprised a systematic review of existing economic analyses on TOF for RA and an economic analysis based on the company's *de novo* model. Following the clarification round,[34] a number of amendments were made to the model which resulted in different ICERs to those presented in the CS, although the broad conclusions of the company's original analyses remain unchanged. The ERG report will discuss only the latest version of the model unless there is a reason to refer back to the original version.

5.1 ERG's comment on company's review of cost-effectiveness evidence

5.1.1 Summary of the company's search strategy

The company performed a literature search in order to identify existing cost-effectiveness/cost-utility/cost-benefit analyses that were related to the decision problem, that is, that included tofacitinib or comparators (combined with RA-related terms and a cost-effectiveness filter). The following sources were searched: MEDLINE [via Ovid], MEDLINE In-Process & Other Non-Indexed Citations [via Ovid], EconLit [via Ovid], NHS EED [via Wiley], the Cochrane Database of Systematic Reviews [via Wiley in the 2016 updates], Health Technology Assessment Database [via Wiley in the 2016 updates]. The original searches covered the period of November 2010 and three review updates up to December 2016.

The company carried out supplementary searches in conference proceedings websites (ACR, EULAR, BSR and International Society for Pharmacoeconomics and Outcomes Research [ISPOR]) and several international HTA websites (NICE, CADTH, PBAC and NIHR). The searches covered the period from 2005 up to December 2016. The ERG considers that the search for cost-effectiveness studies was comprehensive and clearly and fully reported in Appendix 8 of the CS.

The company performed one search to identify the health state utility values for patients with moderate-to-severe RA. The following sources were searched: EMBASE [via Ovid], MEDLINE [via Ovid], MEDLINE In-Process & Other Non-Indexed Citations [via Ovid], EconLit [via Ovid], NHS EED [via Wiley], the Cochrane Database of Systematic Reviews [via Wiley in the 2016 updates], and HTA [via Wiley in the 2016 updates].

In addition, the company searched several conference websites (EULAR, ACR, BSR and ISPOR) from 2013-2016, several international HTA agencies (NICE, SMC, CADTH, PBAC and HAS) and other

relevant websites (EQ-5D, INAHTA, NIHR HTA, CEA registry and RePEc). All the search strategies in both database and website searches were fully reported in Appendix 11 of the CS.

Whilst the translation across the databases appears consistent and there were no consequential errors in the search strategies, the ERG found that the company did not consistently apply the cost-effectiveness filter between the original search (November 2010 and October 2012) and the update searches (in June 2016 and December 2016). The implications of using the filters inconsistently are unclear. Nevertheless, the ERG considers that the searches are sufficiently comprehensive to retrieve all relevant economic studies.

The company performed a search to identify published literature of resource data. The following sources were searched: MEDLINE [via Ovid], MEDLINE In-Process & Other Non-Indexed Citations [via Ovid], EMBASE [via Ovid], the Cochrane Database of Systematic Reviews [via Wiley], HTA [via Wiley], NHS EED [via Wiley].

In addition, the company searched several conference websites (EULAR, ACR, BSR and ISPOR) from 2013-2016, several international HTA agency websites (NICE, SMC, CADTH, PBAC and HAS) and other relevant websites (EQ-5D, INAHTA, NIHR HTA, CEA registry and RePEc. All the search strategies in both database and website searches were fully reported in Appendix 13.

5.1.2 Inclusion and exclusion criteria used in the company's review

A full description of the company's search strategy is provided in Appendix 9 of the CS. The company performed an initial review in November 2010 that searched the following databases: MEDLINE and MEDLINE® In-Process & Other Non-Indexed Citations, from 1950; Embase, from 1974; NHS EED, from 1968 and EconLit, from 1961. These searches were updated, with minor modifications in June 2016 and December 2016. In addition, the company hand-searched key conference proceedings, the websites of national funding bodies to identify previous submissions, and websites that are recommended by NICE. Hand-searching was undertaken initially in November 2010 and was updated in June 2016 and December 2016.

5.1.3 Findings of the cost effectiveness review

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is presented by the company in Figure 56 of the CS. A total of 289 records were identified, of which 91 were full publications, 182 were abstracts only and 16 were previous HTA submissions to funding or reimbursement bodies. A description of the identified studies are provided in Section 5.1.2 of the CS. Two previous evaluations of TOF were identified: one by the CADTH and one by the PBAC.

5.1.4 Conclusions of the cost effectiveness review

Although not explicitly stated, it appears that the company did not believe either of the two identified evaluations of TOF were suitable for the decision problem. As such, the company constructed a *de novo* model to assess the cost-effectiveness of TOF, with or without MTX. The model submitted by the company has many similarities with the model produced by the independent AG in TA375; this model has been published in a peer-reviewed journal,[23] although different data sources have been used, and an appropriate additional strategy for patients with moderate RA has been explored.

The ERG considers that the searches are comprehensive to retrieve all the eligible studies.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

5.2.1 NICE Reference Case checklist

A summary of the key features of the company's *de novo* model relating to the NICE Reference Case[116] is provided in Table 32.

Table 32: Comparison of the company's model with key topics within the NICE reference case

Element	Reference case	Satisfactorily addressed within the CS	ERG Comments
Defining the decision problem	The scope developed by NICE	Yes	-
Comparators	As listed in the scope developed by NICE	Mostly	Some comparators have been excluded from the decision problem including: (1) ABT SC and TCZ SC; (2) CTZ used as monotherapy in the cDMARD-IR population; (3) ADA, ETN, CTZ and IFX in combination with MTX when RTX is contraindicated, and; (4) ADA, CTZ and ETN monotherapies as monotherapy in the bDMARD-IR population.
Perspective on costs	NHS and Personal Social Services (PSS)	Yes	-
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes	Health outcomes are modelled in terms of QALYs gained.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Yes	-
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	Maximum age is 100 years.
Synthesis of evidence on health effects	Based on systematic review	Mostly	The probabilities of response for the intervention are based on a regression model using TOF trial data. The probabilities of EULAR response for the comparators are based on an NMA performed using data identified through a systematic review using TOF as the reference treatment. However, the ERG has concerns with the NMA (see Section 4.3.2).
Measure and valuation of health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Yes	Health effects were expressed in QALYs. HAQ-DI scores were mapped using a mapping algorithm proposed by Hernández-Alava *et al*[117] in the base case. Scenario analyses were included using different mapping algorithms.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	Resource use estimates associated with categories were based on data from the Norfolk Arthritis Register database[118] and were inflated to 2016 values.

Element	Reference case	Satisfactorily addressed within the CS	ERG Comments
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Yes	-
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Not Applicable	No additional equity weighting is applied to the estimated QALY gains.

5.2.2 Population

Patient-level data from the ORAL studies: Standard,[43] Scan,[44] Sync,[45] Solo,[46] and Step[35] were used to populate the company's model. Patients were sampled from the ORAL trial participants that were relevant to the population being evaluated. These data sources differ from the approach used in TA375[24] whereby data from the British Society for Rheumatology Biologics Register (BSRBR) were used. The company states that using the ORAL studies allowed data not recorded in the BSRBR dataset to be used, which allows for the inclusion of more potential predictors of a patient's response levels and allows the correlation between parameters to be maintained. In Table 91 of the CS, the company produces a comparison of the patient characteristics between those in the BSRBR dataset and those in the ORAL studies. The data from the ORAL studies are marked as commercial-in-confidence. Compared with patients in the severe RA and moderate RA groups of the BSRBR, patients in the ORAL studies

[redacted]

The company undertook sensitivity analyses in which the data from the BSRBR were used. Where data were not recorded in the BSRBR, the mean value from the ORAL studies was assumed instead. The ERG are satisfied with the approach taken by the company. The population characteristics used in the model are provided in Table 33.

Table 33: Population characteristics at baseline used in the model

	cDMARD-IR		bDMARD-IR
	Moderate RA	**Severe RA**	**Severe RA**
Age	[redacted]	[redacted]	[redacted]
Proportion female	[redacted]	[redacted]	[redacted]
Weight (Kg)	[redacted]	[redacted]	[redacted]
HAQ-DI score	[redacted]	[redacted]	[redacted]
DAS28	[redacted]	[redacted]	[redacted]
Proportion with prior cDMARD experience	[redacted]	[redacted]	[redacted]
Proportion with prior bDMARD experience	[redacted]	[redacted]	[redacted]
Proportion anti-CCP positive	[redacted]	[redacted]	[redacted]
Disease duration (years)	[redacted]	[redacted]	[redacted]
Haemoglobin	[redacted]	[redacted]	[redacted]
CRP	[redacted]	[redacted]	[redacted]
ESR	[redacted]	[redacted]	[redacted]
Total cholesterol	[redacted]	[redacted]	[redacted]
CDAI	[redacted]	[redacted]	[redacted]
Number of previous DMARDs	[redacted]	[redacted]	[redacted]

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; CCP, cyclic citrullinated peptide; CDAI, clinical disease activity index; cDMARD, conventional disease-modifying anti-rheumatic drug; CRP, c-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; IR, inadequate response.

5.2.3 Interventions and comparators

Descriptions of the intervention and the comparators are provided in Sections 3.2 and 3.3. Table 94 of the CS provides a summary matrix of which interventions are licenced (in combination with MTX or as monotherapy) in each of the moderate RA cDMARD-IR, moderate RA bDMARD-IR, severe RA cDMARD-IR, and severe RA bDMARD-IR populations. This table also includes information on recommendations provided by NICE. Table 34 summarises the comparators presented in the analyses within the CS. The ERG notes that some of the comparators included are currently not recommended by NICE and more importantly that recommended comparators are missing from some of the analyses presented by the company. However, the ERG does not expect this to affect the conclusions of the company's economic analysis.

Table 34: Summary of comparators included in the analyses presented in the CS

Severity	Pathway	MTX tolerant	Comparators	
			Included	**Missing**
Severe	--cDMARD-IR	✓	MTX IFX+MTX* ETN+MTX* ADA+MTX GOL+MTX CTZ+MTX TCZ+MTX ABT+MTX	
		X	SSZ+HQC[#] ETN* ADA TCZ	CTZ
	bDMARD-IR	✓	RTX+MTX GOL+MTX† ABT+MTX†	
		X	TCZ†	ADA CTZ ETN
	bDMARD-IR (RTX-intolerant)	-	GOL+MTX† ABT+MTX† TCZ+MTX	ADA+MTX ETN+MTX*‡ IFX+MTX* CTZ+MTX
Moderate	cDMARD-IR	-	DMC	

*Including its biosimilar
†Not recommended by NICE
‡Included only in the clarification response
[#]Presented as MTX in the CS, the company acknowledged this as an error in the clarification response

ABT: abatacept; TCZ: tocilizumab; ADA: adalimumab; CTZ: certolizumab pegol; ETN: etanercept; GOL: golimumab; IFX: infliximab; RTX: rituximab; MTX: methotrexate; SSZ: sulfasalazine; HCQ: hydroxychloroquine; DMC: cDMARD combination

The ERG comments that SC formulations of ABT and TCZ have not been included in the analyses: in response to a request for clarification [34] (question B26), the company states that it did not identify any studies for ABT SC or TCZ SC that would allow inclusion in the NMA. The company comment that using list prices the SC formulations would be more expensive than the IV formulations and that these would be dominated if clinical equivalence were assumed. The ERG notes that the confidential PAS for these interventions could nullify the company's logic. The ERG also notes that the RTX biosimilar Truxima has not been included as a comparator. However, the ERG acknowledges that this omission does not have an impact on the conclusions of the analyses given that the branded version of rituximab is estimated to dominate TOF according to the company.

The model compares sequences of treatments. The sequences compared in the company's analyses are defined in Tables 96 to 98 of the CS (with the exception of the sequences for the bDMARD-IR MTX-intolerant population, which were missing). The ERG notes that these sequences have shortcomings if

the sequences in TA375 were intended to be replicated. These limitations include: (1) featuring multiple consecutive treatments of the same kind (such as cDMARD combination or SSZ+HCQ); (2) using more than one cDMARD treatment between bDMARDs and palliative care; (3) including non-recommended treatments (such as ABT+MTX after RTX+MTX); and, (4) not assessing all of the possible sequences in the comparison against RTX+MTX. In the clarification response,[34] the company acknowledged these shortcomings as misunderstandings of the sequences in TA375.

In contrast, the ERG considers that the evaluation of a strategy whereby patients with moderate RA are treated with bDMARDs once their RA is classified as severe is a preferable approach to the evaluation undertaken in TA375 and provides a better estimate of the ICER. Among the two possible sequence sets explored for this population, the ERG believes that the combination alternate sequence (which explores the impact of inserting TOF+MTX before MTX and non-biologic therapy [NBT]) is the most appropriate, as any recommendations made within this STA would not impact on the recommendations of other RA drugs.

The ERG presents analyses in Section 5.4 using sequences where these issues have been addressed.

5.2.4 Perspective, time horizon and discounting

The model takes the perspective of the NHS and PSS. The model adopts a lifetime horizon with a maximum age of 100 years. All costs and benefits were discounted at 3.5% per annum in line with the NICE Reference Case.[116]

5.2.5 Model structure

The company used a discrete event simulation (DES) approach which was also used by the AG in TA375.[24] The ERG believes that this an appropriate approach which also removes the need for the definition of time cycles and half-cycle correction. The model structure presented by the company is reproduced in Figure 7.

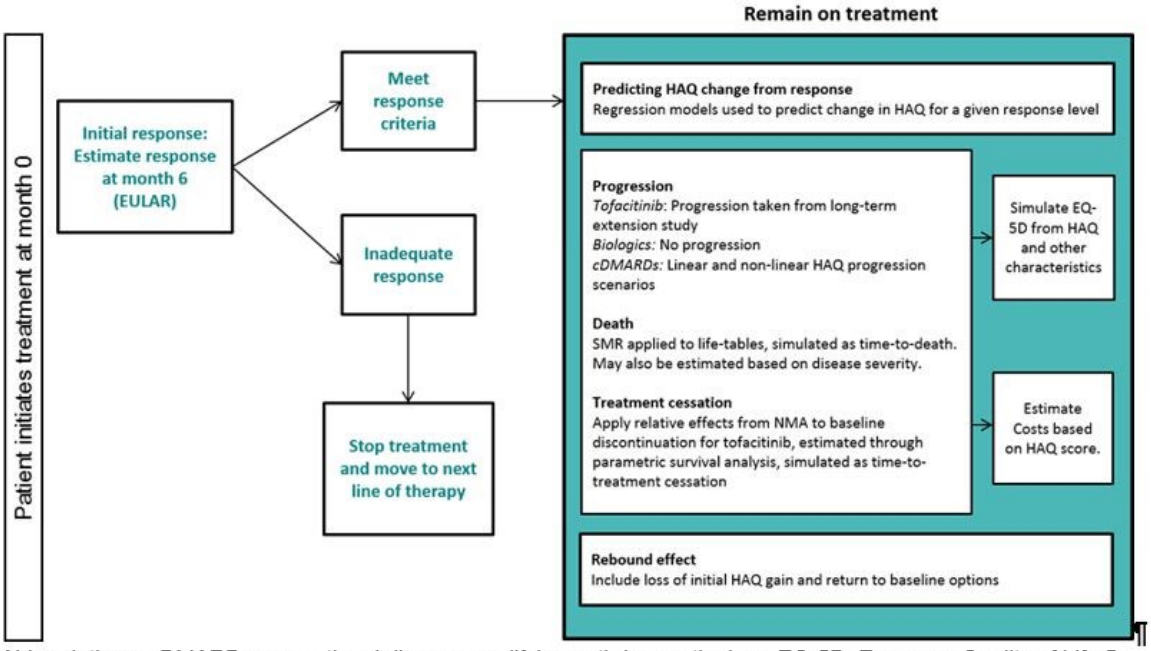
The model presented by the company is similar to the AG's model for TA375.[24] A clinical response in terms of EULAR (good, moderate, or none) is estimated at six months. Patients who experience either a good or a moderate EULAR response remain on treatment, whilst those who experience no response have their treatment withdrawn and move on to the next treatment in the sequence unless the patient is already receiving PALL.

For patients experiencing a good or moderate EULAR response, there is an associated HAQ-DI decrease dependent on patient characteristics, a potential change in HAQ-DI whilst a patient remains on treatment, with HAQ-DI having increased (by the level of the initial decrease) once a patient has

discontinued treatment. Throughout the model, the costs incurred and the utility of the patient are assumed to be related to HAQ-DI score.

The simulated cohort is generated by sampling patients from the Phase III tofacitinib ORAL trials: Standard,[43] Scan,[44] Sync,[45] Solo,[46] and Step[35]. The model randomly samples with replacement from trial participants based on the population chosen (cDMARD-IR or bDMARD-IR). Each sequence compared in the model is run for each patient.

Figure 7: The model structure presented by the company



Abbreviations: cDMARD, conventional disease-modifying anti-rheumatic drug; EQ-5D, European Quality of Life 5 Dimensions; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; NMA, network meta-analysis; SMR, standardised mortality ratio.

For the model that evaluates an option of providing treatment to those who begin with moderate RA when they reach a severe RA state, the model structure was amended to allow the DAS28 score of a patient to be recorded and change over time. This was operationalised [redacted]. In response to a request for clarification[34] (question B14), the company provided further results for the regression model, a scatter plot of fits and residuals versus both DAS28 and HAQ. The ERG was satisfied that the regression used was robust.

5.2.6 Treatment effectiveness, extrapolation and discontinuation

The company estimated the probabilities of EULAR responses for TOF + MTX using a regression model fitted to data from the ORAL trials. The probabilities of EULAR responses for the comparator

treatments were estimated applying the ORs calculated in the NMA to the probabilities of response of TOF + MTX.

The parameters of the multinomial logistic regression model used to estimate the probabilities of moderate or good EULAR response were estimated based on data from the Standard,[43] Scan,[44] and Sync[45] trials. The ERG notes that patients in these trials received TOF in combination with MTX or other cDMARDs but not as monotherapy. Table 35 presents the variables used in the regression model and their coefficients for moderate and good response compared with no response.

Table 35: Results of the multinomial logistic regression company used by the model to estimate moderate or good EULAR responses at Month 6

Variable	Moderate response		Good response	
	Coefficient	SE	Coefficient	SE
Age	[redacted]	[redacted]	[redacted]	[redacted]
Anti CCP positive	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI	[redacted]	[redacted]	[redacted]	[redacted]
DAS28	[redacted]	[redacted]	[redacted]	[redacted]
Prior bDMARDs	[redacted]	[redacted]	[redacted]	[redacted]
CDAI	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]

bDMARD, biologic disease-modifying anti-rheumatic drug; CCP, cyclic citrullinated peptide; DAS28, Disease Activity Score in 28 joints; HAQ-DI, Health Assessment Questionnaire-disability index; RRR, relative risk ratio; SE, standard error.
[†]Significant at the 10% level. [‡]Significant at the 5% level. [§]Significant at the 1% level

The probabilities of moderate or good EULAR response for each patient and treatment were calculated based on the patient's baseline characteristics and the ORs for each treatment calculated in the NMA. Table 36 shows the ORs used in the model together with the average probabilities of moderate or good EULAR response for the MTX-tolerant population. Average probabilities were calculated by averaging the probabilities of all patients in the ORAL Standard,[43] Step,[35] Scan,[44] and Sync[45] trials.

Table 36: ORs and probabilities of good and moderate EULAR response for each treatment used in the MTX-tolerant population

Therapy	ORs compared with TOF		Probabilities of EULAR response*		
	Moderate or good	Good	No response	Moderate response	Good response
TOF + MTX					
ADA + MTX					
CTZ + MTX					
ETN + MTX[#]					
ABT + MTX					
GOL + MTX					
IFX + MTX[#]					
RTX + MTX					
TCZ + MTX					
cDMARD†					

TOF: tofacitinib; ABT: abatacept; TCZ: tocilizumab; ADA: adalimumab; CTZ: certolizumab pegol; ETN: etanercept; GOL: golimumab; IFX: infliximab; RTX: rituximab; MTX: methotrexate; LEF: leflunomide; cDMARD: conventional disease-modifying antirheumatic drug
*Average probabilities based on the full population of ORAL trials (Scan, Standard, Sync and Step)
[#] Biosimilars assumed to have same efficacy
†Includes MTX, LEF and cDMARD combination

Table 37 shows the ORs used in the model together with the average probabilities of moderate or good EULAR response for patients who could not tolerate MTX or for whom MTX was contraindicated. The probabilities of EULAR response for SSZ+HCQ were assumed to be equal to placebo. The ERG notes that this is likely to be an underestimate. Average probabilities were calculated averaging the probabilities of all patients in the ORAL Solo trial.

Table 37: ORs and probabilities of good and moderate EULAR response for each treatment used in the MTX-intolerant population

Therapy	ORs compared with TOF		Probabilities of EULAR response*		
	Moderate or good	Good	No response	Moderate response	Good response
TOF					
ADA					
ETN[#]					
TCZ					
SSZ+HCQ †					

TOF: tofacitinib; TCZ: tocilizumab; ADA: adalimumab; ETN: etanercept; GOL: golimumab; SSZ: sulfasalazine; HCQ: hydroxychloroquine
*Average probabilities based on the full population of ORAL Solo
[#] Biosimilars assumed to have same efficacy
†Assumed equal to placebo

HAQ-DI improvement upon treatment response

After six months, patients are assumed to be assessed for response. Patients who achieved a moderate or good response are assumed to have a reduction in HAQ-DI score. Following the clarification process, the company used the changes in HAQ-DI score conditional on EULAR response reported by the AG in TA375[24] in the base case: these were reductions of 0.672 for patients who experienced a good response, and 0.317 for patients who experienced a moderate response. These values were calculated by the AG in TA375 based on registry data from the BSRBR database. The company used an alternative approach in a scenario analysis based on trial data from ORAL Standard,[43] Scan,[44] and Sync[45]. This alternative approach consisted of a linear regression model which used each patient's baseline characteristics and the treatment class (cDMARD or JAK/bDMARD) as well as the EULAR response category. In this alternative approach, a good EULAR response was associated with a decrease in HAQ-DI of [redacted], a moderate EULAR response was associated with a decrease of [redacted] and no EULAR response was associated with a HAQ-DI reduction of [redacted]. The company also undertook a scenario analysis where the change in HAQ-DI was based on patient characteristics as well as response levels (see CS, Table 104). The explanatory variables were: moderate response; good response; whether the intervention was a JAK inhibitor or a bDMARD; age; weight; HAQ-DI score; disease duration; ESR; and total cholesterol. In this analysis it was assumed [redacted]. The company's clarification response[34] (question B15) provided further information and the ERG was satisfied with these analyses.

HAQ-DI trajectory following initial response

In the base case, patients on bDMARD treatment (and TOF) are assumed to have zero HAQ-DI progression in line with assumptions made in the AG model for TA375.[24] Clinical advice received by the ERG suggested that the assumption that the HAQ-DI trajectory for TOF is equal to that for bDMARDs was reasonable. In a sensitivity analysis, the company assumed that data from two long-term extension studies, NCT00413699 (ORAL Sequel; Study 1024) and NCT00661661 (Study 1041) detailed in Wollenhaupt *et al*.[119] are applicable for TOF up to month 78 after which HAQ-DI was assumed to be constant. These data from the long-term extension studies are marked as academic-in confidence although the company state that '*The analysis of these data shows essentially no progression*'. Figure 58 and Figure 59 of the CS display these data.

For patients on cDMARDs, in the base case, the company used two different approaches to estimate the HAQ-DI trajectory following initial response: one that estimates the HAQ-DI change for average patients and one that estimates the trajectory for 'rapid progressors'. In the first approach, the company used the latent class approach of Norton *et al*.[120] which was subsequently modified and used by the AG in TA375.[24] This approach identifies four classes of HAQ-DI trajectory: (i) low, (ii) moderate, (iii) high

and (iv) severe. Norton *et al*. report a regression model to calculate each patient's probability of belonging to each class based on the patient's baseline characteristics. The company follow the approach used by the AG in TA375 whereby the change in HAQ-DI score for a patient is calculated as the weighted change in HAQ-DI associated with each class. The company provides commercial-in-confidence data that show that the patients in the ORAL trials appear to have a worse prognosis for HAQ-DI trajectory than the ERAS cohort[121] and that assumed within TA375.[24]

In the second approach, the company assumed that 'rapid progressors' could be identified. These patients are assumed to have a worse long-term HAQ-DI prognosis than that for average patients, which was taken from work reported by the NICE Decision Support Unit (DSU).[122] The ERG comments that whether such patients could be identified has been questioned in a report by Stevenson *et al.*[123] considered within TA375. Furthermore, the company producing baricitinib, having analysed academic-in-confidence data on changes in HAQ, stated in its submission to NICE that '*this suggests that the 'rapid-progressor' group discussed in TA375 that might benefit from more aggressive treatment is a small minority of the overall moderate population*.'[124]

An additional scenario analysis was performed that assumed that HAQ-DI progression was linear for patients receiving cDMARDs and that HAQ-DI increased at a rate of 0.045 per year for patients on LEF and at a rate of 0.06 per year for patients on PALL. The ERG believes that these analyses are inappropriate as HAQ-DI progression has been proven to be non-linear[122] in TA375.[24]

HAQ-DI trajectory prior to treatment cessation

The CS states that prior to treatment discontinuation, the HAQ-DI score improvement observed upon treatment response was lost linearly over the six-month period. This is similar to the approach used in TA375,[24] although in TA375 the entire HAQ-DI loss occurred at the time of discontinuation.

After applying changes to HAQ-DI scores, the resulting values were rounded to the nearest valid HAQ-DI score (which is a multiple of 0.125). The ERG notes that this approach can lead to inaccurate results. This contrasts with the approach used in TA375[24] in which scores were rounded to either the higher or the lower valid HAQ-DI score with a probability proportional to their distance to each (e.g. a value twice closer to the upper HAQ-DI score would be twice as likely to be simulated as the upper score than simulated as the lower score). This point was raised by the ERG during the clarification process (see clarification response,[34] question B4) but was misunderstood and therefore not addressed by the company despite the code being contained in the model to perform a probabilistic analysis of HAQ-DI changes. The ERG assessed the impact of this change in its exploratory analyses.

Treatment duration

Patients who fail to achieve moderate or good EULAR response at 6 months discontinue the current treatment and start the next treatment in the sequence. In contrast, patients who achieve moderate or good EULAR response stay on treatment until loss of efficacy. In order to estimate time on treatment for these patients, the company fitted parametric survival curves to data from acute and long-term tofacitinib studies following the guidelines in NICE DSU TSD14.[125] The company's approach is in line with that of the AG's in TA375,[24] which used treatment duration data from the BSRBR database. The company, following the approach taken by the AG in TA375, fitted separate curves for moderate and good EULAR response, independent of treatment. Unlike the AG in TA375, the company used patients' baseline characteristics (age, gender, HAQ-DI, DAS28, disease duration and number of previous DMARDs) as predictor variables in the model. The company fitted several parametric curves (exponential, log normal, Gompertz, Weibull, log logistic and generalised gamma) to the data and concluded that the log normal function provided the best statistical fit in terms of the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC). The company acknowledged that the gamma function had a better AIC score for moderate response and that its BIC was reasonably close to the log normal in the moderate response. The ERG notes that the AG in TA375 used the gamma distribution. The company undertook scenario analyses using different parametric curves.

5.2.7 Mortality

The company applied the mortality ratios per HAQ-DI score at baseline used in TA375[24] to the life tables from the Office for National Statistics (ONS).[126] The company adopted the assumption that only baseline HAQ-DI score, and not changes to the HAQ, affected mortality, as was the case in the AG's model in TA375.[24] This implies that the life expectancy of patients is independent of the treatment option.

5.2.8 Health-related quality of life

The company undertook a literature review, which was last updated in December 2016. This resulted in 204 records (117 full publications and 87 abstracts). Figure 68 of the CS presents the PRISMA diagram for the review. The company identified 23 studies (21 full publications and 2 abstracts) which used a mapping algorithm to derive utilities from HAQ-DI in RA. The CS also states that as of December 2016, there were 22 studies mapping HAQ-DI score to EQ-5D contained in the online HERC database of mapping studies.[127] One of the more recent mappings was that of Hernandez Alava *et al* which estimates EQ-5D based on patient characteristics (HAQ-DI score, pain on a visual analogue scale, age and sex).[117] This mapping was used by the AG in TA375, and is also used in the company's base case. One amendment between the mapping in TA375 and in the CS related to the assumed pain value associated with each HAQ-DI score. In TA375, the AG used the expected pain score at that HAQ-

DI score, whereas a new relationship between pain on a visual analogue scale and HAQ-DI was calculated by the company based on data from the following ORAL trials: Standard;[43] Scan;[44] Sync;[45] Solo;[46] Start[37]; and Step[35], which the company claim is a better predictor of EQ-5D scores within these data sets. The relationship between HAQ-DI and VAS pain is provided in Table 115 of the CS, along with the distributions of HAQ-DI score (see CS, Figure 64) and EQ-5D (see CS Figure 65) within the combined dataset. The company performed an extensive validation of mapping algorithms within Section 5.4.3 of the CS and conclude that the mapping methodology reported by Hernandez Alava *et al*[117] and using data from the ORAL trials is appropriate for use in the base case. The company presented a scenario using an alternative mapping by Soini *et al.*[128] This alternative mapping produced the best fit to the utility data, but uses a simple linear approach, which can, in alternative datasets *'perform poorly'* as reported in Hernandez Alava *et al.*[117]

5.2.9 Adverse events

The company considered the impacts of serious infections on HRQoL and costs. As the model assumes that patients who have a serious infection discontinue treatment, only one such infection can be experienced per treatment. The rates of serious infections for TOF and the OR of serious infections for the comparators were taken from Strand *et al*.[129] and are shown in Table 121 of the CS. A QALY loss of 0.012, discounted at the relevant rate, was assumed for serious infections having been calculated assuming 28 days' duration and a disutility of 0.156, both taken from Oppong *et al*.[130] Sensitivity analyses removing serious infections and doubling the rate were performed and the model was shown not to be sensitive to this parameter. The ERG notes that the CS acknowledged an increased risk of herpes zoster with tofacitinib compared with bDMARD comparators and therefore considers it should be included in the company's economic analysis.

5.2.10 Resources and costs

The company undertook a literature review, which was last updated in December 2016. This resulted in 30 records (19 full publications and 11 abstracts). The PRISMA diagram for this review is presented in Figure 69 of the CS.

The company's model includes costs associated with drug acquisition, drug administration and monitoring, hospitalisation and serious infections. A detailed estimate of the price of each intervention is provided in Table 122 of the CS, with a summary table also presented (Table 123 of the CS) which has been slightly amended and shown in Table 38. These data are split according to the costs incurred within the first six months of treatment and annual costs beyond six months. In line with TA375[24] the retreatment interval for RTX was assumed to be 9 months although the costs of a rituximab biosimilar have not been incorporated. The CS included a typographical error regarding the costs of RTX but this did not affect the modelling and was corrected during the clarification round. Administration costs were

based on TA375[24] and were inflated to 2014/15 prices using the Hospital and Community Health Services Index.[131]

The cost of palliative care was taken from the Pfizer Rheumatoid Arthritis Model, rather than from the TA375,[24] although these different monthly prices (£44 compared with £60) are not expected to affect the ICER to any large degree.

There is a PAS for CTZ that provides the first 12 weeks of treatment free of charge to the NHS; this was incorporated into the first year's acquisition costs. The PAS for GOL, whereby 100mg is provided at the same price of 50mg was also incorporated. The confidential PAS for ABT and TCZ were not included, as recommended by NICE.

Table 38: Drug acquisition costs

Therapy	Modelled cost	
	Cost months 0-6	Subsequent annual costs
TOF (with PAS)	[redacted]	[redacted]
TOF (with PAS) + MTX	[redacted]	[redacted]
ADA	£4,612.92	£9,225.84
ADA + MTX	£4,624.50	£9,250.80
CTZ	£2,153.10	£9,365.20
CTZ + MTX	£2,164.68	£9,390.16
ETN	£4,717.70	£9,435.40
ETN + MTX	£4,729.28	£9,460.36
ABT + MTX	£9,075.98	£13,888.16
GOL + MTX	£4,605.60	£9,213.00
IFX + MTX	£8,153.85	£9,217.39
RTX + MTX	£3,811.00	£5,081.33
TCZ	£5,694.00	£11,388.00
TCZ + MTX	£5,705.58	£11,412.96
Ciclosporin	£814.80	£1,765.40
LEF	£29.68	£55.69
MTX	£11.58	£24.96
PALL	£265.00	£530.00
SSZ	£60.45	£133.77
DMARD combination*	£72.03	£158.73
ETN biosimilar	£4,334.20	£8,668.40
ETN biosimilar + MTX	£4,345.78	£8,693.36
IFX biosimilar + MTX	£7,441.62	£8,424.13

TOF: tofacitinib; ABT: abatacept; TCZ: tocilizumab; ADA: adalimumab; CTZ: certolizumab pegol; ETN: etanercept; GOL: golimumab; IFX: infliximab; RTX: rituximab; MTX: methotrexate; LEF: leflunomide; cDMARD: conventional disease-modifying antirheumatic drug; PALL: palliative care; SSZ – sulfasalazine

* Assumed to be equal in cost to MTX + SSZ

The cost per IV injection was estimated to be £159.20 and the cost per SC injection was estimated to be £2.70. Monitoring costs were also based on TA375[24] and included full blood count, erythrocyte sedimentation rate (ESR), biochemical profile, chest x-ray, urine analysis, C-reactive protein and a tuberculosis test prior to treatment and full blood counts, ESR and biochemical profile every 0.17 years (approximately every 2 months) whilst on treatment. In addition, it was assumed that the outpatient contact would cost £143 per visit, based on NHS Reference Costs.[132] As in TA375,[24] it was assumed

that patients on bDMARDs and cDMARDs incurred the same monitoring cost. The resulting costs from inflating the figures in TA375[24] were £193.63 prior to treatment initiation, and £883.11 monitoring costs per year.

Hospitalisation costs were based on those within the AG's model in TA375,[24] inflated to 2015/2016 prices. In these estimates, hospitalisation costs were dependent on HAQ-DI score band and were calculated based on data from the Norfolk Arthritis Register (NOAR) database on inpatient days and joint replacements and NHS Reference Costs. The costs used in the model are presented in Table 39.

Table 39: The hospitalisation costs used within the model

HAQ-DI score band	Assumed annual cost
0.00 to <0.50	£173.06
0.50 to <1.00	£106.00
1.00 to <1.50	£376.99
1.50 to <2.00	£541.36
2.00 to <2.50	£1288.34
2.50 to <3.00	£2778.72

The cost per serious infection was £1789 per episode estimated using the average of six NHS Reference Costs considered relevant and uplifted to 2014/15 prices. This value is broadly similar to the cost of £1479 used in the AG model for TA375.[24]

5.2.11 Methods of the analysis

The company undertook analyses within the following groups:

- cDMARD-IR patients with severe RA that could receive combination therapy
- cDMARD-IR patients with severe RA that could receive monotherapy only
- bDMARD-IR patients with severe RA (RTX eligible and RTX ineligible)
- bDMARD-IR patients with severe RA who had received RTX + MTX
- bDMARD-IR patients with severe RA that could receive monotherapy only
- cDMARD-IR patients with moderate RA (combination therapy and monotherapy)

The deterministic results in the base case were produced by simulating 10,000 patients. The company ran the model using a wide range of patient numbers and concluded that 10,000 patients provided the best trade-off between stability of the results and computation time. Graphs and standard errors were presented to support the company's conclusion. Given that the biosimilars are assumed to have the same

efficacy as their branded formulations, the differences in the total QALYs estimated between IFX and its biosimilar and ETN and its biosimilar are the result of Monte Carlo sampling error.

The company presented results of the probabilistic sensitivity analyses (PSA) for all sets of analyses except for the bDMARD-IR MTX ineligible population with severe RA and the cDMARD-IR population with moderate RA (the company did not justify these omissions). For each PSA iteration, 100 patients were simulated instead of the 10,000 patients simulated for the deterministic analyses for computational reasons. Draws from the joint posterior distribution (i.e. CODA) of the NMA were taken in each iteration for the ORs of EULAR response. In the clarification response[34] (question B18), the company states that the probabilistic and deterministic values were similar, and the company provides a plot showing that the results were stable at 1000 iterations.

The company also presented scenario analyses using alternative assumptions to those used in the base case analysis for each of the populations.

For the cDMARD-IR populations, the company presented two base cases: one based on the Norton *et al.*[120] HAQ-DI progression for patients on cDMARDs and another one based on the DSU's rapid progressors analysis. The ERG considered that the rapid progressors analysis was not relevant for decision-making as this is likely to reflect a small subgroup that is difficult to identify, as explained in Section 5.2.6. Consequently, only the results based on the Norton *et al.* HAQ-DI progression were considered relevant by the ERG.

As instructed by NICE, the company did not take into account the confidential PAS in place for TCZ and ABT in their analyses.

5.2.12 Cost effectiveness results

5.2.12.1 Company submission

The analyses in the CS contained limitations identified by the ERG, which were acknowledged by the company to be mistakes or misunderstandings. Therefore, the results of the probabilistic analyses included in Table 137 of the CS are only briefly described here.

In cDMARD-IR patients with severe RA who can receive MTX, TOF+MTX was estimated to dominate GOL+MTX, ADA+MTX, ABT+MTX and IFX+MTX. MTX and IFXb are less costly and less effective than TOF+MTX with the cost savings per QALY lost being approximately £41,000 for IFXb and £42,000 per QALY for MTX. The ICERs for ETN+MTX, CTZ+MTX and TCZ+MTX compared with TOF+MTX are all above £80,000 per QALY gained. When patients with rapid progression were

assumed to be identified, the ICER of TOF+MTX compared with MTX reduced to £23,487 per QALY gained (see CS, Table 138).

In cDMARD-IR patients with severe RA for whom MTX was contraindicated or not tolerated, the probabilistic ICER for TOF monotherapy compared with SSZ+HCQ is estimated to be £53,433 per QALY gained (see CS, Table 148). TOF monotherapy dominates ADA and ETN, but is less effective and less expensive than TCZ monotherapy where the costs saved per QALY lost was higher than £50,000. However, ETN biosimilar was not included in this analysis. When patients with rapid progression were assumed to be identified, the ICER for TOF monotherapy compared with SSZ+HCQ, assumed to have the costs and efficacy of MTX, was reduced to £25,094 per QALY gained (see CS, Table 149).

The company presented two different analyses for the bDMARD-IR population with severe RA dependent on whether RTX was an option. In the group of patients for whom RTX was an option, RTX + MTX dominated (see CS, Table 158). The company also analysed the cost-effectiveness of adding a treatment of TOF+MTX after RTX + MTX and before TCZ + MTX, which was estimated to result in an ICER of £29,454 per QALY gained (Table 167 of the CS). The ERG notes that the analysis includes sequences of different lengths, which introduces considerable uncertainty in the comparative analysis. In bDMARD-IR patients with severe RA for whom RTX was not an option, TOF + MTX dominated all of its comparators (see CS, Table 159).

In bDMARD-IR patients with severe RA who cannot tolerate MTX or in whom MTX is contraindicated, the ICER for TOF monotherapy compared with TCZ monotherapy was estimated in a deterministic analysis to be £25,932 per QALY gained. The ERG notes that the sequences used in this analysis were not specified in the CS and that TCZ is not recommended by NICE as monotherapy for bDMARD-IR patients with severe RA who cannot tolerate MTX. ADA, ETN and CTZ are recommended in this population and therefore should have been included as comparators.

In cDMARD-IR patients with moderate RA who can receive MTX, the company estimated deterministically that the ICER for TOF+MTX compared with a sequence of cDMARD combination treatments was £51,693 per QALY gained (see CS, Table 180). When patients with rapid progression were assumed to be identified, the ICER for TOF+MTX compared with MTX reduced to £38,389 per QALY gained (Table 182 of the CS).

In cDMARD-IR patients with moderate RA who cannot tolerate MTX, the ICER for TOF compared with a sequence of cDMARD combination treatments was estimated deterministically to be £51,370 per QALY gained (see CS, Table 184). When patients with rapid progression were assumed to be

identified, the ICER for TOF+MTX compared with MTX reduced to £38,140 per QALY gained (see CS, Table 186).

5.2.12.2 Clarification response

During the clarification round, the ERG questioned the company on some of the aspects of their analyses and asked for a re-analysis of the company's NMA. Table 40 shows the relevant changes in the company's analyses. Within the clarification response,[34] the company admitted to some mistakes and misunderstandings that led to issues in the analyses. The company only provided a set of analyses using one of the NMAs requested by the ERG, using Estimate 2. The company stated in their response that they believed Estimate 1 to be more *"clinically plausible"* than Estimate 2 and therefore, these analyses do not reflect the company's revised base case.

Table 40: Changes in the company's base case for the clarification response

	Company submission	**Clarification response**	**Company approved**	**Comments provided by the company**
NMA	Estimate 1 Fixed effects	Estimate 2 Random effects	X	Estimate 1 *"is clinically more plausible*" p4 of the Clarification Response
Sequences	Tables 96 to 98 of the CS	Tables 32 to 34 of the clarification response[34]	✓	"*This appears to be a misunderstanding on Pfizer part*." Clarification question B5
HAQ-DI score change upon response	Wrong	Corrected	✓	"*This appears to be a mistake in the model*." Clarification question B11
HAQ-DI progression for LEF and NBT	Linear	Non-linear based on Norton et al.	✓	"*This appears to be a misunderstanding on Pfizer's part.*" Clarification question B7
Predictor of HAQ-DI progression	Age	Age at onset	✓	*"This is a mistake in the analysis"* Clarification question B13
Updating the prior_bdmard flag	No	Yes	**Unclear**	No comment. Clarification question B8

The analyses presented in the company's clarification response resulted in different estimates from those in the CS. In the cDMARD-IR patients with severe RA who could tolerate MTX the ICER for TOF+MTX compared with MTX decreased from £41,617 to [redacted] per QALY gained but was less cost-effective compared with other bDMARDs and was extendedly dominated by MTX and IFXb+MTX (see clarification response,[34] Table 20). The reduction in the ICER for TOF+MTX compared with MTX is explained by the changes in the sequences: more specifically, the sequence used for MTX in the CS featured five consecutive lines of treatment in combination cDMARDs and patients could respond to any number of them. The ERG believes that this assumption is not realistic and replaced the five lines of cDMARD combination treatments with a single MTX treatment. Prompted by

the ERG, the company presented an analysis for bDMARD-IR patients for whom RTX was an option comparing different sequences. The company estimated that replacing TCZ + MTX with TOF + MTX after RTX + MTX would result in savings of [redacted] per QALY saved. The ERG notes that this estimate is highly uncertain as it assumes that the efficacy of TOF + MTX and TCZ + MTX remains unchanged after the RTX + MTX treatment. In bDMARD-IR patients with severe RA for whom RTX was not an option, TOF + MTX was slightly less cost-effective than the recommended bDMARDs compared with the analysis included in the CS. However, TOF+MTX still dominates all of its comparators except TCZ+MTX and ETNb+MTX. The results for the cDMARD-IR population with moderate RA changed only slightly, as the ICER for TOF + MTX compared with MTX decreased from £50,169 to £49,704 per QALY gained. The company's clarification response did not provide analyses for cDMARD-IR or bDMARD-IR patients for whom MTX is contraindicated or not tolerated.

5.2.13 Model validation and face validity checks

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic evaluation and the underlying health economic model upon which this was based. These approaches included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists to critically appraise the company's model and analysis.[133-135]
- Scrutiny of the company's model by health economic modellers including:
    - White-box validation: checking of inputs, code and formulae
    - Black-box testing: changing inputs to check whether the output matches expectations
    - Face-validity testing: checking model results match expectations
    - Comparison of deterministic and probabilistic ICERs.
- Replication of the base case results, PSA and scenario analysis presented within the CS.
- Where possible, checking parameter values used in the company's model against the original data sources.
- Examination of concordance between the description of the model reported within the CS and the company's executable model.
- The use of expert clinical input to judge the clinical robustness of the company's economic evaluation and of the assumptions underpinning the model.

5.3 Summary of key limitations identified within the critical appraisal

The main potential limitations identified within the ERG's critical appraisal of the company's economic analysis are summarised in the box below.

1. Limitations with the company's NMA

2. Missing comparators
3. Inadequate sequences of treatments
4. Assuming same efficacy for SSZ+HCQ as for placebo
5. Assuming the efficacy of the first bDMARD applies to all treatment lines of bDMARDs in the cDMARD-IR population
6. Assuming the same efficacy for TOF+MTX and TOF monotherapy
7. Deterministic rounding to nearest HAQ-DI score
8. Linear HAQ-DI trajectory for palliative care

1. Limitations with the company's NMA

The ERG believes that the company's NMA suffers from potential limitations, which have been described in Section 4.4: (i) the ordered categorical EULAR data were dichotomised in the cDMARD-IR population, which ignores the natural ordering and correlations between the EULAR response categories; (ii) a fixed effects model was used in all the analyses in the bDMARD-IR population and for EULAR responses, which underestimates uncertainty in the treatment effect; and, (iii) the imputation approach used in TOF trials potentially overestimates the treatment effect of TOF versus cDMARD, and could have an important impact in the position of TOF among the bDMARDs.

2. Missing comparators

The company's analyses did not include all the relevant comparators for some of the populations as explained in Section 5.2.3 and Table 34. Most importantly, all relevant comparators were missing in the analysis for bDMARD-IR MTX-intolerant patients with severe RA and four comparators (ADA, ETN, IFX and CTZ with concomitant MTX) out of seven were missing from the analysis for bDMARD-IR RTX-ineligible patients with severe RA. The ERG notes the company included neither the RTX biosimilar nor the SC formulations of ABT and TCZ.

3. Inadequate sequences of treatments

The ERG notes that the sequences used by the company were not appropriate for the following reasons:

- The inclusion of multiple consecutive treatments of cDMARD combinations and SSZ+HCQ. Patients only go through one such treatment before progressing to another type of treatment.
- The inclusion of bDMARD treatments in populations and points in the pathway which have not been recommended by NICE, such as:
    - ETN+MTX after TCZ+MTX and RTX+MTX in cDMARD-IR patients with severe RA.
    - ABT+MTX and GOL+MTX in the bDMARD-IR RTX-eligible patients with severe RA.

  - TCZ+MTX after TOF, ABT or GOL concomitant with MTX in the bDMARD-IR RTX-ineligible patients with severe RA.
  - GOL+MTX after TCZ+MTX in the bDMARD-IR RTX-ineligible patients with severe RA.
  - TCZ monotherapy in bDMARD-IR MTX-intolerant patients with severe RA.
  - RTX+MTX and TCZ+MTX after cDMARD combination in cDMARD-IR patients with moderate RA.
- The inclusion of three or four post-biologic treatments before palliative care instead of just one.

4. *Assuming the same efficacy for SSZ as for placebo*

The company used the EULAR response ORs calculated in the NMA for placebo as an estimate for the ORs for SSZ+HCQ. The ERG notes that this is likely to underestimate the effectiveness of SSZ and therefore underestimate the ICER for TOF monotherapy compared with SSZ.

5. *Assuming the same efficacy for TOF as monotherapy and in combination with MTX*

The company assumed that TOF as monotherapy would have the same efficacy as in combination with MTX. However, ORAL Strategy (NCT02187055)[40] showed that TOF monotherapy was statistically inferior to TOF+MTX. The also NMA shows that TOF monotherapy results in slightly lower probabilities of response than TOF + MTX: in cDMARD-IR patients, an average of [redacted]% versus [redacted]% achieved good EULAR response and [redacted]% versus [redacted]% achieved moderate EULAR response (see clarification response,[34] Table 8). However, the ERG acknowledges that the company estimated the efficacies of other monotherapies in comparison with TOF monotherapy and therefore the relative impact of this assumption is likely to be reduced.

6. *Assuming the efficacy of the first bDMARD applies to all treatment lines of bDMARDs in the cDMARD-IR population*

Within the CS, the company assumed that the efficacy of bDMARDs in terms of probabilities of EULAR response would remain unchanged irrespective of whether they were given as first line or subsequent line treatment. However, as demonstrated by the company's own regression model, the efficacy of bDMARDs is lower in bDMARD-IR patients than in cDMARD-IR patients. Therefore, for the second and subsequent lines of treatment in the cDMARD-IR population, it is more appropriate to use the probability of EULAR response calculated in the bDMARD-IR patients. During the clarification process, the ERG asked the company to activate the prior_bdmard flag after patients had gone through their first bDMARD (or JAK inhibitor). The company implemented this change and presented results of new analyses including it. However, the ERG notes that this change in isolation is not enough, as the comparative efficacy of TOF is different in cDMARD-IR population compared to that in the bDMARD-IR population.

7. Deterministic rounding to nearest HAQ-DI score

HAQ-DI scores range from 0 to 3, with higher scores indicating greater disability. HAQ-DI scores lie on a discrete scale with step values of 0.125, resulting in 25 points. In the model, patients start with a baseline HAQ-DI score and the HAQ-DI progression of patients is modified reflecting treatment response, loss of treatment efficacy or disease progression over time. Changes applied to the HAQ-DI score are usually estimates based on average changes observed in trials or registries and therefore are rarely exact multiples of 0.125. Thus, after applying such a change, the resulting HAQ-DI score of a patient has to be assigned to a valid HAQ-DI score. The company approached this issue by rounding the values to the nearest valid HAQ-DI score. The ERG notes that this approach 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. An example would be that of small changes (lower than 0.0625), that would always be rounded down to zero. In order to avoid this problem, the AG in TA375[24] rounded up with a probability inversely proportional to the distance of the value to the closest valid HAQ-DI score, and rounded down otherwise. For example, a change of 0.4 would have a 0.8 probability of being rounded down to 0.375 and a probability of 0.2 of being rounded up to 0.5.

8. Linear HAQ-DI trajectory for palliative care

The company misinterpreted the AG's report in TA375[24] and consequently applied a linear annual increase of 0.045 in HAQ-DI score to palliative care in the analyses presented in the CS. The ERG noted in the clarification round that in the AG's analysis in TA375,[24] the HAQ-DI score of patients on palliative care followed the same trajectories as the rest of patients on cDMARDs. The company acknowledged this and corrected the issue in their revised model.

5.4 Additional exploratory analyses undertaken by the ERG

The ERG undertook additional analyses including the corrections implemented by the company in response to the ERG's clarification questions. The corrections implemented by the company include:

- Corrected changes in HAQ-DI scores upon response.
- Norton *et al.*[120] progression is used instead of linear progression for palliative care (NBT).
- Activating the prior_bdmard flag after the first biologic or JAK inhibitor when calculating the probabilities of EULAR response.

The ERG also applied the following changes to the company's revised model:

- Calculating the ORs for all treatments including monotherapies compared to TOF+MTX. This change only affected sequences that included monotherapies, as the ORs for combination therapies were already being calculated compared to TOF+MTX. The ERG only applied this

change to the analyses based on the clarification NMA, given that it did not have access to the necessary data to apply it to the results of the company's NMA.

- Probabilistic rounding of HAQ-DI scores.

For its analyses, the ERG used the sequences defined in Table 41, Table 42, Table 43 and Table 44. NBT was assumed to be equivalent to the palliative care used in the company's analyses.

Two sets of analyses are presented for each population: one based on the company's NMA and the other one based on the NMA requested by the ERG in the clarification letter. The main difference between the company's NMA and the clarification NMA is that in the former treatment effect was estimated by applying NRI only in the placebo arm (estimate 1), whilst in the latter treatment effect was estimated applying NRI in both arms (estimate 2) – for more details see Section 4.3.2. The ERG believes that the true treatment effect lies between these two estimates, but closer to estimate 1 than to estimate 2, given that, according to the company, [redacted] of non-responders on TOF at month 3 subsequently developed a response at month 6 compared with less than 10% in the placebo arm.

Due to time constraints, the ERG's analyses were undertaken using only the deterministic version of the model; the ERG used the same number of patients (10,000) as the company in their deterministic analyses.

Table 41: Treatment sequences for the cDMARD-IR population with severe RA who can tolerate MTX

	MTX	**ABT+ MTX**	**ADA+ MTX**	**CTZ+ MTX**	**GOL+ MTX**	**TCZ+ MTX**	**TOF+ MTX**	**ETNb+ MTX**	**IFXb+ MTX**
1	MTX	ABT+ MTX	ADA+ MTX	CTZ+ MTX	GOL+ MTX	TCZ+ MTX	TOF+ MTX	ETNb+ MTX	IFX+ 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

Abbreviations: ABT, abatacept; ADA, adalimumab; CTZ, certolizumab pegol; ETNb, etanercept biosimilar; GOL, golimumab; IFXb, infliximab biosimilar; MTX, methotrexate; NBT, non-biologic treatment; RTX, rituximab; TCZ, tocilizumab; TOF, tofacitinib.

Table 42: Treatment sequences for a cDMARD-IR population with severe RA for whom MTX is contraindicated or not tolerated

Treatment	**SSZ**	**TCZ**	**TOF**	**ETNb**	**ADA**

line					
1	SSZ	TCZ	TOF	ETNb	ADA
2	NBT	ETNb	ETNb	ADA	ETNb
3		SSZ	SSZ	SSZ	SSZ
4		NBT	NBT	NBT	NBT

Abbreviations: ADA, adalimumab; ETNb, etanercept biosimilar; NBT, non-biologic treatment; SSZ, sulfasalazine; TCZ, tocilizumab; TOF, tofacitinib.

Table 43: Treatment sequences for a bDMARD-IR population with severe RA

Sequence	RTX intolerant				RTX tolerant			
	TOF+ MTX	**ABT+ MTX**	**TCZ+ MTX**	**GOL+ MTX**	**RTX, TCZ**	**RTX, TOF**	**RTX, TOF, TCZ**	**RTX, TCZ, TOF**
1	TOF+ MTX	ABT+ MTX	TCZ+ MTX	GOL+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX	RTX+ MTX
2	MTX	MTX	MTX	MTX	TCZ+ MTX	TOF+ MTX	TOF+ MTX	TCZ+ MTX
3	NBT	NBT	NBT	NBT	MTX	MTX	TCZ+ MTX	TOF+ MTX
4					NBT	NBT	MTX	MTX
5							NBT	NBT

Abbreviations: ABT, abatacept; ADA, adalimumab; GOL, golimumab; MTX, methotrexate; NBT, non-biologic treatment; RTX, rituximab; TCZ, tocilizumab; TOF, tofacitinib.

Table 44: Treatment sequences for a cDMARD-IR population with moderate RA

Treatment sequence	Moderate sequences†		Severe sequence
	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.

5.4.1 CDMARD-IR patients with severe RA: combination therapy

Table 45 and

Table **46** show the results of the analyses for cDMARD-IR patients with severe RA on combination therapy, using the company's NMA and the clarification NMA respectively. Given that most of the comparators recommended by NICE are not on the cost-effectiveness frontier, in addition to presenting a fully incremental analysis, a column was included to show the ICER of each of the comparators versus TOF+MTX.

TOF+MTX dominated ADA+MTX regardless of the NMA used in the analysis and the ICERs for TOF+MTX versus most of its comparators were favourable: the ICERs of TOF+MTX compared with GOL, CTZ and ETNb with concomitant MTX were higher than £49,000 per QALY gained regardless of the NMA used. However, TOF+MTX was extendedly dominated by MTX and IFXb+MTX in a fully incremental analysis using the clarification NMA.

Table 45: Results for cDMARD-IR patients with severe RA on combination therapy using company's NMA (estimate 1)

Sequences*	Total QALYs	Total costs (£)	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)	ICER vs TOF+MTX (£/QALY)
MTX	[redacted]	[redacted]				£32,883†
TCZ+MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£31,163†
IFXb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£26,161†
ABT+MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£32,883	-
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£563,148
CTZ+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£139,684
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£85,578	£85,578

*Treatments sequences as specified in Table 41
#Does not include confidential PAS
†ICERs in the southwestern 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;

Table 46: Results for cDMARD-IR patients with severe RA: combination therapy using the clarification NMA (estimate 2)

Sequences*	Total QALYs	Total costs (£)	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)	ICER vs TOF+MTX (£/QALY)
MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	£32,826†
TCZ+MTX[#]	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£29,092†
ADA+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	-
ABT+MTX[#]	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£6,572,401
IFXb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£32,481	£209
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£83,259
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£61,037	£49,988
CTZ+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£87,439	£57,326

Treatments sequences as specified in Table 41
[#]Does not include confidential PAS
†ICERs in the southwestern 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;

The absolute QALYs presented in

Table **46** did not appear intuitive in that reducing the relative efficacy of TOF resulted in an increase in QALYs across all strategies. On investigation, this was found to be explained by the fact that TOF was used to determine the baseline response rates. As such, if TOF was relatively less efficacious, then all comparators would be more efficacious. Given that within the TOF+MTX strategy, it is followed by RTX+MTX, and TCZ+MTX, the total QALYs accrued throughout the sequence increased. As expected, relative ICERs for TOF+MTX compared with other strategies were less favourable in

Table **46** compared with those in Table 45. The ERG undertook a scenario analysis using the rates for cDMARD from TA375[24] as a baseline. The results of this scenario analysis were very similar to those presented in Table 45 and

Table **46**, so the ERG chose not to present them here.

5.4.2 CDMARD-IR patients with severe RA: monotherapy

In cDMARD-IR patients with severe RA for whom MTX was contraindicated or not tolerated, the ICERs for TOF monotherapy versus all of its comparators were higher than £50,000 per QALY gained in both analyses, as shown in Table 47 and Table 48.

Table 47: Results for cDMARD-IR patients with severe RA: monotherapy using company's NMA (estimate 1)

Sequences*	Total QALYs	Total costs (£)	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)	ICER vs TOF (£/QALY)
SSZ	[redacted]	[redacted]	[redacted]	[redacted]	-	£35,138†
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£35,138	-
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£99,795
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£79,288
TCZ#	[redacted]	[redacted]	[redacted]	[redacted]	£51,488	£51,488

*Treatments sequences as specified in Table 42
#Does not include confidential PAS
†ICERs in the southwestern quadrant, i.e. representing cost savings per QALY lost.

SSZ: sulfasalazine: TOF: tofacitinib; TCZ: tocilizumab; ADA: adalimumab; ETNb: etanercept biosimilar;

Table 48: Results for cDMARD-IR patients with severe RA: monotherapy using the clarification NMA (estimate 2) and ORs calculated versus TOF+MTX

Sequences*	Total QALYs	Total costs (£)	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)	ICER vs TOF (£/QALY)
SSZ	[redacted]	[redacted]	[redacted]	[redacted]	-	£35,095†
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£35,095	-
ETNb	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£72,201
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£63,881
TCZ#	[redacted]	[redacted]	[redacted]	[redacted]	£50,430	£50,430

*Treatments sequences as specified in Table 42
#Does not include confidential PAS
†ICERs in the southwestern quadrant, i.e. representing cost savings per QALY lost.

SSZ: sulfasalazine: TOF: tofacitinib; TCZ: tocilizumab; ADA: adalimumab; ETNb: etanercept biosimilar;

5.4.3 BDMARD-IR MTX-tolerant RTX-eligible with severe RA

Table 49 and Table 50 present the results of the analyses for bDMARD-IR patients who could tolerate MTX and for whom RTX was an option. In this population, only the "RTX, TCZ" sequence is recommended by NICE and a column was added to tables to present the ICER of the alternative sequences compared with the recommended sequence. As shown in these tables, the sequence where TOF+MTX replaces RTX+MTX (TOF, TCZ) is dominated by the currently recommended sequence (RTX, TCZ). The sequence "RTX, TOF", that is, where TOF replaces TCZ in the currently recommended sequence, is estimated to produce cost savings ranging from £67,852 to £90,846. However, the confidential PAS in place for TCZ has not been included in this analysis.

Table 49: Results for bDMARD-IR MTX-tolerant RTX-eligible patients with severe RA using company's NMA (estimate 1)

Sequences*#	Total QALYs	Total costs (£)	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)	ICER vs RTX,TCZ‡ (£/QALY)
RTX,TOF	[redacted]	[redacted]	[redacted]	[redacted]	-	£67,852†
TOF,TCZ	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
RTX,TCZ‡	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	-
RTX,TOF,TCZ	[redacted]	[redacted]	[redacted]	[redacted]	£44,535	£32,426
RTX,TCZ,TOF	[redacted]	[redacted]	[redacted]	[redacted]	£704,235	£37,657

*Treatments sequences as specified in Table 43. RTX, TOF and TCZ provided with concomitant MTX.
#Does not include confidential PAS of TCZ
†ICERs in the southwestern quadrant, representing cost savings per QALY lost.
‡Currently recommended sequence.

RTX: rituximab, TOF: tofacitinib; TCZ: tocilizumab; MTX: methotrexate

Table 50: Results for bDMARD-IR MTX-tolerant RTX-eligible patients with severe RA using the the clarification NMA (estimate 2)

Sequences*#	Total QALYs	Total costs (£)	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)	ICER vs RTX,TCZ‡ (£/QALY)
RTX,TOF	[redacted]	[redacted]				£90,846†
TOF,TCZ	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
RTX,TCZ‡	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	-
RTX,TOF,TCZ	[redacted]	[redacted]	[redacted]	[redacted]	£43,530	£35,083
RTX,TCZ,TOF	[redacted]	[redacted]	[redacted]	[redacted]	£59,237	£36,202

*Treatments sequences as specified in Table 43
#Does not include confidential PAS of TCZ
†ICERs in the southwestern quadrant, representing cost savings per QALY lost.
‡Currently recommended sequence.

RTX: rituximab, TOF: tofacitinib; TCZ: tocilizumab;

5.4.4 BDMARD-IR MTX-tolerant RTX-ineligible with severe RA

In bDMARD-IR patients for whom RTX was contraindicated or not tolerated but could tolerate MTX, TOF+MTX dominated GOL+MTX and ABT+MTX using the company's NMA (as shown in

Table **51**) and only GOL+MTX using the clarification NMA (Table 52). The ICERs for TOF+MTX versus the other comparators included in the analyses were all higher than £38,000 per QALY. However, the ERG notes that ADA, IFX and CTZ with concomitant MTX have not been included in the analyses despite being recommended by NICE because the ERG did not have access to estimates of their efficacy in this population.

Table 51: Results for bDMARD-IR MTX-tolerant RTX-ineligible patients with severe RA using company's NMA (estimate 1)

Sequences*	Total QALYs	Total costs (£)	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)	ICER vs TOF+MTX (£/QALY)
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]	£75,070	£75,070

*Treatments sequences as specified in Table 43
#Does not include confidential PAS

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

Table 52: Results for bDMARD-IR MTX-tolerant RTX-ineligible patients with severe RA using the clarification NMA (estimate 2)

Sequences*	Total QALYs	Total costs (£)	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)	ICER vs TOF+MTX (£/QALY)
GOL+MTX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	-	-
ABT+MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£12,624,118
TCZ+MTX#	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£99,511
ETNb+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£38,017	£38,017

*Treatments sequences as specified in Table 43
#Does not include confidential PAS

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

5.4.5 BDMARD-IR MTX-intolerant patients with severe RA

The ERG decided not to run any analyses for the bDMARD-IR patients with severe RA who were MTX-intolerant because the company did not provide effectiveness evidence for any of the relevant comparators, namely ADA, ETN and CTZ.

5.4.6 CDMARD-IR patients with moderate RA

In patients with moderate RA who were cDMARD-IR, the ICER of TOF+MTX compared with a sequence starting with MTX ranged from £47,594 to £50,708 per QALY gained as shown in

Table **53** and Table 54.

Table 53: Results for cDMARD-IR patients with moderate RA using the company's NMA (estimate 1)

Sequences*	Total QALYs	Total costs (£)	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)
MTX	[redacted]	[redacted]			
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£47,594

*Treatments sequences defined in Table 44
TOF: tofacitinib; MTX: methotrexate;

Table 54: Results for cDMARD-IR patients with moderate RA using the the clarification NMA (estimate 2)

Interventions*	Total QALYs	Total costs (£)	Inc. QALYs	Inc. costs (£)	ICER (£/QALY)
MTX	[redacted]	[redacted]			
TOF+MTX	[redacted]	[redacted]	[redacted]	[redacted]	£50,708

*Treatments sequences defined in Table 44
TOF: tofacitinib; MTX: methotrexate;

5.5 Discussion

The CS includes a systematic review of economic evaluations of treatments for moderate and severe RA together with a *de novo* model-based economic evaluation of TOF in combination with MTX or as monotherapy versus currently recommended treatments in adult moderate and severe RA, cDMARD-IR and bDMARD-IR patients.

The company's systematic review of existing economic evaluations did not identify any relevant studies that estimated the cost-effectiveness of TOF + MTX or TOF monotherapy.

The company's *de novo* economic model was largely based on the model developed by the AG in TA375.[24] Costs and health outcomes for TOF and its comparators were estimated from the perspective of the NHS over a lifetime horizon. The analyses presented in the CS relate to six different populations of RA patients: (i) severe RA cDMARD-IR MTX-tolerant; (ii) severe RA cDMARD-IR MTX-intolerant; (iii) severe RA bDMARD-IR who are RTX eligible; (iv) severe RA bDMARD-IR who are not eligible for RTX; (v) severe RA bDMARD-IR MTX intolerant; and, (iv) moderate RA cDMARD-IR;.

In the severe RA cDMARD-IR population, TOF + MTX dominated some of its comparators and was estimated to result in [redacted]. In severe cDMARD-IR patients for whom MTX was contraindicated or not tolerated, TOF monotherapy was less effective and less expensive than the recommended bDMARDs (ETN, ADA, and TCZ) but the savings

per QALY lost are estimated to exceed £50,000. CTZ, which is recommended by NICE in this population, was not included in the analysis. In the severe bDMARD-IR population, TOF+MTX was dominated by RTX+MTX if RTX was an option. [redacted] On the other hand, TOF+ MTX dominated most of its comparators when RTX was not an option in bDMARD-IR patients with severe RA. The company did not provide relevant evidence to analyse the cost-effectiveness of TOF monotherapy in severe bDMARD-IR patients for whom MTX is contraindicated or not tolerated. In the moderate RA cDMARD-IR population, the ICER for TOF + MTX compared with MTX ranged from £47,594 to £50,708 per QALY gained.

The ERG's critical appraisal identified a number of issues in the company's analyses: (i) relevant comparators recommended by NICE were not included in the analyses; (ii) the sequences used in the company's original analyses included bDMARD treatments in points in the pathway not recommended by NICE; (iii) the company assumed equal efficacy for tofacitinib as monotherapy and in combination with MTX in terms of the probabilities of achieving moderate and good EULAR responses; (iv) the efficacy of SSZ was estimated to be equal to the results from the NMA for placebo; and, (v), the company rounded modified 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. The company corrected the first two issues in the revised model submitted with the clarification responses but did not present a full set of analyses relating to their revised base case.

The ERG undertook exploratory analyses based on the company's model and alleviating some of the issues identified in the company's analysis: (i) using sequences that the ERG believed reflected the recommendations from NICE; (ii) calculation ORs for the probabilities of EULAR response of all treatments compared with TOF+MTX; (iii) and implementing the probabilistic rounding of the HAQ-DI scores. The ERG presented two sets of analyses, once based on the company's NMA, and the other one based on the NMA requested by the ERG in its clarification letter. The ERG believes that the true treatment effect lies in the middle between the estimates produced by these two NMAs.

For cDMARD-IR patients with severe RA who can tolerate MTX, based on the company's NMA, TOF + MTX dominated all of its bDMARD comparators except ETNb + MTX. Based on the clarification NMA, TOF + MTX dominated ADA+MTX but was extendedly dominated in the full incremental analysis. For cDMARD-IR patients with severe RA for whom MTX was contraindicated or not tolerated, TOF and TCZ monotherapy extendedly dominated ADA and ETN biosimilar regardless of the NMA used. The ICER of TCZ compared with TOF ranged from £50,430 to £51,488 per QALY gained. In the bDMARD-IR patients with severe RA for whom RTX was an option, the currently

recommended sequence starting with RTX+MTX dominated a sequence where TOF + MTX replaced RTX + MTX regardless of the NMA used. In the bDMARD-IR patients with severe RA for whom RTX was not an option, TOF + MTX dominated GOL+MTX regardless of the NMA used, and dominated ABT + MTX when using the company's NMA. The ICER of ETNb and TCZ with concomitant MTX compared with tofacitinib + MTX was higher than £30,000 per QALY gained regardless of the NMA used. Finally, in patients with moderate RA who were cDMARD-IR, the ICER of TOF + MTX compared with MTX ranged from £47,594 to £50,708 per QALY gained. All analyses presented in this report have not taken any commercial-in-confidence PASs into consideration. The ERG presents in a confidential appendix analyses when the confidential PASs currently in place for TCZ IV and ABT IV are incorporated.

There remain several potentially important areas of uncertainty:

1. Cost-effectiveness of TOF monotherapy in the bDMARD-IR MTX-intolerant population with severe RA. The company did not present any efficacy estimates for the comparators in this population. Instead, the company presented an analysis comparing TOF monotherapy with TCZ monotherapy, which is not recommended by NICE at that point in the pathway. However, the ERG acknowledges that the results of this analysis along with those for the cDMARD-IR MTX-intolerant population with severe RA provide an indication of the cost-effectiveness of TOF monotherapy in the bDMARD-IR MTX-intolerant population with severe RA.

2. Cost-effectiveness of TOF + MTX in the bDMARD-IR RTX-ineligible population with severe RA. The company only presented evidence on the effectiveness of TCZ, GOL, and ABT in combination with MTX for the bDMARD-IR population with severe RA. No evidence was presented on the cost-effectiveness of TOF + MTX compared with ETN, IFX, ADA, CTZ with concomitant MTX in the bDMARD-IR RTX-ineligible population with severe RA.

3. Efficacy of bDMARDs after TOF
   No evidence was presented by the company on the effectiveness of bDMARDs after TOF. In the company's economic analysis, it was assumed that the efficacy of bDMARDs after TOF will be equal to their efficacy after another bDMARD. This is a reasonable assumption to make given the lack of evidence, but the ERG notes that it is unknown whether the efficacy of bDMARDs after TOF could be better (or worse) than when following another bDMARD.

5 END OF LIFE

NICE end of life supplementary advice should be applied in the following circumstances and when both the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and;

The company did not include any claim or justification in the CS for tofacitinib to be considered as an end of life treatment. The ERG believes that neither criterion would be met as patients receiving treatment would be expected to have a life expectancy considerably longer than 24 months and there is little robust evidence to suggest that tofacitinib would provide an additional 3 months of life compared with its comparators.

6 OVERALL CONCLUSIONS

The systematic review of clinical effectiveness showed TOF plus MTX to be superior to placebo plus cDMARD in the target population across a number of relevant primary endpoints. The company's NMA of clinical effectiveness showed that TOF plus cDMARD was superior to cDMARD and comparable to bDMARDs. Evidence to support the clinical effectiveness of TOF monotherapy in those who cannot tolerate MTX is less robust. In the ORAL Solo trial TOF monotherapy demonstrated statistical significance versus placebo for only two of its primary endpoints and data were for 3 months only. TOF treatment in combination with MTX was more efficacious than when TOF was used as monotherapy. Safety data for the two different treatment regimens (TOF plus MTX and TOF monotherapy) should be reported individually rather than pooled as they are reported to be different for each regimen by sources that are not referenced in the CS. An NMA of AEs was not presented in the CS but a paper referenced, but not elaborated upon, in the CS found that the incidence of herpes zoster was higher in TOF than in bDMARDs.

According to the company's analyses, in the severe RA cDMARD-IR population who can tolerate MTX, TOF plus MTX dominates some of its comparators and have favourable ICERs compared with most of the rest of comparators. In the severe RA cDMARD-IR patients for whom MTX is contraindicated or not tolerated, TOF monotherapy dominates some of its comparators. In bDMARD-IR patients with severe RA for whom RTX is an option, RTX plus MTX dominates TOF plus MTX. [redacted] In bDMARD-IR RTX-ineligible patients with severe RA, TOF plus MTX dominates most of its comparators. The company did not provide an analysis for the bDMARD-IR patients with severe disease for whom MTX was contraindicated or not tolerated where TOF monotherapy was compared with its relevant comparators. In the cDMARD-IR population with moderate RA, the ICER of TOF plus MTX compared with MTX ranges from £47,594 to £50,708 per QALY gained. However, the commercial in confidence PASs for some comparators could not be included in these analyses.

The ERG's critical appraisal identified a number of issues relating to the company's model and analysis. The ERG believes that: the NMA is subject to potential limitations; relevant comparators recommended by NICE were not included in the analyses; the sequences used in the company's original analyses included bDMARD treatments in points in the pathway not recommended by NICE; the company assumed equal efficacy for TOF as monotherapy and for TOF + MTX; and, the company rounded modified 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.

The ERG undertook exploratory analyses based on the company's model, alleviating some of the issues identified in the company's analysis and providing results based on two alternative NMAs. The results of the exploratory analyses carried out by the ERG were slightly different to those presented by the company but did not significantly impact the conclusions.

[redacted] In the cDMARD-IR population with moderate RA, the ICER of TOF+MTX compared with MTX was always higher than £45,000 per QALY gained in the most appropriate analyses.

There remain several potentially important areas of uncertainty:

1. Cost-effectiveness of TOF monotherapy in the bDMARD-IR MTX-intolerant population.
2. Cost-effectiveness of TOF + MTX in the bDMARD-IR RTX-ineligible population with severe disease.
3. The efficacy of bDMARDs after TOF.

7 REFERENCES

1. Pfizer Inc. Rheumatoid arthritis - tofacitinib citrate – Company Evidence Submission. London: NICE; 2017.
2. National Institute for Health and Care Excellence. Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs - Final scope. 2017.
3. Scott DL, Steer S. The course of established rheumatoid arthritis. *Best Practice & Research Clinical Rheumatology* 2007;21:943-67.
4. Pincus T, Fuchs HA, Callahan LF, Nance EP, Kaye JJ. Early radiographic joint space narrowing and erosion and later malalignment in rheumatoid arthritis: a longitudinal analysis. *The Journal of Rheumatology* 1998;25:636-40.
5. Drossaers-Bakker KW, Kroon HM, Zwinderman AH, Breedveld FC, Hazes JMW. Radiographic damage of large joints in long-term rheumatoid arthritis and its relation to function. *Rheumatology* 2000;39:998-1003.
6. Allaire S, Wolfe F, Niu J, LaValley MP, Zhang B, Reisine S. Current risk factors for work disability associated with rheumatoid arthritis: Recent data from a US national cohort. *Arthritis Care & Research* 2009;61:321-8.
7. Naz SM, Symmons DPM. Mortality in established rheumatoid arthritis. *Best Practice & Research Clinical Rheumatology* 2007;21:871-83.
8. Dadoun S, Zeboulon-Ktorza N, Combescure C, Elhai M, Rozenberg S, Gossec L*, et al.* Mortality in rheumatoid arthritis over the last fifty years: Systematic review and meta-analysis. *Joint Bone Spine* 2013;80:29-33.
9. Meune C, Touzé E, Trinquart L, Allanore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. *Rheumatology* 2009;48:1309-13.
10. National Collaborating Centre for Chronic Conditions. Rheumatoid arthritis: national clinical guideline for management and treatment in adults: Royal College of Physicians (UK); 2009.
11. Symmons D, Turner G, Webb R, Asten P, Barrett E, Lunt M*, et al.* The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. *Rheumatology* 2002;41:793-800.
12. Symmons DPM, Barrett EM, Bankhead CR, Scott DGL, Silman AJ. The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk Arthritis Register. *Rheumatology* 1994;33:735-9.
13. MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K*, et al.* Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. *Arthritis & Rheumatism* 2000;43:30-7.
14. Jones MA, Silman AJ, Whiting S, Barrett EM, Symmons DP. Occurrence of rheumatoid arthritis is not increased in the first degree relatives of a population based inception cohort of inflammatory polyarthritis. *Ann Rheum Dis* 1996;55:89-93.
15. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS*, et al.* The american rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis & Rheumatism* 1988;31:315-24.
16. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M*, et al.* EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007;66:34-45.
17. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO*, et al.* 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580-8.
18. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C*, et al.* American college of rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis & Rheumatism* 1995;38:727-35.
19. van Gestel AM, Prevoo MLL, van't Hof MA, van Rijswijk MH, van de Putte LBA, van Riel PL. Development and validation of the european league against rheumatism response criteria

for rheumatoid arthritis: Comparison with the preliminary american college of rheumatology and the world health organization/international league against rheumatism criteria. *Arthritis & Rheumatism* 1996;39:34-40.
20. Felson DT. Assessing the efficacy and safety of rheumatic disease treatments: Obstacles and proposed solutions. *Arthritis & Rheumatism* 2003;48:1781-7.
21. Prevoo MLL, Van'T Hof MA, Kuper HH, Van Leeuwen MA, Van De Putte LBA, Van Riel PLCM. Modified disease activity scores that include twenty-eight-joint counts development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis & Rheumatism* 1995;38:44-8.
22. van Gestel AM, Anderson JJ, van Riel PL, Boers M, Haagsma CJ, Rich B.*, et al.* ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. American College of Rheumatology European League of Associations for Rheumatology. *Journal of Rheumatology* 1999;26:705-11.
23. Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J*, et al.* Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. *Health Technology Assessment* 2016;20.
24. National Institute for Health and Clinical Excellence (NICE). Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed; 2016.
25. Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). *Clin Exp Rheumatol* 2005;23:S14-S8.
26. National Institute for Health and Clinical Excellence (NICE). Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. London: NICE; 2010.
27. National Institute for Health and Clinical Excellence (NICE). Tocilizumab for the treatment of rheumatoid arthritis.; 2012.
28. National Institute for Health and Care Excellence. Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF inhibitor – Company Submission. London: NICE; 2016.
29. European Medicines Agency. Assessment report Xeljanz; 2015.
30. Xeljanz. Annex I. Summary of Product Characteristics. 2017.
31. Barton JL. Patient preferences and satisfaction in the treatment of rheumatoid arthritis with biologic therapy. *Patient Prefer Adherence* 2009;3:335-44.
32. Louder AM, Singh A, Saverno K, Cappelleri JC, Aten AJ, Koenig AS*, et al.* Patient Preferences Regarding Rheumatoid Arthritis Therapies: A Conjoint Analysis. *American health & drug benefits* 2016;9:84-93.
33. Cohen SB, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P*, et al.* Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. *Ann Rheum Dis* 2017, http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medp&NEWS=N&AN=28143815.
34. Pfizer Inc. Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs [ID526]. Clarification response; 2017.
35. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B*, et al.* Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet (London, England)* 2013;381:451-60.
36. Pfizer Inc. Clinical Study Report A3921032: Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of 2 Doses of CP-690,550 in Patients With Active Rheumatoid Arthritis on Background Methotrexate With Inadequate Response to TNF Inhibitors.; 2012.

37. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, *et al.* Tofacitinib versus methotrexate in rheumatoid arthritis. *The New England Journal of Medicine* 2014;370:2377-86.
38. Pfizer Inc. Clinical Study Report A3921069: Phase 3 Randomized, Double Blind Study of the Efficacy and Safety of 2 Doses of CP-690,550 Compared to Methotrexate in Methotrexate Naïve Patients with Rheumatoid Arthritis.; 2015.
39. Buch MH, Aletaha D, Emery P, Smolen JS. Reporting of long-term extension studies: lack of consistency calls for consensus. *Ann Rheum Dis* 2011;70:886-90.
40. Pfizer Inc. Protocol A3921187. A phase 3b/4 randomized double blind study of 5 mg of tofacitinib with and without methotrexate in comparison to adalimumab with methotrexate in subjects with moderately to severely active rheumatoid arthritis. Statistical analysis plan; 2014.
41. Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z, *et al.* Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. *The Lancet* 2017; 10.1016/S0140-6736(17)31618-5.
42. National Institute for Health and Care Excellence (NICE). Single technology appraisal: User guide for company evidence submission template. *Journal* 2015. https://www.nice.org.uk/article/pmg24/chapter/Instructions-for-companies 6 November 2015
43. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S, *et al.* Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *The New England Journal of Medicine* 2012;367:508-19.
44. van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, *et al.* Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis and Rheumatism* 2013;65:559-70.
45. Kremer J, Li Z-G, Hall S, Fleischmann R, Genovese M, Martin-Mola E, *et al.* Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Annals of internal medicine* 2013;159:253-61.
46. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, *et al.* Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *The New England Journal of Medicine* 2012;367:495-507.
47. Pfizer Inc. Phase 3 Randomized, Double-Blind, Active Comparator, Placebo-Controlled Study of the Efficacy and Safety of 2 Doses of CP-690,550 in Patients with Active Rheumatoid Arthritis on Background Methotrexate. Clinical Study Report.; 2017.
48. Curtis JR, Xie F, Yun H, Bernatsky S, Winthrop KL. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. *Ann Rheum Dis* 2016:annrheumdis-2016-209131.
49. European Medicines Agency. Assessment report Xeljanz; 2017.
50. Winthrop K, Lindsey S, Fan H, Wang L, Gelone D, Mendelsohn A, *et al.* SAT0229 Herpes Zoster and Tofacitinib: The Risk of Concomitant Nonbiologic Therapy. *Ann Rheum Dis* 2015;74:741-.
51. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, *et al.* Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet (London, England)* 2013;381:1541-50.
52. van Vollenhoven RF, Kinnman N, Vincent E, Wax S, Bathon J. Atacicept in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase II, randomized, placebo-controlled trial. *Arthritis and Rheumatism* 2011;63:1782-92.
53. Kremer JM, Blanco R, Brzosko M, Burgos-Vargas R, Halland A-M, Vernon E, *et al.* Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: Results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. *Arthritis & Rheumatism* 2011;63:609-21.
54. Fleischmann RM, Halland A-M, Brzosko M, Burgos-Vargas R, Mela C, Vernon E, *et al.* Tocilizumab Inhibits Structural Joint Damage and Improves Physical Function in Patients with

Rheumatoid Arthritis and Inadequate Responses to Methotrexate: LITHE Study 2-year Results. *The Journal of Rheumatology* 2013;40:113-26.

55. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E*, et al.* Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *The Lancet*;371:987-97.
56. Yoo DH, Hrycaj P, Miranda P, Ramiterre E, Piotrowski M, Shevchuk S*, et al.* A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis* 2013;72:1613-20.
57. van de Putte LBA, Atkins C, Malaise M, Sany J, Russell A, van Riel PLCM*, et al.* Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis* 2004;63:508-16.
58. Miyasaka N. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. *Modern Rheumatology* 2008;18:252-62.
59. Kim H-Y, Lee S-K, Song YW, Yoo D-H, Koh E-M, Yoo B*, et al.* A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. *APLAR Journal of Rheumatology* 2007;10:9-16.
60. Genovese MC, Schiff M, Luggen M, Becker JC, Aranda R, Teng J*, et al.* Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. *Ann Rheum Dis* 2008;67:547-54.
61. Bae SC, Kim J, Choe JY, Park W, Lee SH, Park YB*, et al.* A phase III, multicentre, randomised, double-blind, active-controlled, parallel-group trial comparing safety and efficacy of HD203, with innovator etanercept, in combination with methotrexate, in patients with rheumatoid arthritis: the HERA study. *Ann Rheum Dis* 2016;76:65-71.
62. Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S*, et al.* Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. *Arthritis and Rheumatism* 2012;64:617-29.
63. Smolen JS, Kay J, Doyle MK, Landewe R, Matteson EL, Wollenhaupt J*, et al.* Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet (London, England)* 2009;374:210-21.
64. Kremer JM, Cohen S, Wilkinson BE, Connell CA, French JL, Gomez-Reino J*, et al.* A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. *Arthritis & Rheumatism* 2012;64:970-81.
65. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A*, et al.* IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008;67:1516-23.
66. Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K*, et al.* Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. *Modern rheumatology / the Japan Rheumatism Association* 2014;24:715-24.
67. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E*, et al.* Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *The Lancet* 2008;371:987-97.
68. Keystone E, Heijde DVD, Mason D, Landewé R, Vollenhoven RV, Combe B*, et al.* Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: Findings of a fifty-two–week, phase III,

multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis & Rheumatism* 2008;58:3319-29.

69. Strand V, Mease P, Burmester GR, Nikaï E, Coteur G, van Vollenhoven R*, et al.* Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. *Arthritis Research & Therapy* 2009;11:R170.
70. Smolen J, Landewé RB, Mease P, Brzezicki J, Mason D, Luijtens K*, et al.* Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis* 2009;68:797-804.
71. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM*, et al.* Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. *Arthritis and Rheumatism* 2008;58:S126-35.
72. Durez P, Malghem J, Toukap AN, Depresseux G, Lauwerys BR, Westhovens R*, et al.* Treatment of early rheumatoid arthritis: A randomized magnetic resonance imaging study comparing the effects of methotrexate alone, methotrexate in combination with infliximab, and methotrexate in combination with intravenous pulse methylprednisolone. *Arthritis & Rheumatism* 2007;56:3919-27.
73. Kameda H, Ueki Y, Saito K, Nagaoka S, Hidaka T, Atsumi T*, et al.* Etanercept (ETN) with methotrexate (MTX) is better than ETN monotherapy in patients with active rheumatoid arthritis despite MTX therapy: a randomized trial. *Modern Rheumatology* 2010;20:531-8.
74. Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P*, et al.* Golimumab, a human anti–tumor necrosis factor α monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: Twenty-four–week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis & Rheumatism* 2009;60:2272-83.
75. Detert J, Bastian H, Listing J, Weiß A, Wassenberg S, Liebhaber A*, et al.* Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naïve patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. *Ann Rheum Dis* 2013;72:844-50.
76. Kavanaugh A, Fleischmann RM, Emery P, Kupper H, Redden L, Guerette B*, et al.* Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. *Ann Rheum Dis* 2013;72:64-71.
77. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, Vollenhoven Rv*, et al.* The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis & Rheumatism* 2006;54:26-37.
78. Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK*, et al.* Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study. *Ann Rheum Dis* 2009;68:1146-52.
79. van Vollenhoven RF, Ernestam S, Geborek P, Petersson IF, Cöster L, Waltbrand E*, et al.* Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. *The Lancet* 2009;374:459-66.
80. Dougados M, Kissel K, Sheeran T, Tak PP, Conaghan PG, Mola EM*, et al.* Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). *Ann Rheum Dis* 2013;72:43-50.

81. Dougados M, Kissel K, Conaghan PG, Mola EM, Schett G, Gerli R*, et al.* Clinical, radiographic and immunogenic effects after 1 year of tocilizumab-based treatment strategies in rheumatoid arthritis: the ACT-RAY study. *Ann Rheum Dis* 2014;73:803-9.
82. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA*, et al.* Adalimumab, a fully human anti–tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: The ARMADA trial. *Arthritis & Rheumatism* 2003;48:35-45.
83. Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S*, et al.* Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis* 2008;67:1096-103.
84. Smolen JS, Emery P, Ferraccioli GF, Samborski W, Berenbaum F, Davies OR*, et al.* Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomised, placebo-controlled trial. *Ann Rheum Dis* 2015;74:843-50.
85. Choe JY, Prodanovic N, Niebrzydowski J, Staykov I, Dokoupilova E, Baranauskaite A*, et al.* A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2015;76:58-64.
86. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS*, et al.* Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti–tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: A randomized, placebo-controlled, 52-week trial. *Arthritis & Rheumatism* 2004;50:1400-11.
87. Emery P, Vencovsky J, Sylwestrzak A, Leszczynski P, Porawska W, Baranauskaite A*, et al.* A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2015;76:51-7.
88. Tanaka Y, Harigai M, Takeuchi T, Yamanaka H, Ishiguro N, Yamamoto K*, et al.* Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study. *Ann Rheum Dis* 2012;71:817-24.
89. Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC*, et al.* Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis* 2009;68:789-96.
90. Bingham CO, Weinblatt M, Han C, Gathany TA, Kim L, Lo KH*, et al.* The Effect of Intravenous Golimumab on Health-related Quality of Life in Rheumatoid Arthritis: 24-week Results of the Phase III GO-FURTHER Trial. *The Journal of Rheumatology* 2014;41:1067-76.
91. Machado DA, Guzman RM, Xavier RM, Simon JA, Mele L, Pedersen R*, et al.* Open-label observation of addition of etanercept versus a conventional disease-modifying antirheumatic drug in subjects with active rheumatoid arthritis despite methotrexate therapy in the Latin American region. *J Clin Rheumatol* 2014;20:25-33.
92. Li Z, Zhang F, Kay J, Fei K, Han C, Zhuang Y*, et al.* Efficacy and safety results from a Phase 3, randomized, placebo-controlled trial of subcutaneous golimumab in Chinese patients with active rheumatoid arthritis despite methotrexate therapy. *Int J Rheum Dis* 2015;19:1143-56.
93. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J*, et al.* Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. *Modern rheumatology / the Japan Rheumatism Association* 2009;19:12-9.
94. Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P*, et al.* The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: A large, randomized, placebo-controlled trial. *Arthritis & Rheumatism* 2006;54:1075-86.

95. Kaneko Y, Atsumi T, Tanaka Y, Inoo M, Kobayashi-Haraoka H, Amano K, *et al.* Comparison of adding tocilizumab to methotrexate with switching to tocilizumab in patients with rheumatoid arthritis with inadequate response to methotrexate: 52-week results from a prospective, randomised, controlled study (SURPRISE study). *Ann Rheum Dis* 2016;75:1917-23.
96. Takeuchi T, Yamanaka H, Tanaka Y, Sakurai T, Saito K, Ohtsubo H, *et al.* Evaluation of the pharmacokinetic equivalence and 54-week efficacy and safety of CT-P13 and innovator infliximab in Japanese patients with rheumatoid arthritis. *Modern rheumatology / the Japan Rheumatism Association* 2015;25:817-24.
97. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, *et al.* Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *The New England Journal of Medicine* 2005;353:1114-23.
98. Combe B, Dougados M, Logeart I, Lukas C, Mariette X, Puechal X, *et al.* AB0516 An open-label randomized controlled study to evaluate the efficacy of etanercept (ETN) versus rituximab (RTX), in patients with active rheumatoid arthritis previously treated with RTX and TNF blockers. *Ann Rheum Dis* 2012;71:667.
99. Manders SH, Kievit W, Adang E, Brus HL, Moens HJB, Hartkamp A, *et al.* Cost-effectiveness of abatacept, rituximab, and TNFi treatment after previous failure with TNFi treatment in rheumatoid arthritis: a pragmatic multi-centre randomised trial. *Arthritis Research & Therapy* 2015;17:134.
100. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, *et al.* Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *The Lancet*;381:451-60.
101. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, *et al.* Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis and Rheumatism* 2006;54:2793-806.
102. Gottenberg J, Brocq O, Perdriger A, et al. Non–tnf-targeted biologic vs a second anti-tnf drug to treat rheumatoid arthritis in patients with insufficient response to a first anti-tnf drug: A randomized clinical trial. *JAMA* 2016;316:1172-80.
103. Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: A randomized trial. *Annals of Internal Medicine* 2006;144:865-76.
104. Fleischmann R, Schiff M, Weinblatt M, Maldonado M, Massarotti EM, Yazici H. Effects of subcutaneous abatacept or adalimumab on remission and associated changes in physical function and radiographic outcomes: one year results from the ample (abatacept versus adalimumab comparison in biologic-naive RA subjects with background methotrexate). *Arthritis & Rheumatism* 2012;64.
105. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, *et al.* Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet (London, England)* 1999;354:1932-9.
106. De Filippis L, Caliri A, Anghelone S, Scibilia G, Lo Gullo R, Bagnatoo G. Improving outcomes in tumour necrosis factor α treatment: comparison of the efficacy of the tumour necrosis factor α blocking agents etanercept and infliximab in patients with active rheumatoid arthritis. *Panminerva Medica* 2006;48:129.
107. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis: A randomized, controlled trial. *Annals of Internal Medicine* 1999;130:478-86.
108. O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, *et al.* Therapies for Active Rheumatoid Arthritis after Methotrexate Failure. *New England Journal of Medicine* 2013;369:307-18.
109. Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, *et al.* Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI):

Evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. *Ann Rheum Dis* 2007;66:1162-7.

110. Furst D, Schiff M, Fleischmann R, Strand V, Birbara C, Compagnone D, *et al.* Adalimumab, a fully human anti-tumour necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of star (safety trial of adalimumab in rheumatoid arthritis). *Journal of Rheumatology* 2003;30:2563.
111. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, *et al.* A Trial of Etanercept, a Recombinant Tumor Necrosis Factor Receptor:Fc Fusion Protein, in Patients with Rheumatoid Arthritis Receiving Methotrexate. *New England Journal of Medicine* 1999;340:253-9.
112. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of Clinical Epidemiology* 1997;50:683-91.
113. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins J. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *International journal of epidemiology* 2012;41:818-27.
114. Lee YH, Bae S-C, Song GG. Comparative efficacy and safety of tofacitinib, with or without methotrexate, in patients with active rheumatoid arthritis: a Bayesian network meta-analysis of randomized controlled trials. *Rheumatology international* 2015;35:1965-74.
115. Boyce EG, Vyas D, Rogan EL, Valle-Oseguera CS, O'Dell KM. Impact of tofacitinib on patient outcomes in rheumatoid arthritis - review of clinical studies. *Patient related outcome measures* 2016;7:1-12.
116. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal; 2013.
117. Hernández Alava M, Wailoo A, Wolfe F, Michaud K. The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis. *Rheumatology* 2013;52:944-50.
118. Wiles NJ, Symmons D. Resource Use Within the Norfolk Arthritis Register (NOAR) Cohort During the First Five Years of Disease. Report for Roche. London: NICE; 2005.
119. Wollenhaupt J, Silverfield J, Lee EB, Curtis JR, Wood SP, Soma K, *et al.* Safety and efficacy of tofacitinib, an oral janus kinase inhibitor, for the treatment of rheumatoid arthritis in open-label, longterm extension studies. *The Journal of rheumatology* 2014;41:837-52.
120. Norton S, Fu B, Scott DL, Deighton C, Symmons DPM, Wailoo AJ, *et al.* Health Assessment Questionnaire disability progression in early rheumatoid arthritis: Systematic review and analysis of two inception cohorts. *Seminars in Arthritis and Rheumatism* 2014;44:131-44.
121. Young A, Dixey J, Cox N, Davies P, Devlin J, Emery P, *et al.* How does functional disability in early rheumatoid arthritis (RA) affect patients and their lives? Results of 5 years of follow-up in 732 patients from the Early RA Study (ERAS). *Rheumatology (Oxford, England)* 2000;39:603-11.
122. Gibson L, Hernandez Alava M, Wailoo A. Progression of Disease in People with Rheumatoid Arthritis Treated with Non-Biologic Therapies. Sheffield; 2015.
123. Stevenson M. Additional analyses requested post consultation. [Internet. Accessed December 30, 2016.]. 2015, https://www.nice.org.uk/guidance/ta375/documents/rheumatoid-arthritis-adalimumab-etanercept-infliximab-certolizumab-pegol-golimumab-abatacept-and-tocilizumab-review-id537-committee-papers2.
124. Eli Lilly. Baricitinib for Treating Moderate to Severe Rheumatoid Arthritis [ID979]; 2017.
125. Latimer NR. NICE DSU Technical Support Document 14: Survival Analysis for Economic Evaluations Alongside Clinical Trials - Extrapolation with Patient-Level Data. Sheffield: Report by the Decision Support Unit; 2013.
126. Office for National Statistics. National Life Tables, United Kingdom: 2011-2013. 2014. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2014-09-25 (Accessed 20 June 2017).
127. Dakin H. Review of studies mapping from quality of life or clinical measures to EQ-5D: an online database. *Health and Quality of Life Outcomes* 2013;11:1-6.

128. Soini EJ, Hallinen TA, Puolakka K, Vihervaara V, Kauppi MJ. Cost-effectiveness of adalimumab, etanercept, and tocilizumab as first-line treatments for moderate-to-severe rheumatoid arthritis. *J Med Econ* 2012;15.
129. Strand V, Ahadieh S, French J, Geier J, Krishnaswami S, Menon S*, et al.* Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. *Arthritis research & therapy* 2015;17:362.
130. Oppong R, Kaambwa B, Nuttall J, Hood K, Smith RD, Coast J. The impact of using different tariffs to value EQ-5D health state descriptions: an example from a study of acute cough/lower respiratory tract infections in seven countries. *Eur J Health Econ* 2013;14:197-209.
131. Curtis L, Burns A. Unit costs of health and social care 2015.; 2015.
132. Department of Health. National Schedule of Reference Costs 2015-16 for NHS Trusts. Total average cost of outpatient attendance for Service Code 410 (Rheumatology). Sheet: Total Outpatient Attendances.; 2016.
133. Drummond M, Sculpher M, Torrance G, O'Brien B, G S. Methods for the economic evaluation of health care programmes. 3rd edn. Oxford: Oxford University Press; 2005.
134. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C*, et al.* Principles of Good Practice for Decision Analytic Modeling in Health-Care Evaluation: Report of the ISPOR Task Force on Good Research Practices — Modeling Studies. *Value in Health* 2014;6:9-17.
135. Malottki K, Barton P, Tsourapas A, Uthman A, Liu Z. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. *Health Technology Assessment* 2011;15:278.

8 APPENDICES

Appendix 1: ERG adverse event search conducted on Thursday 27th April 2017

1	exp Arthritis, Rheumatoid/	105432
2	(arthritis adj2 rheumat*).mp.	124223
3	((felty* or caplan* or sjogren*) adj2 syndrome).mp.	17212
4	rheumatoid nodule.mp.	1024
5	still* disease.mp.	2197
6	(spondylitis adj2 ankylosing).mp.	17135
7	or/1-6	152854
8	(tofacitinib or xeljanz or tasocitinib or cp690550* or cp 690550* or cp690 550* or cp 690 550*).mp.	645
9	(ae or to or po or co).fs.	3583595
10	(safe or safety).ti,ab.	615443
11	side effect$.ti,ab.	214180
12	((adverse or undesirable or harms$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.	409820
13	exp product surveillance, postmarketing/	13221
14	exp adverse drug reaction reporting systems/	6608
15	exp clinical trials, phase iv/	255
16	exp poisoning/	148958
17	exp substance-related disorders/	254830
18	exp drug toxicity/	103445
19	exp abnormalities, drug induced/	14381
20	exp drug monitoring/	17941
21	exp drug hypersensitivity/	42975
22	(toxicity or complication$ or noxious or tolerability).ti,ab.	1114500
23	exp Postoperative Complications/	480396
24	exp Intraoperative Complications/	47003
25	or/9-24	5233898
26	7 and 8 and 25	167

Appendix 2: Absolute treatment effects in the cDMARD-IR and bDMARD-IR population

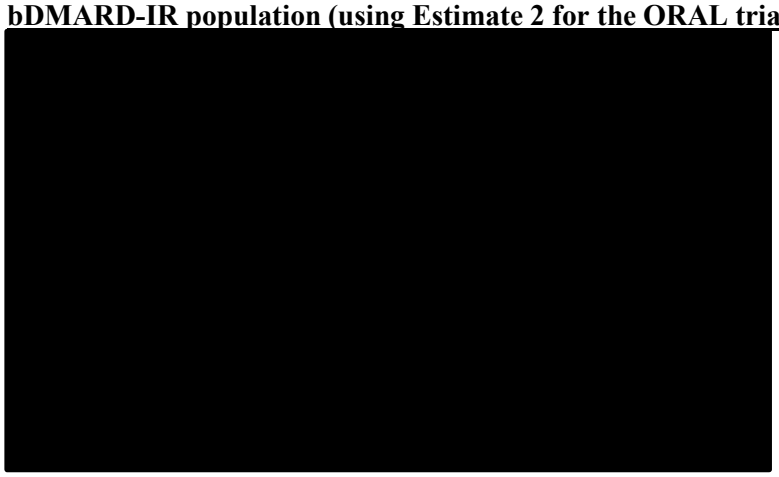
Figure 8: EULAR response in the additional NMA requested by the ERG in the cDMARD-IR population (using Estimate 2 for the ORAL trials)

Figure 9: EULAR response in the additional NMA requested by the ERG in the cDMARD-IR population (using Estimate 2 for the ORAL trials) – monotherapy

Figure 10: EULAR response in the additional NMA requested by the ERG in the cDMARD-IR population (using Estimate 1 for the ORAL trials)

Figure 11: EULAR response in the additional NMA requested by the ERG in the cDMARD-IR population (using Estimate 1 for the ORAL trials) - monotherapy

Figure 12: EULAR response in the additional NMA requested by the ERG in the bDMARD-IR population (using Estimate 2 for the ORAL trials)



tofacitinib at 3 months, there are no placebo-controlled results for 6 months for any of the other relevant endpoints in ORAL Solo. Another recently completed head-to-head RCT including tofacitinib monotherapy versus tofacitinib plus methotrexate or adalimumab plus methotrexate (ORAL Strategy) was presented but only as a preliminary result for the primary endpoint of 50% improvement in the American College of Rheumatology (ACR50) in the CS. This RCT found tofacitinib monotherapy was not shown to be non-inferior in efficacy compared to adalimumab plus methotrexate and tofacitinib plus methotrexate at 6 months whilst tofacitinib plus methotrexate was found to be non-inferior to adalimumab plus methotrexate using ACR50 at 6 months.

A revised summary of safety data for tofacitinib provided by the company following an ERG request showed that the highest incidence rates of adverse events (AEs) were for serious infection events and herpes zoster. Additional data provided by the company indicated bronchitis, pneumonia and all cardiac disorders occurred most commonly in the tofacitinib treatment arms.

Network meta-analyses (NMA) were performed to assess the relative efficacy of tofacitinib compared with the comparators in patients who were inadequate responders (IR) to conventional DMARDs (cDMARD-IR) or to biologic DMARDs (bDMARD–IR) patients with moderate-to-severe RA for EULAR response and change in the Health Assessment Questionnaire disability index (HAQ-DI) at 6 months. For the base case NMA cDMARD-IR population, the odds of achieving a EULAR response were all statistically higher for tofacitinib in combination with methotrexate (tofacitinib plus cDMARD) compared to cDMARD at 6 months. No statistically significant differences were found for tofacitinib plus cDMARD versus bDMARDs plus cDMARD, except for tocilizumab plus cDMARD, which was statistically superior in attaining at least a good EULAR response.

Whilst the odds of all EULAR responses were higher in tofacitinib monotherapy compared to cDMARD, only the effect for a good response was statistically significant. No statistically significant differences were found in tofacitinib versus bDMARDs. Both tofacitinib plus cDMARD and tofacitinib monotherapy were associated with significant reduction in HAQ-DI compared with cDMARD at 6 months.

For the base case NMA bDMARD-IR population, the odds of all EULAR responses were all statistically higher in tofacitinib plus cDMARD compared with cDMARD at 6 months. No statistically significant differences were found for tofacitinib plus cDMARD versus abatacept plus cDMARD. Tofacitinib plus cDMARD was statistically superior compared to golimumab plus cDMARD in attaining both at least a moderate and a good EULAR response; but statistically inferior versus rituximab plus cDMARD, tocilizumab plus cDMARD, non-tumour necrosis factors alpha inhibitors (non-TNFi) plus cDMARD and TNFi plus cDMARD. Tofacitinib in combination with

cDMARD was associated with a significant reduction in HAQ-DI compared with cDMARD at 6 months.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG considers the searches for clinical effectiveness evidence reported in the CS to be adequate, and believes the included RCTs of tofacitinib to be relevant to the decision problem. It is noted that one recently published RCT (ORAL Strategy) was stated to be "ongoing" in the CS and the company indicated in the CS that results will be available in early May 2017. Following a request from the ERG, the company provided an updated NMA of clinical effectiveness that included data from ORAL Strategy.

The eligibility criteria applied in the selection of evidence for clinical effectiveness were considered by the ERG to be reasonable and consistent with the decision problem outlined in the final NICE scope. The quality of the included RCTs was assessed using well-established and recognised criteria. Primary endpoints and selected analyses for clinical efficacy were appropriate.

The ERG considers that the company's safety overview lacks transparency due to pooling both combination and monotherapy trials to produce incidence rates; the lack of consistent comparison to the control arms; the lack of NMA of adverse events versus comparators; and the failure to search for and provide a complete, comprehensive and up-to-date overview of all AEs including serious adverse events (SAEs). Clinical advice received by the ERG indicates that a more informative AE profile would describe the relative occurrence of all adverse events versus the control arm. Clinical advice received by the ERG also stresses the importance of monitoring the occurrence of AEs for new classes of drugs, and in turn, the importance of searching and including up-to-date evidence to inform the AE profile for the current assessment of tofacitinib. Whilst the CS did not provide a NMA of adverse events versus comparators, the company did reference a paper that conducted a NMA showing that the incidence of herpes zoster was significantly higher for tofacitinib versus bDMARD comparators.

The ERG believes that the results presented in NMA of clinical effectiveness should be treated with caution, as the ordered categorical EULAR data were dichotomised in the cDMARD-IR population, which ignores the natural ordering and correlations between the EULAR response categories. A fixed effects model was used in all the analyses in the bDMARD-IR population, and EULAR response (moderate response and good response) in the cDMARD-IR population. Heterogeneity is expected and this approach underestimates uncertainty in the treatment effects. For tofacitinib trials with early escape, the results from non-responder imputation without advancement penalty (non-responder imputation only applied for the placebo arm, not the tofacitinib arm) were used in the base case

However, the analyses presented by the company included a number of limitations. First, relevant comparators recommended by NICE were missing from the company's analyses: adalimumab, etanercept, infliximab and certolizumab pegol with concomitant MTX in bDMARD-IR RTX-ineligible patients with severe RA and all relevant comparators in bDMARD-IR MTX-intolerant patients with severe RA. The CS did not identify publications for inclusion of adalimumab, infliximab and certolizumab pegol for these populations. Second, the sequences used in the company's original analyses were not appropriate for a number of reasons: (i) the inclusion of multiple consecutive lines of the same treatment; (ii) the inclusion of bDMARD treatments in points in the pathway not recommended by NICE; and, (iii) the inclusion of three or four post-biologic treatments before palliative care. Thirdly, the company assumed equal efficacy for tofacitinib as monotherapy and in combination with MTX in terms of the probabilities of achieving moderate and good EULAR responses. However, the results of the NMA show that these probabilities are lower for tofacitinib monotherapy compared with tofacitinib with concomitant MTX. Fourth, the company used the results for placebo from the NMA to estimate the efficacy sulfasalazine for the analysis for the cDMARD-IR MTX-intolerant population. The ERG believes this to lead to an underestimation of the efficacy of sulfasalazine. Finally, the company rounded modified 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. The ERG notes that this approach might lead to inaccurate estimations of HAQ-DI scores, as values might be rounded up more often than they are rounded down or *vice versa.* The company corrected the first two issues in the revised model submitted with the clarification responses but did not present a full set of analyses relating to their revised base case.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The ERG considers the data on clinical effectiveness in the CS to be well-reported and the included trials are of good quality.

The model used appears conceptually appropriate with very few implementation errors, most of which were rectified during the clarification process. The ERG considers that the DES approach taken by the company, which was based on the model used in TA375, was deemed appropriate to represent the disease. The ERG considers the company's analysis of patients with moderate RA that can progress to severe RA and then start with a sequence of bDMARDs to reflect the treatment pathway of these patients better than other previous analyses.

The ERG also notes that the amendments, corrections and different assumptions tested by the ERG do not significantly impact the broad conclusions of the analyses presented in the CS.

1.6.2 Weaknesses and areas of uncertainty

Whilst full data were not available for inclusion into the CS, the ERG believes that the recently published ORAL Strategy trial is also relevant to the decision problem because it has head-to-head evidence at 6 months, demonstrating than tofacitinib monotherapy was not shown to be non-inferior to either adalimumab plus MTX and tofacitinib plus MTX using the primary endpoint of ACR50.

The company focuses its safety profile on whether the AEs were comparable across the tofacitinib treatment arms and whether any new or unexpected safety events have occurred. The ERG considers that a more informative analysis would present all AEs, including SAEs, versus the comparator arm. Additionally the company did not conduct targeted up-to-date literature searches to retrieve evidence for AEs associated with tofacitinib treatment for this appraisal meaning that some relevant analyses of adverse event data for tofacitinib are not included. Pooled analyses of AE data across trials of both tofacitinib monotherapy and tofacitinib in combination with methotrexate are unlikely to provide an accurate reflection of the incidence of adverse event rates from these two treatment regimens, which are noted in sources not referenced in the CS, to be different.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook exploratory analyses based on the company's revised model. The ERG presented two full sets of analyses: one based on the company's preferred NMA and the other based on the NMA undertaken for the clarification response, which the company denoted 'ERG preferred'. As this is not the ERG's preferred analysis we have renamed this the 'clarification NMA'. All analyses presented in this report have not taken any commercial-in-confidence PASs into consideration.

For cDMARD-IR patients with severe RA who can tolerate MTX, based on the company's NMA, tofacitinib + MTX dominated all of its bDMARD comparators except etanercept biosimilar + MTX. Based on the clarification NMA, tofacitinib + MTX dominated ADA+MTX but was extendedly dominated in the full incremental analysis. For cDMARD-IR patients with severe RA for whom MTX was contraindicated or not tolerated, tofacitinib and tocilizumab monotherapy extendedly dominated ADA and ETN biosimilar regardless of the NMA used. The ICER of tocilizumab compared with tofacitinib was £51,488 and £50,430 per QALY gained using the company's NMA and using the clarification NMA, having removed the constraint that TOF monotherapy had the same efficacy as TOF+MTX, respectively.

In the bDMARD-IR patients with severe RA for whom rituximab was an option, rituximab + MTX dominated tofacitinib + MTX regardless of the NMA used. [redacted]. Replacing

tocilizumab + MTX with tofacitinib + MTX after rituximab + MTX was estimated to result in £67,852 and £90,846 per QALY lost using the company's and the clarification NMA respectively. The ERG notes, however, that the confidential PAS of TCZ was not included in these analyses as recommended to the company by NICE at the decision problem meeting. In the bDMARD-IR patients with severe RA for whom RTX was not an option, tofacitinib + MTX dominated golimumab+MTX regardless of the NMA used, and dominated abatacept + MTX also when using the company's NMA. The ICER of etanercept biosimilar and tocilizumab with MTX compared with tofacitinib + MTX was higher than £30,000 per QALY gained regardless of the NMA used.

Finally, in patients with moderate RA who where cDMARD-IR, the ICER of tofacitinib + MTX compared with MTX was £47,594 and £50,708 per QALY gained using the company's and the clarification NMA respectively.

ACR responses,[23] although EULAR is much more closely aligned to the treatment continuation rules stipulated by NICE for treatment in England. These rules require either a moderate or good EULAR response or a DAS28 improvement of more than 1.2 to continue treatment, with the latter criterion applying to RTX. The relationship between change in DAS28 and the absolute DAS28 score and EULAR response is shown in Table 1.

Table 1: Determining EULAR response based on DAS28[22]

	Improvement in DAS 28		
DAS28 at endpoint	>1.2	>0.6 and ≤1.2	≤0.6
≤ 3.2	Good	Moderate	None
>3.2 and ≤5.1	Moderate	Moderate	None
>5.1	Moderate	None	None

Patients with a DAS28 ≤3.2 are regarded as having low disease activity, those with a DAS28 > 3.2 and ≤ 5.1 are regarded as having moderate disease and >5.1 as having very active disease.[21] Within NICE Technology Appraisal (TA) 375, patients with a DAS28 > 3.2 and ≤ 5.1 were considered as having moderate-to-severe disease whilst those with a DAS28 > 5.1 were denoted as having severe disease.[24]

A widely used measure of patient disability is the Health Assessment Questionnaire (HAQ). The HAQ-DI score is a patient completed disability assessment which has established reliability and validity.[25] HAQ-DI scores range from zero to three, with higher scores indicating greater disability The HAQ-DI is a discrete scale with step values of 0.125, resulting in the HAQ-DI scale containing 25 points. The HAQ-DI has been used in many published RCTs in RA.[23]

2.2 Critique of company's overview of current service provision

The company's overview of current service provision is concise but appropriate and relevant to the decision problem set out in the final NICE scope. The ERG provides a summary of current service provision below.

Clinical guidelines

For people with newly diagnosed RA, NICE CG79[10] recommends a combination of cDMARDs (including MTX and at least one other cDMARD plus short-term glucocorticoids) as first-line treatment, ideally beginning within 3 months of the onset of persistent symptoms. Where combination therapies are not appropriate, for example, where there are comorbidities or pregnancy, cDMARD monotherapy is recommended. Where cDMARD monotherapy is used, emphasis should be made on increasing the dose quickly to obtain best disease control. For the purposes of this assessment, the term "intensive cDMARDs" has been used to denote that this involves treatment with multiple cDMARDs simultaneously.

disease-modifying anti-rheumatic drug (tsDMARD). Tofacitinib is available as a 5mg film-coated tablet to be taken by mouth twice a day (BD).

Tofacitinib received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on the 26th January 2017 for the treatment of RA. Prior to this approval, the CHMP had adopted a negative opinion for granting marketing authorisation to tofacitinib in 2013 (25th April) which was confirmed on the 22nd July 2013 on the basis of: (1) Serious and unresolved incidence of infection; (2) Uncertainties in the overall safety profile in relation to incidence and severity of infections, malignancies, lymphoma, gastrointestinal perforations, hepatic enzymes elevations/drug-induced liver injury and lipids and cardiovascular risks; (3) Unresolved safety concerns are not offset by the benefits of the treatment. [29] However, the 2017 CHMP opinion concluded that the safety profile of tofacitinib while remaining complex and clinically challenging can now be considered sufficiently characterised for marketing authorisation.

Tofacitinib was added to the EMA's list of medicines under additional monitoring in April 2017.

Laboratory tests are required for patients undergoing treatment with tofacitinib to monitor:

- neutrophils at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter
- lipid parameters after 8 weeks following initiation of therapy
- lymphocytes (at baseline and every 3 months thereafter)
- haemoglobin (at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter).

The ERG's clinical advisors state that these tests would ordinarily be provided in clinical practice for this patient population.

The Summary of Product Characteristics (SmPC)[30] reports the following contraindications for treatment with tofacitinib:

- patients who are allergic or hypersensitive to ingredients of the medicine
- severe hepatic impairment
- pregnant and breast-feeding
- patients with active infections, including localised infections, tuberculosis (TB), serious infections such as sepsis, or opportunistic infection.

The safety and efficacy of tofacitinib in children aged from 2 years to less than 18 years of age have not yet been established.

A number of additional points regarding tofacitinib are emphasised in the SmPC including:

- A higher rate of infections in patients aged 65 and older and diabetic populations.
- A caution that data in the elderly population of 75 years and over are limited.
- A higher rate of herpes zoster (shingles) in Japanese and Korean patients.

Other potentially relevant comparators such as anakinra [KINERET]; baricitinib [OLUMIANT] sarilumab [KEVZARA] and sirukimab, were excluded in the CS as they are either currently unlicensed, unapproved or yet to be assessed by NICE. Baricitinib is currently under assessment by NICE (ID979) for treating moderate-to-severe RA and, like tofacitinib, is an orally administered JAK inhibitor (4mg once per day).

3.4 Outcomes

The outcome measures in the final scope issued by NICE and those considered in the CS are outlined in Table 2.

Table 2: Outcome measures from the NICE scope considered in the CS

Outcomes as per NICE Scope	Outcomes as defined and measured in the CS
Disease activity	Disease Activity Score (DAS28) American College of Rheumatology (ACR)20; ACR50; ACR70 European League Against Rheumatism (EULAR) response
Physical function	Health Assessment Questionnaire-Disability Index (HAQ-DI)
Joint damage, pain	Visual analogue scale (VAS): Patient's assessment of arthritis pain (PAAP)
Mortality	Death within 30 days of last dose of study drug in pooled safety analysis
Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale
Radiological progression	Sharp-van der Heidje scale modified Total Score (mTSS)
Extra-articular manifestations of disease	Not provided
Adverse effects of treatment	Pooled incidence rates of 19 trials' intervention arms without comparator
Health-related quality of life.	EuroQol 5-dimension questionnaire (EQ-5D)

3.5 Other relevant factors

Adherence

Adherence to treatment is not measured in the CS however, some potential benefits towards adherence are alluded to. The company states (see CS, page 49) that the mode of administration may be important in adherence to RA treatment and that patients with RA have reported a preference for oral administration over other routes including subcutaneous injection. [31] Whilst the CS references a study[32] which reported that RA patients prefer the oral route of administration to other routes, patient preference

does not necessarily equate with increased adherence. Clinical advice to the ERG was that whilst it may be easier for patients to take oral medication, self-administration in itself may be a contributing factor towards non-adherence, whereas the involvement of a third person can sometimes aid adherence. The CS states some valid potential patient groups where an oral therapy presents a useful alternative to clinicians such as those with impaired hand function who may have problems with self-injection.

Ongoing trials of tofacitinib in RA

Ongoing primary research identified from searching clinicaltrials.gov and relevant to the decision problem is documented in **Error! Not a valid bookmark self-reference.**. Nine ongoing studies were noted to be relevant to the long-term safety and efficacy of tofacitinib and plan completion between April2016 and December 2021.

Table 3: Ongoing trials relevant for tofacitinib in RA

Trial no. Sponsor	Aim	Planned enrolment	Planned completion	Comment on relevance to the decision problem.
NCT02157012 Shinshu University	Phase 4 single arm study to examine the safety and effectiveness after tofacitinib treatment in RA patients	100	April 2016	Recruited exclusively at Japanese sites.
NCT03073109 Pfizer	Study of patient-reported outcomes in RA patients treated with tofacitinib or bDMARDs	320	Mar 2018	Exclusively in Latin American patients.
NCT00413699 Pfizer	Phase 3 study of long-term effectiveness and safety of tofacitinib in RA subjects after participating in another "qualifying" study of tofacitinib (ORAL Sequel)	4500	Dec 2018	Included in the list of non-randomised patients evidence supplied by Pfizer.
NCT02831855 Pfizer	Phase 4 study of methotrexate withdrawal on tofacitinib modified release formulation (11mg QD) versus tofacitinib (11mg QD) plus continued methotrexate treatment	580	Mar 2019	Non-licensed formulation in Europe.
NCT03016884 HaEmek Medical Center, Israel	Phase 4 study evaluating the safety, tolerability, and immunogenicity of Zostavax vaccine in the RA population prior to initiation of biologic/tofacitinib therapy for RA	250	May 2019	Recruited exclusively at Israeli sites.
NCT02092467 Pfizer	Phase 3b/4 post-marketing safety study of tofacitinib compared with ADA and ETN for major cardiovascular adverse events, malignancies, hepatic events, infections, and efficacy parameters.	4400	Aug 2019	
NCT02984020 Pfizer	Korean post-marketing surveillance study for the safety and efficacy of Xeljanz during the post-marketing period as required by the Korean Ministry Of Food And Drug Safety.	3000	Jan 2020	Recruited exclusively at Korean sites.
NCT01932372 Pfizer	Special investigation of tofacitinib 5mg in clinical practice of occurrence of adverse reactions/ factors that may potentially affect safety and efficacy and long-term safety vs other bDMARDs	6000	Mar 2021	Registry study not yet recruiting.
NCT03011281 Hanyang University	Prospective study to evaluate the effectiveness and safety of tofacitinib in clinical practice in Korean RA patients	378	Dec 2021	Exclusively in Korean RA patients.

Source: Clinicaltrials.gov

Simple Disease Activity Index (SDAI), DAS 28-4(ESR), and HAQ-DI over time. This trial was completed in December 2016 and results have recently been published.41 In this trial, tofacitinib plus MTX was found to be non-inferior to adalimumab plus MTX. However, tofacitinib monotherapy failed to demonstrate non-inferiority against tofacitinib plus MTX and adalimumab plus MTX for the primary endpoint of ACR50 response rate. The ERG requested effectiveness data for the ORAL Strategy trial and an updated NMA considering these data (see clarification response,34 question A3). The company's clarification response provided DAS28(ESR) EULAR response data for the full trial population but stated [redacted].

As the results have been published in a peer reviewed publication the ERG note that ORAL Strategy can no longer be considered an ongoing trial and consider that further relevant data from this trial were relevant to the decision problem.

The CS also reported a study "A3921041" (NCT00661661) which was completed in December 2013. This was an open-label, long-term extension study to assess safety, but only included Japanese patients. Clinical advice received by the ERG states that data there may be differences between UK and Japanese clinical populations in terms of tolerance and dosage of cDMARD treatment therefore the ERG considers that data from this trial may not be fully applicable to the decision problem.

4.1.3 Critique of data extraction

The CS reported that data were extracted from eligible publications into a predefined table by 'a reviewer', which is not considered as best practice in undertaking systematic reviews. In response to a request for clarification by the ERG (see clarification response,34 question A4), the company responded that two independent reviewers "were involved" in data extraction and quality assessment.

Data extracted from the four included tofacitinib RCTs reported in the CS, and reported below, were checked by the ERG against published trial papers, and were found to be accurate.

4.1.4 Quality assessment

Quality assessment of the four included tofacitinib RCTs is presented in Section 4.6 and Appendix 4 of the CS. The items assessed were taken from the NICE Single Technology Appraisal: User guide for company evidence submission template.42 These are appropriate criteria for assessing the risk of bias in RCTs. Table 6 presents the company's quality assessment of the tofacitinib trials. It is considered good practice for two reviewers either to independently perform quality assessment or to check assessed items, but this was not reported in the CS. The ERG checked the company's quality assessment against the publications of the RCTs relevant to the decision problem, ORAL Standard

Table 4: Characteristics of included tofacitinib RCTs (adapted from Table 12 of the CS)

Trial acronym and trial number	Population	Intervention, N randomised	Comparators, N randomised	Primary outcome(s)
ORAL Standard NCT00853385	cDMARD experienced and MTX-IR adult patients with active moderate-to-severe RA	Tofacitinib 5mg, oral, BID (with background MTX), N=204	Adalimumab 40mg, SC injection, Q2W (with background MTX), N=204 Placebo to tofacitinib 5mg, oral, BID (with background MTX)† N=56	ACR20 response rate at Month 6 (NRI) HAQ-DI score at Month 3 DAS28(ESR) <2.6 at Month 6 (NRI) (Table 21 of CS)
ORAL Scan NCT00847613	cDMARD experienced and MTX-IR adult patients with active moderate-to-severe RA who are	Tofacitinib 5mg, oral, BID (with background MTX), N=321	Placebo to tofacitinib 5mg, oral, BID (with background MTX)†, N=81	ACR20 response rate at Month 6 (NRI) mTSS score at Month 6 (LE) HAQ-DI score at Month 3 DAS28(ESR) <2.6 at Month 6 (NRI) (Table 27 of CS)
ORAL Sync NCT00856544	DMARD-IR (cDMARD including MTX or bDMARD) adult patients with active moderate-to-severe RA	Tofacitinib 5mg, oral, BID (with background cDMARD), N=315	Placebo to tofacitinib 5mg, oral, BID (with background cDMARDs)†, N=79	ACR20 response rate at Month 6 (NRI) HAQ-DI score at Month 3 DAS28(ESR) <2.6 at Month 6 (NRI) (Table 34 of CS)
ORAL Solo NCT00814307	DMARD-IR (cDMARD including MTX or bDMARD) adult patients with active moderate-to-severe RA	Tofacitinib 5mg, oral, BID, N=243	Placebo to tofacitinib 5mg, oral, BID‡, N=61	ACR20 response rate at Month 3 (NRI) HAQ-DI score at Month 3 (Table 40 of CS)

Abbreviations: ACR = American College of Rheumatology; ADA = adalimumab; bDMARD = biologic disease-modifying anti-rheumatic drug; BID = twice daily; cDMARD = conventional disease-modifying anti-rheumatic drug; IR = inadequate response; LE = linear extrapolation; mTSS = van der Heijde modified total sharp score; MTX = methotrexate; NRI = non-responder imputation; ORAL = Oral Rheumatoid Arthritis Phase 3 Trials; Q2W = twice weekly; RA = rheumatoid arthritis; SC = subcutaneous; TNFi = tumour necrosis factor inhibitor; TOF = tofacitinib.

Footnote: †Patients receiving placebo advanced to TOF 5 mg at Month 3 if trial response criteria were not met (defined as 20% reduction in number of tender and swollen joints) or Month 6 regardless of response. ‡All patients receiving placebo advanced to a TOF 5 mg at Month 3

In all four placebo-controlled trials, data for the placebo comparator group is presented in the CS as a "combined placebo group" because patients crossed over to receive either 5 mg (licensed dose) or 10 mg of tofacitinib but results are not provided for the licenced 5 mg dose separately. An early escape design allowed that, at Month 3, placebo non-responders advanced to either 5 mg or 10 mg tofacitinib and at Month 6, all patients receiving placebo advanced to either 5mg or 10mg tofacitinib "*in order to minimise the time patients spent on ineffective treatment*" (CS, page 89). Additionally in the ORAL Standard, Scan and Sync trials an "advancement penalty" was applied whereby patients who did not meet the response criteria at Month 3 were considered to be non-responders for the remainder of the trial. This non-responder imputation (NRI) was also applied to the analysis of patients deemed to be non-responders in the tofacitinib treatment groups at Month 3.

Table 5: Eligibility criteria for the tofacitinib RCTs (reproduced from Table 14 of the CS)

Trial acronym and trial number	ORAL Standard NCT00853385	ORAL Scan NCT00847613	ORAL Sync NCT00856544	ORAL Solo NCT00814307
Inclusion criteria	• Adults aged ≥18 years with a diagnosis of active RA†, consistent with the ACR 1987 Revised Criteria[15] • Ongoing treatment with MTX for ≥4 months with stable dosing (7.5–25 mg/week) ≥6 weeks before receiving the study drug; doses <15 mg were allowed in the case of intolerance or toxicity from higher doses • An inadequate response to MTX (defined as sufficient residual disease activity to meet entry criteria)	• Adults aged ≥18 years with a diagnosis of active RA†, consistent with the ACR 1987 Revised Criteria[15] • Ongoing treatment with MTX for ≥4 months with stable dosing (7.5–25 mg/week) ≥6 weeks before receiving the study drug; doses <15 mg were allowed in the case of intolerance or toxicity from higher doses • An inadequate response to MTX (defined as sufficient residual disease activity to meet entry criteria) • Evidence of ≥3 distinct joint erosions on posteroanterior hand and wrist radiographs or anteroposterior foot radiographs as determined by the investigator, or, if radiographic evidence of joint erosions was unavailable, IgM RF+ or antibodies to CCP	• Adults aged ≥18 years with a diagnosis of active RA‡, consistent with the ACR 1987 Revised Criteria[15] • Ongoing treatment with ≥1 cDMARD therapy – patients receiving MTX required ≥4 months of treatment, with stable dosing (≤25 mg/week) ≥6 weeks before receiving the study drug • An inadequate response to ≥1 cDMARD or bDMARD ([redacted]	• Adults aged ≥18 years and had received a diagnosis of active RA†, consistent with the ACR 1987 Revised Criteria[15] • Discontinued all DMARDs except stable doses of anti-malarial agents • An inadequate response to ≥1 cDMARD or bDMARD (lack of efficacy or occurrence of toxicity)

Exclusion criteria	• Haemoglobin <9.0 gm/dL • Haematocrit <30% • White blood cell count <$3.0x10^9$/L • Absolute neutrophil count <$1.2x10^9$/L • Platelet count <$100x10^9$/L • eGFR rate ≤40 ml/min • AST or ALT levels >1.5 x Upper limit of normal • A history of another autoimmune rheumatic disease except Sjögren's syndrome • Infection that required hospitalisation or parenteral antimicrobial therapy within 6 months of randomisation • Infection requiring antimicrobial therapy within 2 weeks of randomisation • Recurrent or disseminated herpes zoster infection • Recent, current, or chronic infection, including HBV, HCV or HIV • Current infection or evidence of active or inadequately treated infection with Mycobacterium tuberculosis • History of lymphoproliferative disorder or malignancy except for adequately treated non-metastatic basal/squamous cell cancer of the skin or cervical carcinoma in situ • Prior treatment with lymphocyte-depleting therapies or alkylating agents ORAL Standard only: • Prior treatment with ADA • Lack of response to prior anti-TNF biologic treatment • Current treatment with other anti-rheumatic agents, including biologic agents

Abbreviations: ACR = American College of Rheumatology; ADA = adalimumab; ALT = alanine aminotransferase; AST = aspartate aminotransferase; bDMARD = biologic disease-modifying anti-rheumatic drug; CCP = cyclic citrullinated peptide; cDMARD = conventional disease-modifying anti-rheumatic drug; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; ESR = erythrocyte sedimentation rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MTX = methotrexate; ORAL = Oral Rheumatoid Arthritis Phase 3 Trials; RA = rheumatoid arthritis; RF = rheumatoid factor; TNF = tumour necrosis factor.

Footnote: †Active disease was defined as the presence of ≥6 tender or painful joints (of 68 joints examined) and ≥6 swollen joints (of 66 joints examined) and either an ESR ≥28 mm/hr (Westergren method) or a CRP level >7 mg/L. ‡Active disease was defined as the presence of ≥4 tender or painful joints (68 joints examined) and ≥4 swollen joints (of 66 joints examined) and either an ESR ≥28 mm/hr or a CRP level >66.7 nmol/L

Table 6: **Baseline characteristics of participants of ORAL Sync (adapted from Table 18 of the CS)**

ORAL Sync		Placebo to TOF 5mg (N=79)	Placebo to TOF 10mg (N=80)	TOF 5 mg (N=315)
Gender, n (%)	Female, n (%)	[redacted] (79.7)	[redacted] (75.0)	[redacted] (83.8)
	Male, n (%)	[redacted] (79.7)	[redacted] (25.0)	[redacted] (16.2)
Race, n (%)	White	[redacted] (60.8)	[redacted] (55.0)	[redacted] (54.9)
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Region of origin, %	Europe	31.7	28.8	28.9
	North America	22.8	18.8	16
	Latin America	13.9	13.8	14.2
	Rest of world	31.7	38.8	40.9
Age, years (SD)		50.8 (11.2)	53.3 (10.8)	52.7 (11.7)
Mean duration of RA	Years (range)	9.5 (0.3–39.3)	10.2 (0.3–49.0)	8.1 (0.2–39.9)
Rheumatoid factor	n	[redacted]	[redacted]	[redacted]
	Positive, n (%)	[redacted] (73.1)	[redacted] (72.2)	[redacted] (73.9)
Anti-CCP	n	[redacted]	[redacted]	[redacted]
	Positive, n (%)	[redacted]	[redacted]	[redacted]
Tender and swollen joints	n	[redacted]	[redacted]	[redacted]
	Tender joints, mean (SD)	27.2 (16.8)	21.9 (13.0)	25.0 (15.3)
	Swollen joints, mean (SD)	14.6 (9.7)	13.9 (8.6)	14.5 (10.3)
DAS28(ESR)	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	6.44 [redacted])	6.14 [redacted]	6.27 [redacted]
DAS28-3(CRP)	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
HAQ-DI score	n	[redacted]	[redacted]	[redacted]
	Mean (SD)	1.45 (0.64)	1.24 (0.66)	1.44 (0.69)
Prior therapy	TNF inhibitor, n (%)	[redacted] (6.3)	[redacted] (6.3)	[redacted] (7.3)
	Non-TNF inhibitor bDMARD, n (%)	[redacted](7.6)	0	[redacted](2.2)
	MTX, n (%)	[redacted] (83.5)	[redacted] (82.5)	[redacted] (86.7)
	Non-MTX cDMARD, %	55 (69.6)	62 (77.5)	232 (73.7)
	Failed DMARDs, mean	1.3	1.4	1.4
Concomitant therapy = n (%)	MTX	61(77.2)	64 (80.0)	250 (79.4)
	1 cDMARD	[redacted] (73.4)	[redacted] (62.5)	[redacted] (66.7)
	≥2 cDMARDs	[redacted] (25.3)	[redacted] (37.5)	[redacted] (33.3)
	NSAIDs	[redacted] (72.2)	[redacted] (63.8)	[redacted] (75.9)
	Systemic CCS	[redacted] (59.5)	[redacted] (58.8)	[redacted] (61.9)
	Lipid-lowering medication	[redacted]	[redacted]	[redacted]

Abbreviations: bDMARD = biologic disease-modifying anti-rheumatic drug; CCP = cyclic citrullinated peptide; CCS = corticosteroid; cDMARD = conventional disease-modifying anti-rheumatic drug; CRP = C-reactive protein; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire-disability index; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug; ORAL = Oral Rheumatoid Arthritis Phase 3 Trials; RA = rheumatoid arthritis; SD = standard deviation; TNF = tumour necrosis factor; TOF = tofacitinib.
Footnote: [†]In the ORAL trial programme Asian refers to Japanese and Korean patients.

All four RCTs employed modified intention-to-treat (mITT) analyses for effectiveness measures, comprising all randomised patients who received at least one dose of the study drug. All randomised patients in ORAL Standard (n=717) were included in the mITT analyses. Within ORAL Scan, 797/800 (99.6%) patients were included in the mITT analyses. Within ORAL Sync, 792/795 (99.6%) patients were included in the mITT analyses. Within ORAL Solo, 610/611 (99.8%) patients were included in the mITT analyses. All four RCTs are analysed with non-responder imputation and missing data are accounted for using last observation carried forward (LOCF) (see CS, pages 154-159).

4.2.2 Efficacy results for tofacitinib

ACR response data

ACR20 response data for the four included tofacitinib RCTs (ORAL Standard, Scan, Sync and Solo) are reported in Table 8, **Error! Not a valid bookmark self-reference.**, **Error! Reference source not found.** and **Error! Reference source not found.** respectively. A co-primary outcome for ORAL Standard, ORAL Scan and ORAL Sync was the proportion of patients achieving an ACR20 response at six months. A co-primary outcome for ORAL Solo was the proportion of patients achieving an ACR20 response at three months. For ACR20, all four RCTs found a statistically significant advantage for tofacitinib 5mg BID compared with the combined placebo group: ORAL Standard, 51.5% vs 28.3% (p<0.001); ORAL Scan, 51.5% vs 25.3% (p<0.001); ORAL Sync 52.7% vs 31.2% (p<0.001); ORAL Solo 59.8% vs 26.7% (p<0.001) (see Table 8, **Error! Not a valid bookmark self-reference.**, **Error! Reference source not found.**, and **Error! Reference source not found.**).

ACR50 responses for tofacitinib versus placebo were ORAL Standard, [redacted]% vs [redacted]% (p[redacted]); ORAL Scan, 32.4% vs 8.4% (p<0.001); ORAL Sync, [redacted]% vs [redacted]% ($p\leq$[redacted]); ORAL Solo, 31.1% vs 12.5% (p<0.001) (data taken from the CS, Tables 23, 29, 36 and 41).

ACR70 responses for tofacitinib versus placebo were ORAL Standard, [redacted]% vs [redacted]% (p[redacted]); ORAL Scan, 14.6% vs 1.3% (p<0.001); ORAL Sync, [redacted]% vs [redacted]% (p[redacted]); ORAL Solo, 15.4% vs 5.8% (p<0.001) (data taken from the CS, Tables 23, 29, 36 and 41).

For ORAL Standard, the CS (page 106) reported that in terms of comparison between tofacitinib and adalimumab:

“[redacted]”

For the recently completed, head-to-head trial, ORAL Strategy, the CS (page 251) reported the preliminary primary endpoint data (ACR50 response) for tofacitinib plus MTX vs adalimumab plus MTX vs tofacitinib monotherapy. Table 7 shows that tofacitinib plus MTX, but not tofacitinib monotherapy, was non-inferior to adalimumab plus MTX. Data were provided in the CS as academic in confidence but have subsequently been published in an open access peer reviewed publication.[41]

Table 7: ORAL Strategy ACR50 response rates at Month 6 including non-inferiority results (adapted from Table 89 of the CS)

Outcome		**TOF 5 mg Monotherapy (N=384)**	**TOF 5 mg + MTX (N=376)**	**ADA 40 mg + MTX (N=386)**
ACR50 response rate at Month 6, n (%)		147 (38.28)	173 (46.01)	169 (43.78)
Differences in ACR50 response rate				
Comparing with ADA 40 mg + MTX	Absolute difference (TOF – ADA), %	-5.50	2.23	-
	98.34% CI*	-13.98, 2.98	-6.40, 10.86	-
	Non-inferiority criteria met?	No	Yes	-
	p-value†	0.0512	<0.0001	-
Comparing with TOF 5 mg + MTX	Absolute difference (TOF mono – TOF+MTX), %	-7.73	-	-
	98.34% CI*	-16.29, 0.83	-	-
	Non-inferiority criteria met?	No	-	-
	p-value†	0.2101	-	-

Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; MTX, methotrexate; TOF, tofacitinib.
†p-values are from non-inferiority hypothesis testing. The p-values are multiplicity-adjusted and should be compared with 0.05.
* Non-inferiority between groups was shown if the lower bound of the 98·34% CI of the difference between comparators was larger than –13·0%

In the corresponding journal publication (Fleischman *et al.,* 2017)[41] the authors claim that the results suggest that in patients with an inadequate response to MTX, the addition of tofacitinib or adalimumab is equally efficacious and more likely to be effective than switching to tofacitinib monotherapy. The paper further asserts, "[t]*he present analysis suggests that adding tofacitinib 5 mg BID to MTX is as effective as adding adalimumab, a TNFi, to MTX*". The ERG notes that non-inferiority trials do not provide evidence that interventions are therapeutically equal, which is instead the purpose of an equivalence trial. Non-inferiority trials aim to determine whether one treatment is not statistically worse than another. In this case, non-inferiority was only demonstrated for tofacitinib

combination therapy but tofacitinib monotherapy was not found to be non-inferior in the relevant patient population for the current decision problem.

EULAR response data

The CS estimated EULAR response criteria from DAS28 scores as a good or moderate EULAR response (described in the CS as an improvement in DAS28 from baseline) for ORAL Standard, ORAL Scan and ORAL Sync at six months and for ORAL Solo at three months. For this outcome, the responses for tofacitinib 5mg BID compared with the combined placebo group were ORAL Standard, [redacted]% vs [redacted]% (*p*[redacted]); ORAL Scan, vs [redacted]% [redacted]% (*p*[redacted]); ORAL Sync vs [redacted]% [redacted]% (*p*[redacted]); ORAL Solo [redacted]% vs [redacted]% (*p*[redacted]) (see CS, Tables 25, 31, 38 and 43).

Change from baseline in HAQ-DI scores

Mean change from baseline in HAQ-DI scores for the four included tofacitinib RCTs are shown in Table 8, **Error! Not a valid bookmark self-reference.**, **Error! Reference source not found.** and **Error! Reference source not found.**. The primary outcome for ORAL Standard, ORAL Scan, ORAL Sync and ORAL Solo was the mean change from baseline in HAQ-DI score at three months. For this outcome, ORAL Standard, ORAL Sync and ORAL Solo found a statistically significant advantage for tofacitinib 5mg BID compared with the combined placebo group: ORAL Standard, –0.55 vs –0.24 ($p<0.001$); ORAL Sync–0.46 vs –0.21 ($p<0.001$); ORAL Solo–0.50 vs–0.19 ($p<0.001$) (CS Tables 21, 27, 34 and 40). For ORAL Scan, the HAQ-DI scores for tofacitinib 5 mg BD versus placebo were not statistically significant (*p*-value not declared).

Mean change from baseline in HAQ-DI scores to six months for tofacitinib 5mg BID compared with the combined placebo group were: ORAL Standard, [redacted] vs [redacted] (*p*[redacted]); ORAL Scan, [redacted] vs [redacted] (*p*[redacted]); ORAL Sync, [redacted] vs [redacted] (*p*[redacted]); ORAL Solo,–0.50 vs –0.19 ($p<0.001$) (3 month data only available for ORAL Solo) (see CS, Tables 24, 30, 37 and 40).

DAS28(ESR) <2.6 and ≤3.2 response

DAS28(ESR) <2.6 response data for the four included tofacitinib RCTs are shown in Table 8, **Error! Not a valid bookmark self-reference.**, **Error! Reference source not found.** and **Error! Reference source not found.**. The primary outcome for ORAL Standard, ORAL Scan and ORAL Sync was the proportion of patients achieving a DAS28(ESR) <2.6 response at six months. The primary outcome for ORAL Solo was the proportion of patients achieving a DAS28(ESR) <2.6 response at three months. The proportions of patients achieving a response for tofacitinib 5mg BID compared with the combined placebo group were: ORAL Standard, 6.2% vs 1.1% (*p*[redacted]); ORAL Scan, 7.2% vs 1.6% (statistical significance was not declared); ORAL Sync 9.1% vs 2.7% ($p=0.0038$); ORAL Solo 5.6% vs 4.4% ($p=0.62$) (CS Tables 25, 31, 34 and 40).

The proportions of patients achieving a DAS28(ESR) ≤3.2 response for tofacitinib 5mg BID compared with the combined placebo group were: ORAL Standard, [redacted]% vs [redacted]% (p[redacted]); ORAL Scan, [redacted]% vs [redacted]% (p[redacted]); ORAL Sync [redacted]% vs [redacted]% (p[redacted]); ORAL Solo 12.5% vs 5.3% (p<0.001) (see CS, Tables 25, 27, 38 and 43).

Table 8: Summary of primary efficacy results for ORAL Standard (adapted from CS Table 21)

Outcome		**Placebo to tofacitinib 5mg or 10mg BID**	**Tofacitinib 5mg BID**	**Adalimumab 40mg SC Q2W**
ACR20 response rate at Month 6 (NRI with advancement penalty)	n	106	196	199
	Response rate, n (%)	30 (28.3)	101 (51.5)	94 (47.2)
	Difference from placebo, %	-	[redacted]	[redacted]
	95% CI for difference	-	[redacted]	[redacted]
	p-value†	-	<0.001	<0.001
HAQ-DI score at Month 3	n	98	188	190
	LS mean change from baseline	–0.24	–0.55	–0.49
	LS mean difference from placebo	-	[redacted]	[redacted]
	95% CI for difference	-	[redacted]	[redacted]
	p-value†	-	<0.001	<0.001
DAS28(ESR) <2.6 at Month 6 (NRI with advancement penalty)	n	92	177	178
	Response rate, n (%)	1 (1.1)	11 (6.2)	12 (6.7)
	Difference from placebo, %	-	[redacted]	[redacted]
	95% CI for difference	-	[redacted]	[redacted]
	p-value†	-	[redacted]	[redacted]

Abbreviations: ACR = American College of Rheumatology; ADA = adalimumab; CI = confidence interval; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; FAS = full analysis set; HAQ-DI = Health Assessment Questionnaire-disability index; LS = least squares; NRI = non-responder imputation; Q2W = twice weekly; SC = subcutaneous; TOF = tofacitinib.

Footnote: †p-value is subject to the step-down approach

Table 8 shows that both tofacitinib and adalimumab were significantly superior to placebo for the ACR20 and DAS28(ESR) outcomes at 6 months and HAQ-DI at 3 months.

Table 9: Summary of primary efficacy results for ORAL Scan (adapted from CS Table 27)

Outcome		Placebo to tofacitinib 5mg or 10mg BID	Tofacitinib 5mg BID
ACR20 response rate at Month 6 (NRI with advancement penalty)	n	[redacted]	[redacted]
	Response rate, n (%)	[redacted] (25.3)	[redacted] (51.5)
	Difference from placebo, %	-	[redacted]
	95% CI for difference	-	[redacted]
	p-value†	-	<0.001
HAQ-DI score at Month 3	n	[redacted]	[redacted]
	LS mean change from baseline	–0.15	–0.40
	LS mean difference from placebo	-	[redacted]
	95% CI for difference	-	[redacted]
	p-value†	-	Not declared‡
DAS28(ESR) <2.6 at Month 6 (NRI with advancement penalty)	n	[redacted]	[redacted]
	Response rate, n (%)	[redacted] (1.6)	[redacted] (7.2)
	Difference from placebo, %	-	[redacted]
	95% CI for difference	-	[redacted]
	p-value†	-	Not declared‡
mTSS score at Month 6 (LE)	n	[redacted]	[redacted]
	LS mean change from baseline	0.47	0.12
	LS mean difference from placebo	-	[redacted]
	95% CI for difference	-	[redacted]
	p-value†	-	0.0792

Abbreviations: ACR = American College of Rheumatology; ADA = adalimumab; CI = confidence interval; DAS28 = Disease Activity Score in 28 joints; FAS = full analysis set; HAQ-DI = Health Assessment Questionnaire-disability index; LE = linear extrapolation; LS = least squares; NRI = non-responder imputation; mTSS = van der Heijde modified total sharp score; TOF = tofacitinib.
Footnote:†p-value is subject to the step-down approach. ‡Due to the step-down procedure applied to primary efficacy outcomes, significance was not declared for the HAQ-DI score or DAS28(ESR) <2.6 for TOF 5 mg. Nominal p-values (TOF 5 mg vs placebo) for these outcomes were <0.001 and 0.0034, respectively

Table 8 shows that both tofacitinib and adalimumab were significantly superior to placebo for the ACR20 and DAS28(ESR) outcomes at 6 months and HAQ-DI at 3 months.

Table 16 shows that ACR20 was the only outcome where tofacitinib 5 mg BD was declared to be significantly superior to placebo. A step-down approach was used for statistical testing in the order of ACR20, mTSS, HAQ-DI and then DAS28-4(ESR) <2.6. As the mean change from baseline in mTSS score at Month 6 was not significantly different between the tofacitinib 5 mg group (0.12) and the combined placebo group (0.47; p=0.0792), no statements regarding statistical significance could be declared for HAQ-DI score or DAS28-4(ESR) <2.6 for tofacitinib 5 mg.

Table 10: ORAL trials January 2016 data set analysis: tofacitinib safety data (replicated from clarification response, question A1[34])

Event Term	Total number of events	Number of patients affected	Incidence per 100 patient exposure years
Serious Infection Events	[redacted]	[redacted]	[redacted]
Drug Induced Liver Injury (Cases meeting Hy's law†)	[redacted]	[redacted]	[redacted]
Gastrointestinal Perforation Events	[redacted]	[redacted]	[redacted]
Treatment discontinuations as a result of an Adverse Event	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]
Herpes Zoster infection	[redacted]	[redacted]	[redacted]
Interstitial Lung Disease	[redacted]	[redacted]	[redacted]
Malignancies			
All Cancers (other than non-melanomatous cancers of the skin)	[redacted]	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]	[redacted]
Non-melanomatous cancers of the skin	[redacted]	[redacted]	[redacted]
Breast Cancer (Female patients only)	[redacted]	[redacted]	[redacted]
Lung Cancer	[redacted]	[redacted]	[redacted]
Melanoma	[redacted]	[redacted]	[redacted]

Footnote: †prognostic indicator that a pure drug-induced liver injury (DILI) leading to jaundice, without a hepatic transplant, has a case fatality rate of 10% to 50%.

According to the data presented in the company response, the most commonly recorded AE was herpes zoster infection, with an estimated incidence rate per 100 patient years of [redacted]) (Table 10). However, the ERG's own search for AEs in Medline retrieved a study by Winthrop et al., (2014) who reviewed the tofacitinib RA development programme from the Phase II, III and long-term extension studies. This earlier data cut of March 2011 reported the incidence rate of herpes zoster was 4.3 per 100 patient years but was substantially higher within Asia (7.7 per 100 patient years). Clinical advice received by the ERG suggested that increased risk of herpes zoster is elevated about 2-fold in RA generally and the experts considered an increased risk by treatment as therefore more worrying as some instances can be serious, particularly in the elderly. Neither the CS nor the company's response to the clarification letter not provides incidence rates for the comparators arms, instead an analysis is presented which shows that the rate of herpes zoster is relatively stable over time (measured at 6-monthly intervals

tofacitinib 5 mg whilst the proportion of patients experiencing ≥1 treatment-related AE at 3 months in the ORAL Standard, Scan and Sync (tofacitinib plus methotrexate) trials was [redacted] respectively (see CS, Appendix 2). The ERG has tabulated selected AE data deemed as related to the study drug for the tofacitinib treatment arms (data from both 5 mg and 10 mg arms) for the four key ORAL trials. As can be observed in Table 11, the three-tofacitinib combination trials have higher incidences of the selected treatment-related AEs than the monotherapy trial (ORAL Solo).

Table 11: Tofacitinib-related adverse event (data extracted from Appendix 2 of the CS)

Number experiencing event/ Number of patients in tofacitinib (5 mg and 10 mg) treatment arms				
	ORAL Standard	ORAL Scan	ORAL Sync	ORAL Solo
Treatment related SAEs between 0-6 months	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation due to AEs between 0-6 months	40/405 (9.9%)	53/637 (8.3%)	40/633 (6.3%)	14/488 (2.9%)
Deaths attributed to study treatment	1	5	3	0

Interestingly the recently published journal paper for the ORAL Strategy trial[41] describes this same issue (which is not drawn in the CS) when the authors state that "*concomitant csDMARDS augment the risk of herpes zoster with tofacitinib*." They cite an abstract from a study funded by Pfizer which found that "*concomitant use of nonbiologic DMARDs or GCs appears to increase the risk and overall IR per 100* [patient years] *of HZ from 0.56 to 4.82 with 5 mg BID*".[50] This study, published in 2015, is not referenced in the CS.

The ERG considers that a higher toxicity profile of tofacitinib plus methotrexate cannot be fully characterised in a pooled analysis with associated incidence rates from both dosing regimens, as combining the monotherapy and combination therapy trials potentially dilutes the apparent incidence of treatment-related adverse events that occur in tofacitinib combination therapy.

4.3 Critique of trials identified and included in the network-meta-analysis

4.3.1 Included trials for the network meta-analysis

NMAs were performed separately for the cDMARD-IR and bDMARD-IR population. Trials other than the tofacitinib RCTs (ORAL Standard, ORAL Scan, ORAL Sync, ORAL Solo and ORAL Step)

that were included in the NMA are listed in Table 28 (cDMARD-IR population) and Table 29 (bDMARD-IR population) below.

Quality assessments of the included trials (other than ORAL Standard, ORAL Scan, ORAL Sync, ORAL Solo and ORAL Step) were presented in Appendix 4 of the CS. Appropriate quality assessment items were used, however, it was unclear for the double-blind trials in Appendix 4 of the CS, who exactly was blinded (i.e., patients, physicians, outcome assessors). In response to a request for clarification from the ERG regarding who was blinded in the double-blind trials (see clarification response,[34] question A6), the company stated:

> *"patients and investigators were blind in six trials (ADACTA[51], AUGUST II[52], LITHE[53, 54], OPTION[55], PLANETRA [56], Van de Putte 2004[57]); patients and outcome assessors were blind in four trials (DE019, RAPID 1, RAPID 2, GO-FORTH); patients, care providers, and investigators were blind in one trial (GO-FORWARD); patients, care providers, investigators, and outcome assessors were blind in 11 trials (ACT-RAY, ATTEST, CERTAIN, Choe 2015, Emery 2015, Fleischmann 2012, GO-FURTHER, HERA, J-RAPID, Kremer 2012, Li 2015, SATORI); and patients, investigators, and other study personnel, except for pharmacists were blind in one trial (START)."*

It was not reported who was blinded in three of the "double-blind" trials (CHANGE[58], Kim 2007[59] and Van de Putte *2004*[57]).

Trials in the analysis of the cDMARD-IR population were largely the same as those in the NMA undertaken by the independent Assessment Group (AG) in TA375. However, there were some exceptions, which have been grouped into the following categories: (i) trials in the CS that were not included in TA375, and; (ii) trials included in TA375 but excluded from the CS. A similar comparison could not be made for the bDMARD-IR population, as this was not the focus of TA375.

Trials included the CS not in TA375 NMA

In total, 10 trials were included the CS that were not included in the base case analysis of TA375. HERA[61] was published after the search date for TA375. Fleishmann 2012,[62] GO-AFTER,[63] Kremer 2012[64] and RADIATE[65], were excluded from TA375 as participants in these trials had received prior biologic therapy. J-RAPID[66] was excluded as separate 6-month data were not reported for those with concomitant cDMARDs and monotherapy. Four trials were only included in TA375 sensitivity analyses as trial participants had received prior biologics (LITHE,[53, 54] OPTION,[67] RAPID 1,[68, 69] RAPID 2[70]).

Trials in TA375 NMA not in the CS base case

The ERG identified 19 trials that had been included in TA375 that were either excluded or not included in the CS. Of these, 12 trials in TA375 were identified as potentially relevant and full texts were scrutinised by the ERG. Possible reasons for exclusion identified by the ERG for all 12 studies are presented in Table 30.

4.3.2 Critique of the indirect comparison and/or multiple treatment comparison

NMAs were performed separately for the cDMARD-IR and bDMARD-IR population using a Bayesian approach for EULAR response at Month 6 and change from baseline HAQ-DI score at Month 6. For the continuous outcome, HAQ-DI, an identity-link function model was used in the NMA. For the ordered categorical EULAR response, a binomial likelihood with logit link-function model was used for the cDMARD-IR population by dichotomising the data, and a multinomial likelihood with probit link function model was used for bDMARD-IR population. The CS also explores the probit link function model for the cDMARD-IR population in a scenario analysis. The choice of the link function was based on the performance of convergence of the Markov chain Monte Carlo (MCMC). The choice between the fixed effect and random effects model was based on the deviance information criterion (DIC). Table 12 provides a summary of the model used for each outcome measure in the two populations.

Table 12: The model used for each analysis in the CS

Population	Outcome	Model
cDMARD-IR	EULAR response (moderate)	binomial logit (fixed effect)
	EULAR response (good)	binomial logit (fixed effect)
	EULAR response (at least moderate)	binomial logit (random effects)
	HAQ-DI	identity (random effects)
bDMARD-IR	EULAR response	multinomial probit (fixed effect)
	HAQ-DI	identity (fixed effect)

The ERG disagrees with the approach of using two different models for EULAR response in the two populations based on the performance of the convergence of the MCMC. When data are sparse, poor convergence may be caused by the use of a reference/vague prior. The choice of the likelihood function/link function should be based on the data generating process. A multinomial likelihood with probit link function is preferred to a binomial likelihood with logit link function for the ordered categorical EULAR data because it accounts for natural ordering and correlations between the EULAR categories. This is important to the decision problem when EULAR results are used to populate the economic model. When data are sparse, comparing DIC of a fixed effect model with DIC of a random effects model using a reference/vague prior for the between-study standard deviation may not be appropriate since the reference/vague prior may lead to implausible posterior uncertainty for the results. The choice between the fixed effect and random effects model should be determined by the objective of the analysis and the conduct of the included studies. The fixed effect model was used for a moderate EULAR response and a good response, but the random effects model was used for at least a moderate

response in the cDMARD-IR population. It may not be reasonable to believe that heterogeneity exists in at least a moderate EULAR response network but not in a moderate response or a good response network.

In response to a request for clarification (question A11), the company clarified that placebo + cDMARD/cDMARD was used as the reference treatment across all the NMAs.

For tofacitinib (TOF) trials with early escape, two non-responder imputation (NRI) approaches were applied. Estimate 1 of treatment effect was calculated by applying NRI to Month 3 non-responders from the placebo arm (termed NRI without advancement penalty). Estimate 2 of treatment effect was calculated by applying NRI to Month 3 placebo non-responders as well as the Month 3 TOF non-responders (termed NRI with advancement penalty). The primary analysis for the ORAL Standard, Scan and Sync trials was based on NRI with advancement penalty (Estimate 2).

Estimate 1 was used in the base case NMA for the ORAL Standard, Scan and Sync trials with the justification that, using the data combined from these three trials, [redacted] of non-responders treated with TOF at Month 3 subsequently developed a response to treatment at Month 6. The CS states that clinical expert opinion estimates that less than 10% of the Month 3 placebo-treated non-responders would have subsequently developed a EULAR response by Month 6 (CS page 156). Estimate 1 was also used in the base case NMA for the ORAL Solo and Step trials with the reason that it is expected that few patients would go on to develop any subsequent response to treatment beyond that already seen by Month 3 (CS page 158) in the absence of any form of active DMARD treatment. The ERG believes that Estimate 1 overestimates the relative treatment effect of TOF and Estimate 2 underestimates the treatment effect of TOF.

In response to a request for clarification (question A12), the company stated that there was a typographical error in the CS regarding the prior used for the treatment effect relative to the reference treatment. The vague prior used for the relative treatment effect was a normal distribution with mean 0 and variance 100^2. In RE models, a uniform [0, 5] prior was used for the between-study standard deviation. The ERG notes that when data are sparse, this uniform prior would lead to implausible posterior uncertainty in the results.

The I^2 statistic was used to assess the heterogeneity for the pairwise treatment comparisons. [redacted]

Because a probit model was used in the bDMARD-IR population for EULAR response, it was not clear how the OR was calculated in this case. In response to a request for clarification from the ERG (question A11), the company stated that the WinBUGS code presented included code for generating the absolute treatment effects but these were not generated. Hence, it was still unclear how ORs were calculated from the probit model.

The base case NMA results in the CS should be interpreted with caution since Estimate 1 (NRI without advancement penalty) was used for calculating the relative treatment effect of TOF in the ORAL trials, which overestimated the relative treatment effect of TOF in these trials. A fixed effect model was used for moderate EULAR response, good EULAR response in the cDMARD-IR population and all the outcomes in the bDMARD-IR population, which underestimated treatment uncertainty. Two different models were used for EULAR response in the two populations.

To incorporate etanercept into the cDMARD-IR networks, the company assumed that the intensified cDMARD arm in the LARA study was the same as the cDMARD node, based on the assumptions involved in incorporating LARA to the central node were less of a risk to bias in the network than changing the inclusion criteria for the NMA to include the SWEFOT trial (disease duration <1 year) in the base case analysis. The ERG notes that this may not be an appropriate assumption to make, because this could overestimate the treatment effect of cDMARD.

Six sensitivity analyses were performed in the CS, which included:

1. Exclusion of predominantly Asian populations trials/lower dose MTX
2. Exclusion of trials that included patients with prior bDMARD exposure
3. Exclusion of trials with milder disease
4. Separating intensified cDMARDs from central node
5. Alternative modelling approach (probit) for cDMARD-IR
6. Alternative modelling approach (probit) for cDMARD-IR, using Estimate 2

The company concluded that results were sensitive to the trials included in the base case network, but less influenced by the modelling approach.

The ERG requested the company to perform additional analysis for EULAR response in both populations (clarification question A7) with the following settings:

- Using a random effects probit model with an informative prior for the between-study variance (log normal with mean of -2.56 and variance of 1.74^2, proposed by Turner *et al.,* (2012).[113] The log normal is truncated so that the OR in one study would not be ≥50 times than in another, and re-scaled to match the probit scale).

- EULAR response for ORAL trials derived using DAS ESR with all trial data by applying non-responder imputation Estimate 2 in the CS Table 53. Use the individual EULAR results from trials in the NMA, i.e. not pooling individual patient-level data from ORAL trials.
- Excluding studies which only reported DAS (i.e. did not report EULAR) from the NMA.
- Not assuming intensified DMARD arm is equivalent to the central DMARD node in the LARA trial and including the SWEFOT trial. [redacted]Choosing PBO plus cDMARD/cDMARD as the reference treatment (treatment 1) in the analyses.

The ERG also requested a sensitivity analysis for the requested NMA as above by excluding patients with prior biologic use in the ORAL trials and excluding studies that enrolled a proportion of patients with prior bDMARD use (clarification question A8). In addition to the two analyses the ERG has requested, the company also provided the results using the settings suggested by the ERG as above but applying Estimate 1 (NRI without advancement penalty) to the ORAL trial **Error! Reference source not found.** to **Error! Reference source not found.** show the EULAR results from the additional analyses conducted by the company (clarification question A7 and A8). All the results were interventions relative to cDMARD on the probit scale, with larger negative numbers being associated with better health outcomes.

Using Estimate 2 (NRI with advancement penalty), which is consistent with the primary analysis of the ORAL Standard, Scan and Sync trials, the effect of TOF plus cDMARD was the smallest among the bDMARDs in the cDMARD-IR population (**Error! Reference source not found.**). Using Estimate 1 (NRI without advancement penalty), the effect of TOF + cDMARD compared to cDMARD was smaller than that of TCZ, CTZ, GOL, ETN and ETN's biosimilars in combination with cDMARD, but larger than ADA, ABT, IFX and IFX's biosimilars in combination with cDMARD in the cDMARD-IR population (**Error! Reference source not found.**).

For TOF as monotherapy, the effect of TOF compared with cDMARD was the smallest among the active treatments using Estimate 2, but had a larger effect than intensified cDMARD and ETN using Estimate 1 in the cDMARD-IR population (**Error! Reference source not found.**).

The analyses including patients with and without prior biologics use provide very similar results for the cDMARD-IR population, except that the treatment effect of TCZ plus cDMARD versus cDMARD reduced noticeably using the studies without prior biologics and the effect of ADA monotherapy became statistically significant (**Error! Reference source not found.** and **Error! Reference source not found.**).

The effect of TOF plus cDMARD compared with cDMARD was bigger than GOL plus cDMARD, but smaller than non-TNFi, ETN, TNFi, RTX, TCZ and ABT in combination with cDMARD in the bDMARD-IR population using Estimate 2 (**Error! Reference source not found.**). None of the treatment effects versus cDMARD were statistically significant, but the ERG suspects that a vague prior was used because the estimated between-study standard deviation was reported to have mean 1.21 with 95% credible interval (0.02, 4.52) which does not reflect the prior that the ERG has suggested. The company did not provide the results using Estimate 1.

The absolute treatment effects, including at least a moderate and at least a good EULAR response for both populations, are presented in Appendix 2.

A primary endpoint of radiographic progression using the mTSS in ORAL Scan was not significant at either 6 or 12 months (p=0.0792). Further statistically significant benefits for tofacitinib in combination with methotrexate (at 6 months) and for tofacitinib monotherapy (at 3 months) over placebo were observed using the EQ-5D, FACIT-F and pain assessed VAS outcomes ($p \leq 0.001$).

ACR20 at 3 months was significant for tofacitinib monotherapy versus placebo at 3 months in one trial (ORAL Solo) but not significant for the primary endpoint of the proportion achieving remission using DAS28(ESR) at 3 months. As all patients crossed over from placebo to receive tofacitinib at 3 months in ORAL Solo, there are no placebo-controlled results at 6 months for the other relevant endpoints. The ERG consider that the recently completed head-to-head trial, ORAL Strategy, has data relevant to the decision problem. The ORAL Strategy trial showed tofacitinib combination therapy with methotrexate to be non-inferior to adalimumab plus methotrexate but tofacitinib monotherapy was not found to be non-inferior to both tofacitinib plus methotrexate and adalimumab plus methotrexate for the primary endpoint of ACR50 at 6 months.

Safety data for tofacitinib were presented in the CS from a pooled analysis of tofacitinib trial data up to March 2015 which was two years prior to the current appraisal. Whilst the company were able to provide some up-to-date safety data following a request, the ERG note that a full and transparent safety profile of tofacitinib versus comparators, which contains comprehensive data for all AEs including SAEs, was not provided. The company stated that they were "*unable to update the incidence of Serious Adverse Events within the timelines provided as these are listed in a separate data base*". One of the most common AEs for tofacitinib was herpes zoster, which was also noted from a published NMA to be significantly higher than bDMARD comparators. [48] Incidence rates in the company's safety set were highest for serious infection events, bronchitis, pneumonia and all cardiac disorders. The ERG considers that pooling trials to produce incidence rates of AEs with tofacitinib may dilute the appearance of adverse events for tofacitinib plus cDMARD, which are noted by several sources[41, 49, 50, 114] to be higher than for tofacitinib monotherapy, which are not referenced or discussed in the CS. Moreover, the company's reliance on AE data from their own trial programme without performing targeted searches for relevant safety literature for tofacitinib means that relevant studies regarding safety, such as NMAs versus other bDMARDs, are missed.

The ERG believes that the results presented in NMA should be treated with caution, as the ordered categorical EULAR data were dichotomised in the cDMARD-IR population, which ignores the natural ordering and correlations between the EULAR response categories. A fixed effect model was used in all the analyses in the bDMARD-IR population and EULAR response (moderate response and good response) in the cDMARD-IR population. Heterogeneity is expected and this approach underestimates uncertainty in the treatment effect. For tofacitinib trials with early escape, the results

Table 13: Population characteristics at baseline used in the model

	cDMARD-IR		bDMARD-IR
	Moderate RA	**Severe RA**	**Severe RA**
Age	[redacted]	[redacted]	[redacted]
Proportion female	[redacted]	[redacted]	[redacted]
Weight (Kg)	[redacted]	[redacted]	[redacted]
HAQ-DI score	[redacted]	[redacted]	[redacted]
DAS28	[redacted]	[redacted]	[redacted]
Proportion with prior cDMARD experience	[redacted]	[redacted]	[redacted]
Proportion with prior bDMARD experience	[redacted]	[redacted]	[redacted]
Proportion anti-CCP positive	[redacted]	[redacted]	[redacted]
Disease duration (years)	[redacted]	[redacted]	[redacted]
Haemoglobin	[redacted]	[redacted]	[redacted]
CRP	[redacted]	[redacted]	[redacted]
ESR	[redacted]	[redacted]	[redacted]
Total cholesterol	[redacted]	[redacted]	[redacted]
CDAI	[redacted]	[redacted]	[redacted]
Number of previous DMARDs	[redacted]	[redacted]	[redacted]

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; CCP, cyclic citrullinated peptide; CDAI, clinical disease activity index; cDMARD, conventional disease-modifying anti-rheumatic drug; CRP, c-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; IR, inadequate response.

5.3.2 Interventions and comparators

Descriptions of the intervention and the comparators are provided in Sections 3.2 and 3.3. Table 94 of the CS provides a summary matrix of which interventions are licenced (in combination with MTX or as monotherapy) in each of the moderate RA cDMARD-IR, moderate RA bDMARD-IR, severe RA cDMARD-IR, and severe RA bDMARD-IR populations. This table also includes information on recommendations provided by NICE. Table 34 summarises the comparators presented in the analyses within the CS. The ERG notes that some of the comparators included are currently not recommended by NICE and more importantly that recommended comparators are missing from some of the analyses presented by the company. The CS did not identify publications for inclusion of adalimumab, infliximab and certolizumab pegol for the bDMARD-IR populations. However, the ERG does not expect this to affect the conclusions of the company's economic analysis.

Table 14: ORs and probabilities of good and moderate EULAR response for each treatment used in the MTX-tolerant population

Therapy	ORs compared with TOF		Probabilities of EULAR response*		
	Moderate or good	Good	No response	Moderate response	Good response
TOF + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTZ + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABT + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX + MTX#	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cDMARD†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TOF: tofacitinib; ABT: abatacept; TCZ: tocilizumab; ADA: adalimumab; CTZ: certolizumab pegol; ETN: etanercept; GOL: golimumab; IFX: infliximab; RTX: rituximab; MTX: methotrexate; LEF: leflunomide; cDMARD: conventional disease-modifying antirheumatic drug

*Average probabilities based on the full population of ORAL trials (Scan, Standard, Sync and Step)

Biosimilars assumed to have same efficacy

†Includes MTX, LEF and cDMARD combination

Table 15 shows the ORs used in the model together with the average probabilities of moderate or good EULAR response for patients who could not tolerate MTX or for whom MTX was contraindicated. The probabilities of EULAR response for SSZ+HCQ were assumed to be equal to placebo. The ERG notes that this is likely to be an underestimate. Average probabilities were calculated averaging the probabilities of all patients in the ORAL Solo trial.

Table 15: ORs and probabilities of good and moderate EULAR response for each treatment used in the MTX-intolerant population

Therapy	ORs compared with TOF		Probabilities of EULAR response*		
	Moderate or good	Good	No response	Moderate response	Good response
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN#	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SSZ+HCQ †	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TOF: tofacitinib; TCZ: tocilizumab; ADA: adalimumab; ETN: etanercept; GOL: golimumab; SSZ: sulfasalazine; HCQ: hydroxychloroquine

*Average probabilities based on the full population of ORAL Solo

Biosimilars assumed to have same efficacy

†Assumed equal to placebo

moderate, (iii) high and (iv) severe. Norton *et al*. report a regression model to calculate each patient's probability of belonging to each class based on the patient's baseline characteristics. The company follow the approach used by the AG in TA375 whereby the change in HAQ-DI score for a patient is calculated as the weighted change in HAQ-DI associated with each class. The company provides commercial-in-confidence data that show that the patients in the ORAL trials are more likely to be in a worse HAQ-DI progression class than the ERAS cohort[121] and that assumed within TA375.[24] This may be due to the recruitment of patients with established RA in the ORAL trials.

In the second approach, the company assumed that 'rapid progressors' could be identified. These patients are assumed to have a worse long-term HAQ-DI prognosis than that for average patients, which was taken from work reported by the NICE Decision Support Unit (DSU).[122] The ERG comments that whether such patients could be identified has been questioned in a report by Stevenson *et al.*[123] considered within TA375. Furthermore, the company producing baricitinib, having analysed academic-in-confidence data on changes in HAQ, stated in its submission to NICE that '*this suggests that the 'rapid-progressor' group discussed in TA375 that might benefit from more aggressive treatment is a small minority of the overall moderate population*.'[124]

An additional scenario analysis was performed that assumed that HAQ-DI progression was linear for patients receiving cDMARDs and that HAQ-DI increased at a rate of 0.045 per year for patients on LEF and at a rate of 0.06 per year for patients on PALL. The ERG believes that these analyses are inappropriate as HAQ-DI progression has been proven to be non-linear[122] in TA375.[24]

HAQ-DI trajectory prior to treatment cessation

The CS states that prior to treatment discontinuation, the HAQ-DI score improvement observed upon treatment response was lost linearly over the six-month period. This is similar to the approach used in TA375,[24] although in TA375 the entire HAQ-DI loss occurred at the time of discontinuation.

After applying changes to HAQ-DI scores, the resulting values were rounded to the nearest valid HAQ-DI score (which is a multiple of 0.125). The ERG notes that this approach can lead to inaccurate results. This contrasts with the approach used in TA375[24] in which scores were rounded to either the higher or the lower valid HAQ-DI score with a probability proportional to their distance to each (e.g. a value twice closer to the upper HAQ-DI score would be twice as likely to be simulated as the upper score than simulated as the lower score). This point was raised by the ERG during the clarification process (see clarification response,[34] question B4) but was misunderstood and therefore not addressed by the company despite the code being contained in the model to perform a probabilistic analysis of HAQ-DI changes. The ERG assessed the impact of this change in its exploratory analyses.

1. Limitations with the company's NMA
2. Missing comparators
3. Inadequate sequences of treatments
4. Assuming same efficacy for SSZ+HCQ as for placebo
5. Assuming the efficacy of the first bDMARD applies to all treatment lines of bDMARDs in the cDMARD-IR population
6. Assuming the same efficacy for TOF+MTX and TOF monotherapy
7. Deterministic rounding to nearest HAQ-DI score
8. Linear HAQ-DI trajectory for palliative care

1. Limitations with the company's NMA

The ERG believes that the company's NMA suffers from potential limitations, which have been described in Section 4.4: (i) the ordered categorical EULAR data were dichotomised in the cDMARD-IR population, which ignores the natural ordering and correlations between the EULAR response categories; (ii) a fixed effects model was used in all the analyses in the bDMARD-IR population and for EULAR responses, which underestimates uncertainty in the treatment effect; and, (iii) the imputation approach used in TOF trials potentially overestimates the treatment effect of TOF versus cDMARD, and could have an important impact in the position of TOF among the bDMARDs.

2. Missing comparators

The company's analyses did not include all the relevant comparators for some of the populations as explained in Section 5.3.2 and Table 34. Most importantly, all relevant comparators were missing in the analysis for bDMARD-IR MTX-intolerant patients with severe RA and four comparators (ADA, ETN, IFX and CTZ with concomitant MTX) out of seven were missing from the analysis for bDMARD-IR RTX-ineligible patients with severe RA. The CS did not identify publications for inclusion of adalimumab, infliximab and certolizumab pegol for the bDMARD-IR populations. The ERG notes the company included neither the RTX biosimilar nor the SC formulations of ABT and TCZ.

3. Inadequate sequences of treatments

The ERG notes that the sequences used by the company were not appropriate for the following reasons:

- The inclusion of multiple consecutive treatments of cDMARD combinations and SSZ+HCQ. Patients only go through one such treatment before progressing to another type of treatment.
- The inclusion of bDMARD treatments in populations and points in the pathway which have not been recommended by NICE, such as:
    - ETN+MTX after TCZ+MTX and RTX+MTX in cDMARD-IR patients with severe RA.

- ABT+MTX and GOL+MTX in the bDMARD-IR RTX-eligible patients with severe RA.
- TCZ+MTX after TOF, ABT or GOL concomitant with MTX in the bDMARD-IR RTX-ineligible patients with severe RA.
- GOL+MTX after TCZ+MTX in the bDMARD-IR RTX-ineligible patients with severe RA.
- TCZ monotherapy in bDMARD-IR MTX-intolerant patients with severe RA.
- RTX+MTX and TCZ+MTX after cDMARD combination in cDMARD-IR patients with moderate RA.

- The inclusion of three or four post-biologic treatments before palliative care instead of just one.

4. *Assuming the same efficacy for SSZ as for placebo*

The company used the EULAR response ORs calculated in the NMA for placebo as an estimate for the ORs for SSZ+HCQ. The ERG notes that this is likely to underestimate the effectiveness of SSZ and therefore underestimate the ICER for TOF monotherapy compared with SSZ.

5. *Assuming the same efficacy for TOF as monotherapy and in combination with MTX*

The company assumed that TOF as monotherapy would have the same efficacy as in combination with MTX. However, ORAL Strategy (NCT02187055)[40] showed that TOF monotherapy was not found to be non-inferior to TOF+MTX. The also NMA shows that TOF monotherapy results in slightly lower probabilities of response than TOF + MTX: in cDMARD-IR patients, an average of [redacted] versus [redacted] achieved good EULAR response and [redacted] versus [redacted] achieved moderate EULAR response (see clarification response,[34] Table 8). However, the ERG acknowledges that the company estimated the efficacies of other monotherapies in comparison with TOF monotherapy and therefore the relative impact of this assumption is likely to be reduced.

6. *Assuming the efficacy of the first bDMARD applies to all treatment lines of bDMARDs in the cDMARD-IR population*

Within the CS, the company assumed that the efficacy of bDMARDs in terms of probabilities of EULAR response would remain unchanged irrespective of whether they were given as first line or subsequent line treatment. However, as demonstrated by the company's own regression model, the efficacy of bDMARDs is lower in bDMARD-IR patients than in cDMARD-IR patients. Therefore, for the second and subsequent lines of treatment in the cDMARD-IR population, it is more appropriate to use the probability of EULAR response calculated in the bDMARD-IR patients. During the clarification process, the ERG asked the company to activate

the prior_bdmard flag after patients had gone through their first bDMARD (or JAK inhibitor). The company implemented this change and