NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs [ID1220]

The final scope and matrix are available on the NICE website

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

Tofacitinib for treating active psoriatic arthritis following inadequate response to disease-modifying anti-rheumatic drugs

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

Abbreviations

AEs	Adverse events
ACR	American College of Rheumatology
bDMARD	Biological disease-modifying antirheumatic drug
cDMARD	Conventional disease-modifying antirheumatic drug
HAQ-DI	Health assessment questionnaire- disability index
Hrqol	Health-related quality of life
NMA	Network meta-analysis
PASI	Psoriasis area and severity index
PsA	Psoriatic arthritis
PsARC	Psoriatic arthritis response criteria
TNF-αi	Tumour necrosis factor alpha inhibitor

Psoriatic arthritis (PsA)

- Psoriatic arthritis = inflammatory arthritis closely associated with psoriasis
- Chronic progressive condition with flare-ups and periods of remission
- Psoriatic arthritis causes multiple distressing symptoms including chronic pain, exhaustion, swelling and joint damage
- Symptoms range from mild inflammation to severe erosion of the joints
- Up to 24% patients with psoriasis may go on to develop PsA
- Peak age of onset is 30 to 50 years

Patient perspectives

- Submissions received from Psoriasis Association and Psoriasis and Psoriatic Arthritis Alliance
- Onset is often between 20-40 years old, adding a substantial burden to carers who may be in full time employment
- There is unmet need for additional options for:
  - when the disease does not respond to treatment
  - when other treatments loses efficacy and,
  - treatments which improve fatigue and nail disease
- Patients with PsA may reduce their working hours, change careers to reduce pain/mobility issues or require sick leave
- PsA reduces quality of life, sociability and affects relationships with family and friends
- Goals = maintaining mobility, stopping further deterioration and joint destruction
- Oral therapy → ease of administration compared to subcutaneous injection (benefit people with affected hand & finger joints)

Tofacitinib (Xeljanz)

Pfizer

Mechanism of action	Targeted janus kinase (JAK) inhibitor
Positive CHMP opinion	Tofacitinib in combination with methotrexate is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug therapy
Administration and dose	• Oral administration • 1 x 5mg tablet twice daily
Cost	• List price: £690.03 per 56-tablet pack • Average annual cost of treatment £9,001.19* • A confidential patient access scheme is in place for tofacitinib

Identified sub-populations covered by CHMP-positive indication:

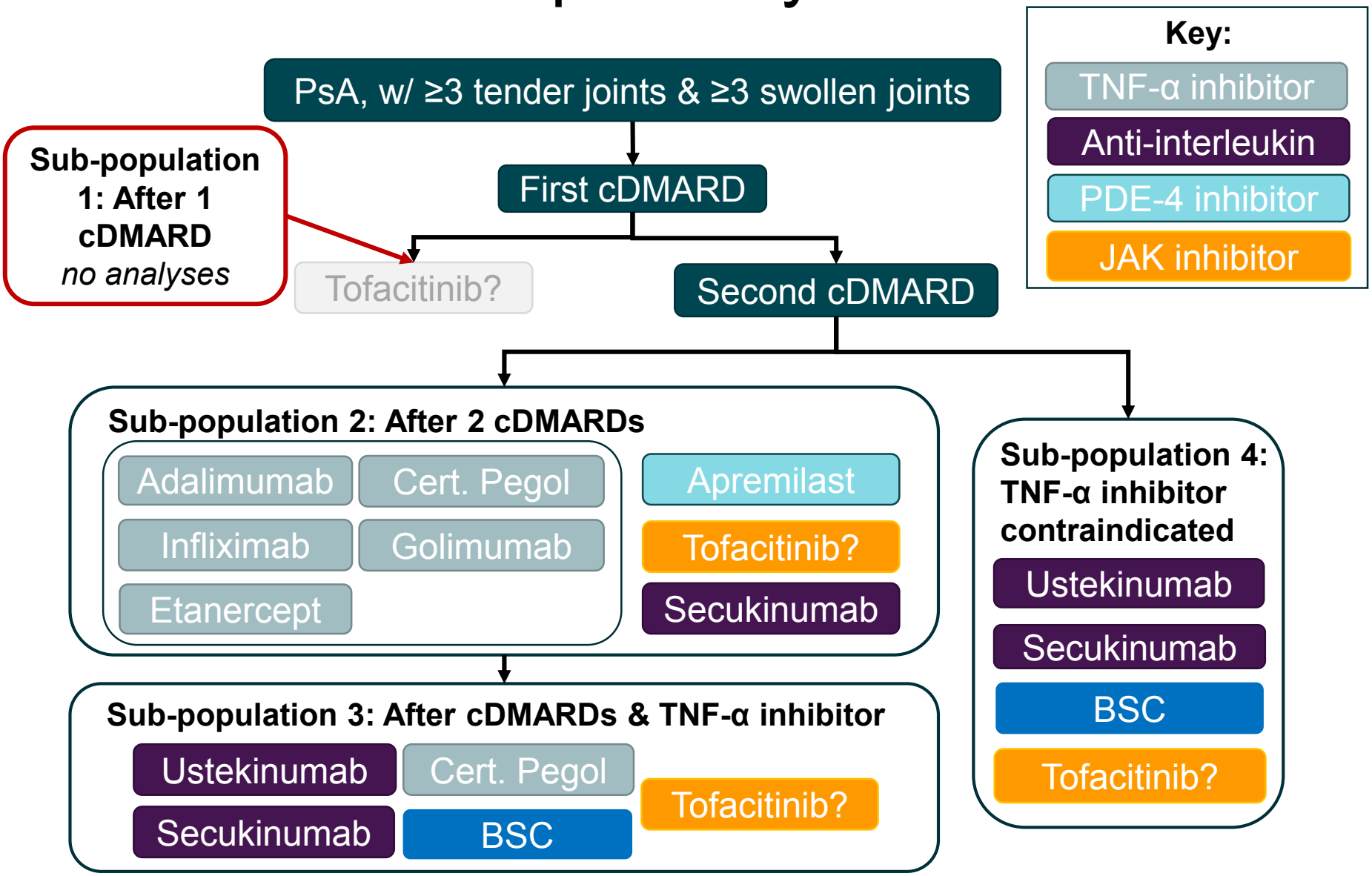
1. No adequate response to at least 2 prior conventional DMARDS (cDMARDs)
2. No adequate response to cDMARDs and at least 1 biological DMARD/TNF-αi
3. TNF-αi contraindicated/not-tolerated
4. No adequate response to 1 cDMARD

**Factual inaccuracy updated by NICE technical team after committee meeting*

Clinical expert comments

- Aim of treatment is to reduce symptoms and improve quality of life
- An increasing number of people have run out of options and are left with unremitting symptoms, a very poor quality of life and disease progression
- Tofacitinib mode of action is unique in psoriatic arthritis
  - PsA is a heterogeneous disease, and the available treatment options have different strengths e.g. the skin/enthesitis/dactylitis responses vary across agents
- Tofacitinib may be particularly effective at treating joint disease
- Only other treatment that can be taken orally is apremilast – so tofacitinib may be a useful option for needle phobic patients or those allergic to parenteral preservatives

Clinical pathway of care



Decision problem

NICE scope		Company submission
Intervention: *'tofacitinib…*		
…(alone/combination with csDMARD)'		*…(in combination with a csDMARD)'*
Sub-population	**Comparators**	
(**1**) No response w/ 1 cDMARD	• cDMARDs	No analyses (insufficient data to separate from '≥2 cDMARDs')
(**2**) No response w/ ≥2 cDMARDs:	• bDMARDs • Apremilast	✓
(**3**) No response w/ cDMARDs and ≥1 TNF-αi:	• Ustekinumab • Secukinumab • Certolizumab pegol • BSC	• Ustekinumab, secukinumab & BSC • No analysis vs cert. peg. as trial only included subset of population
(4) TNF-αi contraindicated:	• Ustekinumab • Secukinumab • BSC	✓

- ERG comment: Population & outcomes consistent with NICE scope
- Deviations in intervention and comparators reasonable

Clinical trial evidence

OPAL Broaden	OPAL Beyond
Multicentre, phase 3, randomised, double-blinded	
• Tofacitinib 5mg twice daily (n=107) • Placebo* (n=105) • Adalimumab (n=106)	• Tofacitinib 5mg twice daily (n=131) • Placebo* (n=131)
• ≥3 tender joints, ≥3 swollen joints • Active psoriatic plaques • Prior cDMARD • No prior TNF-αi treatment	• ≥3 tender joints, ≥3 swollen joints • Active psoriatic plaques • Inadequate response to 1 TNF-αi [redacted]
• 12 month + 36 month extension	• 6 month + 36 month extension
• 1° outcomes: ACR 20 and HAQ-DI at 3 months • Other outcomes used in model: PsARC, HAQ-DI, PASI 50, 75, 90	
*Patients taking placebo were able to crossover to tofacitinib at 3 months	

- ERG comment: All arms received concomitant cDMARD (CHMP-positive indication for tofacitinib is in combination with **methotrexate** only)
- In clinical practice, not all patients receiving adalimumab would have cDMARD
- OPAL Broaden not powered to test non-inferiority tofacitinib vs adalimumab

Key outcome measures and definitions

% of patients with ACR 20 (American College of Rheumatology)

- 7 disease activity measures
- Response: ≥20% improvement in tender joint count and swollen joint count and ≥20% improvement in at least 3 of the other measures

% of patients with PASI 75 (psoriasis area & severity index)

- Assessment of the skin in 4 areas of the body, higher score = greater severity
- Response: 75% reduction in PASI score

% of patients with PsARC (psoriatic arthritis response criteria)

- 4 disease activity measures
- Response if improvement on ≥2 of the measures, 1 must be joint tenderness or swelling score, no worsening in any of the 4 measures
- NICE TA guidance for biological DMARDs specifies that PsARC should be assessed at 12 weeks to inform continued treatment decision

Mean Δ from baseline HAQ-DI (health assessment questionnaire- disability index): 8 measures of daily activities, higher score indicates increased disability

All key outcomes assessed months 3 & 6 (& 12 for OPAL Broaden only)

Key baseline characteristics

	OPAL Broaden			OPAL Beyond	
	TOF	ADA	PBO	TOF	PBO
n	107	106	105	131	131
Mean age	49.4	47.4	47.4	49.5	49.0
Female, %	53.0	47.0	53.0	49.0	61.0
Mean PsA duration, years	7.3	5.3	6.4	9.6	9.4
Current methotrexate, %	85.0	75.0	88.0	75.0	77.0
≥1 prior cDMARD, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 2 prior cDMARDS, %	[redacted]	[redacted]	[redacted]	NR	NR
1 prior TNF-αi, %	0	0	0	[redacted]	[redacted]
≥ 2 prior TNF-αi,%	0	0	0	[redacted]	[redacted]
Mean tender joint count	20.5	17.1	20.6	20.5	19.8
Mean swollen joint count	12.9	9.8	11.5	12.1	10.5
Mean HAQ-DI score	1.2	1.1	1.1	1.3	1.3

TOF= tofacitinib, ADA= adalimumab, PBO=placebo

Key clinical effectiveness results

	OPAL Broaden					OPAL Beyond		
3 month results	Response rate %			p-value for comparison		Response rate %		p-value for comparison
	TOF	**ADA**	**PBO**	**TOF v PBO**	**TOF v ADA**	**TOF**	**PBO**	**TOF vs PBO**
ACR 20	50.0	52.0	33.0	0.01	[redacted]	50.0	24.0	<0.001
ACR 50	28.0	33.0	10.0	0.001	[redacted]	30.0	15.0	0.003
ACR 70	17.0	19.0	5.0	0.004	[redacted]	17.0	10.0	[redacted]
PsARC	51.4	61.3	44.8	[redacted]	[redacted]	58.8	29.0	[redacted]
HAQ-DI Δ	-0.35	-0.38	-0.18	0.006	[redacted]	-0.39	-0.14	<0.001
PASI 50	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	
PASI 75	43.0	39.0	15.0	<0.001	[redacted]	21.0	14.0	[redacted]*

**Factual inaccuracy updated by NICE technical team after committee meeting*

Results of open-label extension study

- OPAL Balance includes patients that have previously participated in OPAL Broaden and OPAL Beyond
- Initially all patients have tofacitinib 5mg regardless of previous treatment (could then be ↑ to 10mg at investigator's discretion)
- Follow-up is still ongoing

	Month 6		Month 12		Month 18		Month 24	
ACR 20: n, %	634	70.7	570	74.0	341	77.4	82	67.1
ACR 50: n, %	633	47.1	570	49.8	342	53.5	82	50.0
ACR 70: n, %	636	30.5	570	32.1	341	36.1	82	26.8
Change in HAQ-DI: n, mean	636	-0.5	571	-0.5	342	-0.5	81	-0.6
PASI 75: n, %	433	60.7	396	63.1	242	61.2	58	69.0

ERG comment:

- [redacted] daily, whereas licensed dose = 5mg

Tofacitinib & radiographic disease progression

- FDA calculated non-inferiority margins for TOF vs ADA on radiographic outcomes (based on meta-analyses of TNF-αis & ADEPT trial [ADA vs PBO])
- Although upper CI for radiographic progression from OPAL Broaden is within NI margin, FDA did not consider this strong evidence because:
  - Comparison based on only 1 trial
  - Imputation methods underestimated standard error (∴ wide CIs)
  - Heterogeneity between OPAL Broaden and other trials
- Company attempted to address uncertainties with population-adjusted analyses

ERG comment:

- Adjusting for baseline characteristics does not address other areas of trial heterogeneity (eg. use of concomitant csDMARDs with tofacitinib)
- Company analyses still based on only 1 trial
- Available tofacitinib data has much shorter follow-up than for TNF-αi data
- Upper CIs for outcomes crossed the upper & lower NI margins
- Cannot conclude that tofacitinib is non-inferior to adalimumab on radiographic progression outcomes

ERG comment on clinical trial evidence

- OPAL Broaden & OPAL Beyond = well conducted, phase III RCTs
- TNF-αi naive population: tofacitinib significantly more effective than placebo in all outcomes apart from PSARC (although placebo PSARC response rate was high [44.8%])
- TNF-αi experienced population: tofacitinib significantly more effective than placebo in all outcomes
- No statistically significant differences in tofacitinib vs adalimumab, but OPAL Broaden not powered to test non-inferiority → interpret results with caution
- 18% of OPAL Broaden and 24% of OPAL Beyond were treated in combination with sulfasalazine or leflunomide (CHMP-positive indication for tofacitinib is in combination with methotrexate only) → generalisability?
- In clinical practice, not all patients receiving adalimumab would have csDMARD
- OPAL Broaden & Beyond had 12- & 6- month follow-up but placebo controlled phase was only 3 months
- % and distribution of previous TNF-αis in OPAL Beyond might not be reflective of how tofacitnib will be used in current practice

Adverse events

- Most frequent adverse events in the Phase III trials:
  - nasopharyngitis, upper respiratory infection and headache
- Types and rates of common adverse events generally comparable to those seen in the rheumatoid arthritis clinical programme, for which there is 8 years of observation
- No new risks or safety signals identified in long-term extension study (OPAL Balance)
- Safety profile broadly consistent with other NICE-recommended biological DMARDs

- ERG comment: Adverse events profile similar to adalimumab
- Tofacitinib tolerability shown in low rate of withdrawals due to AEs
- ↑ risk of herpes zoster seems to be specific AE of tofacitinib

Network meta-analysis (NMA)

- Data split into bDMARD-naive & bDMARD-experienced (consistent with AG approach in TA445)
- bDMARD-naive NMA = evidence to support sub-populations 2 & 4
- bDMARD-experienced NMA = evidence to support sub-population 3
- Bayesian NMA with uninformative prior
- Fixed- and random- effect analyses explored for each model
- TA445 identified heterogeneity in placebo arms for some outcomes (appearing to change over time) → placebo-adjusted models explored
- Class effect analyses explored in 2 different model specifications:
  1. tofacitinib 5mg, apremilast, TNF-αi & anti-IL as separate classes
  2. tofacitinib 5mg, apremilast, TNF-αi/antiI-IL as separate classes

Combined

Placebo adjustment in NMA

- OPAL Broaden had highest placebo PsARC response rate of all NMA trials
- Consistent with TA445 (found that placebo response rates ↑ over time)
- Could be due to changes in inclusion criteria/concomitant medicines
- Company split placebo arms into 2 categories based on age of trial:

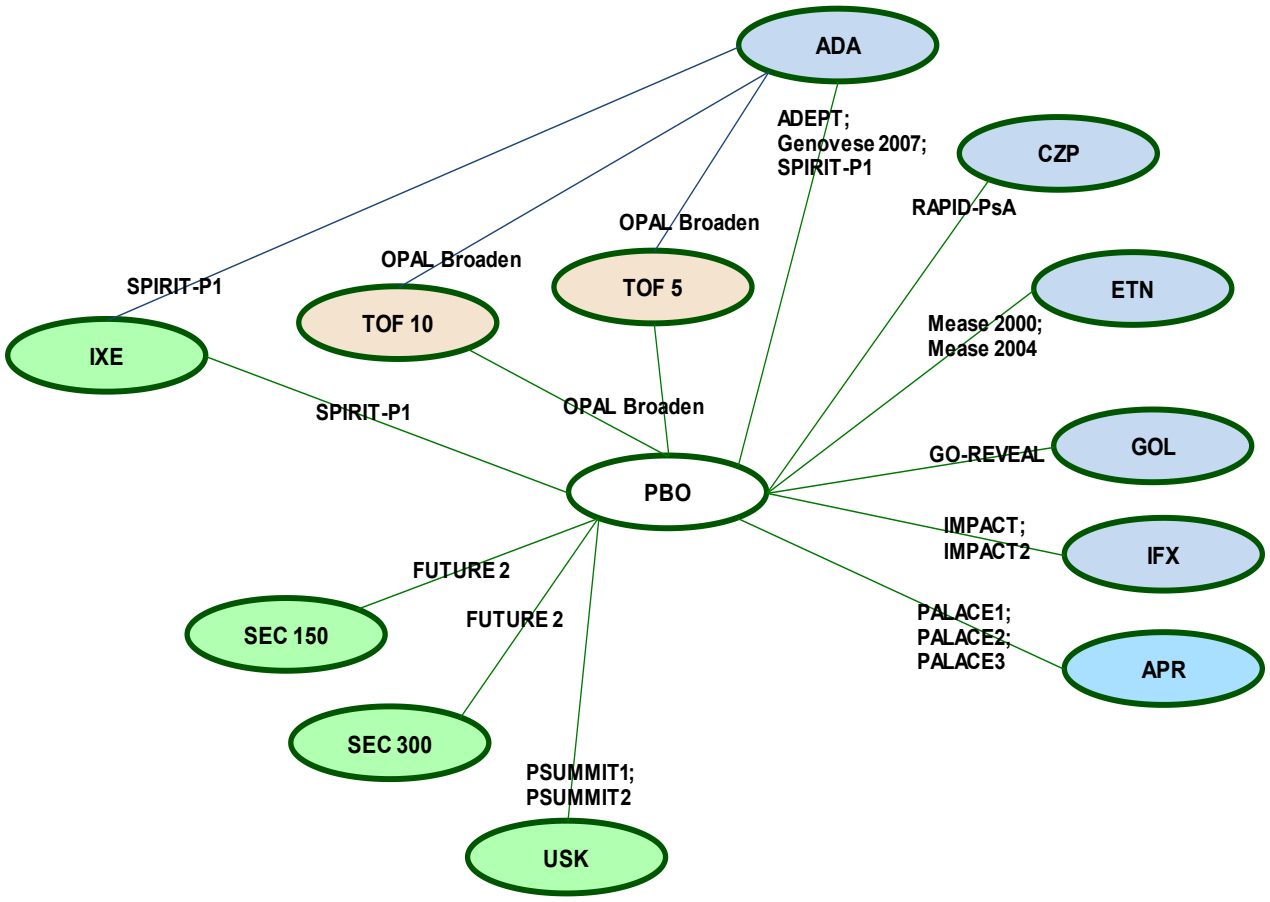
PBO1 = older trials & apremilast

PBO2 = newer trials, PSUMMIT1, RAPID-PSA, FUTURE2 & OPAL Broaden

- Company also allowed NMA placebo-adjustment to differ by treatment

- ERG consider apremilast trial placebo arm should be in PBO2
- Implementation of placebo-adjusted model in bDMARD-naive analysis incorrect (ERG corrected; updated results presented)
- Following ERG correction, placebo-adjustment improves model fit
- However, rationale for heterogeneity in placebo-response not clear → interpret placebo-adjusted model results with caution

NMA: biological DMARD-naive



ERG corrected implementation of placebo adjusted PSARC analyses (results presented slide 21)

- Includes a mixed population of patients who have had 1 or 2 prior cDMARDs, as insufficient data for separate networks
- Overall population data used for some comparators: ~50% (cert. peg) ~20% (secukinumab) 14-30% (apremilast) had prior bDMARDs
- Network used for:
  -PsARC response
  -PASI 50/75/90
  -ΔHAQ-DI conditional on PSARC response

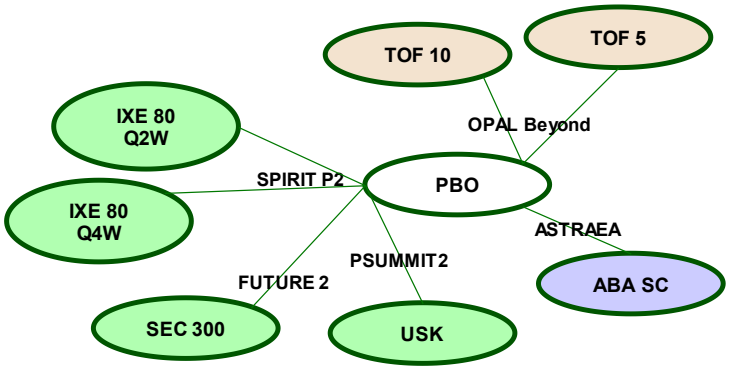
Key NMA results: biological DMARD-naive

	Company analyses			
	Probability of response		Absolute change from baseline	
	PsARC*	PASI 75	ΔHAQ-DI: PsARC responders	ΔHAQ-DI: PsARC non-responders
PBO	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]
APR	[redacted]	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]	[redacted]
INF	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]
GOL	[redacted]	[redacted]	[redacted]	[redacted]
TOF	[redacted]	[redacted]	[redacted]	[redacted]
SEC 150 mg	[redacted]	[redacted]	-0.43	-0.09
SEC 300 mg	[redacted]	[redacted]	-0.51	-0.08
CTZ	[redacted]	[redacted]	-0.47	-0.12

From TA445

* Implementation corrected by ERG

NMA: biological DMARD-experienced



To include secukinumab in model:

- PsARC: odds ratio vs. placebo from TA445 used resulting in probability of [redacted]
- HAQ-DI: values from TA445 NMA used, -0.38 for responders and -0.43 for non-responders

	PsARC	PASI 75	ΔHAQ-DI: PsARC responders	ΔHAQ-DI: PsARC non-responders
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	-0.38	-0.43

Bold = 95% credible interval does not overlap with tofacitinib

From TA445

Company conclusions on the clinical effectiveness evidence

	No prior bDMARD	Prior bDMARD
PsARC	• Tofacitinib not statistically significantly better than placebo • Etanercept/infliximab/golimumab statistically significantly better than tofacitinib	• [redacted] • Similar to ustekinumab
PASI 75	• [redacted]	• [redacted] • Odds of response significantly lower than ustekinumab

- Tofacitinib significantly improved ACR20 and HAQ-DI vs. placebo at 3 months
  - significant improvements occurred as early as week 2 for ACR20
- Tofacitinib associated with a reduction in fatigue and itch severity and improved overall quality of life
- Long-term extension study suggests efficacy generally sustained at 24 months

ERG comment on NMA

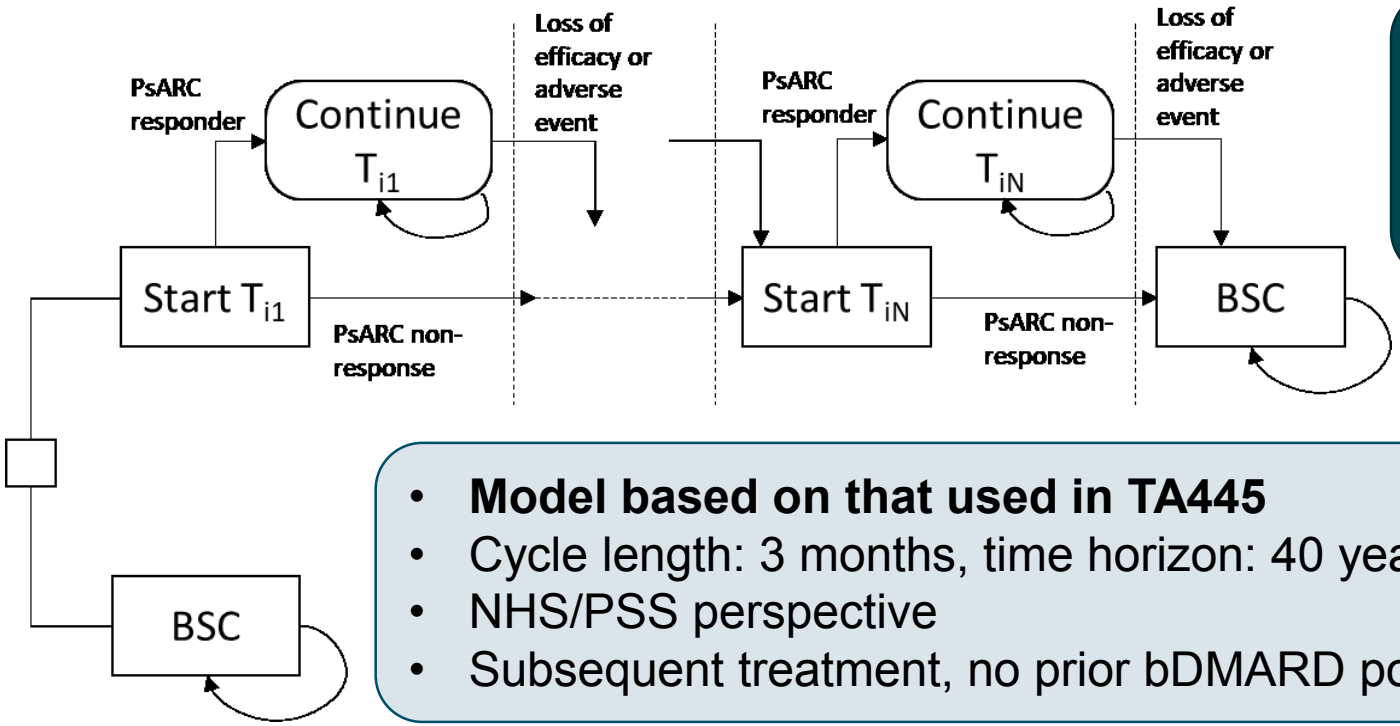
bDMARD-naive population:

- ERG-corrected company PsARC analysis shows tofacitinib in lower effectiveness group (comparable to apremilast)
- ERG preferred PsARC model = class effect separating TOF 5mg & TOF 10mg (classes = tofacitinib 5mg, tofacitinib 10mg, apremilast, combined TNF-αi/antiI-IL → 5mg can be interpreted independently of 10mg group)
- bDMARD-experienced population:
- No significant issues with bDMARD-experienced analysis

Effectiveness of tofacitinib:

- Tofacitinib consistently ranked among the least effective treatments for PsARC
- Tofacitinib associated with a higher level of effectiveness for PASI response, and HAQ-DI response conditional on PsARC (more comparable to adalimumab)

Economic model



Data from no prior bDMARD NMA used for TNF-αi contraind.

- **Model based on that used in TA445**
- Cycle length: 3 months, time horizon: 40 years
- NHS/PSS perspective
- Subsequent treatment, no prior bDMARD pop: ustekinumab

Key difference vs TA445 = psoriasis subgroups modelled together

- Licensed secukinumab dose depends on severity of psoriasis (no/moderate psoriasis = 150mg, severe psoriasis = 300mg)
- Because of this, psoriasis levels modelled as separate subgroups in TA445
- Tofacitinib company model → subgroups modelled together (PASI response assessed separately for each subgroup and weighted average calculated for overall population)

Health states in model

Initial treatment period

- PsARC response assessed at 3 months for all treatments to determine whether treatment continues
  - this does not reflect the continuation rule for all comparators e.g. NICE guidance for secukinumab recommends response assessed at 16 weeks

Continued treatment period

- Constant risk of discontinuation (12-week probability 3.96%, from TA445) due to any cause applied
- On discontinuing HAQ-DI and PASI scores revert to baseline
- Patients move to initial treatment period of ustekinumab (no prior bDMARD population only) or BSC

BSC

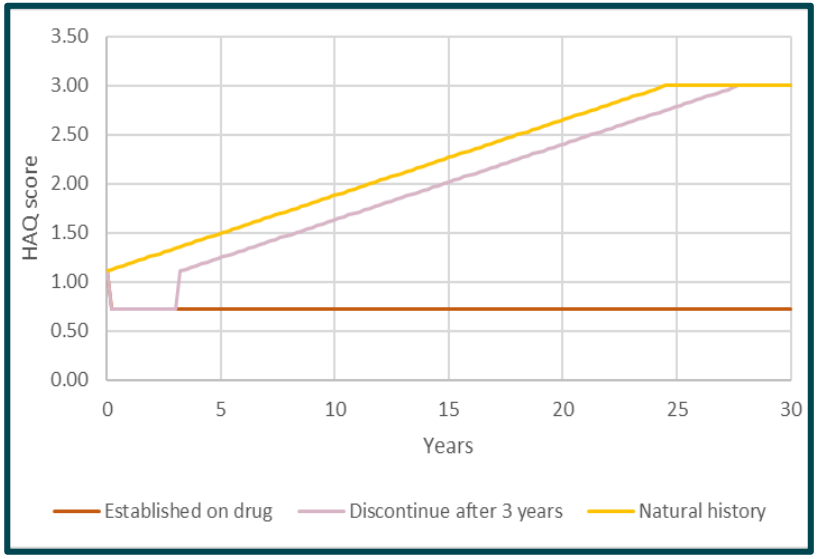
- Assumed to be a mix of cDMARDs and palliative care
- Placebo rates from the NMAs used as a proxy for BSC
- Corresponding BSC PsARC and PASI response maintained until death but HAQ-DI progresses according to natural history

Disease progression over time

- Arthritis element of PsA progressive, psoriasis element not progressive → under BSC, HAQ-DI scores worsens over time but PASI scores don't

HAQ-DI:

- Patients have treatment specific HAQ-DI change based on PsARC response
- Improvement maintained whilst on-treatment (excluding apremilast)
- For patients without response/ who stop treatment, HAQ-DI score is assumed to rebound (equal to initial gain) and then progress in line with BSC



- ERG concerned about assumption that patients responding to tofacitinib do not experience HAQ progression → no long term data to support
- Explored with scenario analyses using different rates of HAQ-DI progression
- Unlikely that HAQ has linear progression over entire extrapolation period
- BSC practice may change over time → assumptions about HAQ progression should be updated (assumptions based on research from 2009)

Key assumptions in company model

- PsARC non-responders discontinue at 3 months for all therapies
- Patients treated with tofacitinib & bDMARDs have no HAQ-DI progression
- PASI scores do not progress after initial 3 months of treatment
- PASI75 response correlated with PsARC response
- HAQ & PASI scores return to baseline level after discontinuation of all treatments apart from apremilast & BSC
- All populations categorised into no psoriasis (50%), mild/moderate psoriasis (25%) and moderate to severe psoriasis (25%) → subgroups modelled together with weighted average calculated for overall population (different approach to TA445)
- Company modelled weighted average PASI score for the three psoriasis categories → sub-populations were not defined on psoriasis levels

- ERG concerned with assumption of no on-treatment HAQ progression (slide 27)
- ERG concerned as baseline PASI scores can impact cost-effectiveness results
- Severity of psoriasis determines which dose of SEC is appropriate comparator
- ERG explored by defining the sub-populations by psoriasis level (in line with TA445)

Treatment sequences

Patient sub-population	Treatment sequence		
	1st	2nd	3rd
Sub-population 2	TOF, ADA, APR, CZP, ETN, GOL, INF, SEC (188mg), BSC	UST	BSC
Sub-population 3:	TOF, SEC (300mg), UST, BSC	BSC	-
Sub-population 4:	TOF, SEC (188mg), UST, BSC	BSC	-

- Response rates for subsequent lines of treatments taken from bDMARD-experienced NMAs to reflect differences in efficacy between lines of therapy

- ERG concerned that for treatments other than UST & SEC, model does not account for treatment effect degradation for subsequent lines of treatment
- In TA455 committee concluded assumption of no degradation unlikely (although recognised not enough data to estimate magnitude of degradation)
- For patients with low PsARC response, assumption could overestimate tofacitinib cost-effectiveness; ERG could not quantify due to lack of flexibility in model

Utility values

- EQ-5D data collected in OPAL, but utility algorithm from TA445 used in base case
- Scenario analyses with algorithm derived from OPAL data presented
- OPAL clinical data applied to tofacitinib alone & tofacitinib and comparators

Utility algorithms	Intercept	HAQ-DI	PASI
TA445 algorithm ☆	0.897	-0.298	-0.004
bDMARD naive (OPAL Broaden)	[redacted]	[redacted]	[redacted]
bDMARD experienced (OPAL Beyond)	[redacted]	[redacted]	[redacted]

- Impact of adverse events on health-related quality of life not modelled (as in TA445) → assumed to be captured in withdrawal rate
- Upon withdrawal HAQ-DI and PASI score is assumed to return to baseline

- [redacted]

☆ = company base case

Costs and health care resource use

Psoriasis management costs			
	No psoriasis	Mild to mod	Mod to severe
Uncontrolled psoriasis	£0	£224.18	£640.83
Controlled psoriasis (PASI 75)	£0	£18.12	£18.12

- Administration costs in 1st cycle =
  - £45.00 (nurse time) for ADA, CZP, ETN, GOL, SEC (all doses)
  - £241.00 (intravenous infusion) for INF
- Administration costs in 2nd+ cycle =
  - £241.00 (intravenous infusion) for INF
- Monitoring costs in 1st cycle = £212.22 for all treatments
- Monitoring costs in 2nd+ cycle = £4.01 for all treatments
- Cost per unit increase in HAQ-DI = £1,547.04 + (£466.47 x HAQ)
  - based on Kobelt et al algorithm for rheumatoid arthritis
- Costs of adverse events not modelled

Cost effectiveness results

- Some comparator technologies have confidential discounts
- Because of this, results incorporating all intervention and comparator discounts are confidential → presented in a confidential appendix for committee members
- Results presented here incorporate:
  - confidential **tofacitinib** patient access scheme (**PAS**) discount
  - publically available **PAS** discounts for **certolizumab pegol & golimumab**
  - publically available **biosimilar** prices for **etanercept & infliximab**
  - publically available **list price** for **ustekimumab** (no PAS)
  - publically available **list prices** for **apremilast & secukinumab** (technologies have confidential PAS discounts → analyses in confidential discount)

Cost effectiveness results

1. Company base-case sub-population 2 (corrected by ERG)
2. Company base-case sub populations 3 & 4
3. Company scenario analyses
4. ERG sensitivity analysis: NMA PsARC model specifications (sub-population 2)
   - No placebo adjustment, random effects
   - Placebo adjustment, class effects (tof 5mg & 10mg doses separated)
6. ERG sensitivity analysis: severity of psoriasis (sub-populations 2 & 4)
7. ERG sensitivity analysis: on-treatment HAQ-DI progression (sub-populations 2, 3 & 4)
   - Tofacitinib progression = apremilast progression
   - 11% tofacitinib patients progress at BSC rate
   - 11% tofacitinib patients progress at apremilast rate

Company base case (corrected by ERG)

Sub-population 2: bDMARD naive

	Total costs £	Total QALYs	Pairwise comparison v BSC			ICER: fully inc. £
			Δ costs £	Δ QALYs	ICER £	
BSC	[redacted]	[redacted]	-	-	-	-
Tofacitinib	[redacted]	[redacted]	£32,822	2.52	£13,029	£13,029
Apremilast	[redacted]	[redacted]	£39,434	2.02	£19,555	D
Adalimumab	[redacted]	[redacted]	£47,275	2.67	£17,701	ED
Cert Pegol	[redacted]	[redacted]	£49,490	2.89	£17,145	ED
Etanercept	[redacted]	[redacted]	£50,598	3.20	£15,799	£26,006
Secukinumab	[redacted]	[redacted]	£51,143	2.85	£17,931	D
Golimumab	[redacted]	[redacted]	£53,774	2.91	£18,507	D
Infliximab	[redacted]	[redacted]	£69,389	3.26	£21,270	£315,590

D = Dominated, ED = Extendedly dominated

Company base case

Sub-populations 3 & 4: prior-bDMARD & TNF-αi contraindicated

	Total costs £	Total QALYs	Pairwise comparison v BSC			ICER: fully inc. £
			Δ costs £	Δ QALYs	ICER £	
Sub-population 3: prior-bDMARD						
BSC	[redacted]	[redacted]	-	-	-	-
Tof	[redacted]	[redacted]	£11,732	1.30	£9,001	£9,001
Ust	[redacted]	[redacted]	£26,709	1.42	£18,761	£124,510
Sec	[redacted]	[redacted]	£54,206	1.60	£33,914	£157,429
						[redacted]
BSC	[redacted]	[redacted]	-	-	-	-
Tof	[redacted]	[redacted]	£8,930	1.14	£7,825	£7,825
Ust	[redacted]	[redacted]	£24,979	1.33	£18,837	ED
Sec	[redacted]	[redacted]	£30,153	1.62	£18,557	£43,872

D = Dominated, ED = Extendedly dominated

Company scenario analyses

Tofacitinib ICER vs BSC (£/QALY)			
Scenario	**bDMARD naïve***	**prior bDMARD**	**TNF-αi contraind.**
Base case	£13,419	£9,001	£7,825
Pessimistic NMA: using alternative NMAs with worst outcomes for tofacitinib	£14,124	£9,001	£8,599
Optimistic NMA: using alternative NMAs with best outcomes for tofacitinib	£12,013	£7,908	£6,089
ACR20 stopping rule (instead of PsARC)	£12,996	£8,968	£7,516
Data for BSC, tofacitinib and adalimumab from OPAL Broaden direct comparison	£15,016	-	-
OPAL Broaden direct comparison data for tofacitinib and adalimumab, NMA data for other treatments	£12,913	-	-
Utility values from OPAL (all treatments)	£18,235	£10,522	£10,655
Utility values from OPAL (tofacitinib only)	£13,582	£9,229	£8,032

* Results for bDMARD-naive population have not been corrected by ERG

ERG sensitivity analysis (NMA model)

Sub-population 2: bDMARD naive

	No placebo adjustment, random effects			Placebo adjustment, class effect assumed ★		
	Total costs	Total QALYs	ICER: fully inc. £	Total costs	Total QALYs	ICER: fully inc. £
BSC	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Tof	[redacted]	[redacted]	£13,355	[redacted]	[redacted]	£13,011
Apr	[redacted]	[redacted]	D	[redacted]	[redacted]	D
Ada	[redacted]	[redacted]	ED	[redacted]	[redacted]	ED
Czp	[redacted]	[redacted]	ED	[redacted]	[redacted]	ED
Sec	[redacted]	[redacted]	D	[redacted]	[redacted]	£28,866
Etn	[redacted]	[redacted]	£21,186	[redacted]	[redacted]	D
Gol	[redacted]	[redacted]	D	[redacted]	[redacted]	D
Inf	[redacted]	[redacted]	£156,878	[redacted]	[redacted]	£320,148

D = Dominated, ED = Extendedly dominated ★ = ERG preferred

ERG sensitivity analysis (psoriasis level)

Sub-population 2: bDMARD naive

	No psoriasis (sec 150mg)			Mild-mod (sec 150mg)			Mod-severe (sec 300mg)		
	Costs	QALYs	ICER: fully inc.	Costs	QALYs	ICER: fully inc.	Costs	QALYs	ICER: fully inc.
BSC	[redacted]	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Tof	[redacted]	[redacted]	£14,396	[redacted]	[redacted]	£12,896	[redacted]	[redacted]	£10,477
Apr	[redacted]	[redacted]	D	[redacted]	[redacted]	D	[redacted]	[redacted]	D
Sec	[redacted]	[redacted]	ED	[redacted]	[redacted]	ED	[redacted]	[redacted]	D
Ada	[redacted]	[redacted]	D	[redacted]	[redacted]	D	[redacted]	[redacted]	ED
Czp	[redacted]	[redacted]	ED	[redacted]	[redacted]	D	[redacted]	[redacted]	ED
Etn	[redacted]	[redacted]	£28,530	[redacted]	[redacted]	£28,925	[redacted]	[redacted]	£29,483
Gol	[redacted]	[redacted]	D	[redacted]	[redacted]	D	[redacted]	[redacted]	ED
Inf	[redacted]	[redacted]	£732,175	[redacted]	[redacted]	£256,411	[redacted]	[redacted]	£146,891

ERG sensitivity analysis (psoriasis level)

Sub-population 4: TNF-αi contraindicated

	No psoriasis (sec 150mg)			Mild-mod (sec 150mg)			Mod-severe (sec 300mg)		
	Costs	QALYs	ICER: fully inc.	Costs	QALYs	ICER: fully inc.	Costs	QALYs	ICER: fully inc.
BSC	[redacted]	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Tof	[redacted]	[redacted]	£8,972	[redacted]	[redacted]	£7,769	[redacted]	[redacted]	£5,680
Sec	[redacted]	[redacted]	£32,789	[redacted]	[redacted]	£29,262	[redacted]	[redacted]	ED
Ust	[redacted]	[redacted]	D	[redacted]	[redacted]	D	[redacted]	[redacted]	£75,660

- Psoriasis level sensitivity analyses uses the ERG preferred NMA model
- Tofacitinib cost-effectiveness appears to increase with severity of psoriasis

ERG sensitivity analysis (progression)

Sub-population 2: bDMARD naive

	TOF progression = APR progression			11% patients progress at BSC rate			11% patients progress at APR rate		
	Costs	QALYs	ICER: fully inc.	Costs	QALYs	ICER: fully inc.	Costs	QALYs	ICER: fully inc.
BSC	[redacted]	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Tof	[redacted]	[redacted]	£15,706	[redacted]	[redacted]	£13,531	[redacted]	[redacted]	£13,266
Apr	[redacted]	[redacted]	D	[redacted]	[redacted]	D	[redacted]	[redacted]	D
Ada	[redacted]	[redacted]	ED	[redacted]	[redacted]	ED	[redacted]	[redacted]	ED
Czp	[redacted]	[redacted]	ED	[redacted]	[redacted]	ED	[redacted]	[redacted]	ED
Etn	[redacted]	[redacted]	£16,191	[redacted]	[redacted]	£24,735	[redacted]	[redacted]	£26,650
Gol	[redacted]	[redacted]	D	[redacted]	[redacted]	D	[redacted]	[redacted]	D
Sec	[redacted]	[redacted]	D	[redacted]	[redacted]	D	[redacted]	[redacted]	D
Inf	[redacted]	[redacted]	£320,148	[redacted]	[redacted]	£320,148	[redacted]	[redacted]	£320,148

ERG sensitivity analysis (progression)

Sub-populations 3 & 4: prior-bDMARD & TNF-αi contraindicated

	TOF = APR			11% at BSC rate			11% at APR rate		
	Costs	QALYs	ICER: fully inc.	Costs	QALYs	ICER: fully inc.	Costs	QALYs	ICER: fully inc.
Sub-population 3:									
BSC	[redacted]	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Tof	[redacted]	[redacted]	£15,400	[redacted]	[redacted]	£9,984	[redacted]	[redacted]	£9,472
Ust	[redacted]	[redacted]	£23,287	[redacted]	[redacted]	£64,441	[redacted]	[redacted]	£85,041
Sec	[redacted]	[redacted]	£157,429	[redacted]	[redacted]	£157,429	[redacted]	[redacted]	£157,429
Sub-population 4:									
BSC	[redacted]	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Tof	[redacted]	[redacted]	£13,266	[redacted]	[redacted]	£8,670	[redacted]	[redacted]	£8,230
Ust	[redacted]	[redacted]	ED	[redacted]	[redacted]	ED	[redacted]	[redacted]	ED
Sec	[redacted]	[redacted]	£22,849	[redacted]	[redacted]	£36,554	[redacted]	[redacted]	£39,888

Equality and innovation

- No equality issues identified by stakeholders
  - Tofacitinib is oral therapy whereas most comparators are injected subcutaneously → improved accessibility for people with affected joints vs comparators
- Company's view on innovation:
  - 1st JAK inhibitor: modulates multiple cytokines specifically associated with the pathogenesis of PsA
  - Oral treatment, convenient and may improve adherence
  - In the OPAL trials tofacitinib demonstrated efficacy across the spectrum of relevant disease domains: peripheral arthritis, enthesitis, dactylitis, and skin manifestations, as well as physical functioning and patient-reported outcomes
  - No benefits not captured in the QALY highlighted

Key clinical issues

- How is tofacitinib used in clinical practice? When would clinicians choose tofacitinib?
- Are the OPAL trials generalisable? Uncertainty with…
  - Concomitant use of other cDMARDs instead of methotrexate
  - Distribution of previous TNF-αi use
  - OPAL Broaden & Beyond had 12- & 6- month follow-up but placebo controlled phase was only 3 months
- Which is the most appropriate NMA model for bDMARD-naive PsARC outcome?
  - Placebo-adjustment & random effects
  - No placebo-adjustment & random effects
  - Class effect, placebo-adjustment & random effects
- Is tofacitinib an effective treatment?
  - PsARC not stat. significantly different from placebo in OPAL Broaden
  - One of the least effective treatments for PsARC in all NMA analyses
  - Longer term evidence from OPAL Balance

Key cost effectiveness issues

- Should psoriasis subgroups be modelled separately?
- Treatment effect degradation…
  - Are assumptions about treatment effectiveness plausible?
  - Would treatment effect differ by line of use?
- Any there any equalities issues?
- Is tofacitinib innovative?
- Are there any benefits not captured in the QALY calculations?

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tofacitinib for treating active psoriatic arthritis following disease-modifying anti-rheumatic drugs [ID1220]

Document B

Company evidence submission

6th April 2018

File name	Version	Contains confidential information	Date
	1.0	**Yes**	**05 April 2018**

Contents

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Abbreviations

Δ	Change from baseline
AAC	Arthritis Advisory Committee
ABA	Abatacept
ACR	American College of Rheumatology
ADA	Adalimumab
AE	Adverse event
AG	Assessment Group
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
Anti-IL	Anti-interleukin
APR	Apremilast
AS	Ankylosing spondylitis
AST	Aspartate transaminase
ATP	Adenosine triphosphate
BD	Twice-daily
bDMARD	Biologic disease-modifying anti-rheumatic drug
BHPR	British Health Professionals in Rheumatology
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
BSR	British Society for Rheumatology
CADTH	Canadian Agency for Drugs and Technologies in Health
CASPAR	Classification Criteria for Psoriatic Arthritis
CCP	Cyclic citrullinated peptide
cDAPsA	Clinical Disease Activity in Psoriatic Arthritis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CrI	Credible interval
CRP	C-Reactive protein
csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug
COX	Cyclooxygenase
CSR	Clinical study report
CZP	Certolizumab pegol
Dl	Decilitre
DIC	Deviance information criteria
DLQI	Dermatology Life Quality Index
DMARD	Disease-modifying anti-rheumatic drug
DSS	Dactylitis Severity Score
DSU	Decision Support Unit
EMA	European Medicines Agency
eMIT	Electronic market information tool
ETN	Etanercept
EQ-5D	EuroQoL
EULAR	European League Against Rheumatism

FACIT-F	Functional Assessment of Chronic Illness Therapy- Fatigue Scale
FAS	Full analysis set
FDA	Food and Drug Administration
FE	Fixed effect
G	Gram
GLM	Generalised linear model
GMMRM	Generalised mixed model for repeated measures
GOL	Golimumab
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health Assessment Questionnaire- Disability Index
Hb	Haemoglobin
IA	Intra-articular
ICER	Incremental cost-effectiveness ratio
IL	Interleukin
IM	Intra-muscular
INF	Infliximab
IPD	Individual patient data
IQR	Interquartile range
IR	Inadequate response
ISI	Itch Severity Item
IV	Intravenous
JAK	Janus kinase
LEI	Leeds Enthesitis Index
L	Litre
LS	Least squares
LTE	Long-term extension study
LYG	Life years gained
M	Mean
MA	Meta-analysis
MACE	Major Adverse Cardiac Event
MDA	Minimal Disease Activity
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MI	Multiple imputation
MNAR	Missing not at random
mTSS	Modified Total Sharp Score
MTX	Methotrexate
N/A	Not applicable
nbDMARD	Non-biological DMARD
NHS	National Health Service
NI	Non-inferiority
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NSAID	Non-steroidal anti-inflammatory drug
OL	Open label
OR	Odds ratio

PASI	Psoriatic Area and Severity Index
PBAC	Pharmaceutical Benefits Advisory Committee
PBO	Placebo
PDE4	Phosphodiesterase type-4
PF	Physical functioning
PICOS	Population, interventions, comparators, outcomes, study design
PP	Per protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PsA	Psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
PsO	Plaque psoriasis
RE	Random effect
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QALY	Quality-adjusted life year
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RE	Random-effect
RR	Relative risk
SA	Sensitivity analysis
SAE	Serious adverse event
SAS	Safety analysis set
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SEC	Secukinumab
SF-36	36-item Short Form Survey
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
SPARCC	Spondyloarthritis Research Consortium of Canada
SUCRA	Surface Under the Cumulative Ranking Curve
TEAE	Treatment-emergent adverse event
TNFi	Tumour necrosis factor inhibitor
TOF	Tofacitinib
TSD	Technical specification document
tsDMARD	Targeted synthetic disease-modifying anti-rheumatic drug
UK	United Kingdom
ULN	Upper limit normal
UST	Ustekinumab
UVB	Ultraviolet B treatment
VAT	Value-added tax
WinBUGs	Bayesian inference Using Gibbs Sampling (for Windows)
Wk	Week
WMD	Weighted mean difference

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The decision problem for this appraisal asks if tofacitinib is clinically and cost-effective in line with its full (anticipated) marketing authorisation:

[redacted]

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 active PsA whose disease has not responded adequately to previous DMARD therapy or for whom DMARDs are not tolerated or contraindicated	Adults with active PsA whose disease has not responded adequately to previous DMARD therapy or for whom DMARDs are not tolerated or contraindicated	This was considered consistent with the final scope
Intervention	Tofacitinib (alone or in combination with non-biological DMARD)	Tofacitinib (in combination with a csDMARD)	Marketing authorisation is anticipated for tofacitinib in combination with a csDMARD
Comparator(s)	Sub -population 1 – For people whose disease has not responded adequately to 1 non-biological DMARD • Non-biological DMARDs Sub-population 2 – For people whose disease has not responded adequately to at least 2 non-biological DMARDs: • Biological DMARDs (with or without methotrexate, including etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, secukinumab); apremilast Sub-population 3 – For people whose disease has not responded adequately to non-biological DMARDs and 1 or more TNFis: • Ustekinumab; certolizumab pegol; secukinumab; best supportive care Sub-population 4 – For people in whom TNFis are contraindicated or not tolerated:	Sub-population 2 – For people whose disease has not responded adequately to at least 2 non-biological DMARDs • Biological DMARDs; apremilast; best supportive care Sub-population 3 – For people whose disease has not responded adequately to non-biological DMARDs and 1 or more TNFis: • Ustekinumab; secukinumab; best supportive care Sub-population 4 – For people in whom TNFis are contraindicated or not tolerated • Ustekinumab; secukinumab; best supportive care	Pfizer seek to align the sub-populations assessed in this appraisal to those populations that have received positive recommendations from NICE in previous TAs (i.e., sub-populations 2, 3, and 4); consequently, we have not submitted results for sub-population 1. There were insufficient data to subdivide patients into those who had failed 1 non-biological DMARD and those who had failed 2 non-biological DMARDs, as per the NICE scope. Therefore, as per the approach taken by the AG in TA445, two populations are included in the submission NMAs: bDMARD-naïve and bDMARD-experienced. If a study had been included in the TA445 NMA bDMARD-naïve network, we assumed that the majority of patients had received at least 1 previous non-biological DMARD. Best supportive care was included as a comparator for all sub-populations to serve as a benchmark against which cost-effectiveness may be assessed. This is

	• Ustekinumab; secukinumab; best supportive care		consistent with previous appraisals from TA199 (2) and TA445 (3). Certolizumab pegol has been excluded from sub-population 3 because the data available from the RAPID PsA trial informs only a subset of patients in this sub-population (i.e., primary responders to a prior TNFi who were secondary failures [primary non-responders were explicitly excluded from this trial]) (4).
Outcomes	The outcome measures to be considered include: • disease activity • functional capacity • disease progression • periarticular disease (for example, enthesitis, tendonitis, dactylitis) • mortality • adverse effects of treatment • health-related quality of life	The outcome measures include: • disease activity: ACR20, ACR50, ACR70, ACR response criteria components, PASI50/75/90, PsARC, MDA • functional capacity: HAQ-DI, HAQ-DI conditional on PsARC response status • disease progression: van der Heijde-mTSS • periarticular disease (for example, enthesitis, tendonitis, dactylitis): DSS, LEI, SPARCC • health-related quality of life: SF-36 (physical functioning component), FACIT-F (total score), DLQI, ISI • mortality • adverse effects of treatment	N/A
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be	The cost effectiveness of treatments was expressed in terms of incremental cost per QALY. Economic analyses have taken a lifetime approach (40 years) in line with TA199/445 (2, 3) and have considered	This was considered consistent with the final scope

	sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and Personal Social Services perspective. • The availability of any patient access schemes for the intervention or comparator technologies will be taken into account. • For the comparators, the availability and cost of biosimilars should be taken into consideration.	biosimilar prices and net discounts where publicly-accessible patient access schemes (PAS) were available.	
Subgroups to be considered	If evidence allows, the following subgroups will be considered: • Reason for treatment failure (for example, lack of efficacy, intolerance or adverse events). • Presence or severity of concomitant psoriasis (no psoriasis, mild, moderate or severe psoriasis)	The economic evaluation considers three sub-populations, as detailed above. The economic model also accounts for a distribution of patients with no psoriasis, mild to moderate psoriasis and moderate to severe psoriasis, as per TA445 (3).	Evidence in the subgroups contained within the final scope (i.e., reason for treatment failure and presence/severity of concomitant psoriasis) was not identified for comparator products
Special considerations including issues related to equity or equality	No equality issues are anticipated if tofacitinib is recommended for use in England and Wales.	No equality issues are anticipated.	This is considered consistent with the final scope

Abbreviations: ACR, American College of Rheumatology; bDMARD, biologic disease-modifying anti-rheumatic drug; csDMARD (~non-biological DMARD), conventional synthetic disease-modifying anti-rheumatic drug; DLQI, Dermatology Life Quality Index; DMARD, disease-modifying anti-rheumatic drug; ; DSS, Dactylitis Severity Score; FACIT-F, Functional Assessment of Chronic Illness Therapy- Fatigue Scale; HAQ-DI, Health Assessment Questionnaire Disability Index; ISI, Itch Severity Index; LEI, Leeds Enthesitis Index; MDA, Minimal Disease Activity; mTSS, modified Total Sharp Score; NICE, National Institute for Health and Care Excellence; NMA, network meta analysis; NHS, National Health Service; PAS, Patient Access Scheme; PASI, Psoriasis Area and Severity Index ; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Criteria; QALY, quality-adjusted life year; SPARCC, Spondyloarthritis Research Consortium of Canada; TA, technology appraisal; TNFi, tumour necrosis factor inhibitor.

B.1.2 Description of the technology being appraised

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
Mechanism of action	Tofacitinib offers a novel mechanism of action for the treatment of PsA through the potent, selective and reversible inhibition of the JAK family (5). 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 RA, psoriasis, PsA, and axial spondyloarthritis. In enzymatic assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2 (6). 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 results in modulation of the immune and inflammatory response in PsA.
Marketing authorisation/CE mark status	• Regulatory submission to EMA: The application was submitted on [redacted]. • CHMP positive opinion is expected on [redacted]. • Marketing authorisation: expected [redacted] • UK availability: [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	[redacted] Contraindications for tofacitinib are: • Hypersensitivity to the active substance or to any of the excipients; • Active tuberculosis, serious infections such as sepsis, or opportunistic infections; • Severe hepatic impairment; and • Pregnancy and lactation. 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.

Method of administration and dosage	The recommended dose of tofacitinib is available in 5 mg film-coated tablets for twice daily oral administration. A dose of 5 mg once daily is appropriate for patients with severe renal impairment (creatinine clearance <30 mL/min). A dose of 5 mg once daily is appropriate for patients with moderate hepatic impairment (Child–Pugh B).
Additional tests or investigations	The monitoring requirements specific to tofacitinib are included as elements of standard NHS Trust policies for bDMARDs and should therefore not be considered as additional to current clinical practice.
List price and average cost of a course of treatment	The list price of a 56-tablet pack of 5 mg tofacitinib is £690.03 (excluding VAT; BNF online [2017]). The average cost per patient for the first 6 months is estimated at £4,500.60 based on the list price. The average cost per patient for subsequent years is estimated at £9001.19 based on the list price.
Patient access scheme	For the previously NICE-approved RA indication (TA480), the company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount of [redacted] to the list price of tofacitinib, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; BNF, British National Formulary; CHMP, Committee for Medicinal Products for Human Use; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; DMARD, disease-modifying anti-rheumatic drug; EMA, European Medicines Agency; IL, interleukin; JAK, Janus kinase; mg, milligram; mL, millilitre; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TA, technology appraisal; VAT, value-added tax.

B.1.2.1 Regulatory approval outside the UK

Tofacitinib was approved in the US by the Food and Drug Administration (FDA) in December 2017 for treatment of adult patients with active PsA who have had an inadequate response or intolerance to MTX or other DMARDs (7). Tofacitinib may be used in combination with MTX or other non-biologic DMARDs (7).

B.1.2.2 Ongoing HTAs in the rest of the UK

Submission to the Scottish Medicines Consortium is planned for [redacted] 2018.

B.1.2.3 Changes in service provision and management

Tofacitinib is an orally-administered treatment option for patients with PsA who may otherwise progress to a parenteral bDMARD, which are predominantly administered subcutaneously. To self-inject subcutaneous bDMARDs, patients are typically required to undergo thorough training in injection technique and attain endorsement

from the relevant healthcare professional that their self-administration is appropriate (8-13). Consequently, as an oral treatment, tofacitinib is likely to have a positive impact on service provision compared with the most frequently used treatments currently recommended by NICE for PsA. In addition, as a small molecule, tofacitinib does not require refrigeration (i.e., it does not have the cold chain requirements necessary for parenteral treatment options) and, as an oral option, is easy for patients to self-administer.

B.1.2.3.1 Additional tests/investigations

No additional tests or investigations are required beyond those that are already part of current clinical practice for bDMARDs (that is, included as elements of standard NHS Trust policies) and comprehensive checklists can be found in the risk minimisation materials associated with the online Summary of Product Characteristics (SmPC) available at: https://www.medicines.org.uk/emc/. These are detailed below in **Section B.1.2.3.4.**

B.1.2.3.2 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 both non-biological DMARDs (conventional synthetic DMARDs; csDMARDs) and bDMARDs and include:

- Full blood count (pre- and on-treatment)
- Erythrocyte sedimentation rate or C-reactive protein (pre- and on-treatment) for disease activity assessment
- Biochemical profile (pre- and on-treatment)
- Chest X-ray (pre-treatment)
- Tuberculosis test (pre-treatment)

The time between monitoring visits for tofacitinib is typically three months after initial stabilisation, as it is with bDMARDs and csDMARDs currently used by the NHS.

B.1.2.3.3 Additional infrastructure requirements

Not applicable.

B.1.2.3.4 Patient monitoring requirements

Currently, the SmPCs of all NICE-recommended bDMARDs state that patients should be monitored for signs of infection (8-14).

In line with the European League Against Rheumatism (EULAR) recommendations, clinicians should be aware of the higher risk for cardiovascular disease in patients with rheumatoid arthritis (RA), compared with the general population, which may also be applicable to patients with ankylosing spondylitis (AS) and PsA (15). As a result, cardiovascular disease risk assessment is recommended for all patients with RA, AS or PsA at least once every five years and should be reconsidered following major changes in anti-rheumatic therapy (15).

A summary of tofacitinib monitoring requirements is presented in **Table 3** below (and described in detail in the SmPC and associated risk minimisation materials).

Table 3: Tofacitinib monitoring requirements

[redacted]

B.1.2.3.5 Need for concomitant therapies

Tofacitinib is indicated for treatment of active PsA in combination with a csDMARD.

B.1.3 Health condition and position of the technology in the treatment pathway

- PsA is the second most common inflammatory joint disease in early arthritis clinics (after RA), and has a substantial detrimental impact on the physical function and quality of life of patients (17-19). In England in 2016, PsA was estimated to affect over 105,000 adults (20, 21).
- PsA is a heterogeneous inflammatory arthritis with broad musculoskeletal phenotypes and extra-articular manifestations (e.g., skin psoriasis) (22) and may result in permanent joint damage (23, 24).
- PsA primarily affects working age adults (25) and, as a consequence, imposes a substantial economic burden on patients, the health care system, workplaces and society (26-36). Approximately 42% of patients with PsA also have multiple comorbid conditions, such as hyperlipidaemia and hypertension (26, 27).
- The heterogeneous nature of PsA necessitates a broad range of treatment options, with no single agent capable of achieving key treatment goals such as minimal disease activity (MDA) in all patients (22).
- Forty-six percent of PsA patients report that currently-available therapies can actually be worse than the condition itself, with 85% reporting that there is a need for better therapies (37). There is preference amongst PsA patients for oral treatments over those administered subcutaneously or intravenously (38).
- Patients with PsA rarely achieve PsA-specific remission (39) and frequently discontinue their TNFi treatment due to lack of efficacy/tolerability. Consequently, a need exists for additional medications beyond those currently-available that work across multiple cytokines involved in the pathogenesis of PsA (40).
- Tofacitinib provides patients with active PsA who have had an inadequate response to previous treatment (csDMARD and TNFi) with:
    - an orally-administered treatment option;

- a novel mechanism of action;
- a proven efficacy profile across multiple PsA domains; and
- an acceptable safety profile.

B.1.3.1 Disease overview

PsA is a complex inflammatory condition which has a significant detrimental impact on physical function and quality of life through a range of characteristic clinical manifestations, including peripheral arthritis, axial arthritis, dactylitis, enthesitis, skin psoriasis, and nail disease (17-19). In early arthritis clinics, PsA has been reported to be the second most common inflammatory joint disease after RA (41, 42). Men and women are equally likely to be affected by PsA, which principally affects adults of working-age, with a peak onset between the ages of 30 and 50 years (43). In England in 2016, PsA was estimated to affect 105,010 adults (20, 21). PsA is associated with psoriasis, and up to 24% of patients with psoriasis may go on to develop PsA (44). The proportion of patients who have psoriasis before their PsA diagnosis has been found to range from 61.3% to 82.3%, and the majority of cases of PsA in these patients occur within 7 to 15 years of the onset of psoriasis (45). Irreversible joint damage occurs as affected joints become chronically inflamed, leading to bone erosion (23, 24).

PsA imposes a substantial economic burden on patients, health care resources, and society (26-36). The multiple clinical manifestations associated with PsA result in physical disability and confer a significant psychosocial impact (40). Patients with PsA are often additionally affected by a range of comorbidities including hyperlipidaemia (47.5%), hypertension (47.3%), depression (21.2%), type 2 diabetes mellitus (20.2%), and fibromyalgia (16.6%), with 42% of patients estimated to have multiple comorbid conditions (26, 27). Patients with PsA also experience substantial functional limitations, including pain, sleep disturbances, fatigue, severe stiffness, and reduced mobility (34). In a recent study involving 13 countries, EULAR designed a questionnaire that can be used to calculate a score reflecting the impact of PsA from the perspective of patients (46). This identified the five most important domains of health impacted by PsA from the patients' perspective, which were pain (in the joints and spine), skin problems (including itching), fatigue (both physical and

mental), ability to pursue work and leisure activities, and functional capacity (i.e., the ability to perform daily tasks) (46).

A 2010 study performed in the UK demonstrated that the total mean annual observed health care costs for PsA ranged from £1252 per person, for the least severely affected patients (Health Assessment Questionnaire: HAQ ≤2), to £2947 per person for the most severely affected patients (HAQ >2). This was slightly higher than the annual cost previously found to be associated with RA (~£579.94 per person for patients with a HAQ score between 1 and 2 and £1673.41 for patients with a HAQ score >2), suggesting a potentially greater economic burden related to PsA than RA (30, 31). In the workplace, PsA is associated with a loss of productivity, as well as high levels of unemployment and work disability (34, 35).

B.1.3.2 Clinical pathway of care

B.1.3.2.1 NICE guidance

A variety of tumour necrosis factor inhibitors (TNFis) are approved by NICE for treating PsA. NICE technology appraisals (TA) 199 (2) and 220 (47) recommend etanercept, infliximab and adalimumab, and golimumab, respectively, when a patient has peripheral arthritis with three or more tender joints and three or more swollen joints, and the PsA has not responded to at least two csDMARDs, given alone or in combination. Ustekinumab (an IL-12 and IL-23 inhibitor) is recommended in NICE TA 340 (48) when treatment with TNFis is contraindicated, but would otherwise be considered (as per TA199 (2) and TA220 (47)), or the person has had treatment with one or more TNFi. Apremilast (a PDE4 inhibitor; targeted synthetic DMARD [tsDMARD]) and certolizumab pegol (a PEGylated FAB' fragment of a TNFi) and secukinumab (an IL-17A inhibitor) are recommended in NICE TA 433 (49) and 445 (3), respectively, for patients whose disease has not responded to at least two csDMARDs. In TA445, certolizumab pegol is also recommended when a TNFi has stopped responding after the first 12 weeks of therapy, whilst secukinumab is recommended when the disease has not responded to TNFi treatment within the first 12 weeks, or after 12 weeks, or if TNFis are contraindicated. NICE appraisals are ongoing for two treatments which may soon be added to the PsA treatment pathway: ixekizumab, an anti-IL-17A (NICE guidance publication is expected in October 2018),

and abatacept, a T-cell inhibitor (NICE guidance publication is expected in July 2018). Full details of relevant NICE guidance are presented in Appendix L.

Biosimilars of etanercept and infliximab are currently available for use in the NHS for PsA (1, 50).

B.1.3.2.2 Clinical guidelines for treatment of PsA

Clinical guidelines for PsA (22, 51-54) emphasise several common treatment goals: control of symptoms, prevention of structural damage, and normalisation of functional and social participation.

An international task force of experts has recommended a 'treat-to-target' approach for spondyloarthritis, including PsA (55, 56), which is an approach also recommended by EULAR (22). The strategy proposes disease remission as the therapeutic target. However, as remission may be a difficult goal to achieve, low/minimal disease activity (LDA/MDA) has been considered a useful alternative target (22, 55). The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA; a non-profit consortium of rheumatologists, dermatologists, radiologists, geneticists, methodologists, epidemiologists, patient research partners, and biopharmaceutical industry representatives) propose a set of six standards and an individualised treatment pathway for six clinical domains: peripheral arthritis, axial disease, enthesitis, dactylitis, nails and skin; which along with comorbid conditions influence therapy recommendations (55). NICE recommend the use of bDMARDs/tsDMARDs in adults with active and progressive PsA when they have peripheral arthritis with three or more tender and three or more swollen joints, and when the disease has not responded to a trial of at least two csDMARDS, alone or in combination (57). The guidelines recommend discontinuation of bDMARDs/tsDMARDs for patients whose disease has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 12 (2, 3, 47), 16 (3, 49) and 24 weeks (48). The British Society for Rheumatology/British Health Professionals in Rheumatology (BSR/BHPR) guidelines (for peripheral arthritis in PsA) are broadly similar in terms of patient eligibility for TNFis and response assessment using PsARC (54).

The clinical guidelines for treatment of PsA outlined above are summarised more comprehensively in **Appendix L**.

B.1.3.3 Issues relating to current clinical practice

PsA is a heterogeneous disease (22) and thus requires a broad range of drug interventions to optimally manage patients. Although bDMARDs are effective in the treatment of PsA, these therapies are associated with limitations. These limitations include the injectable administration of these agents requires training by a healthcare professional, and injections or infusions can also be associated with injection site/infusion site reactions (9-11, 14). In the Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey of over 3,000 patients conducted in the US, Canada, France, Germany, Italy, Spain, and the UK (n=327) (58), more than 50% of respondents found oral csDMARDs (e.g. MTX) or injectable bDMARDs (e.g. adalimumab, etanercept) to be burdensome (37). Thirty percent of patients who have ever used oral therapies and 15% of patients who have ever used bDMARDs reported that oral csDMARDs were burdensome due to side effects/abnormal laboratory tests. Biologic DMARDs were burdensome primarily due to fear and anxiety of injections and the physical preparation for self-injection (26%), inconvenience (15%), adverse events (15%), pain/discomfort (7%), and a lack/loss of effectiveness (2%). Forty-six percent of respondents reported that currently-available therapies can actually be worse than the condition itself, and 85% of respondents felt that there was a need for better therapies (37). A recent U.S survey of treatment preferences among patients with PsA suggested that route of administration was the most important consideration, with patients reporting a preference for oral formulation over self-injection and intravenous infusion (38).

Among PsA patients treated with TNFis, treatment persistence is generally low, with approximately 30% to 50% discontinuing their index TNFi therapy during the first year of treatment (59-62). In one study, 44% of patients discontinued their index TNFi therapy during the first year primarily due to lack of efficacy (52%) and adverse effects (28%) (61). Data specifically from the British Society of Rheumatology Biologics Register (BSRBR) indicate that only 59% of patients remain on their first TNFi for PsA after three years of treatment (63), and there is evidence of clinically significant immunogenicity in some PsA patients receiving infliximab and

adalimumab, correlating with low therapeutic drug levels and worsening disease activity (64, 65). Furthermore, Norwegian hospital survey data reports that only one in ten patients achieve PsA specific remission (39). The challenges of achieving therapeutic targets (and maximising persistence of therapy) in patients with PsA suggests that additional treatment options with a new mechanism of action and oral route of administration would be valuable to patients.

B.1.3.3.1 The need for additional treatment options in TNFi-naïve patients

Recent GRAPPA guidelines concluded that PsA patients who have adverse prognostic risks factors (e.g., multiple swollen or tender joints or elevated C-reactive protein) are at high risk for structural progression (53). The chosen therapy for these patients should address as many active domains as possible and the guidelines recommend TNFis (which have proven efficacy in multiple PsA domains) as first-line treatment. However, some TNFi-naïve patients may not be comfortable with the use of a parenterally-administered treatment (40), and patient acceptability is highlighted in the same guidelines as an important criterion for treatment selection. Several studies in RA have assessed patient preferences with respect to mode of administration of treatments and indicated a preference for oral versus parenteral therapy (66-68). Similarly, as mentioned above, PsA patients report a preference for oral formulation over self-injection and intravenous infusion (38). Currently, apremilast is the only NICE-approved oral therapy for PsA. However, apremilast demonstrated equivocal efficacy for ACR50 and 70 response rates at the 16-week clinical assessment time-points in the PALACE 1, 2, and 3 clinical trials, (≤10% of enrolled or randomised patients were TNFi efficacy/therapeutic failures) and lacks any radiographic data by which to assess joint damage progression in PsA (49, 69-71). Therefore, there is a need for an oral, small molecule medication with an acceptable safety profile and similar efficacy, both in magnitude and domain coverage, to a TNFi for patients with active PsA who are TNFi-naïve and have had an inadequate response to csDMARD treatment. Tofacitinib addresses these unmet needs.

B.1.3.3.2 The need for additional treatment options in TNFi-IR patients

Many PsA patients will eventually require additional treatment options, in the event they no longer respond to or tolerate their TNFi treatment; however, treatment alternatives for TNFi-IR patients are limited. Observational data suggest that efficacy, safety, and drug survival rates of a second TNFi are inferior to that reported for first time treatment with a TNFi (72, 73). An observational trial of PsA subjects in Sweden demonstrated that ACR20 response at Month 3 was achieved by 47% of first-time, and 22% of second-time TNFi switchers; ACR50 response rates were 21% and 14%; and ACR70 response rates were 12% and 2% for first time and second time switchers, respectively. Median drug survival time for patients in this study switching TNFis for the first time was 64 months (95% CI 31–97), compared with 14 months (95% CI 5–23) for second-time switchers (74), implying a need for interventions with alternative mechanisms of action.

Currently-approved non-TNFi bDMARD treatments (such as ustekinumab and secukinumab) demonstrate similar efficacy to TNFis on PsA musculoskeletal domains, and superior efficacy on plaque psoriasis (75). However, the majority of patients in clinical trials for these treatments were TNFi-naïve, not TNFi-IR. Further, a subset of data on these agents suggests lower efficacy in TNFi-IR patients as compared to the rest of the study population (76, 77). These treatments also require a parenteral route of administration (38). Furthermore, as previously discussed, some TNFi treatments have been associated with clinically significant immunogenicity in some patients, which has been shown to be an important mechanism underlying treatment failure and loss of response over time across multiple inflammatory diseases (78-82). As a synthetic, small molecule JaK inhibitor (in contrast to a bDMARD), tofacitinib would not be expected to induce any immunogenicity (83).

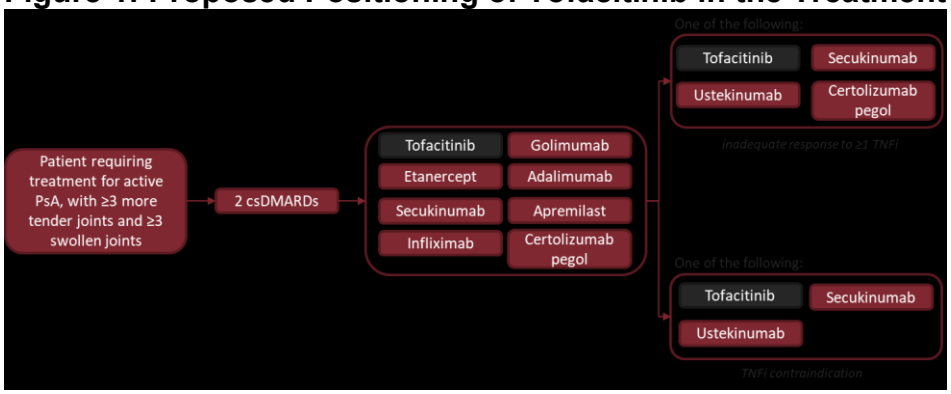
There are currently no NICE-recommended oral treatment options for PsA patients who are TNFi-IR. There is therefore a clear unmet medical need for an oral, small molecule treatment with a novel mechanism of action that has efficacy across multiple PsA domains, and an acceptable safety profile, that can be used to effectively treat TNFi-IR, as well as csDMARD-IR patients. Tofacitinib addresses these unmet needs.

B.1.3.3.3 Proposed positioning of tofacitinib within the clinical pathway

The proposed positioning of tofacitinib (Figure 1) is after csDMARDs as an alternative to other currently recommended bDMARD/tsDMARDs; and after treatment failure, intolerance or contraindication to a TNFi.

Tofacitinib offers a broad and novel mode of action through its inhibition of JAK, which modulates multiple cytokines specifically associated with the pathogenesis of PsA (5).

Figure 1: Proposed Positioning of Tofacitinib in the Treatment Pathway



Abbreviations: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug, PsA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitor

B.1.4 Equality considerations

No equality issues are anticipated if tofacitinib is recommended for use in England and Wales in accordance with its expected marketing authorisation.

B.2 Clinical effectiveness

- Results from the OPAL clinical trial programme demonstrated efficacy of tofacitinib 5 mg BD across multiple PsA domains including minimal disease activity (84), signs and symptoms of PsA, physical functioning, and radiographic progression.
- The clinical effectiveness of tofacitinib 5 mg BD in PsA was informed by two pivotal trials, OPAL Broaden (csDMARD-IR and TNFi-naïve population in a 12-month, randomised, placebo- and active-controlled clinical trial) and OPAL

Beyond (TNFi-IR population in a 6-month, randomised, placebo-controlled clinical trial).

- Sustained efficacy and safety of tofacitinib 5 mg BD is supported by an ongoing study, OPAL Balance, which is a long-term extension (LTE) study lasting 36 months and includes patients who had completed the OPAL Broaden and OPAL Beyond clinical trials.

OPAL Broaden (csDMARD-IR and TNFi-naïve)

- The ACR20 (50% vs 33%, p=0.01), ACR50 (28% vs 10%, p<0.001) and ACR70 (17% vs 5%, p=0.004) response rates at Month 3 were all significant in the tofacitinib 5 mg BD group when compared with placebo, were numerically similar to adalimumab (ACR20 ~ 52%; [redacted]; ACR50 ~ 33%; [redacted]; ACR70 ~ 19%, [redacted]) at Month 3, and were sustained up to Month 12.
- The change in HAQ-DI score from baseline at Month 3 in the tofacitinib 5 mg BD group was -0.35 vs -0.18 in the placebo group (p=0.006), which was numerically similar to adalimumab (-0.38; [redacted]) and was sustained up to Month 12 (LSM change=-0.54).
- The LSM change from baseline in van der Heijde mTSS at Month 12 in the tofacitinib 5 mg BD group was 0.01 vs -0.07 in the adalimumab group ([redacted]), a difference which was not considered to be clinically significant by clinical experts.
- The PsARC response rate at Month 3 in the tofacitinib 5 mg BD group was 51.4% vs 44.8% in the placebo group ([redacted]), a rate that was at least sustained through Month 12 (64.5%). For adalimumab, the respective PsARC response rates at Month 3 and Month 12 were 61.3% and 65.1% (comparison of tofacitinib 5 mg BD with adalimumab of [redacted] at Month 3 and [redacted] at Month 12).

- The PASI75 response rate at Month 3 in the tofacitinib 5 mg BD group was 43% vs 15% in the placebo group (p<0.001), which was numerically similar to adalimumab (39%; [redacted]) and was sustained up to Month 12.

- The MDA response rate at Month 3 in the tofacitinib 5 mg BD group was 26% vs 7% in the placebo group ([redacted]), which was numerically similar to adalimumab (25%, [redacted]) and was sustained up to Month 12.

(Please note: OPAL Broaden was not sufficiently powered to make formal statistical comparisons between tofacitinib and adalimumab; these are presented as a guide to interpretation rather than to declare statistical significance).

OPAL Beyond (TNFi-IR)

- The ACR20 (50% vs 24%, p<0.001) and ACR50 (30% vs 15%; p=0.003) response rates were significantly improved in the tofacitinib 5 mg BD group compared with placebo, and ACR 70 (17% vs 10%; [redacted]) had a numerically higher response rate. The improvements in the tofacitinib 5 mg BD group were sustained up to Month 6.

- The change in HAQ-DI score from baseline at Month 3 in the tofacitinib 5 mg BD group was -0.39 vs -0.14 in the placebo group (p<0.001) and was sustained up to Month 6.

- The PsARC response rate at Month 3 in the tofacitinib 5 mg BD group was 58.8% vs 29.0% in the placebo group ([redacted]) and was sustained up to Month 6.

- The PASI75 response rate in the tofacitinib 5 mg BD group at Month 3 was 21% vs 14% in the placebo group ([redacted]) and was at least sustained up to Month 6 (34%).

- The MDA response rate at Month 3 in the tofacitinib 5 mg BD group was 23% vs 15% in the placebo group ([redacted]) and was sustained up to Month 6.

OPAL Balance (csDMARD-IR/TNFi-naïve and TNFi-IR)

Interim data from the LTE study OPAL Balance indicate that improvements in HAQ-DI are largely sustained throughout an approximate two-year time period.

Adverse Reactions

- The clinical trial programme (OPAL Broaden, OPAL Beyond, and OPAL Balance) demonstrates that treatment with tofacitinib 5 mg BD is well tolerated.
- Across the OPAL Phase III clinical trial programme (OPAL Broaden, Beyond and Balance) treatment with tofacitinib 5 mg BD was well tolerated. The most frequent adverse events (AE) reported throughout the Phase III trials were headache, upper respiratory tract infections and nasopharyngitis.
- The safety profile of tofacitinib 5 mg BD is stable over time and consistent with bDMARDs currently recommended by NICE for the treatment of PsA.
- The tofacitinib safety profile in PsA is consistent with that of the tofacitinib RA programme (which has more than eight years (85, 86) of observation in clinical studies, more than 19,400 patient-years of drug exposure (85, 86), and includes the incidence and stability (that is, incidence over time) of adverse events of special interest.
- Safety events of special interest were infrequent and generally similar to those observed with bDMARDs, with the exception of an elevated incidence of Herpes Zoster.

B.2.1 Identification and selection of relevant studies

B.2.1.1 Search Strategy

Pfizer conducted a SLR to identify all relevant clinical data from the published literature regarding the clinical effectiveness of treatments in PsA. The SLR was performed in accordance with the methodological principles of conduct for systematic reviews as detailed in the University of York Centre for Reviews and

Dissemination's (CRD) "Guidance for Undertaking Reviews in Health Care" and is described in **Appendix D**.

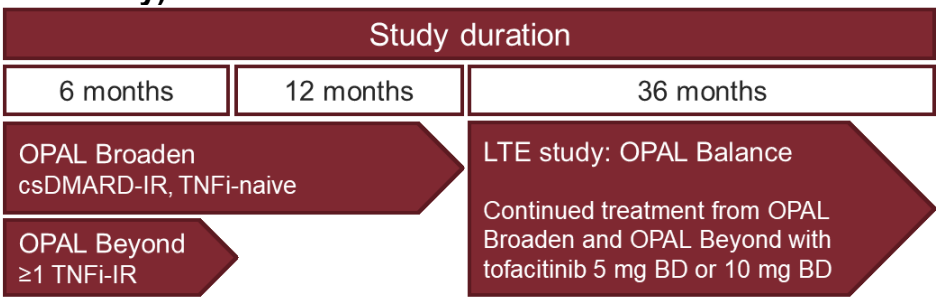
B.2.1.2 Study selection

The methods discussed in **Appendix D** for study selection were further refined to studies which included the licensed formulation of tofacitinib (5 mg, BD).

B.2.2 List of relevant randomised clinical effectiveness evidence

The SLR of clinical evidence identified two randomised controlled trials (RCTs) of tofacitinib in the populations relevant to the decision problem. The OPAL clinical trial programme consisted of two Phase III RCTs: OPAL Broaden (NCT01877668) and OPAL Beyond (NCT01882439) (**Table 4**, **Figure 2**). OPAL Broaden studied adult subjects with PsA who had previously had an inadequate response to csDMARDs and were TNFi-naïve; OPAL Beyond studied subjects who had previously had an inadequate response to at least one TNFi (TNFi-IR). Both trials contribute to the evidence base for tofacitinib's PsA indication.

Figure 2: Overview of the tofacitinib OPAL clinical trial programme (Phase III to LTE study)



Abbreviations: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; IR, inadequate response; LTE, long term extension study; TNFi, tumour necrosis factor inhibitor

Throughout **Section B.2** of this document, the publications for OPAL Broaden and OPAL Beyond are used as the primary source where possible; additional detail from the Clinical Summary Reports (CSRs) supplement the published data where required (87-90).

Both OPAL Broaden and OPAL Beyond studied 5 mg and 10 mg doses of tofacitinib twice daily (BD). As only the 5 mg dose has been submitted for regulatory approval in PsA, no results for the 10 mg dose BD are presented in this submission, with the exception of data from the open-label extension study, OPAL Balance

(NCT01976364), which consist of pooled findings for tofacitinib 5 mg BD and 10 mg BD doses. The 10 mg dose is referred to only where necessary, such as in descriptions of the trial designs.

Table 4: Clinical effectiveness evidence for OPAL Broaden and OPAL Beyond

Study	OPAL Broaden (2017)	OPAL Beyond (2017)
Study design	Phase 3 randomised, multicentre, 12-month, double-blind, double-dummy, active-controlled and placebo-controlled, parallel treatment group	Phase 3 randomised, multicentre, 6-month, double-blind, placebo-controlled, parallel-group
Population	Subjects with active PsA who had an IR to at least one csDMARD due to lack of efficacy or toxicity/lack of toleration and had not previously received any TNFi treatment	Subjects with active PsA who had an IR to at least one TNFi, as determined by a lack of efficacy or the occurrence of an AE that was considered by the treating physician to be related to treatment
Intervention(s)	TOF 5 mg BD (N=107) TOF 10 mg BD (N=104)	TOF 5 mg BD (N=131) TOF 10 mg BD (N=132)
Comparator(s)	ADA 40 mg SC q 2 weeks (N=106) PBO (for 3 months; N=105) At the end of the 3-month placebo-controlled period, the PBO group separated into two groups that switched either to TOF 5 mg BD (N=52) or TOF 10 mg BD (N=53)	PBO (for 3 months; N=131) At the end of the 3-month placebo-controlled period, the placebo group separated into two groups that switched either to TOF 5 mg BD (N=66) or TOF 10 mg BD (N=65)
Trial supports application for MA	Both trials support application for marketing authorisation	
Trial used in the economic model	Both trials were used in the economic model	
Rationale for use in the model	Both trials were included in the model because they include a population directly relevant to the decision problem	
Reported outcomes specified in the decision problem[§]	• Disease activity o **ACR20/50/70,** ACR response criteria components, **PASI50/75/90, PsARC**, MDA • Functional capacity o HAQ-DI, **HAQ-DI conditional on PsARC response status** • Periarticular disease (e.g., enthesitis, tendonitis, dactylitis) o DSS, LEI, SPARCC • Health-related quality of life. o SF-36 (PF component), FACIT-F (total score), DLQI, ISI • Mortality • Adverse effects of treatment • Disease progression (van der Heijde-mTSS in OPAL Broaden only)	

Abbreviations: ACR, American College of Rheumatology; BD, twice daily; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; AE, adverse event; DLQI, Dermatology Life Quality Index; DSS, Dactylitis Severity Score; FACIT-F, Functional Assessment of Chronic Illness Therapy- Fatigue Scale; HAQ-DI, Health Assessment Questionnaire Disability Index; IR, inadequate response; ISI, Itch Severity Index; LEI, Leeds Enthesitis Index; MA, marketing authorisation; MDA, Minimal Disease Activity; mTSS, modified Total Sharp Score; N, number; PASI,

Psoriasis Area and Severity Index; PF, physical functioning; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Criteria; SPARCC, Spondyloarthritis Research Consortium of Canada; TNFi, tumour necrosis factor Inhibitor
§Bolded outcomes were used to inform the economic model

B.2.3 Summary of methodology of the relevant randomised clinical effectiveness evidence

B.2.3.1 Comparative summary of RCT methodology

The methodology for the pivotal Phase III RCTs are summarised in **Table 5**.

Table 5: Comparative summary of trial methodology

Trial number (acronym)	NCT01877668 (OPAL Broaden)	NCT01882439 (OPAL Beyond)
Location	[redacted]	[redacted]
Trial design	Phase 3 randomised, multicentre, 12-month, double-blind, double-dummy, active-controlled and placebo-controlled, parallel treatment group	Phase 3 randomised, multicentre, 6-month, double-blind, placebo-controlled, parallel-group
Eligibility criteria for participants	Adult subjects aged ≥18 years with active PsA who had an inadequate response to at least 1 csDMARD and had not previously received any TNFi. Details of inclusion and exclusion criteria are provided in **Table 6**.	Adult subjects aged ≥18 years with active PsA who had an inadequate response to at least one TNFi. Details of inclusion and exclusion criteria are provided in **Table 6**.
Settings and locations where the data were collected	The study was collected across 126 study centres across 16 countries (Australia, Belgium, Bulgaria, Canada, Czech Republic, France, Germany, Hungary, Mexico, Poland, Russian Federation, Slovakia, Spain, Taiwan, UK, US) UK centres enrolling at least 5 patients: 1	The study was collected across 98 study centres across 15 countries (Australia, Belgium, Brazil, Canada, Czech Republic, France, Germany, Mexico, Poland, Russian Federation, Slovakia, Spain, Taiwan, UK, US) UK centres enrolling at least 5 patients: 2
Trial drugs **Permitted and disallowed concomitant medication**	TOF 5 mg BD (N=107) TOF 10 mg BD (N=104) ADA 40 mg SC Q2W (N=106) PBO to TOF 5 mg BD (N=52)§	TOF 5 mg BD (N=131) TOF 10 mg BD (N=132) PBO to TOF 5 mg BD (N=66)§ PBO to TOF 10 mg BD (N=65)§

	PBO to TOF 10 mg BD (N=53)§ Subjects were instructed to administer their injectable study medication (ADA or PBO) once every two weeks according to the instructions provided to them. Subjects were instructed to take one tablet from the study medication bottle (TOF or PBO) twice daily (once in the morning and once in the evening approximately 12 hours apart). **Permitted and disallowed concomitant medication** Patients were required to receive a stable background dose of a single csDMARD throughout the trial. Permitted background csDMARDs were methotrexate (maximum dose of 20 mg/week; minimum duration 4 months and stable dose for 4 weeks prior to first dose of study drug), sulfasalazine (maximum dose of 3 g/day; minimum duration 2 months and stable dose for 4 weeks prior to first dose of study drug) and leflunomide (maximum dose of 20 mg/day; minimum duration 4 months and stable dose for 4 weeks prior to first dose of study drug). Other csDMARDs were considered after discussion with the study clinician. Prohibited medications during the study period included: • [redacted] • [redacted] • [redacted] • [redacted]	Subjects were instructed to take one tablet from the study medication bottle (TOF or PBO) twice daily (once in the morning and once in the evening approximately 12 hours apart). **Permitted and disallowed concomitant medication** Patients were required to receive a stable background dose of a single csDMARD throughout the trial. Permitted background csDMARDs were methotrexate (maximum dose of 20 mg/week; minimum duration 4 months and stable dose for 4 weeks prior to first dose of study drug), sulfasalazine (maximum dose of 3 g/day; minimum duration 2 months and stable dose for 4 weeks prior to first dose of study drug) and leflunomide (maximum dose of 20 mg/day; minimum duration 4 months and stable dose for 4 weeks prior to first dose of study drug). Other csDMARDs were assessed on a case-by-case basis by the study Investigator and Sponsor. Prohibited medications during the study period included: • [redacted] • [redacted] • [redacted] • [redacted]
Primary outcomes used in the economic model and/or specified in the scope¶	**Primary outcomes[a]** • **ACR20 response rate at Month 3** • **ΔHAQ-DI at Month 3** **Supportive analysis of primary outcomes** • HAQ-DI responder analysis (≥0.35 as the cutpoint for response) at Month 3	**Primary outcomes[a]** • **ACR20 response rate at Month 3** • **ΔHAQ-DI at Month 3** **Supportive analysis of primary outcomes** • HAQ-DI responder analysis (≥0.35 as the cutpoint for response) at Month 3

Other outcomes used in the economic model and/or specified in the scope¶	**Secondary outcomes** • ACR20 response rate[a]: Week 2, Month 6, 12 • Δvan der Heijde-mTSS, progressor rates, and non-progressor rates: Month 12 • ΔACR components: Month 3 • ACR50/70 response rate[a]: Month 3, 6, 12 • **PASI75 response rate: Month 3**, 6, 12 • **PsARC response rate: Month 3**, 6, 12 • ΔLEI, ΔSPARCC, ΔDSS: Month 3, 6, 12 • ΔSF-36 (PF component), FACIT-F (total score): Month 3, 6, 12 **Other outcomes** • MDA response rate: Month 3, 6, 12 • ΔDLQI, ΔISI: Month 3, 6, 12 • ΔHAQ-DI: Month 6, 12 • ΔACR components: Month 6, 12 **Post-hoc analyses used in the economic model[b]** • **PASI50/90 response rate: Months 3**, 6, 12 • **ΔHAQ-DI conditional on PSARC response status: Month 3**, 6, 12	**Secondary outcomes** • ACR20 response rate[a]: Week 2, Month 6 • ΔACR components at Month 3 • ACR50/70 response rate[a]: Month 3, 6 • **PASI75 response rate: Month 3**, 6 • **PsARC response rate: Month 3**, 6 • ΔLEI, ΔSPARCC, ΔDSS: Month 3, 6 • ΔSF-36 (PF component), FACIT-F (total score): Month 3, 6 **Other outcomes** • MDA response rate: Month 3, 6 • ΔDLQI, ΔISI: Month 3, 6 • ΔHAQ-DI: Month 6 • ΔACR components: Month 6 **Post-hoc analyses used in the economic model[b]** • **PASI50/90 response rate: Month 3**, 6 • **ΔHAQ-DI conditional on PSARC response status: Month 3**, 6
Pre-planned subgroups	[redacted]	[redacted]

Abbreviations: Δ, change from baseline; ACR, American College of Rheumatology; ADA, adalimumab; BD, twice daily; bDMARD, biologic disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; DLQI, Dermatology Life Quality Index; DSS, Dactylitis Severity Score; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; HAQ-DI, Health Assessment Questionnaire Disability Index; IA, intraarticular; IM, intramuscular; ISI, Itch Severity Item; IR, inadequate response; IV, intravenous; LEI, Leeds Enthesitis Index; MDA, Minimal Disease Activity; mTSS, modified Total Sharp Score; N, number; PASI, Psoriatic Area and Severity Index; PBO, placebo; PsA, psoriatic arthritis; PsARC, Psoriatic Arthritis Response Criteria; SC, subcutaneous; SF-36, 36-item Short Form Survey; SPARCC, Spondyloarthritis Research Consortium of Canada; TNFi, tumour necrosis factor inhibitor; TOF, tofacitinib

§All subjects receiving placebo advanced to a predetermined dose of TOF (5 mg BD or 10 mg BD) at Month 3.

[a]As described in Section 2.4.2., a hierarchical testing procedure was applied to the primary endpoints of ACR20 and HAQ-DI; a hierarchical testing was also applied to the ACR family endpoints (ACR20, ACR50, and ACR70) at Month 3, and to ACR20 from 3 months to earlier time points

[b]The following outcomes were not pre-specified endpoints in the study but were calculated post-hoc for inclusion in the economic model.

¶Bolded outcomes were examined in the economic model

B.2.3.3 Eligibility criteria

Key eligibility criteria for the pivotal Phase III RCTs are summarised in **Table 6**, with additional eligibility criteria detailed in **Table D8** in **Appendix D**.

Table 6: Eligibility criteria for RCTs

Trial no. (acronym)	NCT01877668 (OPAL Broaden)	NCT01882439 (OPAL Beyond)
Inclusion criteria	• Adults aged ≥18 years; • Diagnosis of PsA for ≥6 months, meeting the CASPAR (91) criteria at screening; • Active arthritis (≥3 tender/painful and ≥3 swollen joints) and active plaque psoriasis at screening and baseline; • IR to ≥1 csDMARD and no previous TNFi treatment; • Prior use of non-TNFi bDMARDs for treatment of psoriasis must have been discontinued for ≥6 months prior to the first dose of study drug.	• Adults aged ≥18 years (≥20 years in Taiwan); • Diagnosis of PsA for ≥6 months; meeting CASPAR criteria at screening; • Active plaque psoriasis (diagnosed or confirmed by a dermatologist or a sponsor-approved rheumatologist) at screening and active arthritis (≥3 tender/painful joints and ≥3 swollen joints) at screening and baseline; • IR to ≥1 TNFi (lack of efficacy and/or treatment-related adverse event determined by or reported to the physician and recorded on the case report form).
Exclusion criteria	• Current non-plaque forms of psoriasis (except nail psoriasis); • Current or recent history of severe, progressive, or uncontrolled renal, hepatic, haematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, or neurologic disease; • Evidence of active or latent or inadequately treated *Mycobacterium tuberculosis*; • Blood dycrasias within 3 months of first study drug dose including confirmed haemoglobin <10 g/dL; white blood cell count <3.0 × 10^9/L (<3000/mm^3); absolute neutrophil count ≤1.5 × 10^9/L (≤1500/mm^3); absolute lymphocyte count <1.0 × 10^9/L (<1000/mm^3); platelet count <100 × 10^9/L (<100,000/mm^3). • AST or ALT >1.5x ULN at screening; • Estimated creatinine clearance <40 mL/min; • History of any autoimmune rheumatic disease other than PsA; • History of lymphoproliferative disorder; • History of recurrent herpes zoster, disseminated herpes zoster, or disseminated herpes simplex; • History of active infection requiring hospitalisation or parenteral antimicrobial therapy within 6 months prior to first study drug dose; • Current or history of malignancies (except adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ); • Prior treatment with a non-B-cell-specific lymphocyte-depleting agent.	

Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; bDMARD, biologic disease-modifying anti-rheumatic drug; CASPAR, Classification Criteria for Psoriatic Arthritis; COX-2, Cycloocygenase-2; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; DMARD, disease-modifying anti-rheumatic drug; IR, inadequate response; L, litre; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitor; ULN, upper limit norm

B.2.3.4 Baseline characteristics and demographics

B.2.3.3.1 OPAL Broaden

Data on baseline characteristics and demographics for the two placebo groups in OPAL Broaden (placebo switching to tofacitinib 5 mg BD and placebo switching to tofacitinib 10 mg BD) were pooled and are presented below in **Table 7**. In OPAL Broaden, the demographic and baseline disease characteristics were similar across treatment groups, with the exception of significant differences between groups in the mean swollen-joint count (unadjusted p=0.03 for the comparison among all four trial groups), mean Leeds Enthesitis Index (LEI) score (unadjusted p=0.02 for the comparison among all four groups), and the rate (%) of MTX use at baseline (unadjusted p=0.02 for the comparison among all four groups), which were all lower in the adalimumab group, and significant differences among trial groups in the rate of glucocorticoid use at day 1 (unadjusted p=0.02 for the comparison of the 10-mg tofacitinib BD group with other groups), which was 27% for tofacitinib 5 mg BD, 22% for adalimumab, 17% for placebo, and 11% for tofacitinib 10 mg BD. The majority of the subjects were white (97 to 99%); the mean age ranged from 47.4 to 49.4 years and the mean duration of PsA ranged from 5.3 to 7.3 years. Out of the 318 subjects, 216 (67.92%) had enthesitis and 177 (55.66%) had dactylitis; 262 (82.39%) of subjects were receiving concomitant MTX. Key subject baseline characteristics are summarised in **Table 7**, with additional baseline characteristics presented in **Appendix N**. Data on tofacitinib 10 mg BD dose group are available in the Mease et al., publication (87) and in the OPAL Broaden CSR but have not been presented here.

Table 7: Characteristics of participants across treatment groups in OPAL Broaden and OPAL Beyond

	OPAL Broaden			OPAL Beyond	
Baseline characteristic	**TOF 5 mg (N=107)**	**ADA 40 mg (N=106)**	**PBO (N=105)**	**TOF 5 mg (N=131)**	**PBO (N=131)**
Age (years), M (SD)	49.4 (12.6)	47.4 (11.3)	47.4 (12.3)	49.5 (12.3)	49.0 (12.6)
Sex, Female, N (%)	57 (53)	50 (47)	56 (53)	64 (49)	80 (61)
Race (white), N (%)	105 (98)	103 (97)	104 (99)	121 (92)	118 (90)
Duration of PsA (years), M (SD)	7.3 (8.2)	5.3 (5.3)	6.4 (6.4)	9.6 (7.6)	9.4 (8.1)
Tender/painful joints, M (SD)	20.5 (12.6)	17.1 (11.2)	20.6 (14.4)	20.5 (13.0)	19.8 (14.9)
Swollen joints, M (SD)	12.9 (9.9)	9.8 (7.9)	11.5 (8.8)	12.1 (10.6)	10.5 (9.0)
HAQ-DI, M (SD)	1.2 (0.6)	1.1 (0.6)	1.1 (0.6)	1.3 (0.7)	1.3 (0.8)
BSA affected with psoriasis, ≥3, N (%)	82 (77)	78 (74)	82 (78)	80 (61)	86 (66)
SPARCC, Score >0, N (%)	81 (75.7)	82 (77.4)	79 (75.2)	96 (73.3)	100 (76.3)
SPARCC, M (SD)	5.0 (3.3)	4.5 (2.8)	5.3 (3.8)	5.8 (4.1)	5.4 (3.5)
LEI, Score >0, N (%)	75 (70)	76 (72)	65 (62)	83 (63)	93 (71)
LEI, M (SD)	2.5 (1.4)	2.3 (1.2)	2.8 (1.5)	3.0 (1.6)	2.8 (1.6)
DSS, Score >0, N (%)	61 (57)	58 (55)	58 (55)	66 (50)	63 (48)
DSS, M (SD)	9.1 (8.0)	8.0 (7.4)	9.9 (8.4)	7.8 (9.9)	6.8 (5.7)
PASI for subjects with BSA ≥3% and PASI >0				[redacted]	[redacted]
N (%)	82 (77)	77 (73)	82 (78)	7.6 (0.6-32.2)	7.1 (1.6-66.0)
Median (range)	5.6 (0.4-46.0)	7.0 (2.0-47.1)	6.6 (0.8-41.4)		
CRP (mg/L) >2.87, N (%)	68 (64)	64 (60)	63 (60)	85 (65)	80 (61)
Rheumatoid factor positive, Yes, N (%)	8 (7.5)	5 (4.7)	1 (1.0)	[redacted]	[redacted]
CCP antibody positive, Yes, N (%)	8 (7.5)	4 (3.8)	3 (2.9)	[redacted]	[redacted]
van der Heijde-mTSS >0					
N	96	99	95	--	--
M (SD)	17.1 (28.6)	14.4 (39.2)	17.6 (43.4)	--	--
Prior non-TNFi bDMARD therapy, N (%)	3 (3)	1 (1)	3 (3)	[redacted]	[redacted]
Prior bDMARD therapy (TNFi only), N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Oral glucocorticoid use on day 1, N, (%)	29 (27)	23 (22)	18 (17)	37 (28)	31 (24)
Concomitant csDMARD therapy up to month 3, n (%)					
Methotrexate	91 (85)	79 (75)	92 (88)	98 (75)	101 (77)
Sulfasalazine	8 (7)	15 (14)	9 (9)	21 (16)	20 (15)
Leflunomide	7 (7)	10 (9)	4 (4)	12 (9)	9 (7)
Hydroxychloroquine	0	1 (1)	0	[redacted]	[redacted]
Other[3]	1 (1)	1 (1)	0	2 (2)	1 (1)
Methotrexate dose, mg/wk, M (SD)	16.4 (3.8)	15.8 (4.4)	15.5 (4.1)	14.7 (4.4)	14.1 (4.3)

Abbreviations: ADA, adalimumab; BSA, body surface area; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; bDMARD, biologic disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug DMARD, disease-modifying anti-rheumatic drug; DSS, Dactylitis Severity Score; HAQ-DI, Health Assessment Questionnaire - Disability Index; LEI, Leeds Enthesitis Index; M, mean; mg, milligram; mTSS, modified Total Sharp Score; N, number of subjects in Safety Analysis Set; n, number; PASI, Psoriasis Area and Severity Index; PBO, Placebo; PsA, psoriatic arthritis; SD, standard deviation; SPARCC, Spondyloarthritis Research Consortium of Canada; TNFi, tumour necrosis factor inhibitor; TOF, tofacitinib; wk, week

[3]Subjects who were treated with >1 DMARD(s) are counted in the "other" category

B.2.3.3.2 OPAL Beyond

Data on baseline characteristics and demographics for the two placebo groups in OPAL Beyond (placebo switching to tofacitinib 5 mg BD and placebo switching to tofacitinib 10 mg BD) were pooled and are presented above in **Table 7**. In OPAL Beyond, the demographic and baseline disease characteristics were similar across treatment groups, with the exception of the mean number of tender/painful joint, which was significantly different across all trial groups (unadjusted p=0.03 for the comparison among all four trial groups, including tofacitinib 10 mg BD) and was highest in the tofacitinib 10 mg BD group (25.5, SD=17.5), followed by the tofacitinib 5 mg BD group (20.5, SD=13.0) and the placebo group (19.8, SD=14.9). There were more female subjects in the placebo group (61%) than the tofacitinib 5 mg BD group (49%); the majority of the subjects were white (90 to 92%); the mean age ranged from 49.0 to 49.5 years; and the mean duration of PsA ranged from 9.4 to 9.6 years. Out of the 262 subjects, 176 (67.18%) had enthesitis and 129 (49.24%) had dactylitis; 199 (75.95%) of subjects were receiving concomitant MTX. Key subject baseline characteristics are summarised in **Table 7**, with additional baseline characteristics presented in in Appendix N. Data on the tofacitinib 10 mg BD dose group are available in the Gladman et al., publication (88) and the OPAL Beyond CSR but have not been presented here.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis sets

The main analysis sets in the OPAL RCTs are defined below, with additional analysis sets detailed in **Appendix M**.

The Full Analysis Set (FAS): All subjects who were randomised to the study and received at least one dose of the randomised study drug (tofacitinib, adalimumab, or placebo). The FAS was used for all analyses of all efficacy (including PRO) endpoints and was the primary dataset for the primary endpoints.

The Safety Analysis Set (Safety): This set included all subjects who received at least one dose of the randomised study drug (tofacitinib or placebo).

[redacted]

B.2.4.2 Statistical information

A summary of the statistical methods used in the OPAL RCTs are presented in **Table 8**.

Table 8: Summary of statistical analyses

Trial number (acronym)	NCT01877668 (OPAL Broaden)	NCT01882439 (OPAL Beyond)
Hypothesis objective	[redacted]	[redacted]
Multiple comparisons and multiplicity	In order to control for Type I error rate at the 5% level in the primary analysis, a step-wise testing procedure was used to adjust for multiple comparisons of two TOF doses (5 mg BD and 10 mg BD) against PBO for the co-primary endpoints of ACR20 and ΔHAQ-DI at Month 3. A similar step-down procedure was also applied to certain secondary endpoints in the following order (after ACR20 and HAQ-DI): PASI75, ΔLEI, ΔDSS, ΔSF-36 Physical Functioning Domain and ΔFACIT-F total score at Month 3. Because the endpoints ACR50 and ACR70 can be viewed as extensions of the ACR20, and all belong to the ACR family of endpoints, a step-down approach to testing the ACR20, ACR50 and ACR70 at Month 3 was used for each endpoint and doses within each endpoint. In order to be more rigorous about establishing the onset of efficacy, a step-down approach with the ACR20 from 3 months to earlier time points was also utilised. No preservation of the type I error rate was applied for the remainder of secondary endpoints or other endpoints.	

Statistical analysis of primary endpoints	For each endpoint, TOF 10 mg BD was tested versus PBO first, followed by TOF 5 mg BD vs PBO. Testing stopped at the first instance in which statistical significance was not achieved. Primary Analysis: For ACR20 response at Month 3, the normal approximation for the difference in binomial proportions was used to test the superiority of each dose of TOF to PBO on the FAS. Primary Analysis: For the change from baseline in HAQ-DI at Month 3, a mixed-effect model with repeated measures was used on the FAS. [redacted]	
Statistical analysis of secondary and other endpoints	Analyses of all secondary/other endpoints used the FAS [redacted](as indicated in **Table M20** in **Appendix M**). Binary endpoints were analysed with the use of the normal approximation for the difference in binomial proportions (i.e., normal approximation for binomial distribution). Continuous endpoints were analysed with the use of a mixed model for repeated measures with trial group, visit, interaction of the trial group by visit, geographic location, and baseline value as fixed effects.	
Sample size, power calculation	For the ACR20 analysis, a sample size of 100 per arm was planned to yield 92% power, assuming a difference in response rates between TOF and PBO of ≥20% (with the placebo response at 15%). For the analysis of the ΔHAQ-DI, the sample size of 100 per arm results in over 94% power for differences of 0.3 or greater between a TOF dose and PBO, assuming a SD of 0.6. For estimating the difference between two treatments in progressor rate (defined as Δvan der Heijde mTSS >0.5, an increase), a sample size of 100 per arm was planned to result in a 95% CI with a half width of approximately 8.5% assuming the true progressor rate in the two treatments (e.g., a TOF dose and ADA) were both 10%.	For the ACR20 analysis, a sample size of 130 per arm was planned to yield 84% power, assuming a difference in response rates between TOF and PBO of ≥15% (with the placebo response at 15%) and 97% power, assuming a difference in response rates between TOF and PBO of ≥20%. For the analysis of the ΔHAQ-DI, the sample size of 130 per treatment arm results in approximately 98% power for differences of 0.3 or greater between a TOF dose and PBO, assuming a SD of 0.6.

Data management, subject withdrawals	NRI was applied to response-type/binary endpoints: ACR20, ACR50, ACR70, ΔHAQ-DI (decrease) ≥0.35, PsARC, PASI75, and MDA. No imputation was applied to missing HAQ-DI data. Missing mTSS values at Month 12 (OPAL Broaden only) were imputed via linear extrapolation.

Abbreviations: Δ, change from baseline; ACR, American College of Rheumatology; ADA, adalimumab; BD, twice daily; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; DSS, Dactylitis Severity Score; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire - Disability Index; LEI, Leeds Enthesitis Index; PASI, Psoriasis Area and Severity Index; PBO, placebo; SD, standard deviation; SF-36, 36-item Short Form Survey; TNFi, tumour necrosis factor inhibitor; TOF, tofacitinib

B.2.4.3 Participant flow in the relevant randomised controlled trials

See **Section D.1.2.2** (**Appendix D**), for details of the numbers of participants eligible to enter the trials.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

See **Section D.1.3** (**Appendix D**) for quality assessment of the relevant trials in the OPAL trial programme.

B.2.6 Clinical effectiveness results of the relevant randomised controlled trials

A decision was made to present efficacy results from OPAL Broaden and OPAL Beyond that inform the economic model in **Sections B.2.6.1** and **B.2.6.2** below.

Data for additional efficacy measures, i.e., Minimal Disease Activity (MDA), Dactylitis Severity Score (DSS), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), 36-item Short Form Survey – Physical Functioning component (SF-36 PF), Functional Assessment of Chronic Illness Therapy- Fatigue Scale (FACIT-F) Total Score, Dermatology Life Quality Index (DLQI), and Itch Severity Item (ISI)) and post-hoc analyses conducted to inform the economic model (Health Assessment Questionnaire – Disability Index; HAQ-DI conditional on Psoriatic Arthritis Response Criteria (PsARC) , Psoriatic Area and Severity Index (PASI) 50/90), are presented in **Appendix M**. However, given that treat to target recommendations now

exist in clinical guidelines for PsA (22, 55, 56), a summary of the effect of tofacitinib 5 mg BD on MDA is also reported in **Section B.2.6.1.2** and **B.2.6.2.2** below.

An overview of the scoring criteria for the outcome measures included in this submission is presented in **Appendix L** (**Section L.2.1**).

For endpoints not included in the hierarchical testing procedure (see **Table 8**) due to failure to achieve significance on the previous endpoint, or those not included in the procedure, such as for comparisons between tofacitinib 5 mg BD and adalimumab and adalimumab and placebo, nominal p-values are presented to guide interpretation rather than to declare statistical significance. As OPAL Broaden was not powered to assess non-inferiority or superiority between tofacitinib and adalimumab, no formal conclusions can be made.

B.2.6.1 Summary of outcome measures in OPAL Broaden (csDMARD-IR and TNFi-naïve)

B.2.6.1.1 Main efficacy outcomes

- ***Signs and symptoms of PsA: Proportion of subjects achieving ACR20 response at Month 3 (Trial primary outcome)***

A significantly greater percentage of subjects in the tofacitinib 5 mg BD (50%) group achieved an ACR20 response at Month 3 compared with subjects in the placebo group (33%; p=0.010; the difference compared to placebo was 17.1% ([redacted]; 95% CI: 4.1, 30.2) (**Table 9**). The rate of response in the tofacitinib 5 mg BD group was numerically comparable to adalimumab (52%; [redacted]). As shown by the secondary/other endpoints (see **Section B.2.6.1.2**), the ACR20 response rate in the tofacitinib 5 mg BD group was sustained at Months 6 and 12; a significantly higher ACR20 response rate in the tofacitinib 5 mg BD group compared to placebo was seen as early as Week 2 ([redacted] p<0.001).

- ***Physical functioning: Mean change from baseline in HAQ-DI score at Month 3 (Trial primary outcome)***

The mean change from baseline in HAQ-DI score at Month 3 was significantly greater in the tofacitinib 5 mg BD group (–0.35) compared with the placebo group (–0.18; p=0.006); the difference from placebo was -0.2 [redacted]; 95% CI: -0.3, -0.05) (**Table 9**). The improvement in HAQ-DI score in the tofacitinib 5 mg BD group was numerically comparable to adalimumab (-0.38; [redacted]). As shown by the secondary/other endpoints (see **Section B.2.6.1.2**), the change in HAQ-DI score in the tofacitinib 5 mg BD group observed at Month 3 was sustained at Months 6 and 12.

In a supportive analysis, a decrease (indicating clinical improvement) in the HAQ-DI score that was greater than or equal to the minimum clinically important difference (a decrease from baseline ≥0.35) occurred in 53% of the subjects in the tofacitinib 5 mg BD group, as compared with 31% of subjects in the placebo group at Month 3 ([redacted]); such a decrease occurred in 53% of the subjects in the adalimumab group ([redacted] for the comparison between tofacitinib 5 mg BD and adalimumab).

[redacted]

Table 9: Summary of primary efficacy results for OPAL Broaden (FAS)

Outcome	TOF 5mg	ADA	PBO
ACR20 response rate at Month 3			
N	107	106	105
Response rate, n (%)	54 (50)	55 (52)	35 (33)
Difference from placebo, %	17.1	18.6	--
95% CI for difference	4.1, 30.2	5.5, 31.7	--
p-value	0.01[§]	[redacted][†]	--
HAQ-DI score at Month 3			
N*	103	101	102[a]
LS mean change from baseline	-0.35	-0.38	-0.18
LS mean difference from placebo	-0.2	-0.2	--

95% CI for difference	-0.3, -0.05	-0.3, -0.1	--
p-value	0.006§	[redacted]†	--

Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-disability index; LS, least squares; N, number of subjects in FAS; N*, number of subjects evaluable at Month 3; n, number of responders; PBO, placebo; TOF, tofacitinib.
§p-value is subject to the step-down approach; †nominal p-value for comparison between adalimumab and placebo;
[a]One placebo subject was excluded from the analysis (no post-baseline assessments)

[redacted]

B.2.6.1.2 Secondary and other efficacy outcomes

- ***Signs and symptoms of PsA***: ***Proportion of subjects achieving ACR20, ACR50, and ACR70 response at Week 2 (ACR20 only), Month 3 (excluding ACR20), Month 6, and Month 12***

A rapid response to tofacitinib 5 mg BD was observed: after 2 weeks, the ACR20 response rate in the tofacitinib 5 mg BD group was significantly higher than in the placebo group (p<0.001).

At Month 3, tofacitinib 5 mg BD significantly improved ACR50 and ACR70 response rates compared with the placebo group (p=0.001 and p=0.004, respectively).

ACR20, ACR50, and ACR70 response rates in the tofacitinib 5 mg BD group were sustained at Months 6 and 12 and were comparable to adalimumab, with the exception of ACR70 response rates at Month 6, for which tofacitinib 5 mg BD response rates were smaller than adalimumab ([redacted]). The Week 2 (ACR20 only), Month 3 (except ACR20), Month 6, and Month 12 ACR20, ACR50 and ACR70 response rates for OPAL Broaden are summarised in **Table 10**.

Table 10: ACR20, ACR50, and ACR70 response rates for OPAL Broaden (FAS)

Outcome	TOF 5mg	ADA	PBO*
ACR20 response rate, n/N (%)			
Week 2	[redacted]	[redacted]	[redacted]
Difference from placebo	[redacted]	[redacted]	--
95% CI for difference	[redacted]	[redacted]	--
p-value	<0.001	[redacted]	--
Month 6	[redacted]	[redacted]	--
Month 12	73/107 (68)	64/106 (60)	--
ACR50 response rate, n/N (%)			
Month 3	30/107 (28)	35/106 (33)	10/105 (10)
Difference from placebo	18.5	23.5	--

95% CI for difference	8.3, 28.7	12.9, 34.1	--
p-value	0.001	[redacted]	--
Month 6	[redacted]	[redacted]	--
Month 12	48/107 (45)	43/106 (41)	--
ACR70 response rate, n/N (%)			
Month 3	18/107 (17)	20/106 (19)	5/105 (5)
Difference from placebo	12.1	14.1	--
95% CI for difference	3.9, 20.2	5.6, 22.6	--
p-value	0.004	[redacted]	--
Month 6	[redacted]	[redacted]	--
Month 12	25/107 (23)	31/106 (29)	--

Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; FAS, full analysis set; n, number of responders; N, number of subjects in FAS; PBO, placebo; TOF, tofacitinib
[§]nominal p-value ≤0.05 for comparison of tofacitinib 5 mg BD with adalimumab; [†]nominal p-value for the comparison between adalimumab and placebo; [redacted]*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

[redacted]

- ***Signs and symptoms of PsA***: ***Change from baseline across ACR criteria components at Month 3, Month 6, and Month 12***

Tofacitinib 5 mg BD was significantly superior to placebo across ACR Swollen Joint Count, C-Reactive Protein, Patient's Assessment of Arthritis Pain, and Patient's Global Assessment of Arthritis criteria and numerically superior to placebo across ACR Tender/Painful Joint Count and Physician's Global Assessment of Arthritis criteria at Month 3. These response rates were sustained up to Months 6 and 12 (see **Appendix M** for further detail).

- ***Physical functioning: Change from baseline in HAQ-DI scores at Month 6 and Month 12***

Changes from baseline in HAQ-DI scores in the tofacitinib 5 mg BD group were sustained up to Months 6 and 12, were numerically similar to adalimumab ([redacted] at Month 6 and [redacted] and Month 12) and are summarised in

Table 11.

Table 11: Change in HAQ-DI from baseline for OPAL Broaden (FAS)

Outcome	TOF 5mg	ADA
HAQ-DI score, LS Mean (SE) [n/N]		
Month 6	[redacted]	[redacted]
Month 12	-0.54 (0.05) [96/107]	-0.45 (0.05) [94/106]

Abbreviations: ADA, adalimumab; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; LS, Least Squares; mg, milligram; N, total number of unique subjects in the longitudinal model; n, number of subjects evaluable at each visit; SE, standard error; TOF, tofacitinib

[redacted]

- ***Structural preservation: Change from baseline in van der Heijde-mTSS scores, non-progression rates, and progressor rates at Month 12***

Tofacitinib 5 mg BD was associated with a mean change from baseline in total van der Heijde mTSS score at Month 12 of 0.01 vs -0.07 for adalimumab ([redacted]), as shown in Figure 3. According to clinical experts consulted as part of this evidence submission, the difference between tofacitinib 5 mg BD and adalimumab was unlikely to be clinically significant, suggesting that the two treatments were similar in a numerical sense. Progressor rates (defined as >0.5 increase from baseline in van der Heijde mTSS) at Month 12 for tofacitinib 5 mg BD ([redacted]) were similar to adalimumab ([redacted]) ([redacted]). Change from baseline and progressor rates are presented in **Table 12** below.

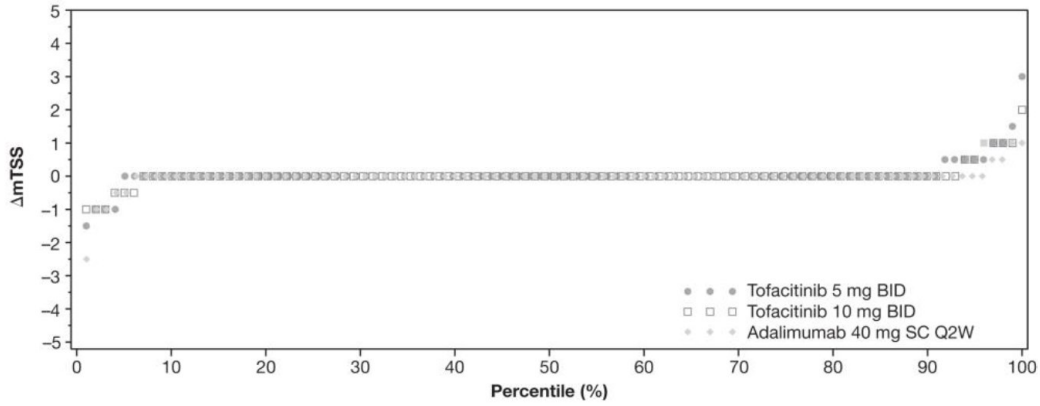
Table 12: Change in van der Heijde-mTSS from baseline and progressor rate for OPAL Broaden (FAS)

Outcome	TOF 5mg	ADA
mTSS, LS Mean (SE) [N*]		
Month 12	0.01 (0.07) [98]	-0.07 (0.07) [95]
Difference from ADA	[redacted]	--
95% CI for difference	[redacted]	--
p-value	[redacted]†	--
mTSS progressor rate, n/N (%)		
Month 12	[redacted]	[redacted]
Difference from ADA	[redacted]	--
95% CI for difference	[redacted]	--
p-value	[redacted]†	--

Abbreviations: ADA, adalimumab; LS, least squares; mg, milligram; mTSS, modified Total Sharp Score; N, number of subjects evaluable at Month 12 after linear extrapolation; N*, total number of unique subjects in ANCOVA analysis; n, number of progressors; SE, standard error; TOF, tofacitinib

†nominal p-value for the comparison between tofacitinib 5 mg BD and adalimumab;

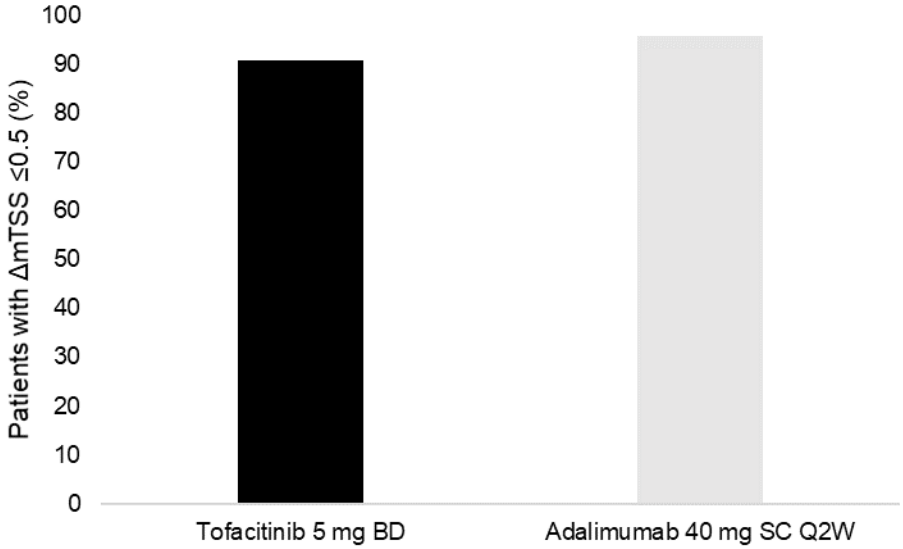
Figure 3: Cumulative probability of van der Heijde-mTSS in OPAL Broaden



Abbreviations: BID, twice daily; mTSS, modified Total Sharp Score; SC, subcutaneous; Q2W, every 2 weeks

Similarly, as shown in Figure 4, the proportion of subjects with radiographic non-progression (defined as ≤0.5 increase in van der Heijde mTSS from baseline) at Month 12 was numerically similar between the tofacitinib 5 mg BD (96%) and adalimumab (98%) groups.

Figure 4: Rates of van der Heijde-mTSS non-progression in OPAL Broaden



Abbreviations: BD, twice daily; mTSS, modified Total Sharp Score; SC, subcutaneous; Q2W, every 2 weeks

- ***Signs and symptoms of PsA***: ***Proportion of subjects achieving PsARC response at Month 3, Month 6, and Month 12***

Tofacitinib 5 mg BD numerically improved the PsARC response rate compared to placebo at Month 3 ([redacted]), which was at least sustained through Month 6 and Month 12. PsARC response rate in the adalimumab group was 61.3% at month 3 ([redacted]; tofacitinib 5mg BD vs adalimumab).The PsARC response rates for OPAL Broaden are summarised in **Table 13**.

Table 13: PsARC response rates for OPAL Broaden (FAS)

Outcome	TOF 5mg	ADA	PBO*
PsARC response rate, n/N* (%)			
Month 3	55/107 (51.4)	65/106 (61.3)	47/105 (44.8)
Difference from placebo	6.6	16.6	--
95% CI for difference	-6.8, 20.1	3.3, 29.8	--
p-value	[redacted]	[redacted]†	--
Month 6	[redacted]	[redacted]	--
Month 12	69/107 (64.5)	69/106 (65.1)	--

Abbreviations: ADA, adalimumab; FAS, full analysis set; n, number of responders; N*, number of subjects in FAS; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; TOF, tofacitinib
*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period
†nominal p-value

[redacted]

- ***Signs and symptoms of PsA***: ***Proportion of subjects achieving PASI75 response at Month 3, Month 6, and Month 12***

Tofacitinib 5 mg BD significantly improved the PASI75 response rate compared to placebo at Month 3 (p<0.001), which was comparable to adalimumab ([redacted]) and was sustained through Month 6 and Month 12. The PASI75 response rates for OPAL Broaden are summarised in

Table 14.

Table 14: PASI75 response rates for OPAL Broaden (FAS)

Outcome	TOF 5mg	ADA	PBO*
PASI75 response rate, n/N (%)			
Month 3	35/82 (43)	30/77 (39)	12/82 (15)
Difference from placebo	28.1	24.3	--
95% CI for difference	14.9, 41.2	11.0, 37.6	--
p-value	<0.001	[redacted]†	--
Month 6	[redacted]	[redacted]	--
Month 12	46/82 (56)	43/77 (56)	--

Abbreviations: ADA, adalimumab; FAS, full analysis set; n, number of responders; N*, number of subjects in FAS; N, number of subjects in FAS with baseline BSA≥3% and baseline PASI>0; PASI, Psoriatic Area and Severity Index; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; TOF, tofacitinib
*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period
†nominal p-value

[redacted]

- ***Other secondary measures of disease activity (MDA), signs and symptoms of PsA (LEI, SPARCC, and DSS) and quality of life (SF-36, FACIT-F, DLQI, and ISI) at Month 3, Month 6, and Month 12***

The MDA response rate at Month 3 in the tofacitinib 5 mg BD group was 26% vs 7% in the placebo group ([redacted]), which was numerically similar to adalimumab (25%, [redacted]) and was sustained up to Month 12 (see **Appendix M** for further detail).

Tofacitinib 5 mg BD was numerically superior to placebo across measures of enthesitis (LEI, SPARCC) and dactylitis (DSS) at Month 3, with responses sustained up to Month 6 and Month 12 (see **Appendix M** for further detail).

Tofacitinib 5 mg BD was numerically (SF-36 PF, FACIT-F total score) and significantly (DLQI, ISI) superior to placebo at Month 3, with responses sustained up to Month 6 and Month 12 (see **Appendix M** for further detail).

B.2.6.2 Summary of outcome measures from OPAL Beyond (TNFi-IR)

Main efficacy outcomes

- ***Signs and symptoms of PsA: Proportion of subjects achieving ACR20 at Month 3 (Trial primary outcome)***

A significantly greater percentage of subjects in the tofacitinib 5 mg BD group (50%) achieved an ACR20 response at Month 3 compared with subjects in the placebo group (24%; p<0.001); the difference from placebo was 26.0% ([redacted] 95% CI: 14.7, 37.2) (

Table 15). As shown by the secondary/other endpoints (see **Section B.2.6.2.2**) the ACR20 response rate in the tofacitinib 5 mg BD group was sustained at Month 6; a rapid response in the form of a significantly higher ACR20 response rate in the tofacitinib 5 mg BD group compared to placebo was seen as early as Week 2 ([redacted] p=0.005).

- ***Physical functioning: Mean change from baseline in HAQ-DI score at Month 3 (Trial primary outcome)***

The mean change from baseline in HAQ-DI score at Month 3 was significantly greater in the tofacitinib 5 mg BD group (–0.39) compared with the placebo group (–0.14; p<0.001); the difference from placebo was -0.3 ([redacted] 95% CI: -0.4, -0.1) (

Table 15). As shown by the secondary/other endpoints (see **Section B.2.6.2.3**), this change in HAQ-DI score in the tofacitinib 5 mg BD group observed at Month 3 was sustained at Month 6.

In a supportive analysis, a decrease (indicating clinical improvement) in the HAQ-DI score that was greater than or equal to the minimum clinically important difference (a decrease from baseline ≥0.35) occurred in 50.0% of the subjects in the tofacitinib 5 mg BD group, as compared with 27.6% of the subjects in the placebo group at Month 3 ([redacted]); the difference from placebo was 22.4% ([redacted]; 95%CI: 10.2, 34.6).

Table 15: Summary of primary efficacy results for OPAL Beyond (FAS)

Outcome	TOF 5mg	PBO
ACR20 response rate at Month 3		
N	131	131
Response rate, n (%)	65 (50)	31 (24)
Difference from placebo, %	26.0	--
95% CI for difference	14.7, 37.2	--
p-value†	<0.001	--
HAQ-DI score at Month 3		
N*	124	117
LS mean change from baseline	-0.39	-0.14
LS mean difference from placebo	-0.3	--
95% CI for difference	-0.4, -0.1	--
p-value†	<0.001	--

Abbreviations: ACR, American College of Rheumatology; CI, confidence interval; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-disability index; LS, least squares; N, number of subjects in FAS; N*, number of subjects evaluable at Month 3; n, number of responders; PBO, placebo; TOF, tofacitinib.
†p-value is subject to the step-down approach.

[redacted]

Secondary and other efficacy outcomes

- ***Signs and symptoms of PsA***: ***Proportion of subjects achieving ACR20, ACR50, and ACR70 response at Week 2 (ACR20 only), Month 3 (excluding ACR20), and Month 6***

A rapid response to tofacitinib 5 mg BD was observed; after 2 weeks, the ACR20 response rate in the tofacitinib 5 mg BD group was significantly improved compared with the placebo group (p=0.005).

At Month 3, tofacitinib 5 mg BD significantly improved the ACR50 response rate compared with the placebo group (p=0.003) and numerically improved the ACR70 response rate compared to placebo ([redacted]).

ACR20, ACR50, and ACR70 response rates were sustained up to Month 6 and are summarised in **Table 16**.

Table 16: ACR20, ACR50, and ACR70 response rates for OPAL Beyond (FAS)

Outcome	TOF 5mg	PBO*
ACR20 response rate, n/N (%)		
Week 2	[redacted]	[redacted]
Difference from placebo	[redacted]	--
95% CI for difference	[redacted]	--
p-value	0.005	--
Month 6	78/131 (60)	--
ACR50 response rate, n/N (%)		
Month 3	39/131 (30)	19/131 (15)
Difference from placebo	15.3	--
95% CI for difference	5.4, 25.2	--
p-value	0.003	--
Month 6	50/131 (38)	--
ACR70 response rate, n/N (%)		
Month 3	22/131 (17)	13/131 (10)
Difference from placebo	6.9	--
95% CI for difference	-1.3, 15.1	--
p-value	[redacted]	--
Month 6	28/131 (21)	--

Abbreviations: ACR, American College of Rheumatology; FAS, full analysis set; mg, milligram; N, number of subjects in FAS; n, number of responders; PBO, placebo; TOF, tofacitinib
[†]nominal p-value; [redacted]*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

- ***Signs and symptoms of PsA***: ***Change from baseline across ACR criteria components at Month 3 and Month 6***

Tofacitinib 5 mg BD was significantly superior to placebo across ACR Tender/Painful Joint Count, Swollen Joint Count, C-Reactive Protein, Patient's Assessment of Arthritis Pain, Patient's Global Assessment of Arthritis, and Physician's Global Assessment of Arthritis criteria at Month 3. These response rates were sustained up to Month 6 (see **Appendix M** for further detail).

- ***Physical functioning: Change from baseline in HAQ-DI scores at Month 6***

The significantly greater decrease (indicating clinical improvement) from baseline in HAQ-DI score in the tofacitinib 5 mg BD group (discussed in **Section B.2.6.2.1**) was sustained up to Month 6 (**Table 17**).

Table 17: Change in HAQ-DI from baseline for OPAL Beyond (FAS)

Outcome	TOF 5mg	PBO*
HAQ-DI score, LS Mean (SE) [n/N]		
Month 6	-0.44 (0.05) [122/131]	--

Abbreviations: FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; LS, least squares; N, total number of unique subjects in the longitudinal model; n, number of subjects evaluable at each visit; PBO, placebo; SE, standard error; TOF, tofacitinib
*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

- ***Signs and symptoms of PsA***: ***Proportion of subjects achieving PsARC response at Month 3 and Month 6***

Tofacitinib 5 mg BD significantly improved the PsARC response rate at Month 3 compared to placebo ([redacted]), which was sustained up to Month 6. PsARC response rates at Month 3 and Month 6 for OPAL Beyond are summarised in

Table 19.

Table 18: PsARC response rates for OPAL Beyond (FAS)

Outcome	TOF 5mg	PBO*
PsARC response rate, n/N* (%)		
Month 3	77/131 (58.8)	38/131 (29.0)
Difference from placebo	29.8	--
95% CI for difference	18.3, 41.2	--
p-value	[redacted]	--
Month 6	77/131 (58.8)	--

Abbreviations: FAS, full analysis set; n, number of responders; N*, number of subjects in FAS; mg, milligram; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; TOF, tofacitinib
*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

- ***Signs and symptoms of PsA***: ***Proportion of subjects achieving PASI75 response at Month 3 and Month 6***

Tofacitinib 5 mg BD numerically improved the PASI75 response rate at Month 3 compared to placebo ([redacted]), which was at least sustained through Month 6. PASI75 response rates at Month 3 and Month 6 for OPAL Beyond are summarised in

Table 19.

Table 19: PASI75 and PsARC response rates for OPAL Beyond (FAS)

Outcome	TOF 5mg	PBO*
PASI75 response rate, n/N (%)		
Month 3	17/80 (21)	12/86 (14)
Difference from placebo	7.3	--
95% CI for difference	-4.3, 18.9	--
p-value	[redacted]	--
Month 6	27/80 (34)	--

Abbreviations: FAS, full analysis set; n, number of responders; N*, number of subjects in FAS; N, number of subjects in FAS with baseline BSA≥3% and baseline PASI>0; mg, milligram; PASI, Psoriatic Area and Severity Index; PBO, placebo; TOF, tofacitinib
*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

[redacted]

- ***Other secondary measures of disease activity (MDA), signs and symptoms of PsA (LEI, SPARCC, and DSS) and quality of life (SF-36, FACIT-F, DLQI, and ISI) at Month 3 and Month 6***

The MDA response rate at Month 3 in the tofacitinib 5 mg BD group was 23% vs 15% in the placebo group ([redacted]) and was sustained up to Month 6 (see **Appendix M** for further detail).

Tofacitinib 5 mg BD was significantly superior than placebo with regard to SPARCC and numerically superior across LEI and DSS at Month 3, with responses sustained up to Month 6 (see **Appendix M** for further detail).

Tofacitinib 5 mg BD was numerically (SF-36 PF, FACIT-F total score) and significantly (DLQI, ISI) superior to placebo at Month 3, with responses sustained up to Month 6 (see **Appendix M** for further detail).

B.2.7 Subgroup analysis

The OPAL Broaden and OPAL Beyond trials present data in csDMARD-IR (TNFi-naïve) and TNFi-IR patients, respectively. Data on patient demographics in these two respective populations are presented in **Section B.2.3.3**. Data for the primary and secondary outcomes are presented in **Section B.2.6**; post-hoc analyses data for

inclusion in the economic model in the UK NICE submission are presented in **Sections M.1.1.3** (OPAL Broaden) and **M.1.2.3** (OPAL Beyond). Data for the trials identified through the systematic literature review are presented in **Appendix E**.

B.2.8 Non-randomised and non-controlled clinical evidence

B.2.8.1 List of relevant non-randomised and non-controlled evidence

The long-term safety and efficacy of tofacitinib was evaluated in one study (**Table 20**). Study A3921092 (OPAL Balance) was a Phase III, open-label extension study involving long-term follow-up of patients who had previously participated in randomised Phase III tofacitinib trials (OPAL Broaden and OPAL Beyond). OPAL Balance is ongoing.

Table 20: Relevant non-RCT study: OPAL Balance

Study number	A3921092 (OPAL Balance; study ongoing)
Objective	To assess the long-term safety, tolerability, and efficacy of TOF
Population	Subjects with active PsA qualifying from Phase III TOF RCTs (OPAL Broaden and OPAL Beyond)
Intervention(s)	TOF 5 mg BD and TOF 10 mg BD Upon entry into the LTE study, patients were to receive TOF 5 mg BD for one month: After one month, doses could be increased to 10 mg BD for efficacy reasons at the investigator's discretion; Doses could be reduced back to 5 mg BD for safety reasons at the investigator's discretion
Comparator(s)	None

Outcomes specified in the decision problem	• Adverse effects of treatment
	• Disease activity
	  ○ ACR20, ACR50, ACR70, ACR response criteria components, PASI75
	• Functional capacity
	  ○ HAQ-DI
	• Periarticular disease (for example enthesitis, tendonitis, dactylitis)
	  ○ DSS, LEI
	• Health-related quality of life (data are not yet available)
	• Mortality

Primary study reference	Nash et al, 2017 (92, 93); Pfizer data on file
Justification for inclusion	Provides long-term data on the safety and efficacy of TOF

Abbreviations: BD, twice daily; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; LTE, long term extension; mg, milligram; PsA, psoriatic arthritis; RCT, randomised controlled trial; TNFi, tumour necrosis factor inhibitor; TOF, tofacitinib

B.2.8.2 List of non-RCTs excluded from further discussion

No non-RCTs of tofacitinib in the relevant patient populations were excluded from further discussion.

B.2.8.3 Summary of methodology of the relevant non-randomised and non-controlled evidence

A summary of the methodology of the LTE study, OPAL Balance, is presented in **Appendix M**.

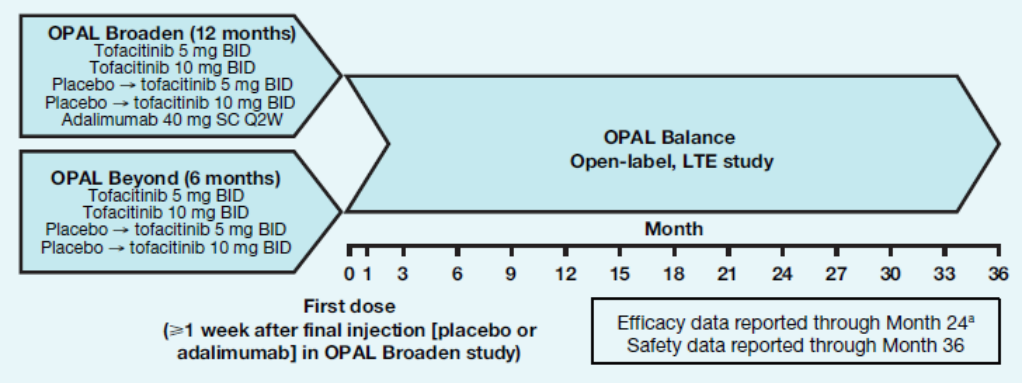
B.2.8.4 Statistical analysis of the non-randomised and non-controlled evidence

A summary of statistical analyses of the LTE study, OPAL Balance, is presented in **Appendix M**.

B.2.8.5 Participant flow in the relevant non-randomised studies

See **Section D.1.2.2** (**Appendix D**), for details of the numbers of participants eligible to enter the OPAL Balance trial and **Appendix M** for baseline characteristics of the participants.

Figure 5: OPAL Balance study design



[a]Sample sizes were too small beyond this point for meaningful analysis
Abbreviations: BID, twice daily; LTE, long-term extension; Q2W, every other week; SC, subcutaneous
Source: Nash 2017(92, 93)

B.2.8.6 Quality assessment of the relevant non-randomised and non-controlled evidence.

Quality assessment of the OPAL Balance study is presented in **Appendix M**; however, it is only preliminary as the study is ongoing.

B.2.8.7 Clinical effectiveness results of the relevant non-randomised and non-controlled evidence

B.2.8.7.1 Long-term effect of tofacitinib on signs and symptoms of the disease, physical functioning, enthesitis and dactylitis

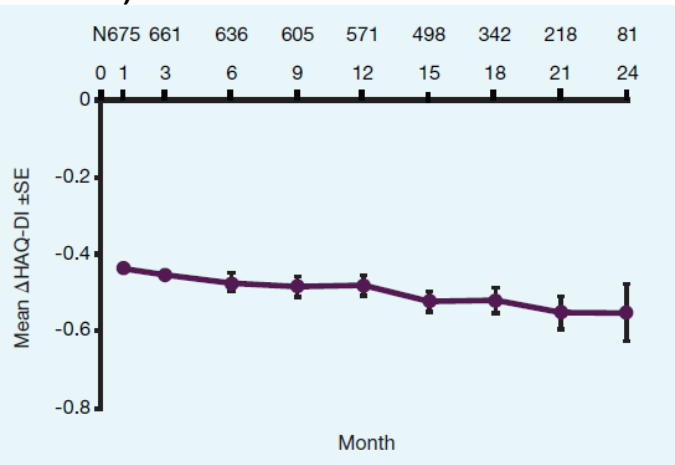
The results for the change from baseline in ACR20 and HAQ-DI up to Month 24 (interim data analysis up to 25 January 2017) in the pooled tofacitinib group (5 mg and 10 mg BD doses) are shown in **Table 21** and **Figure 6**. These results demonstrated that improvements in signs and symptoms of the disease and physical functioning achieved by tofacitinib treatment are generally sustained long term (92, 93). Similar improvements were demonstrated for other measures of signs and symptoms of the disease (ACR50, ACR70, and PASI75), as well as measures of enthesitis (LEI), dactylitis (DSS), and pain.

Table 21: Summary of efficacy through to Month 24 in OPAL Balance

Outcome	TOF (all patients, N=686)			
Timepoint	**Month 6**	**Month 12**	**Month 18**	**Month 24**
ACR20, n/N1 (%)	448/634 (70.7)	422/570 (74.0)	264/341 (77.4)	55/82 (67.1)
ACR50, n/N1 (%)	298/633 (47.1)	284/570 (49.8)	183/342 (53.5)	41/82 (50.0)
ACR70, n/N1 (%)	194/636 (30.5)	183/570 (32.1)	123/341 (36.1)	22/82 (26.8)
∆HAQ-DI, mean (SD) [N]	-0.5 (0.6) [636]	-0.5 (0.6) [571]	-0.5 (0.6) [342]	-0.6 (0.7) [81]
PASI75 response rate, n/N1 (%)	263/433 (60.7)	250/396 (63.1)	148/242 (61.2)	40/58 (69.0)
∆LEI, mean (SD) [N1]	-1.7 (1.8) [418]	-1.7 (1.8) [371]	-1.8 (1.8) [220]	-1.8 (1.9) [56]
∆DSS, mean (SD) [N1]	-7.2 (7.9) [336]	-7.7 (7.8) [300]	-7.1 (7.2) [186]	-7.3 (6.6) [48]
∆Pain, mean (SD) [N1]	-26.0 (28.0) [634]	-26.8 (27.6) [570]	-29.4 (29.4) [342]	-32.6 (30.2) [81]

Abbreviations: Δ, change from baseline; ACR, American College of Rheumatology; ACR20/50/70, ACR20%/50%/70% response rate; BSA, body surface area; DSS, Dactylitis Severity Score; HAQ-DI, Health Assessment Questionnaire-Disability Index; LEI, Leeds Enthesitis Index; n, number of responders; N, number of patients in full analysis set; N1, number of evaluable patients at a visit; PASI, Psoriasis Area and Severity Index; PASI75, Psoriasis Area and Severity Index 75% improvement; SD, standard deviation
Source: Nash 2017(92, 93)

Figure 6: Change in HAQ-DI score from baseline up to Month 24 (25 January 2017 data cut) - FAS



Abbreviations: HAQ-DI, Health Assessment Questionnaire-Disability Index; M, mean; SE, standard error
Source: Nash 2017(92, 93)

[redacted]

Figure 7 [redacted]

Figure 7: Change in HAQ-DI score from baseline up to Month 27 (4 April 2016 data cut) – FAS and constant tofacitinib 5 mg BD subjects only

[redacted]

B.2.9 Meta-analysis

Direct meta-analyses for tofacitinib (in combination with a csDMARD) versus placebo are presented in forest plots in **Appendix E**. As there was only one trial per population (OPAL Broaden for bDMARD-naïve and OPAL Beyond for bDMARD-experienced, see **Section B.2.10** below), the results are the same as those reported above in **Section B.2.6.**

B.2.10 Indirect and mixed treatment comparisons

Indirect comparisons between tofacitinib (in combination with a csDMARD) and other treatments of interest were also undertaken to examine the relative effects of tofacitinib in relation to those treatments and are presented in **Appendix E**.

In the absence of head-to-head comparisons, network meta-analyses (NMA) were performed, using RCTs identified in the SLR (see **Appendix D** for SLR methodology),

to estimate the efficacy of tofacitinib (in combination with a csDMARD) relative to other treatments for PsA.

For consistency with the approach taken by the Assessment Group (AG) for TA445, data were subdivided into two populations: bDMARD-naïve and bDMARD-experienced, (94) and these informed the sub-populations specified in the NICE scope (Table 1):

- Sub-populations 2 and 4 were informed by the bDMARD-naïve evidence synthesis with data for tofacitinib from OPAL Broaden (csDMARD-IR and TNFi-naïve), and

- Sub-population 3 was informed by the bDMARD-experienced evidence synthesis with data for tofacitinib from OPAL Beyond (TNFi-IR).

Note that trials identified in the SLR were conducted across an 18-year period and a variation in placebo response across these trials was evident for some important outcomes, with larger placebo response rates seen in more recent trials (94). A variation was also noted across trials regarding patients' previous use of bDMARD therapy, with bDMARD-experienced populations recruited only in the more recent trials. Furthermore, there were insufficient data available from all trials to subdivide patients into those who had failed one non-biological DMARD (csDMARD) and those who had failed two non-biological DMARDs, as per the NICE scope. Therefore, NMAs in this evidence submission were performed on the bDMARD-naïve and bDMARD-experienced populations separately (see **Section B.2.10** above). The included models adjust for and explore the different rates of placebo response across trials.

B.2.10.1 Summary of the trials used to carry out the indirect or mixed treatment comparisons (NMAs)

Studies were identified from the SLR using the scope set out by NICE for this appraisal (see **Appendix D**). The SLR yielded 21 studies for inclusion in the NMA. One abatacept IV study was not included (Mease et al., 2011 (95)) because it was not clear whether the population was bDMARD-naïve. Another study (McInnes et al., 2014 (96)) was

excluded as the active treatment arm (an IV preparation of secukinumab) was not licensed for PsA. Therefore, 19 studies were taken forward into the NMA evidence network for the entire population.

Where possible, data were extracted from the primary publications; if the data were not available from a primary publication, they were extracted from the TA445 AG report, which was a secondary source (94). Redacted data from the AG report were requested from NICE and the respective manufacturers but had not been made available at the time of submission. Studies informing the NMA are summarised below in **Table 22**.

Table 22: Summary of the trials used to carry out the indirect or mixed treatment comparison (n=21)

Main Author, Year [TRIAL ID]; sponsor	Previous treatment(s)	Number of patients: screened/ randomised/ treated / completed	Study arms (n, ITT)	Concomitant DMARD treatment during trial
Mease et al., 2017 [ASTRAEA]	≥1 DMARD IR† TNFi IR 60%	NR/424/NR/382	PBO (211); ABA SC 125 mg QW (213);	+ 1 csDMARD (unclear%)
Mease et al., 2011	≥1 DMARD IR† (TNFi IR =unclear)	NR/170/NR/147	PBO (42); ABA IV 3 mg/kg Q4W (45); ABA IV 10 mg/kg Q4W (40)+ ABA IV 2 x 30 mg/kg then10 mg/kg (43).	+ 1 MTX (60%)
Genovese et al., 2007	≥1 csDMARD IR	NR/100/NR/96	PBO (49) ADA SC 40 mg Q2W (51)	+ 1 MTX (66%)
Mease et al., 2005 [ADEPT]	csDMARD IR +/- NSAID	NR/313/NR/289	PBO (162) ADA SC 40 mg Q2W (151)	+ 1 MTX (50%)
Cutolo et al., 2016 [PALACE 2]	1 or 2 DMARD IR† (TNFi IR ≤ 10%)	NR/484/NR/361	PBO up to 16 wks (159); APR 20 mg BD oral (163); APR 30 mg BD oral (162)	+ 1 csDMARD (79%)
Edwards et al., 2016 [PALACE 3]	≥1 DMARD IR† (TNFi IR ≤ 10%)	NR/505/NR/438	PBO up to 16 wks (159); APR 20 mg BD oral (163); APR 30 mg BD oral (162)	+ 1 csDMARD (unclear%)
Kavanaugh et al., 2014 [PALACE 1]	csDMARD IR +/- bDMARD IR (TNFi-IR ≤ 10%)	NR/504/NR/444	PBO (168) APR 20 mg BD oral (168); APR 30 mg BD oral (168)	+ 1 csDMARD (70%)
Mease et al., 2014 [RAPID-PsA]	≥1 DMARD IR† primary TNFi IR excluded*	NR/409/NR/309	PBO up to 12 wks (136); CZP SC 200 mg Q2W (138); CZP SC 400 mg Q4W (135)	+ 1 MTX (64%)
Mease et al., 2004	NSAID +/- csDMARD IR	NR/205/NR/165	PBO (104) ETN 25 mg BIW (101)	+ 1 MTX (42%)
Mease et al., 2000	NSAID +/- csDMARD IR	NR/60/NR/56	PBO (30) ETN 25 mg BIW (30)	+ 1 MTX (47%)
Kavanaugh et al., 2009 [GO-REVEAL]	csDMARD IR +/- NSAID	NR/405/405/380	PBO (113) GOL 50 mg (146) GOL 100 mg (146)	+ 1 MTX (49%)
Antoni et al., 2005 [IMPACT]	≥1 csDMARD IR	NR/104/NR/99	PBO up to 16 wks (52) IFX IV 5 mg/kg (wks 0, 2, 6 & 14) (52)	+ 1 MTX (55%)
Antoni et al., 2005 [IMPACT 2]	≥1 csDMARD IR	NR/200/NR/134	PBO (100) IFX IV 5 mg/kg (100)	+ 1 csDMARD (71%)

Main Author, Year [TRIAL ID]; sponsor	Previous treatment(s)	Number of patients: screened/ randomised/ treated / completed	Study arms (n, ITT)	Concomitant DMARD treatment during trial
Mease et al. 2017 [SPIRIT P1]	NSAID +/- DMARD IR	NR/417/NR/382	PBO (106) ADA SC 40 mg Q2W (101) IXE SC 80 mg Q2W (103) IXE SC 80 mg Q4W (107)	+ 1 csDMARD (64%)
Nash et al., 2017 [SPIRIT-P2]	≥1 TNFi IR + ≥1 csDMARD	NR/363/NR/314	PBO (118) IXE SC 80 mg Q2W (123) IXE SC 80 mg Q4W (122)	+ 1 csDMARD (50%)
McInnes 2015 [FUTURE 2]	csDMARD IR +/- bDMARD IR (up to 3)	NR/397/NR/335	PBO (98) SEC 75 mg (99) SEC 150 mg (100) SEC 300 mg (100)	+ 1 MTX (47%)
McInnes et al., 2014‡	≥1 DMARD IR†	NR/42/NR/35	PBO (14) SEC IV 10 mg /kg (wk 0, 6) (28)	+ 1 csDMARD (64%)
Gladman et al., 2017 [OPAL Beyond]; Pfizer	≥1 TNFi IR	546/395/394/345	PBO →TOF 5 mg BD oral after 3 mths (66); PBO →TOF 10 mg BD oral after 3 mths (65); TOF 5 mg BD oral (131); TOF 10 mg BD oral (132).	+ 1 csDMARD (100%)
Mease et al., 2017 [OPAL Broaden]; Pfizer	≥1 csDMARD IR	611/422/422/373	PBO →TOF 5 mg BD oral after 3 mths (52); PBO →TOF 10 mg BD oral after 3 mths (53); TOF 5 mg BD oral (107); TOF 10 mg BD oral (104); ADA SC 40 mg Q2W (106).	+ 1 csDMARD (100%)
McInnes et al., 2013 [PSUMMIT 1]	≥1 csDMARD IR	NR/615/NR/NR	PBO up to 16 wks (205); USK SC 45 mg (wks 0, 4, 16) (204); USK SC 90 mg (wks 0, 4, 16) (206)	+ 1 MTX (49%)
Ritchlin et al., 2014 [PSUMMIT2]	csDMARD IR +/- bDMARD IR	NR/312/NR/NR	PBO (104) USK SC 45 mg (103); USK SC 90 mg (105)	+ 1 csDMARD (50%)

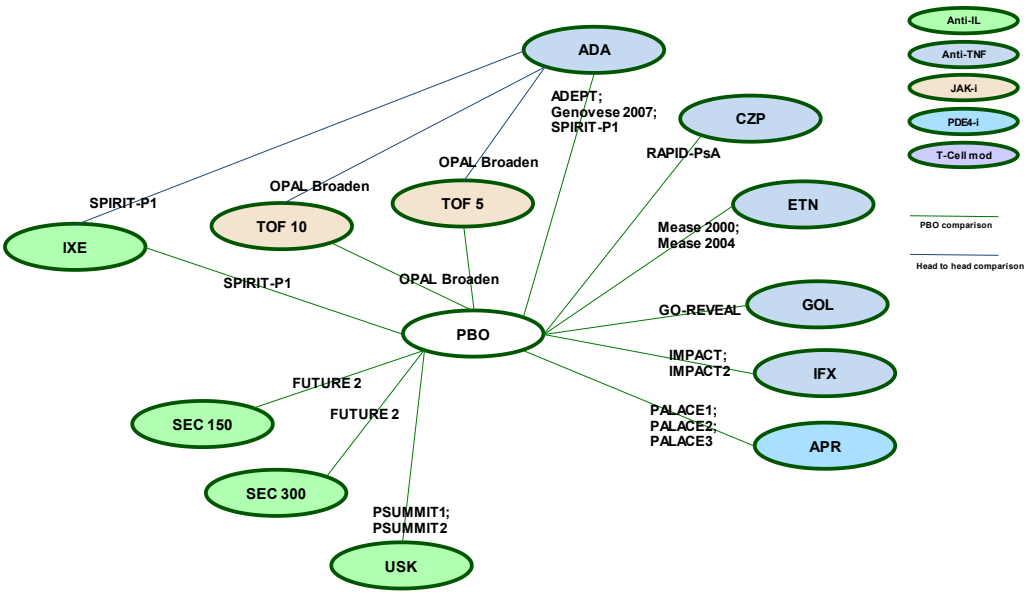
Treatment arms underlined were not included in the analysis (are not of interest, or not a licensed dose and are not needed to connect the networks);
† csDMARD and/or bDMARD;
‡ study dropped out of the NMA because secukinumab IV is not licensed as a treatment in PsA;
+ licensed dose for ABA IV in PsA for a 60-100kg adult ~ 750 mg wk 0, 2, 4, then monthly which is approximating 10mg/kg.
* primary non-responders excluded but study included secondary non-responders to TNFi;
ABA, abatacept; ADA, adalimumab; APR, apremilast; bDMARD, biologic disease modifying anti-rheumatic drugs; BD, twice daily; csDMARD, conventional synthetic disease modifying anti-rheumatic drugs; CZP, certolizumab pegol; DMARD, disease modifying anti-rheumatic drugs; IFX, infliximab; IR, inadequate response; IV, intravenous; IXE, ixekizumab ; MTX; methotrexate; NSAID, non-steroidal anti-inflammatory drug; PBO, placebo; Q2W, every 2 weeks; Q3W, every three weeks; Q4W, every 4 weeks; QW, once weekly; SC, subcutaneous; SEC, secukinumab; TNFi, tumour necrosis factor inhibitor; TOF, tofacitinib; USK, ustekinumab

B.2.10.2 Evidence networks

B.2.10.2.1 Summary of bDMARD-naïve evidence network

Sixteen studies reported data for at least one of the key efficacy outcomes for this population. All studies were connected via a placebo control arm. See **Figure 8** below for the general network diagram and **Appendix E** for the network diagram for each outcome. Ixekizumab was not NICE approved in the UK for PsA at the time of this review. However, a TA was in progress (ID1194) and the phase III study SPIRIT P1 had been published (97). This study was therefore included in the network.

Figure 8: General network diagram for all studies with bDMARD-naïve population data

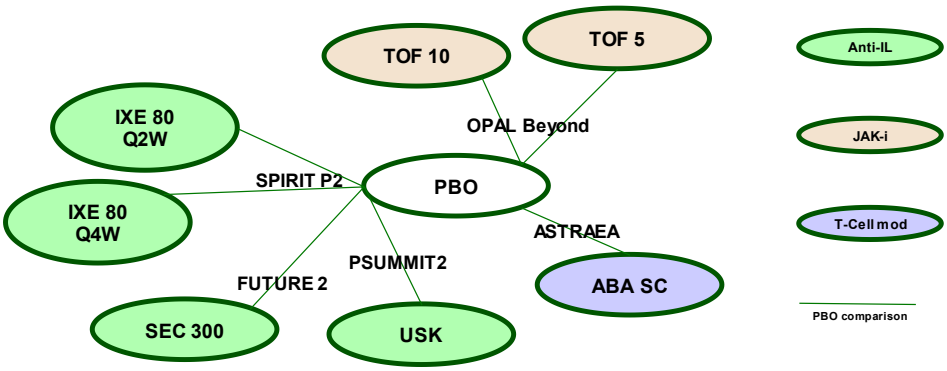


B.2.10.2.2 Summary of bDMARD-experienced evidence network

Five studies reported at least one of the key efficacy outcomes for this population and were connected via a placebo control arm. See **Figure 9** below for the general network diagram and **Appendix E** for the network diagram for each outcome. Abatacept and ixekizumab were not NICE-approved in the UK for PsA at the time of this review; however, TAs in PsA were in progress (ID993 and 1194, respectively) and key Phase III clinical trial data (ASTRAEA for abatacept, and SPIRIT P2 for ixekizumab) had been

published; therefore, these trials were included in the network. As in TA445, RAPID-PsA (the certolizumab pegol trial) was not included in the bDMARD-experienced network, because the population was not comparable with the other bDMARD-experienced trials (94).

Figure 9: General network diagram for all studies with bDMARD-experienced population data



B.2.10.3 Network meta-analysis methodology

The general approach for this meta-analysis was as per the NICE Decision Support Unit (DSU) recommendations (98-101). Specifically, we adopted an approach that was similar to the one used by the TA445 AG (94). A summary of the methodology is presented below, with full details presented in **Appendix D**.

B.2.10.3.1 Direct meta-analysis with Bucher Indirect Comparisons (IC):

Direct comparisons of all drugs versus placebo were calculated using frequentist pairwise direct meta-analysis in Stata MP v14.2 (102, 103). Indirect comparisons of tofacitinib 5 mg BD versus all drugs were calculated from the direct comparisons above using the Bucher method (104, 105). Details of the associated methods are presented in **Appendix D**.

B.2.10.3.2 Network Meta-Analysis:

Bayesian NMA methodology as recommended by NICE in DSU TSD 2 (98) was conducted to estimate comparisons of all treatments simultaneously. Data were fitted to generalised linear models via Bayesian Markov Chain Monte Carlo methods using WinBUGs (106) and published code (**Table D19** in **Appendix D**). The burn-in was 100,000 to ensure convergence, with estimates drawn from three chains of 10,000 samples. A plot of the sampling history and posterior distributions can be provided for selected endpoints as evidence of adequate convergence upon request. There were no issues with convergence, unless otherwise stated.

The mean residual deviance (total residual deviance divided by number of data points) and the deviance information criteria (DIC) were provided as estimates of how well the predicted values fitted the observed dataset.

Fixed effect (FE) models were tested for all outcomes. Random effect (RE) analyses were conducted where feasible, using a uniform (i.e., uninformative) prior for the between-studies standard deviation (SD) (Hasselblad (107) and Gelman (108)) and assuming that heterogeneity is the same across all comparisons. Relative treatment effects were expressed as (log) odds ratio (OR) for dichotomous outcomes; treatment effect relative to ‘no response’ for the reference treatment was expressed on the probit scale for the categorical outcomes (PASI and ACR) and weighted mean differences (WMD) for the continuous outcomes (HAQ-DI). The generalised linear models (GLMs) and link functions for each outcome are presented in

Table 23 below.

Absolute effects (T[k]) were calculated as recommended in TSD2 (98), using the relative effects (d[k]) calculated in the main part of the WinBUGs NMA and the baseline effect (A) for the reference treatment, which in this analysis was placebo.

- For continuous outcomes: T[k] = A+d[k]
- For dichotomous outcomes: Logit(T[k]) = A+d[k] (98)
- For categorical outcomes on the probit scale: T[k,cut-off]=1-phi(A+d[k]+z[cut-off]) (98)

In addition to the relative and absolute treatment effects, the NMA calculated treatment rankings, such that the best treatment was ranked 1, and worst treatment ranked N (N = number of treatments). The rankings across all the samples were pooled to calculate the probability of achieving each rank. Surface Under the Cumulative Ranking Curves (SUCRA) were provided to express the percentage of efficacy for each treatment compared to an ideal treatment ranked first without uncertainty (see **Appendix E**) (109). For the key models, the probability of each rank has been summarised in a rankogram, following the presentation of the model results (see **Appendix E**).

Covariate and class-level analyses were conducted using the general methodology recommended in DSU TSD3 (110), with adaptations based on the analysis in TA445 (94). NMA model details are presented in

Table 23 below. Class-level models were run to compare with the TA445 results.

For the HAQ-DI conditional on PsARC response status analyses, an alternative model to the Rodgers (111) and Cummins (112) code was also analysed; this model adjusts the trial variance to account for multi-arm studies. In this alternative model, the PsARC responders subgroup data were analysed separately from the PsARC non-responders subgroup data.

In the TA445 short-term efficacy NMAs, the rate of placebo response was identified as a source of heterogeneity for some outcomes. For example, for PsARC response, higher placebo rates were associated with lower relative effectiveness estimates. Placebo-adjusted models were therefore explored to mitigate the impact of potential population-level differences (e.g., different severity of disease, different duration of disease, mixed background treatment) on estimates of treatment effect.

Table 23: NMA Model Assumptions (including placebo-adjusted and class-level effect NMA models)

Endpoints GLM; link function	ID	Exchangeable treatment effects?	Classes†	PBO-adjusted
PsARC **Binomial; logit**	***A***	No, independent treatment effects	No class effect	No
	B	No, independent treatment effects	No class effect	Yes
	C	Yes, exchangeable within class 1	TOF, APR, TNFi, Anti-IL	Yes
	D	Yes, exchangeable within class 2	TOF, APR, bDMARDs	Yes
PASI 50/75/90 **Multinomial; probit**	***E***	No, independent treatment effects	No class effect	No
	F	No, independent treatment effects	No class effect	Yes
HAQ-DI | PsARC **Normal; identity**	***G***	No, independent treatment effects; effects are added to PBO non-responders (Rodgers 2011 (111) and Cummins 2011 (112))	No class effect	No
	H	Yes, exchangeable within class 1; effects are added to PBO non-responders (Rodgers 2011 (111) and Cummins 2011 (112))	TOF, APR, TNFi, Anti-IL	No
ACR 20/50/70 **Multinomial; probit**	***E***	No, independent treatment effects	No class effect	No
	F	No, independent treatment effects	No class effect	Yes
	I	Yes, exchangeable within class 1	TOF, APR, TNFi, Anti-IL	Yes
	J	Yes, exchangeable within class 2	TOF, APR, bDMARDs	Yes
HAQ-DI **Normal; identity**	***K***	No, independent treatment effects	No class effect	No

Models highlighted in grey were not used in the economic analysis
†The TOF class models accounted for tofacitinib 5 mg and 10 mg doses.
Abbreviations: ACR, American College of Rheumatology; Anti-IL Anti-interleukin; APR, apremilast; bDMARD, biologic disease-modifying antirheumatic drug; GLM, generalised linear model; HAQ-DI, Health Assessment Questionnaire Disability Index; PASI, Psoriatic Area and Severity Item; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; TNFi, tumour necrosis factor inhibitor; TOF, tofacitinib

Table 24: Overview of models selected

Endpoints GLM; link function	bDMARD-naïve	bDMARD-experienced
PsARC **Binomial; logit**	A1 FE, A2 RE (pessimistic); A1* FE, A2* RE (optimistic) B1 FE, B2 RE (base case)	A1 (base case)
PASI 50/75/90 **Multinomial; probit**	E1 FE (optimistic), E2 RE (pessimistic; base case)	E1 FE with 24-wk data (optimistic), E1 FE without 24-wk data (pessimistic; base case)
HAQ-DI | PsARC **Normal; identity**	G FE (pessimistic); K1 FE (optimistic), K2 RE (base case)	G FE (optimistic); K1 FE (pessimistic; base case)

ACR 20/50/70 Multinomial; probit	E1 FE (optimistic), E2 RE (pessimistic; base case) F FE	E1 FE with 24-wk data (pessimistic), E1 FE without 24-wk data (optimistic; base case)

Abbreviations: ACR, American College of Rheumatology; bDMARD, biologic disease-modifying antirheumatic drug FE, fixed-effects; HAQ-DI, Health Assessment Questionnaire Disability Index; PASI, Psoriatic Area and Severity Item; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; RE, random effects

* for the alternative network analysis, the PBO arm from the OPAL Broaden trial was excluded on the basis that this arm had a poor fit in all of the previous models (see Appendix E for more detail). This was also considered a reasonable approach (but with limitations) by a clinical expert.

B.2.10.4 Network meta-analysis results

Base case models for use in the assessment of clinical and cost-effectiveness were selected primarily on the basis of 'best' statistical model fit (goodness of fit) after considering the average residual deviance and/or, where data sets were analogous, the deviance information criteria (DIC). Clinical expert advice was also considered in model selection (see **Section D.2.3** in **Appendix D** for discussion). There was no evidence to support class-level models, and placebo-adjusted models were only found to be justified for PsARC. Clinical expert advice suggested that class effect models were not likely to be appropriate, particularly for anti-IL therapies and bDMARDs as a class, due to differences in response profiles (see **Section D.2.3** in **Appendix D** for discussion).

To assess sensitivity of effectiveness estimates, and for scenario analyses in section B.3, optimistic models were selected based on results with the "best" data for tofacitinib 5 mg BD (that is, where tofacitinib 5 mg BD had the highest probability of response); pessimistic models were selected based on results with the "worst" data for tofacitinib 5 mg BD (i.e., lowest probability of response).

Clinical expert opinion was sought to inform selection of the optimistic model for PsARC, which excluded the placebo arm from OPAL Broaden (due to elevated placebo response and poor model fit in terms of residual deviance); the clinical opinion stated that this was a logical choice based on clinical experience (see **Section D.2.3** in **Appendix D** for discussion). Choice of RE versus FE models was informed by other measures of heterogeneity. For example, for PsARC, the [redacted] and consideration of the reduced between-trials SD and narrower credible interval were used in selecting the base case PsARC model (selecting Model B2 vs Model A2). **Table 24** and **Table 24**

above provide a comprehensive overview of the model variations run for each patient population and each outcome; optimistic, pessimistic and base case models are also indicated; full model details are presented in **Appendix E.**

Results from the base case models are described in the following sections. Results from the optimistic and pessimistic scenarios are described as sensitivity analyses and presented in **Section B.2.10.5.2**. Results for the remaining models are presented in **Appendix E** only. Model fit statistics are also provided in **Appendix E**.

B.2.10.4.1 Analyses from bDMARD-naïve evidence network

- ***PsARC response analysis***

In TA445, the AG noted that the PsARC response data indicated that higher placebo rates were associated with lower relative effectiveness estimates and that placebo response rates appeared to have increased over time (94). [redacted] As described above (**Table 24**), additional analyses were undertaken to explore this effect. Placebo-adjusted model B2 RE (

Table 23) was selected as a base model because it had the lowest DIC and reduced the between study SD (with a narrower CI) compared to the non-placebo-adjusted model A2, explaining some heterogeneity (see **Section 2.10.5.1.1**). A RE model was selected on the basis that a RE model is generally preferable to a FE model, as it includes uncertainty within and between trials. The preference for a RE model was further considered appropriate in the context of the heterogeneity observed in the direct meta-analyses for the etanercept and adalimumab trials PsARC responses [redacted]

Model A2 in the alternative network was the optimistic model, given that a [redacted] however, we could not remove the placebo arm from Future 2, as we would have lost secukinumab as a comparator. This model had a lower average residual deviance than model A1 in the alternative network, but as a RE model, it allowed for uncertainty between trials, compared to the FE model. Results for all models evaluated are presented in **Appendix E**.

The results of the base case model (placebo-adjusted B2 RE) showed that all comparators were significantly better than placebo except for tofacitinib 5 mg BD [redacted] The ORs [redacted] tofacitinib 5 mg BD with adalimumab, apremilast, ustekinumab, secukinumab, and certolizumab pegol, with [redacted] (see **Table E14** in **Appendix E**). The probability of PsARC response with tofacitinib 5 mg BD was [redacted]

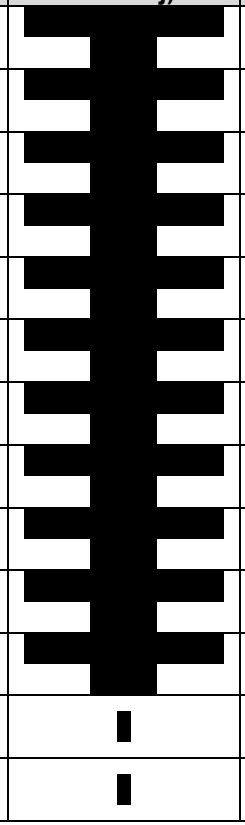
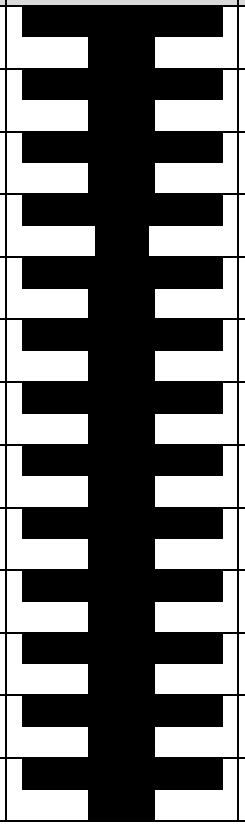
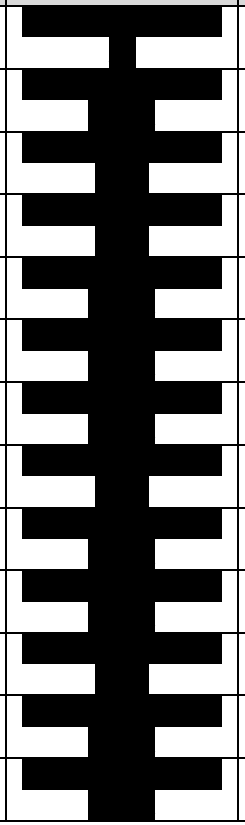
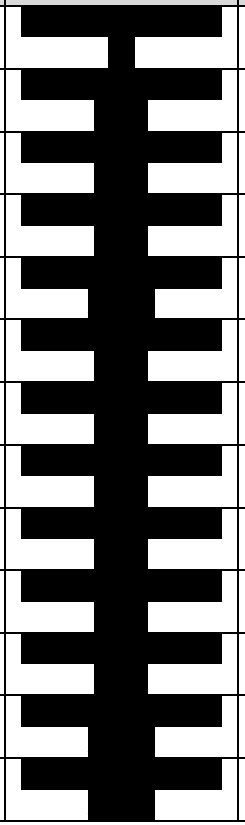
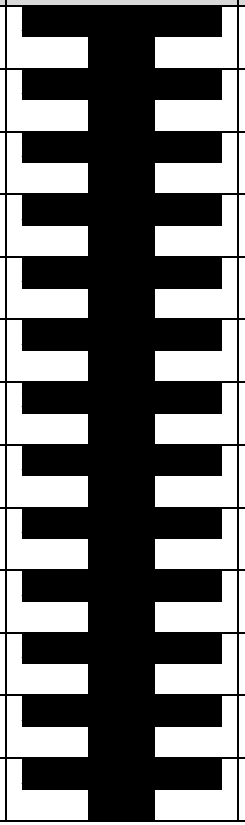
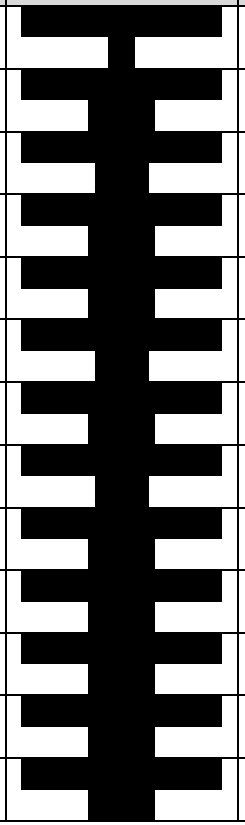
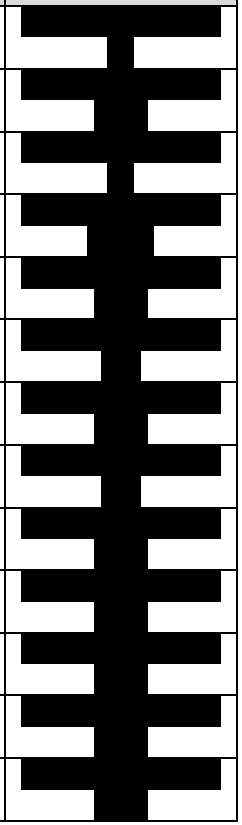
The analyses used data for all patients (bDMARD-naïve and bDMARD-experienced) for Future 2 and RAPID-PsA, as the bDMARD-naïve data were redacted in TA445 and were not available in the primary publications. When comparing the ORs from our model (using all patient data) with the ORs from the TA445 NMA (using the bDMARD-naïve data), it was noted that our results may have overestimated the treatment effects for certolizumab pegol and secukinumab.

There was only one trial (OPAL Broaden) that compared tofacitinib 5 mg BD with an active treatment (adalimumab as an active control). The adalimumab versus placebo comparisons were smaller in OPAL Broaden compared to Genovese et al., 2007 and ADEPT for PsARC (and for many outcomes explored in the NMAs).

[redacted]

[redacted]Excluding the OPAL Broaden placebo arm improved model fit and resulted in the model being selected as the optimistic model (**Appendix E**, **Table E20**, Model A2 alternative network).

Table 25: Summary results for bDMARD-naïve population: Probability of PsARC, PASI 50/75/90, ACR 20/50/70 response (base case model data)

Comparator	PsARC: Model B2 (RE & PBO adj)†	PASI 50: Model E2 (RE)‡	PASI 75: Model E2 (RE) ‡	PASI 90: Model E2 (RE) ‡	ACR 20: Model E2 (RE)‖	ACR 50: Model E2 (RE)‖	ACR 70: Model E2 (RE)‖
PBO							
ADA							
APR							
ETN							
IFX							
USK 45							
GOL 50							
TOF 5							
SEC 150							
SEC 300							
CZP							
IXE 80 Q2W							
IXE 80 Q4W							

† PsARC data for all patients for Future 2 and RAPID-PsA were used as data for bDMARD-naïve population are redacted in TA445 and not published elsewhere. PsARC data for PSUMMIT 1 & 2 were 24-week population data as per TA445.
‡ The 12-week PASI 50/75/90 data for Future 2 bDMARD-naïve population are redacted in TA445, 16-week data used instead. PASI 50/75/90 data for PSUMMIT 1 & 2 (PSUMMIT 2 only reports PASI75 data) were 12-week population data as per TA445. NMA excluded IMPACT due to extreme values.
‖ The 12-week ACR 20/50/70 data for Future 2 and RAPID-PsA bDMARD-naïve population are redacted in TA445, 24-week data used instead. ACR 20/50/70 data for PSUMMIT 1 & 2 were 12-week population data as per TA445. NMA excluded IMPACT due to extreme values.

- ***HAQ-DI conditional on PsARC response status analysis***

Model K2 RE (

Table 23) was used as a base case model because it included an adjustment for multi arm studies (alternative code to the code previously-used by Rodgers (111) and Cummins (112)) and because a RE model would take a better account of heterogeneity (vs model K1 FE; see **Appendix E**). Results for all models evaluated are presented in **Appendix E**. Placebo-adjusted models were not undertaken in line with TA445, as HAQ-DI change in the current submission was assessed based on PsARC response/non-response.

The results of the base case model (K2 RE) showed that tofacitinib 5 mg BD [redacted]

The analyses did not include Future 2 and RAPID-PsA, as the bDMARD-naïve data were redacted in TA445 and were not available in the primary publications. Therefore, our NMA had no results for certolizumab pegol and secukinumab for HAQ-DI.

Table 26: HAQ-DI | PsARC summary results for bDMARD-naïve population: Absolute change from baseline (base case model data)

Comparator	HAQ-DI: Model K2 (RE, alternative code)	HAQ-DI: Model K2 (RE, alternative code)
	PsARC responders	PsARC non-responders
PBO	[redacted]	[redacted]
ADA	[redacted]	[redacted]
APR	[redacted]	[redacted]
ETN	[redacted]	[redacted]
IFX	[redacted]	[redacted]
USK 45	[redacted]	[redacted]
GOL 50	[redacted]	[redacted]
TOF 5	[redacted]	[redacted]
SEC 150	[redacted]	[redacted]
SEC 300	[redacted]	[redacted]
CZP	[redacted]	[redacted]
IXE 80 Q2W	[redacted]	[redacted]
IXE 80 Q4W	[redacted]	[redacted]

Note: data for Future 2 and RAPID-PsA for bDMARD-naïve population are redacted in TA445 and not published elsewhere. Data for PSUMMIT 1 & 2 were 24-week population data as per TA445. † significant difference based on 95% CrI

- ***PASI 50/75/90 response analysis***

Since the placebo response may be an effect modifier for the PsARC endpoint, we explored the relationship between the placebo and treatment effects for the PASI outcome, following the same methodology as the TA445 AG (94). Model E2 RE (

Table 23) was selected as a base case model because it had the lowest DIC and average residual deviance. Results for all models evaluated are presented in **Appendix E**.

The results of the base case model (E2 RE) showed that tofacitinib 5 mg BD [redacted] Tofacitinib 5 mg BD was also [redacted] Tofacitinib 5 mg BD had a probability of PASI 50 response [redacted] PASI 75 response of [redacted] and PASI 90 response of [redacted] 25

The analyses used PASI 75 and PASI 90 data at week 16 for Future 2, as the week 12 bDMARD-naïve data were redacted in TA445 and were not available in the primary publication. When comparing the results from our NMA with the equivalent model result from TA445, it was noted that the use of the week 16 data may have underestimated the treatment effects for secukinumab. As the percentage of placebo treated patients achieving PASI 50 response in IMPACT (infliximab) and PASI 75 response in Mease et al 2000 (etanercept) was zero, the convergence for the infliximab and etanercept treatment effects was less than satisfactory leading to wide CrIs. The IMPACT study was excluded from the NMA due to the extreme values reported in the trial (PASI 50 response was 0% for placebo and 100% for infliximab, making PASI 75 and PASI 90 not estimable), which generated an error in WinBUGs. Estimates of response in the NMA were possible for etanercept.

- ***ACR 20/50/70 response analysis***

Since the placebo response may be an effect modifier for the PsARC endpoint, we explored the relationship between the placebo and treatment effects for the ACR

response outcome, following the same methodology as the TA445 AG (94). Model E2 RE (

Table 23) was selected as the base case model because it had the lowest DIC and average residual deviance; furthermore, the RE model accounted for considerable heterogeneity in adalimumab trials (OPAL Broaden). Results for all models evaluated are presented in **Appendix E**.

The results of the base case model (E2 RE) showed that tofacitinib 5 mg BD [redacted] OR for ACR20 response was [redacted] ACR50 response was [redacted] Tofacitinib 5 mg BD was [redacted]

Our analyses used week 24 data for Future 2 and RAPID-PsA, as the 12-week data were redacted in TA445 and were not available in the primary publications. When comparing the results from our NMA with the equivalent model results from TA445, it was noted that the use of the week 24 data may have overestimated the treatment effects for certolizumab pegol and secukinumab.

B.2.10.4.2 Analyses from bDMARD-experienced evidence network

- ***PsARC response analysis***

The bDMARD-experienced population data for PSUMMIT2 were sourced from the TA445 AG report (94). As per the TA445 analysis, "the inclusion of the 24-week PsARC data for ustekinumab was based on an assumption that they fairly reflected the 12-week results (bDMARD-experienced population results for PsARC at 12 weeks in PSUMMIT2 were not available, though 12-week data for the full population were available)" (see Appendix 12.3.2 of the TA445 AG report) (4). Only one analysis was conducted examining the PsARC response in this population; base case model A1 FE (

Table 23) used data from PSUMMIT 2 (24-week data available in AG report from TA445) and OPAL Beyond.

The results of the base case model (A1 FE) showed that tofacitinib 5 mg BD [redacted] Tofacitinib 5 mg BD had a probability of PsARC response [redacted] Error! Not a valid bookmark self-reference. [redacted]

Table 27: Summary results for bDMARD-experienced population: Probability of PsARC, PASI 50/75/90, ACR 20/50/70 response (base case model data)

Comparator	PsARC: Model A1 FE (RE & PBO adj)	PASI 50: Model E1 (FE)	PASI 75: Model E1 (FE)	PASI 90: Model E1 (FE)	ACR 20: Model E1 (FE)	ACR 50: Model E1 (FE)	ACR 70: Model E1 (FE)
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
APR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
USK 45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC 150	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC 300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE 80 Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IXE 80 Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: the above uses data for PSUMMIT2 for the bDMARD-experienced population from TA445 Table 44 (94)

- ***HAQ-DI conditional on PsARC response status analysis***

The bDMARD-experienced population data for PSUMMIT2 were sourced from the TA445 AG report (94). As per the TA445 AG analysis, the PSUMMIT2 bDMARD-experienced population data at 24-weeks were included in the analysis, as the AG had determined that 24-week data was equivalent to the 12-weeks outcome. Data for FUTURE2 were redacted in TA445 and were not available from the primary publication.

Analyses for two models were conducted; model G FE and model K1 FE. Model K1 FE was an alternative model to the Rodgers (111) and Cummins (112) code and included an adjustment for multi-arm studies. DICs for the two models were not comparable, but the average residual deviance for model K1 (**Table 28**) [redacted] was thus selected as the base case model. Results for the two models evaluated are presented in **Appendix E**.

The results of the base case model (K1 FE) showed that tofacitinib 5 mg BD [redacted] from baseline in HAQ-DI in PsARC non-responders (see **Table E76** in **Appendix E**). Tofacitinib 5 mg BD was [redacted] in PsARC responders of non-responders.

Table 28: HAQ-DI | PsARC summary results for bDMARD-experienced population: Absolute change from baseline (base case model data)

Comparator	HAQ-DI: Model K1 (FE, alternative code)	HAQ-DI: Model K1 (FE, alternative code)
	(PsARC responders)	(PsARC non-responders)
PBO	[redacted]	[redacted]
USK 45	[redacted]	[redacted]
TOF 5	[redacted]	[redacted]
SEC 150	[redacted]	[redacted]
SEC 300	[redacted]	[redacted]
CZP	[redacted]	[redacted]
IXE 80 Q2W	[redacted]	[redacted]
IXE 80 Q4W	[redacted]	[redacted]

† significant difference based on 95% CrI; Note: data for Future 2 bDMARD-experienced population are redacted in TA445 and not published elsewhere

- ***PASI 50/75/90 response analysis***

The bDMARD-experienced population data for PSUMMIT2 were sourced from the TA445 AG report Table 54 (only PASI 75 response data at 12 weeks were available); for FUTURE-2, the 16-week bDMARD-experienced population data reported in Table 11 of the TA445 AG report were used (only PASI 75 and PASI 90 response data were available; 12-week data were redacted) (94). We were unable to assess whether the 24-week data from SPIRIT-P2 and ASTRAEA were comparable to 12-week data (unaffected by cross-over/early escape). However, there were sufficient data to do an analysis both with and without the 24-week data. Model E1 FE without 24-week data was selected as the base model because it had comparable average residual deviance to model E1 FE with 24-week data and, in part, for consistency with the model choice for ACR. Results for the two models evaluated are presented in **Appendix E**.

The results of this base case model showed that tofacitinib 5 mg BD was [redacted] Tofacitinib 5 mg BD had [redacted] Tofacitinib 5 mg BD had a probability of PASI 50 response of [redacted] PASI 75 response of [redacted] and PASI 90 response of [redacted] bDMARD-experienced population data for PSUMMIT2 were sourced from the TA445 AG report (94). As per the TA445 analysis, "the inclusion of the 24-week PsARC data for ustekinumab was based on an assumption that they fairly reflected the 12-week results (bDMARD-experienced population results for PsARC at 12 weeks in PSUMMIT2 were not available, though 12-week data for the full population were available)" (see Appendix 12.3.2 of the TA445 AG report) (4). Only one analysis was conducted examining the PsARC response in this population; base case model A1 FE (

Table 23) used data from PSUMMIT 2 (24-week data available in AG report from TA445) and OPAL Beyond.

The results of the base case model (A1 FE) showed that tofacitinib 5 mg BD [redacted] Tofacitinib 5 mg BD had a probability of PsARC response [redacted] Error! Not a valid bookmark self-reference. [redacted]

Table 27[redacted]

- ***ACR 20/50/70 response analysis***

The bDMARD-experienced population data for PSUMMIT2 were sourced from the TA445 AG report Table 54 (12-week data) (94); for FUTURE-2, the 24-week bDMARD-experienced population data reported in Table 10 of TA445 were used (12-week data were redacted) (94). We were unable to assess whether the 24-week data from SPIRIT-P2 and ASTRAEA were comparable to 12-week data (unaffected by cross-over/early escape). However, there were sufficient data for an analysis both with and without the 24-week data. DICs for the two models (with and without the 24-week data) were not comparable, but the average residual deviance in model E1 FE without 24-week data was [redacted] Results for the two models evaluated are presented in **Appendix E**.

The results of the base case model (E1 FE without 24-week data; **Table 27**) showed that tofacitinib 5 mg BD was [redacted] Tofacitinib 5 mg BD had a probability of ACR 20 response of [redacted]

B.2.10.5 Uncertainties in the indirect and mixed treatment comparisons

B.2.10.5.1 Statistical assessment of heterogeneity

B.2.10.5.1.1 bDMARD-naïve studies

- ***Statistical heterogeneity***

PsARC: There was [redacted] of [redacted]

[redacted] for PsARC, [redacted] I^2 was not estimable for tofacitinib, secukinumab, golimumab or certolizumab pegol, as there was only one trial per treatment analysed (see forest plot in **Figure E2** in **Appendix E**).

PASI 50/75/90: [redacted] of PASI 50/75/90 [redacted]. For PASI 50 and PASI 90 this was [redacted](see forest plot in **Figure E12** in **Appendix E**).

ACR 20/50/70:
[redacted] ACR 20 [redacted]: [redacted](see forest plot in **Figure E30** in **Appendix E**). In all cases, the [redacted] were [redacted]

HAQ-DI by PsARC: For change in HAQ-DI by PsARC response, [redacted](see forest plot in **Figure E24** in **Appendix E**).

- ***Between-study standard deviation***

For the bDMARD-naïve network, RE NMA models were used where feasible.

PsARC: The between study SD for the basic RE model (A2) [redacted] The placebo-adjusted base case model (B2) [redacted]

PASI 50/75/90: The between study SD for the basic RE model (E2)

[redacted]

ACR 20/50/70: The between study SD for the basic RE model (E2)

[redacted]

HAQ-DI by PsARC: The between study SD for the alternative RE model (K2)

[redacted]

B.2.10.5.1.2 bDMARD-experienced studies

For bDMARD-experienced studies, there was only one study per treatment, hence we were unable to conduct a statistical assessment of heterogeneity.

B.2.10.5.2 Sensitivity analysis

The sensitivity analyses (optimistic and pessimistic models) performed for each network are summarised below, with results presented in Appendix E. See **Table 24** above for model summary. Additional model results are also presented in **Appendix E**.

B.2.10.5.2.1 bDMARD-naive

- **PsARC**: The optimistic model was similar to the base case model, except [redacted] The pessimistic model was similar to the base case model.

- **PASI 50/75/90:** The optimistic model was similar to the base case model (also pessimistic), except [redacted]
- **HAQ-DI conditional on PsARC response:** The optimistic and pessimistic models were similar to base case, except [redacted]
- **ACR 20/70/90:** The optimistic model was similar to the base case model (also pessimistic) except [redacted]

Table 29: Sensitivity analyses for the bDMARD-naïve network

Outcome	Sensitivity analyses: optimistic/pessimistic models in Appendix E
PsARC	• **Base case**: Model B 2 (RE) main network – PBO adjusted • **Optimistic**: Model A 2 (RE) alternative network – excluding OPAL Broaden PBO arm. • **Pessimistic**: Model A 2 (RE) – main network
PASI 50/75/90	• **Optimistic**: Model E 1 (FE) • **Pessimistic (also base case**): Model E 2 (RE)
HAQ| PsARC response	• **Pessimistic**: Model G (FE, Rodgers (111) and Cummins (112) model) • **Optimistic**: Model K 1 (FE, alternative code) • **Base case**: Model K 2 (RE, alternative code)
ACR 20/50/70	• **Optimistic**: Model E 1 (FE) • **Pessimistic (also base case**): Model E 2 (RE)

Abbreviations: ACR, American College of Rheumatology; FE, fixed-effects; HAQ-DI, Health Assessment Questionnaire Disability Index; PASI, Psoriasis Area and Severity Index; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; RE, random effects

B.2.10.5.2.2 bDMARD-experienced

- **PsARC**: No sensitivity analyses were conducted.
- **PASI 50/75/90:** The optimistic model was similar to the base case model (also pessimistic), excep [redacted]
- **HAQ-DI conditional on PsARC response:** The optimistic model was similar to the base case model (also pessimistic), except [redacted]
- **ACR 20/70/90:** The pessimistic model was similar to the base case model (also optimistic), except [redacted]

Table 30: Sensitivity analyses for the bDMARD-experienced network

Outcome	Full results in Appendix E
PsARC	• **Base case:** Model A 1 (FE)
PASI 50/75/90	• **Pessimistic (also base case):** Model E 1 (FE) excluding 24-week data • **Optimistic**: Model E 1 (FE) including 24-week data
HAQ| PsARC response	• **Optimistic**: Model G (FE, Rodgers (111) and Cummins (112) model) • **Pessimistic (also base case**): Model K 1 (FE, alternative code)
ACR 20/50/70	• **Optimistic (also base case):** Model E 1 (FE) excluding 24-week data • **Pessimistic**: Model E 1 (FE) including 24-week data

Abbreviations: ACR, American College of Rheumatology; FE, fixed-effects; HAQ-DI, Health Assessment Questionnaire Disability Index; PASI, Psoriasis Area and Severity Index; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; RE, random effects

B.2.10.5.3 Discussion of heterogeneity

Heterogeneity can be defined as variation in the same pairwise comparison between trials.

- ***Heterogeneity***

Statistical heterogeneity was discussed in **Section B.2.10.5.1**, with further limitations discussed in **Appendix E**. Potential sources of clinical and methodological heterogeneity within the NMAs are discussed below.

There was no evidence of inconsistency between the direct and indirect evidence. It should be noted that the loops in the evidence network arise from multi-armed trials (OPAL Broaden: tofacitinib 5mg BD – adalimumab – placebo, and SPIRIT-P1: ixekizumab – adalimumab - placebo) and data from multi-armed trials are internally consistent. Only one part of these loops contain evidence from independent trials (i.e., adalimumab – placebo in ADEPT (115) and Genovese 2007 (116)) and there was evidence of heterogeneity between studies for this contrast (see forest plots in **Appendix E** and discussion in **Section B.2.10.5.1**), which is likely to be due to the differences in placebo effects (see placebo creep discussion in **Section B.2.14.2.2**).

We were unable to subdivide patients into those who had failed one non-biological DMARD (csDMARD) and those who had failed two non-biological DMARDs (csDMARDs), as per the NICE scope; indeed, for some of the studies included in this review it was unclear from the publications whether all patients met the criterion of at least one previous csDMARD failure. To address this issue, we used the same approach as the one used by the AG for TA445, stratifying the data broadly into bDMARD-naïve and bDMARD-experienced populations.

There were methodological differences between the studies included in the NMA. A quality assessment of the studies included in the NMA (**Appendix D**) revealed that, in a number of studies, treatment groups differed at the outset of the study in terms of prognostic factors (e.g., imbalances between groups in concomitant methotrexate use

and swollen joint count in OPAL Broaden (87); radiographic disease progression at baseline in Mease et a.., 2004 (117)), and a number of studies had unexpected imbalances in drop-out between groups. One half of the studies did not specify whether care providers, study participants, and outcome assessors were blind to treatment allocation. Similarly, in half of the studies, it was not clear whether the concealment of treatment allocation was adequate. Lastly, for several studies, it was not clear whether treatment randomisation was carried out appropriately; sequence generation methods were not described and/or no/few details regarding the randomisation process were provided.

Trial design was also a factor in terms of cross-over/early escape design and time points for assessment. We attempted to mitigate this by including data before cross-over at around 12 weeks of treatment wherever possible (12 weeks of treatment is also an appropriate follow-up time since treatment guidelines recommend that PsARC be assessed at 12 weeks (2, 54)).

There were unexplained differences in placebo response in some of the studies included in the NMAs. In the TA445 short-term efficacy NMAs, rate of placebo PsARC response was identified as a source of heterogeneity, with higher placebo rates associated with lower relative effectiveness estimates; however, the source of any relationship between placebo response and treatment effect was unclear. To address this, we adopted the same approach as the AG for TA445 and conducted the placebo-adjusted models (see model summary in **Table 24**).

The reporting of [redacted] for some of the outcomes [redacted] had an impact on some parts of the analysis. Similarly, it was noted that, [redacted] across many outcomes, though the [redacted] were [redacted] See the direct meta-analysis forest plots in **Appendix E**

B.2.10.6 Concluding remarks

Results from the base case NMAs indicate that tofacitinib 5 mg BD is similarly efficacious to comparator b/tsDMARDs in the bDMARD-naïve population, with the exception of PsARC response where the odds of response were significantly lower compared with etanercept, infliximab and golimumab. In the bDMARD-experienced population base case NMAs, tofacitinib 5 mg BD was similarly efficacious to ustekinumab with the exception of PASI50/75/90, where odds of responses were significantly lower.

B.2.10.7 Supplementary analyses of radiographic progression outcomes

A NMA of radiographic disease progression was not feasible, owing to placebo cross-over in the tofacitinib and comparator trials and resultant lack of a connecting treatment. Alternatively, a multivariate population-adjusted regression analysis of individual patient data from the OPAL Broaden trial was conducted in an attempt to estimate whether the lack of clinically (and statistically) significant difference observed between tofacitinib 5 mg BD and adalimumab 40 mg Q2W at week 52, in relation to radiographic outcomes in OPAL Broaden, could be replicated in a population at higher risk of radiographic progression. These analyses used pre-specified effect modifiers and prognostic factors (c.f. Gladman et al 2010; (118)) centred using baseline characteristics from the ADEPT trial to adjust the OPAL Broaden data to a target population more at risk of progression. Full analysis methodology, results, and limitations are presented in **Appendix D**.

- ***Difference in mTSS***

The difference in mTSS at 12 months between tofacitinib 5 mg BD versus adalimumab was [redacted] using the best fitting multivariate model. Full model results are presented in **Appendix D**.

- ***Odds of progression***

The odds of progression (change in mTSS from baseline of >0.5 at 12 months) is [redacted] for tofacitinib 5 mg BD versus adalimumab using unadjusted data, and [redacted] when using the best fitting multivariate model. Full model results are presented in **Appendix D**.

- ***Conclusions***

The results of this analysis suggest there is no difference between tofacitinib 5 mg BD and adalimumab with respect to radiographic progression, when estimating the effects of tofacitinib in a population similar to the trial population in ADEPT (a study considered to have demonstrated that adalimumab inhibits radiographic progression in PsA) (115). The primary limitation of this analysis was that the OPAL Broaden trial was underpowered for detecting differences between tofacitinib 5 mg BD and adalimumab, given that the observed progression rate was just 2-4% at 12 months (see **Appendix D** for further discussion of the limitations).

B.2.11 Adverse reactions

As with the efficacy and quality of life data, the safety data for tofacitinib 5 mg BD for the treatment of active PsA in adults who have had an inadequate response to csDMARDs or who have been intolerant to a prior TNFi therapy are from OPAL Broaden and OPAL Beyond clinical trials. Long-term safety data for tofacitinib in support of this technology appraisal are drawn from the LTE study OPAL Balance; safety data reported up to Month 36 are presented for interim data up to January 25, 2017, which are pooled for tofacitinib 5 mg BD and tofacitinib 10 mg BD subjects, due to flexible dosing between 5 mg and 10 mg BD. As of January 25, 2017, no new risks or safety signals were identified in the LTE study compared with those previously reported in the randomised controlled trials and LTE data from the tofacitinib RA development programme. The types and rates of common AEs (including infections and malignancies) were generally comparable to those seen in the RA clinical programme.

In OPAL Broaden and OPAL Beyond, at the end of the 3-month placebo-controlled period, the placebo groups were separated into two groups: subjects switching to

tofacitinib 5 mg BD and subjects switching to tofacitinib 10 mg BD. The group that switched from placebo to tofacitinib 5 mg BD after the placebo-controlled period (PBO → TOF 5 mg) was used to complement tofacitinib 5 mg BD safety profile data at 12 months in OPAL Broaden and 6 months in OPAL Beyond.

Treatment-emergent adverse events (TEAEs), hereafter referred to as adverse events (AEs), are defined as any events that had onset after the start of the first dose of study treatment, or onset prior to the first dose of study treatment and worsened in severity after the first dose of study treatment. Safety data are presented for all-causality AEs; safety data for treatment-related AEs are presented in Appendix M.

A NMA for safety was not performed for several reasons: there were too few RCTs reporting AEs of interest; too few studies reporting specific AEs using the same definition of the event (e.g., cardiovascular events ranged from hypertension through to major cardiovascular events); and some studies reported zero events in either one or both arms. An NMA was thus considered not feasible or reliable.

B.2.11.1 OPAL Broaden

B.2.11.1.1 Common AEs (all causalities)

- ***Common AEs reported up to Month 3***

Up to Month 3 (that is, during the placebo-controlled period), the percentage of subjects with all-causalities AEs was higher in the adalimumab group (46%) than the tofacitinib 5 mg BD (39%) and placebo (35%) groups. A summary of AEs reported up to Month 3 is presented in

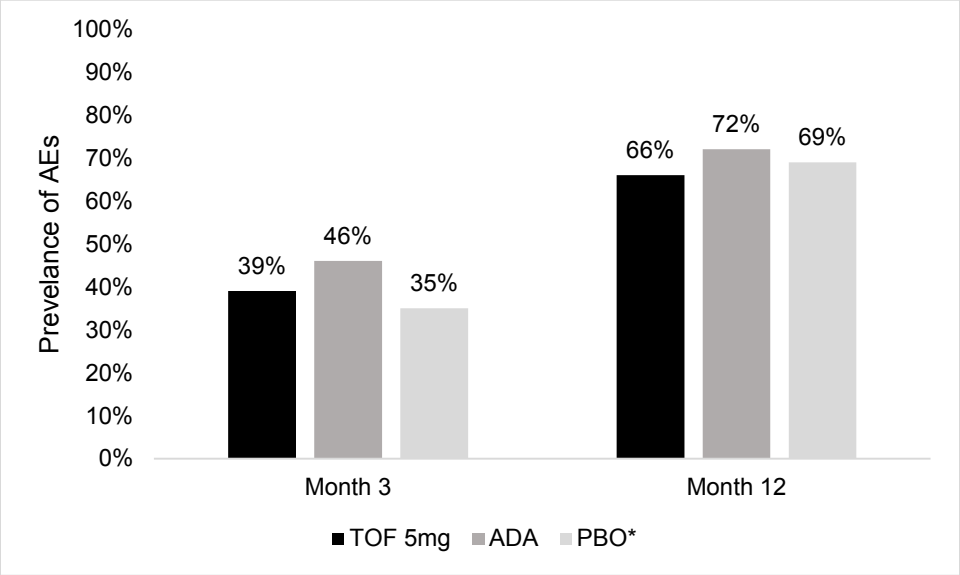
Table 31.

Table 31: Summary of AEs Reported up to Month 3 (Safety Analysis Set, All Causalities) for OPAL Broaden

Number (%) of Subjects:	TOF 5mg, n (%)	ADA, n (%)	PBO, n (%)
Subjects evaluable for AEs	107	106	105
[redacted]	[redacted]	[redacted]	[redacted]
Subjects with AEs	42 (39)	49 (46)	37 (35)
Subjects with SAEs	3 (3)	1 (1)	1 (1)
[redacted]	[redacted]	[redacted]	[redacted]

Except for the Number of AEs, subjects are counted only once per treatment in each row. MedDRA (v18.1) coding dictionary applied. SAEs – according to the Investigator's assessment.
Abbreviations: ADA, adalimumab; AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; mg, milligram; n, number of subjects that met the criteria; PBO, placebo; SAE, serious adverse event, TOF, tofacitinib

Figure 10: Total Prevalence (%) of All Causality AEs (Including SAEs) Reported up to 3 Months and 12 Months for OPAL Broaden



Abbreviations: AE, adverse event; mg, milligram; SAE, serious adverse event
*PBO indicates the group that received placebo treatment during the 3-month placebo-controlled period and was switched to tofacitinib 5mg BD treatment at Month 3

The incidence of the most common all causalities AEs up to Month 3 was generally similar between groups, with the most common AEs being headache, nasopharyngitis, and upper respiratory tract infection.

- Headache: 3.7% of subjects in the tofacitinib 5 mg BD group, 4.7% of subjects in the adalimumab group, and 3.8% of subjects in the placebo group.

- Nasopharyngitis: 3.7% of subjects in the tofacitinib 5 mg BD group, 4.7% of subjects in the adalimumab group, and 2.9% of subjects in the placebo group.
- Upper respiratory tract infection: 1.9% of subjects in the tofacitinib 5 mg BD group, 2.8% of subjects in the adalimumab group, and 4.8% of subjects in the placebo group.

Relative risk (RR) ratios up to Month 3 for tofacitinib 5 mg BD vs placebo and adalimumab vs placebo comparisons could only be calculated for the following AEs: [redacted] (**Table 32**, **Figure 11** and **Figure** 12). Compared to the placebo group, [redacted] Compared to the placebo group, [redacted] Compared to placebo, [redacted]

Table 32: Incidence of AEs Up to Month 3 in OPAL Broaden (Tier 2, Occurring in >=4 Subjects in Any Treatment Group) (Safety Analysis Set, All Causalities)

Outcome: System Organ Class (preferred term)	TOF 5mg (N=107) n (%)	ADA (N=106) n (%)	PBO (N=105) n (%)	RR for TOF vs PBO		RR for ADA vs PBO	
				RR	95% CI	RR	95% CI
Gastrointestinal disorders							
Nausea	2 (1.9)	4 (3.8)	0	[redacted]			
General disorders and administration site conditions							
[redacted]							
Infections and infestations							
Nasopharyngitis	4 (3.7)	5 (4.7)	3 (2.9)				
Upper respiratory tract infection	2 (1.9)	3 (2.8)	5 (4.8)				
Investigations							

Alanine aminotransferase increased	1 (0.9)	4 (3.8)	0	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders							
Headache	4 (3.7)	5 (4.7)	4 (3.8)	[redacted]	[redacted]	[redacted]	[redacted]

Note: The Mease publication (87) reports data for AEs that occurred at a rate of ≥5% in at least one of the treatment groups (TOF 5mg, TOF 10mg, PBO, or ADA); AEs that occurred at a rate lower than 5% are reported in the CSR only, and therefore are marked as confidential.
Abbreviation: ADA, adalimumab; AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; mg, milligram; [redacted]; PBO, placebo; RR, relative risk; TOF, tofacitinib
They are not adjusted for multiplicity and should be used for estimation purposes only. MedDRA (v18.1) coding dictionary applied.[redacted]

Figure 11: AEs Up to Month 3 (Tier 2, Occurring in >=4 Subjects in Any Treatment Group) Comparing Tofacitinib 5 mg BD and Placebo Groups in OPAL Broaden (Safety Analysis Set, All Causalities)

[redacted]

Figure 12: AEs Up to Month 3 (Tier 2, Occurring in >=4 Subjects in Any Treatment Group) Comparing Adalimumab and Placebo in OPAL Broaden (Safety Analysis Set, All Causalities)

- ***Common AEs reported up to Month 12***

Up to Month 12, the percentage of subjects with AEs (all causalities) was higher in the adalimumab group (72%) than the tofacitinib 5 mg BD (66%) and placebo→tofacitinib 5 mg BD (69%) groups. A summary of AEs reported up to Month 12 is presented in **Table 33**.

Table 33: Summary of AEs Reported up to Month 12 (Safety Analysis Set, All Causalities) for OPAL Broaden

Number (%) of Subjects:	TOF 5mg, n (%)	ADA, n (%)	PBO→TOF 5mg, n (%)*
Subjects evaluable for AEs	107	106	52
[redacted]	[redacted]	[redacted]	[redacted]
Subjects with AEs	71 (66)	76 (72)	36 (69)
Subjects with SAEs	8 (7)	9 (8)	3 (6)
[redacted]	[redacted]	[redacted]	[redacted]

Except for the Number of AEs, subjects are counted only once per treatment in each row. MedDRA (v18.1) coding dictionary applied. SAEs – according to the Investigator's assessment.
Abbreviations: ADA, adalimumab; AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; mg, milligram; n, number of subjects that met the criteria; PBO, placebo; SAE, serious adverse event, TOF, tofacitinib

*Group that received placebo treatment during the 3-month placebo-controlled period and was switched to tofacitinib 5 mg BD treatment at Month 3

The incidence of the most common all-causalities AEs up to Month 12 was generally similar between groups, with the most common AEs being headache, nasopharyngitis, and upper respiratory tract infection.

- Headache: 4.7% of subjects in the tofacitinib 5 mg BD group, 6.6% of subjects in the adalimumab group, and 3.8% of subjects in the placebo→tofacitinib 5 mg BD group.
- Nasopharyngitis: 7.5% of subjects in the tofacitinib 5 mg BD group, 10.4% of subjects in the adalimumab group, and 7.7% of subjects in the placebo→tofacitinib 5 mg BD group.
- Upper respiratory tract infection: 9.3% of subjects in the tofacitinib 5 mg BD group, 7.5% of subjects in the adalimumab group, and 9.6% of subjects in the placebo→tofacitinib 5 mg BD group.

B.2.11.1.2 AEs of special interest

A summary of events of special interest is presented in **Table 34**. No cases of tuberculosis, non-melanoma skin cancer, or interstitial lung disease were reported. Full details of AEs of special interest are reported in **Appendix M**.

Table 34: Summary of adverse events of special interests for OPAL Broaden (Safety Analysis Set, All Causalities)

	Up to Month 3			Up to Month 12		
	TOF 5 mg (N=107)	**ADA (N=106)**	**PBO (N=105)**	**TOF 5 mg (N=107)**	**PBO→TOF 5 mg (N=52)***	**ADA (N=106)**
AE of special interest, n (%) [day of onset]†						
Serious infection	0	0	0	0	2 (4) [days 102 and 331]	1 (1) [day 170]
Herpes zoster infection	1 (1) [day 61]	0	0	2 (2) [days 61 and 173]	0	0
Opportunistic infection	1 (1) [day 61]	0	0	1 (1) [day 61]	0	0
Cancer, excluding non-melanoma cancer	2 (2) [days 1 and 11]	0	0	3 (3) [days 1, 11, and 232]	0	0
Cardiovascular event	0	0	0	0	1 (2) [day 139]	2 (2) [days 263 and 345]
Gastrointestinal perforation	0	0	0	0	1 (2) [day 102]	0

Abbreviations: ADA, adalimumab; AE, adverse event; mg, milligram; n, number of subjects that met the criteria; PBO, placebo; TOF, tofacitinib.
† Among the adverse events of special interest, the cases of herpes zoster infection were not judged to be serious adverse events, and the events of opportunistic infection, cancer, cardiovascular event, and gastrointestinal perforation were all adjudicated.
*Group that received placebo treatment during the 3-month placebo-controlled period and was switched to tofacitinib 5 mg BD treatment at Month 3

B.2.10.1.3 Deaths

No subject died up to Month 3. One death due to cardiac arrest occurred during month 4 in a subject in the placebo→tofacitinib 5 mg BD group.

B.2.11.2 OPAL Beyond

B.2.11.2.1 Common AEs (all causalities)

- ***Common AEs reported up to Month 3***

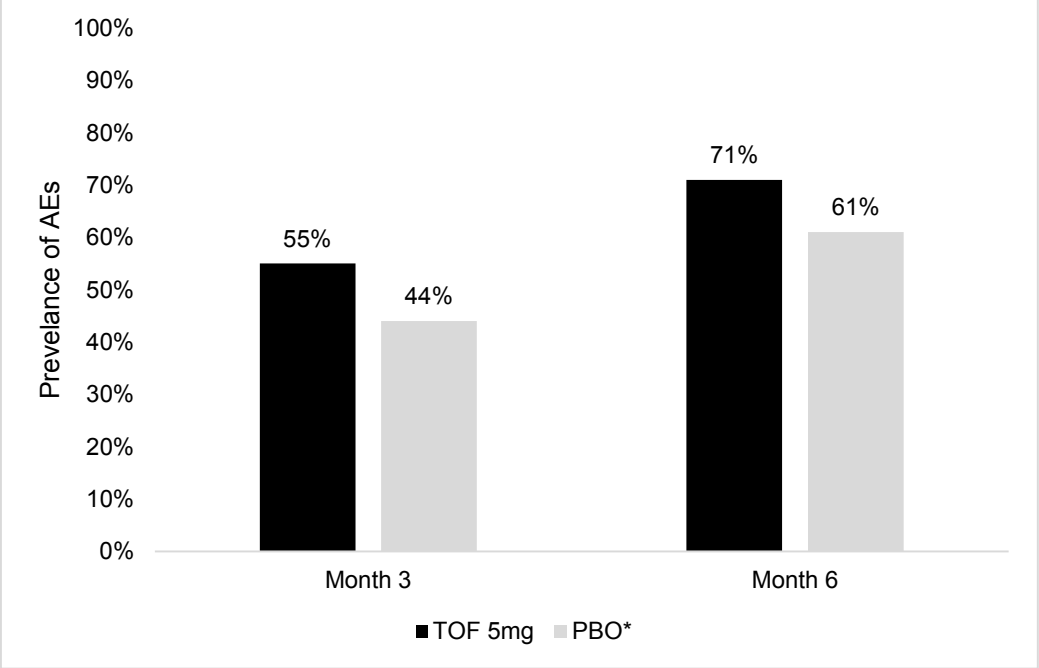
Up to Month 3 (placebo-controlled period), the percentage of subjects with AEs (all causalities) was higher in the tofacitinib 5 mg BD (55%) than in the placebo group (44%). A summary of AEs reported up to Month 3 is presented in **Table 35**.

Table 35: Summary of AEs Reported Up to Month 3 (Safety Analysis Set, All Causalities) for OPAL Beyond

Outcome	TOF 5mg n (%)	PBO n (%)
Subjects evaluable for AEs	131	131
[redacted]	[redacted]	[redacted]
Subjects with AEs	72 (55)	58 (44)
Subjects with SAEs	1 (1)	3 (2)
[redacted]	[redacted]	[redacted]

Except for the Number of AEs, subjects are counted only once per treatment in each row. SAEs – according to the Investigator's assessment. MedDRA (v18.1) coding dictionary applied.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; mg, milligram; n, number of subjects that met the criteria; PBO, placebo; SAE, serious adverse event, TOF, tofacitinib

Figure 13: Total Prevalence (%) of All Causality AEs (Including SAEs) Reported up to 3 Months and 6 Months for OPAL Beyond



Abbreviations: AE, adverse event; mg, milligram; SAE, serious adverse event
*PBO indicates the group that received placebo treatment during the 3-month placebo-controlled period and was switched to tofacitinib 5 mg BD treatment at Month 3[redacted]

The incidence of all causalities AEs up to Month 3 was generally similar between groups, with the most-common AEs being headache, nasopharyngitis, and upper respiratory tract infection.

- Headache: 3.8% of subjects in the tofacitinib 5 mg BD group and 5.3% of subjects in the placebo group.
- Nasopharyngitis: 7.6% of subjects in the tofacitinib 5 mg BD group and 2.3% of subjects in the placebo group.
- Upper respiratory tract infection: 7.6% of subjects in the tofacitinib 5 mg BD group and 4.6% of subjects in the placebo group.

[redacted]RR ratios up to Month 3 for tofacitinib 5 mg BD vs placebo comparisons are summarised in **Table 36** and **Figure 14**. Compared to the placebo group, [redacted]Compared to the placebo group, [redacted]

Table 36: Incidence of AEs Up to Month 3 in OPAL Beyond (Tier 2, Occurring in >=4 Subjects in Any Treatment Group) (Safety Analysis Set, All Causalities)

Outcome: System Organ Class (preferred term)	TOF 5mg (N=131) n (%)	PBO (N=131) n (%)	RR for TOF vs PBO	
			RR	95% CI
Gastrointestinal disorders				
Diarrhoea	6 (4.6)	1 (0.8)	[redacted]	[redacted]
Nausea	4 (3.1)	7 (5.3)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations				
Nasopharyngitis	10 (7.6)	3 (2.3)	[redacted]	[redacted]

Upper respiratory tract infection	10 (7.6)	6 (4.6)	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders				
Dizziness	6 (4.6)	1 (0.8)	[redacted]	[redacted]
Headache	5 (3.8)	7 (5.3)	[redacted]	[redacted]
Vascular disorders				
Hypertension	4 (3.1)	2 (1.5)	[redacted]	[redacted]

Note: The Gladman publication (88) reports data for AEs that occurred at a rate of ≥5% in at least one of the treatment groups (TOF 5mg, TOF 10mg, or PBO); AEs that occurred at a rate lower than 5% are reported in the CSR only, and therefore are marked as confidential.

Abbreviation: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; mg, milligram; [redacted] PBO, placebo; RR, relative risk; TOF, tofacitinib

Only displaying AEs with a frequency of at least 4 counts in any treatment group. They are not adjusted for multiplicity and should be used for estimation purposes only.

[redacted]

Figure 14: AEs Up to Month 3 (Tier 2, Occurring in >=4 Subjects in Any Treatment Group) Comparing Tofacitinib 5 mg BD and Placebo in OPAL Beyond (Safety Analysis Set, All Causalities)

[redacted]

- ***Common AEs reported up to Month 6***

Up to Month 6, the percentage of subjects with AEs (all causalities) was higher in the tofacitinib 5 mg BD (71%) than in the placebo→tofacitinib 5 mg BD (61%) group. A summary of AEs reported up to Month 6 is presented in **Table 37**.

Table 37: Summary of AEs Reported Up to Month 6 (Safety Analysis Set, All Causalities) for OPAL Beyond

Outcome	TOF 5mg, n (%)	PBO →TOF 5mg, n (%)*
Subjects evaluable for AEs	131	66
[redacted]	[redacted]	[redacted]
Subjects with AEs	93 (71)	40 (61)
Subjects with SAEs	5 (4)	2 (3)
[redacted]	[redacted]	[redacted]

Except for the Number of AEs, subjects are counted only once per treatment in each row.
SAEs – according to the Investigator's assessment. MedDRA (v18.1) coding dictionary applied.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; mg, milligram; n, number of subjects that met the criteria; PBO, placebo; SAE, serious adverse event, TOF, tofacitinib
*Group that received placebo treatment during the 3-month placebo-controlled period and was switched to tofacitinib 5 mg BD treatment at Month 3

The incidence of all-causalities AEs up to Month 6 was generally similar between groups, with the most common AEs being headache, nasopharyngitis, and upper respiratory tract infection.

- Headache: 7.6% of subjects in the tofacitinib 5 mg BD group and 4.5% of subjects in the placebo→tofacitinib 5 mg BD group.
- Nasopharyngitis: 10.7% of subjects in the tofacitinib 5 mg BD group and 6.1% of subjects in the placebo→tofacitinib 5 mg BD group.
- Upper respiratory tract infection: 9.2% of subjects in the tofacitinib 5 mg BD group and 6.1% of subjects in the placebo→tofacitinib 5 mg BD group.

B.2.11.2.2 AEs of special interest

Full details of AEs of special interest are reported in Appendix M. No cancers, gastrointestinal perforations, interstitial lung disease, or cases of M. tuberculosis infection were reported.

Table 38: Summary of adverse events of special interests for OPAL Beyond (Safety Analysis Set, All Causalities)

	Up to Month 3		Up to Month 6	
	TOF 5 mg (N=131)	PBO (N=131)	TOF 5 mg (N=131)	PBO→TOF 5 mg (N=66)*
AE of special interest, n (%) [day of onset]†				
Serious infection	0	0	2 (2) [days 166 and 135]‡	0
Herpes zoster infection§	1 (1) [day 77]	0	1 (1) [day 77]	0
Adjudicated opportunistic infection	1 (1) [day 77]	0	1 (1) [day 77]	0
Adjudicated major cardiovascular event¶	0	0	1 (1) [day 245]‖	0

Abbreviations: AE, adverse event; mg, milligram; n, number of subjects that met the criteria; PBO, placebo; TOF, tofacitinib
‡ One patient had pneumonia and one had oral candidiasis.
§ The cases of herpes zoster infection were not judged to be serious adverse events.
¶ A major adverse cardiovascular event included any myocardial infarction, cerebrovascular event (nonfatal stroke), or cardiovascular death.
‖ One patient had a myocardial infarction.
*Group that received placebo treatment during the 3-month placebo-controlled period and was switched to tofacitinib 5 mg BD treatment at Month 3

B.2.11.2.3 Deaths

There were no deaths reported during the course of the study.

B.2.11.3 OPAL Balance

B.2.11.3.1 Common AEs reported up to Month 36

Up to Month 36, 1,685 AEs had been reported in 502 (73.2%) subjects. The most common AEs were respiratory tract infection (11.4%), nasopharyngitis (10.6%), and urinary tract infection (6.4%). A summary of AEs reported up to Month 36 is presented in **Table 39**.

Table 39: Summary of AEs Reported up to Month 36 (Safety Analysis Set, All Causalities) for OPAL Balance

Outcome	TOF (5 mg and 10 mg), n (%)
Subjects evaluable for AEs	686
Number of AEs	1685
Subjects with AEs	502 (73.2)
Subjects with SAEs	72 (10.5)
Subjects with severe AEs	57 (7.6)

Abbreviations: AE, adverse event; mg, milligram; n, number of subjects that met the criteria; SAE, serious adverse event, TOF, tofacitinib

B.2.11.3.2 AEs of special interest up to Month 36

Full details of AEs of special interest are reported in **Appendix M**. No cases of gastrointestinal perforation or inflammatory bowel disease were reported. One case of uveitis was reported.

- ***Tuberculosis***

Up to Month 36, four AEs of latent TB were reported in subjects whose previously negative QuantiFERON response became positive; however, no cases of active TB were reported.

- ***Serious infection/herpes zoster***

Up to Month 36, 11 (1.6%) subjects reported serious infection events. There were 19 (2.8%) cases of herpes zoster reported, of which a case of facial herpes zoster was a SAE. There were 17 cases of single dermatome herpes zoster and two cases of multidermatomal herpes zoster. The two cases of multidermatomal herpes zoster were adjudicated as opportunistic infections; no non-herpes zoster, non-TB opportunistic infections were reported.

- ***Cardiovascular events***

Up to Month 36, two (0.3%) subjects reported major cardiovascular AEs.

- ***Cancer***

Thirteen (1.9%) subjects reported malignancies.

B.2.11.3.3 Deaths up to Month 36

Four (0.6%) subjects died up to Month 36: one subject died due to pancreatic adenocarcinoma, one subject died due to acute cardiac failure secondary to hypertensive heart disease, one subject died due to chronic obstructive pulmonary disease, and one subject died due to pulmonary embolism.

B.2.11.4 Safety overview

Over eight years of observation through the tofacitinib RA clinical programme of studies (85, 119) and more than 19,400 patient-years of experience (85, 119) have demonstrated that the rates of AEs are stable over time and are similar to bDMARDS for RA, with the exception of herpes zoster (85, 119-143). Overall, tofacitinib 5 mg BD demonstrated an acceptable safety profile in PsA across the Phase III clinical trial programme (OPAL Broaden and OPAL Beyond) that is well-characterised, stable, and clinically manageable. The rate of SAEs was low across OPAL Broaden and OPAL Beyond; the most frequent AEs reported throughout the Phase III trials were nasopharyngitis, upper respiratory infection, and headache. The types and rates of common AEs (including infections and malignancies) were generally comparable to those seen in the RA clinical programme.

[redacted]

To provide long-term safety information, interim data from the LTE study OPAL Balance were analysed. As of January 25, 2017, no new risks or safety signals were identified in the LTE data from the tofacitinib PsA 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. Recommendations on how to appropriately manage risks associated with tofacitinib (including vaccinations and risks of serious infection) are outlined within the SmPC (16).

In a health claims database study conducted in an American cohort of PsA patients, the incidence of most AEs reported in tofacitinib PsA phase III studies was generally comparable with that observed in a general PsA population, with the exception of the rates of herpes zoster, which were somewhat higher in the tofacitinib cohort than in the real-world comparison cohort (Truven Marketscan Comparison Cohort) (144).

B.2.12 Ongoing studies

B.2.12.1 OPAL Balance

Patients from OPAL Broaden and OPAL Beyond studies were eligible to enter the OPAL Balance (3-year LTE study) ≤3 months after completing or discontinuing the qualifying study for reasons not related to the study drug. Interim data for OPAL Balance are available up to April 4, 2016 for tofacitinib 5 mg BD group and pooled tofacitinib 5 mg BD and 10 mg BD group efficacy data, as measured by the HAQ-DI, up to Month 27 (see **Section B.2.7.1** and **Appendix M**), and January 25, 2017 for pooled efficacy and safety data on tofacitinib 5 mg BD and 10 mg BD doses (see **Section B.2.8.8** for efficacy data up to Month 24 and **Section B.2.10.3** and **Appendix M** for safety data up to Month 36).

B.2.13 Innovation

Following the era of bDMARDs, there is a re-emergence of small-molecule clinical development programmes in PsA. Additionally, as our understanding of the pathogenesis of PsA increases, the parallel evolution of increasingly selective therapies may provide patients with an optimal balance between increased clinical benefit and the reduced risk for side effects (145). Large-molecule bDMARDs disrupt cytokine signalling in the extracellular space by inhibiting receptor activation usually causing complete blockade (145-147). Small-molecule agents target intracellular signal transduction pathways and have important dose-response relationships (the extent of target inhibition may vary with dose of drug) (147, 148). Tofacitinib acts intracellularly to inhibit the phosphorylation and activation by preferentially inhibiting signalling by heterodimeric cytokine receptors associated with JAK1 and JAK3 (6, 149, 150).

As a first-in-class oral treatment with a novel mechanism of action, tofacitinib represents a step-change in the management of PsA. Tofacitinib provides a rapid onset, highly-efficacious, orally-administered treatment option for adult patients with active PsA who have previously had an inadequate response to csDMARDs and are TNFi-naïve, and those patients with an inadequate response to a TNFi. In the OPAL trial programme, tofacitinib demonstrated efficacy across the spectrum of relevant disease domains: peripheral arthritis, enthesitis, dactylitis, and skin manifestations, as well as physical functioning and patient-reported outcomes. Tofacitinib offers a broad and novel mode of action through its inhibition of JAK, which modulates multiple cytokines specifically associated with the pathogenesis of PsA. As a targeted small molecule (i.e., a tsDMARD), tofacitinib would be expected to lack the clinically significant immunogenicity often observed with parenterally-administered TNFis in PsA (83, 151).

The mode of administration may be important in adherence to treatment in RA (152, 153), and oral therapy has been reported to be preferential over subcutaneous injection and intravenous infusion in patients with PsA (38, 154). As an oral therapy, tofacitinib represents a convenient treatment option for working-age adults, especially those with frequent national or international travel because it does not require refrigeration, is easy to travel with, and would be an option for cases of needle phobia (25).

Due to its convenient and preferential route of administration, tofacitinib may have the potential to improve treatment adherence and support the medicines optimisation agenda. In a recent NHS England update (2018) on prescribing responsibility across interfaces, disease –specific shared care arrangements are described as a mechanism of providing access, choice and convenience for patients (155). With appropriate and robust agreements in place, tofacitinib has the potential to offer an alternative PsA treatment in community settings.

B.2.14 Interpretation of clinical effectiveness and safety evidence

B.2.14.1 Principal findings from the clinical evidence highlighting the clinical benefits and harms of the technology

Overall, tofacitinib 5 mg BD has been shown to be an effective treatment for patients with active PsA who previously had an inadequate response to csDMARDs and were TNFi-naïve and patients who previously had an inadequate response to a TNFi. This evidence supports the submission for reimbursement in patients with active PsA whose disease has not responded adequately to previous DMARD therapy or for whom DMARDs are not tolerated or contraindicated. Tofacitinib 5 mg BD resulted in significant improvements in the signs and symptoms of PsA and physical functioning compared with placebo at Month 3. Significant improvements occurred as early as week 2 for ACR20, a key measure of the signs and symptoms of PsA. Among those patients who had previously had an inadequate response to at least one csDMARD and were TNFi naïve, OPAL Broaden revealed efficacy of tofacitinib 5 mg BD that was similar in a numerical sense to adalimumab for primary outcomes and radiographic progressor/non-progressor rates (although it is important to note that the study was not powered to formally compare tofacitinib with adalimumab). Tofacitinib 5 mg BD was also associated with a reduction in patients' levels of fatigue and itch severity and improved overall quality of life in patients. Results from the LTE study, OPAL Balance, demonstrated that the efficacy of tofacitinib was generally sustained for up to 24 months (January 2017 data cut, FAS) with respect to signs and symptoms of PsA and physical functioning; however, the preliminary findings from that data cut were not separated by tofacitinib dose (that is, the 5 mg BD and 10 mg BD doses were combined). An earlier interim data-set from OPAL Balance

([redacted] Results from the base case NMAs indicated that tofacitinib 5mg BD was similarly efficacious to comparator b/tsDMARDs in the bDMARD-naïve population, with the exception of PsARC response where the odds of

response were significantly lower compared with etanercept, infliximab and golimumab. In the bDMARD-experienced population (base case NMAs), tofacitinib 5mg BD was similarly efficacious to ustekinumab with the exception of PASI 50/75/90 where odds of responses were significantly lower (see **Section B.2.10**).

Tofacitinib 5mg BD is an oral therapy that is well tolerated in patients with active PsA and has a safety profile which is broadly consistent with other NICE-approved bDMARDs (69, 156-162) (see **Section B.2.11**).

B.2.14.2 Strengths and limitations of the clinical evidence base for the technology

B.2.14.2.1 Strengths of the evidence base

The two Phase III clinical trials (OPAL Broaden and OPAL Beyond) of tofacitinib were multicentre, 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 active PsA (≥3 tender/painful and ≥3 swollen joints), which represents the patients that may receive tofacitinib 5 mg BD 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. Furthermore, the relevance of the trial population to the UK PsA population was apparent in both trials, with [redacted] and [redacted] of patients receiving tofacitinib 5 mg BD in OPAL Broaden and OPAL Beyond, respectively, having previous exposure to MTX. This level of previous csDMARD use (e.g., MTX) would be consistent with the recommendations of NICE and BSR clinical guidelines (54). The dose of MTX provided across the trials was also consistent with UK prescribing practice (163).

The endpoints measured across the Phase III trials were well-recognised, clinically-relevant outcomes and were consistent with clinical practice in the UK (2, 164). These outcomes also covered aspects identified as important in the treat-to-target recommendations of PsA, including minimal disease activity (MDA), signs and symptoms of the disease, physical functioning, radiographic progression, and quality of life (22, 55, 56). All co-primary endpoints were met for the tofacitinib 5 mg BD group in OPAL Broaden and OPAL Beyond. Furthermore, the LTE study, OPAL Balance, demonstrates that the magnitude of response achieved with tofacitinib is generally sustained up to 24 months. This includes HAQ-DI data which were used to inform the economic model presented in **Section B.3.2**.

The statistical analyses employed across the tofacitinib clinical trials were robust and conservative in nature. Due to the number of 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 B.2.4.2**). At a given endpoint, tofacitinib 5 mg BD could only achieve significance if both tofacitinib 10 mg BD at the same endpoint and tofacitinib 10/5 mg BD at the prior endpoint were significant.

The data supporting the safety of tofacitinib 5 mg BD are comprehensive and include interim data of a LTE study reporting safety data up to 36 months. Overall, tofacitinib 5 mg BD is well tolerated with a stable AE profile over time. The potential increased risk of infections has been well-characterised across the tofacitinib clinical development programme and shows that the incidence rate of infections is low and stable over time. An elevated risk of infections is well established with bDMARDs (and routinely managed by clinical teams) in RA and PsA.

B.2.14.2.2 Potential limitations of the evidence base

Although a comparison with adalimumab was made in OPAL Broaden, no other active comparators were included in the tofacitinib PsA clinical trials. As the OPAL Broaden study was not designed or powered for evaluation of non-inferiority or superiority between tofacitinib and adalimumab, no formal conclusions can be made regarding their comparability.

A relatively high rate of placebo response was observed in the OPAL trials with regard to the primary efficacy measure of ACR20, as well as other semi-subjective outcomes, such as PsARC and PASI responses. Both Phase III trials were powered under the assumption of a placebo response rate for ACR20 of 15%; however, the placebo group had a higher ACR20 response at Month 3 than anticipated (33.0% in OPAL Broaden and 24.0% in OPAL Beyond). This so called placebo creep effect has been observed in previous studies involving patients with PsA and may have impacted the conclusions that could be drawn from the differences between tofacitinib 5 mg BD and placebo (97, 160). It is also likely to have created greater uncertainty in the interpretation of the differences between tofacitinib 5 mg BD compared to placebo and relevant comparators in the NMAs.

As previously discussed in the TA445 AG report (3), examination of the patient baseline characteristics across trials offers no clear reason as to why placebo response rates in trials of bDMARD treatments have increased over time. In the case of PsARC, response rates have noticeably increased from 2013 onwards, starting with the PSUMMIT trials that examined ustekinumab for the treatment of PsA (94). It has been suggested that patient and clinician expectations may have been increasing in recent years, as a result of growing confidence in the benefits of bDMARDs, and that semi-subjective patient- and clinician-reported outcomes such as the PsARC, ACR response and PASI may be particularly susceptible to such expectation effects (94). The theory of growing confidence in the benefit of bDMARDs may explain why an elevated placebo PsARC response rate at Month 3 was observed in OPAL Broaden (45%) and an elevated placebo PASI75 and ACR70 response rate was observed in OPAL Beyond at Month 3 (14% and 10%, respectively).

Similarly, beginning with the PSUMMIT trials, there has been a trend for increases in the number of active treatment arms offered in clinical trials, with the number of active arms growing from one active arm in the early trials to two or more active arms in more recent trials; as a result, patients in the more recent trials may be more confident and optimistic about the likelihood that they are receiving an active treatment (94). Lastly,

anecdotal feedback from clinical experts consulted as part of the UK NICE company evidence submission, suggested that the placebo creep in PsA trials may be explained by: anecdotal pressure to stay in clinical trials where medication provision is poor; co-medication effects through greater encouragement to take DMARDs to improve medication adherence/compliance; and potentially having to find “milder” patients in a competitive clinical trial environment. A meta-regression analysis was undertaken to explore the effect of differences in trial-specific placebo responses on treatment effect, based on the approach used in TA445; results are presented above in **Section B.2.10**.

Demonstrating radiographic outcomes has become more difficult in the modern era, as early access to treat-to-target strategies have become more commonplace. The design of a study is also complicated by the ethical necessity to limit patient exposure to placebo. The efficacy of tofacitinib 5 mg BD (combined with a background csDMARD) with regard to radiographic outcomes was examined in OPAL Broaden. The radiographic progressor rates (ΔmTSS>0.5) and the mean change from baseline in mTSS comparing tofacitinib 5 mg BD and adalimumab 40 mg Q2W were not significant (note: the study was not powered to assess the efficacy of tofacitinib with adalimumab, so no formal conclusions can be made); clinical experts indicated that the difference in mean change from baseline in mTSS would not be considered clinically significant. Furthermore, the OPAL Broaden study was powered under the assumption of a true progression rate of 10% with a half-width 95% CI of 8.5% in the tofacitinib and adalimumab groups; given that the progressor rates were considerably smaller in the actual study ([redacted] for adalimumab 40 mg Q2W and tofacitinib 5 mg BD, respectively), this may have further impacted the conclusions that could be drawn regarding the impact of the two treatments on radiographic progression.

Despite the statistical limitations of OPAL Broaden in relation to formal conclusions that could be drawn on comparisons of tofacitinib 5 mg BD with adalimumab 40 mg Q2W, mean change from baseline in mTSS was minimal (tofacitinib 5mg BD = 0.01 at month 12), numerically and clinically similar, and mTSS progressor rates were low and numerically similar, comparing the two groups. However, it has been reported that

prognostic factors for radiographic progression in the OPAL Broaden clinical trial were different (lower) (e.g., baseline CRP levels, baseline mTSS, baseline erosion and joint space narrowing scores) than a number of previous bDMARD studies in PsA (165). Coupled with the different trial designs and patient characteristics of some of these previous bDMARD studies (e.g., different requirements for concomitant csDMARD use), this has raised questions about assay sensitivity of the OPAL Broaden trial (165). Nonetheless, these results were observed in a trial population where a large proportion of patients were at high risk for structural progression, i.e., 64% and 60% of patients had an elevated hsCRP level (>2.87 mg/l) and 90% and 93% of patients had a mTSS score greater than 0 at baseline in the tofacitinib 5 mg BD and adalimumab 40 mg Q2W groups, respectively (40, 87).

Previous research suggests that there may be a link between radiographic damage and physical function in PsA patients, which is particularly evident in patients whose disease is not controlled (166). Results from a recent study suggest that physical function is affected by structural damage, particularly joint space narrowing, as evidenced by HAQ-DI scores that increase (indicating a decrease in physical function) with higher van der Heijde mTSS; however, the relationship is not strong (166). In a clinical context, the analysis conducted in the cohort of patients in DAPSA (Disease Activity Index for Psoriatic Arthritis) remission (to mitigate the impact that disease activity may have on HAQ-DI), indicated that a patient with a van der Heijde mTSS of 10, 50, 100 and 150 would have predicted residual HAQ-DI values of 0.02, 0.1, 0.2, and 0.3, respectively (a similar trend was also found in the analysis of all patients, adjusted for DAPSA). It was therefore asserted that patients with longstanding PsA and/or substantial radiographic damage would experience a clinically meaningful change (MCID ≥0.3) in HAQ-DI. To further contextualise this, the baseline mean mTSS in OPAL Broaden was 17.6 (placebo), 17.1 (tofacitinib 5 mg BD) and 14.4 (adalimumab 40 mg Q2W). Given a potential relationship between structural damage progression and functional outcomes, the stability of the improvement in physical functioning in the OPAL Broaden study may be suggestive of a positive impact of tofacitinib 5 mg BD oral therapy on disease progression in PsA.

B.3 Cost effectiveness

- A Markov cohort model was developed to evaluate the cost-effectiveness of tofacitinib 5 mg BD versus NICE-recommended comparators from the perspective of the NHS and PSS.
- The model followed a two-step approach, utilising PsARC (and PASI) response criteria to assess short-term efficacy at week 12 post-treatment initiation, and HAQ-DI to capture longer-term outcomes.
- The model structure, methods, and assumptions reflect the approach taken by the York Assessment Group in the recent NICE multiple technology appraisal, TA445, published in May 2017 (3).
- To align with current NICE guidance, three of the four sub-populations outlined in the final NICE scope have been considered:
    - Sub-population 2: People whose disease has not responded adequately to at least 2 non-biological DMARDs
    - Sub-population 3: People whose disease has not responded adequately to non-biological DMARDs and 1 or more TNFis
    - Sub-population 4: People in whom TNFis are contraindicated or not tolerated
- Tofacitinib clinical data from OPAL Broaden (bDMARD-naïve population), OPAL Beyond (bDMARD-experienced population), and OPAL Balance (open label, LTE study) were used to inform the key clinical outcomes considered in the analysis.

Base Case Analysis:

The base case analysis considers PAS prices for tofacitinib 5 mg BD (PAS for RA; TA480) and comparators, where publicly available.

Sub-population 2: People whose disease has not responded adequately to at least 2 non-biological DMARDs

- The ICERs for tofacitinib 5 mg BD vs BSC were [redacted] per QALY (deterministic) and [redacted] per QALY (mean of probabilistic); tofacitinib 5mg BD was extendedly dominated in fully incremental analyses [redacted].
- Probabilistic sensitivity analyses showed that the mean of 10,000 ICERs for tofacitinib 5 mg BD [redacted] per QALY) was consistent with the deterministic ICER and [redacted] of the 10,000 ICERs were below £20,000 and £30,000 per QALY, respectively.

Sub-population 3: People whose disease has not responded adequately to non-biological DMARDs and one or more TNFis

- The ICERs for tofacitinib 5 mg BD vs BSC were [redacted] per QALY (deterministic) and [redacted] per QALY (mean of probabilistic).
- Probabilistic sensitivity analyses showed that the mean of 10,000 ICERs for tofacitinib 5 mg BD was consistent with the deterministic ICER. Of those 10,000 ICERs, [redacted] were below £20,000 and £30,000 per QALY, respectively.

Sub-population 4: People in whom TNFis are contraindicated or not tolerated

- The ICERs for tofacitinib 5 mg BD vs BSC were [redacted] per QALY (deterministic) and [redacted] per QALY (mean of probabilistic).
- Probabilistic sensitivity analyses showed that the mean of 10,000 ICERs for tofacitinib 5 mg BD was consistent with the deterministic ICER, and [redacted] of the 10,000 ICERs were below £20,000 and £30,000 per QALY, respectively.

Scenario Analyses:

- In scenario analyses, the ICER for the tofacitinib 5mg BD sequence vs BSC did not exceed £30,000 per QALY under any scenario and was generally under £20,000
- In a scenario using clinical effect estimates for tofacitinib 5mg BD and adalimumab directly from the OPAL Broaden clinical trial, tofacitinib 5mg BD was more cost effective than adalimumab

Conclusion:

- Results of the base case analysis show the tofacitinib 5 mg BD sequence to be a cost-effective option (at conventional willingness to pay thresholds) vs BSC for sub-populations 2, 3 and 4. In each of the three sub-populations assessed, the deterministic and probabilistic ICER for tofacitinib 5 mg BD vs BSC was below £20,000 per QALY.
- Probabilistic analysis confirmed the deterministic results, suggesting that the tofacitinib 5 mg BD sequence was associated with a high probability of being cost-effective in all sub-populations versus BSC, and was associated with the highest probability of being the optimal treatment at conventional willingness to pay thresholds in sub-populations 3 and 4.
- These results suggest that tofacitinib 5 mg BD represents a cost-effective use of NHS resources in sub-populations 2, 3, and 4.

B.3.1.1 Identification of studies

A systematic review was conducted to identify cost-effectiveness studies relevant to the decision problem from the published literature. The systematic review was performed in accordance with the methodological principles of conduct for systematic reviews as

detailed in the University of York Centre for Reviews and Dissemination's (CRD) "Guidance for Undertaking Reviews in Health Care." A complete description of the search strategy is presented in **Appendix G**.

B.3.1.2 Description of identified studies

No previously published cost-effectiveness studies of tofacitinib for PsA were identified.

The systematic review identified 17 studies that met the inclusion criteria for the broader set of comparators. From those, 14 UK studies were identified. These are summarised in **Appendix G**. Five of the UK studies were HTA monographs or indexed publications of the ERG reports related directly to the following previous appraisals: TA199 (2, 111), TA220 (47, 167), TA340 (168), TA445 (4), and the original appraisal of infliximab and etanercept, TA104 (169, 170). Three were review articles summarising previous appraisals: TA220 (171), TA340 (172), and TA433 (173). A further two were subsequent journal publications based on past appraisals (174, 175). Cawson et al., 2014 (176) provided an update to the systematic review, evidence synthesis and model from TA199 (2, 111). Cummins et al., 2011 (177) and Cummins et al., 2012 (112) presented analyses of infliximab and golimumab, respectively. Bansback et al., 2006 (178) compared etanercept to sequences beginning with either leflunomide or methotrexate plus cyclosporin. The three remaining studies (179-181) were from Canada (n=2) and Italy (n=1).

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the overall flow of studies across the review is shown in Figure 1 in **Appendix G**. A complete list of studies excluded after the full-text review stage is presented in **Appendix G**.

B.3.1.2.1 Health Technology Appraisals

Summaries of the most recent HTA appraisals for relevant comparators (n=28) are included in **Appendix G**. Of the four HTA bodies searched, CADTH had six relevant appraisals (biosimilar appraisals not included), NICE had six, PBAC had six and SMC had eight, all ranging from 2005–2017.

Table 40: Health Technology Assessments

	CADTH	NICE	SMC	PBAC	Total
Abatacept			✓		1
Adalimumab	✓	✓	✓	✓	4
Apremilast	✓	✓	✓	✓	4
Certolizumab Pegol	✓	✓	✓		3
Etanercept		✓	✓	✓	3
Golimumab	✓	✓	✓		3
Infliximab		✓		✓	2
Secukinumab	✓	✓	✓	✓	4
Ustekinumab	✓	✓	✓	✓	4

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; SMC, Scottish Medicines Consortium

B.3.2 Economic analysis

As indicated above, no existing economic analyses were identified that considered the cost-effectiveness of tofacitinib in combination with a csDMARD for this indication. Therefore, a *de novo* economic evaluation (model) was required. Previous economic analyses in PsA have been used to inform the model's structure, assumptions and data sources, as outlined below.

B.3.2.1 Patient population

The patient population represented in the cost-effectiveness analysis includes adults with active PsA who have not responded adequately to previous DMARDs or for whom DMARDs are not tolerated or contraindicated. Four sub-populations were requested in the NICE scope:

1. People whose disease has not responded adequately to 1 non-biological DMARD

Please note: Pfizer seek to align the sub-populations assessed in the technology appraisal (TA) of tofacitinib for treating active PsA following csDMARDs to the populations that have received positive recommendations from NICE in previous TAs (i.e., sub-populations 2, 3, and 4); consequently, we have not submitted results for sub-population 1.

2. People whose disease has not responded adequately to at least 2 non-biological DMARDs

3. People whose disease has not responded adequately to non-biological DMARDs and 1 or more TNFis

4. People in whom TNFi are contraindicated or not tolerated

Relevant end-points for these sub-populations were informed by two key Phase III clinical trials, OPAL Broaden and OPAL Beyond (87, 88). Sub-populations 2 and 4 were informed by the bDMARD-naïve evidence synthesis with data for tofacitinib from OPAL Broaden (csDMARD-IR and TNFi-naïve) (87); and sub-population 3 was informed by the bDMARD-experienced evidence synthesis with data for tofacitinib from OPAL Beyond (TNFi-IR) (88).

B.3.2.2 Model structure

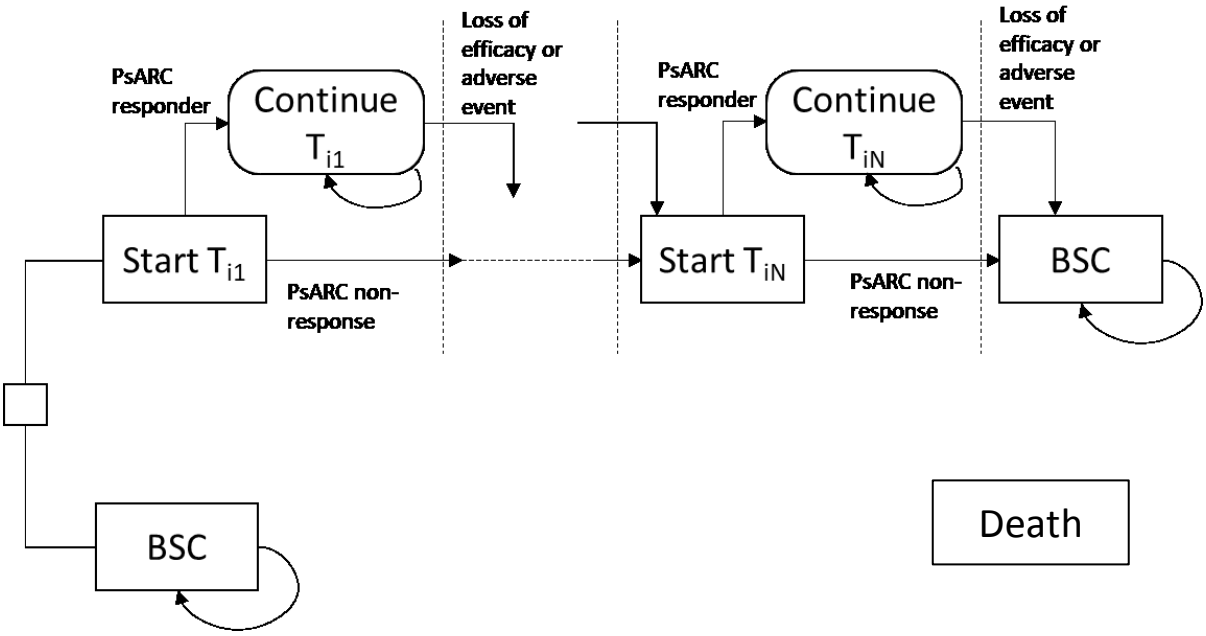
A Markov cohort model was developed in Microsoft Excel® to evaluate the cost-effectiveness of tofacitinib 5 mg BD and comparators from the perspective of the NHS and PSS. Markov cohort models have been used in many previous NICE appraisals in PsA (2, 3, 47); the model structure is based on the modelling approach used by the York Assessment Group (AG) (4) in TA445 (3).

The model compares the cost-effectiveness of treatment sequences including either tofacitinib 5 mg BD or its licensed comparators for the treatment of adults with active PsA in the sub-populations defined in the NICE scope, with the exception of sub-population 1 (**Section B.3.2.1**). The treatment sequences used for each sub-population are reflective of current NICE guidance and reflect the sequences used in TA445 (3) (as detailed in **Section B.3.2.3** and **Table 42**).

The model allows patients to cycle through lines of therapy, with patients remaining on a treatment after the first 3 months if they have met the required response criteria (i.e., a Psoriatic Arthritis Response Criteria [PsARC] response) (**Section B.3.3.1.1**). After initial

response to treatment, patients remain on therapy until either a loss of efficacy, the occurrence of particular adverse events, or death (**Figure 15**).

Figure 15: Model schematic



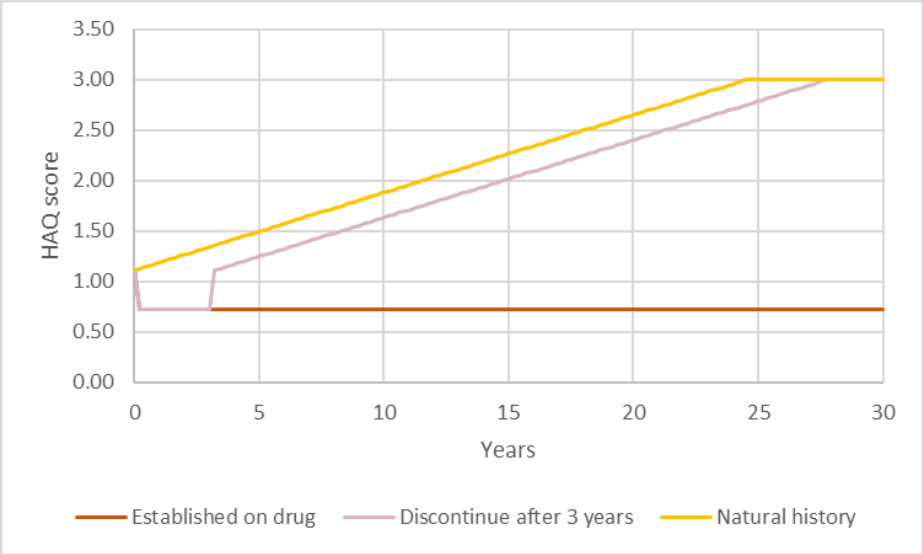
Patients may transition to the death state from any other state. Abbreviations: BSC, best supportive care; PsARC, Psoriatic Arthritis Response Criteria; T_{i1}, first therapy in the i^{th} sequence; T_{iN}, n^{th} therapy in the i^{th} sequence.

In the base case, the model uses PsARC response rates at 3 months (**Section B.3.3.1.1**) to determine the proportion of patients remaining on treatment. This approach reflects clinical management of the condition as recommended by NICE (2, 3, 47-49) and the BSR (54). Following the initial response (or non-response) to treatment at 3 months, the arthritis- and psoriasis-specific components of PsA are modelled separately.

The arthritis component of PsA is modelled via a change in Health Assessment Questionnaire-Disability Index (HAQ-DI) score conditional on PsARC response (**Section B.3.3.1.3**); at 3 months, patients are assigned a HAQ-DI change based on their response to treatment and the particular treatment they received. In PsARC responders, HAQ-DI change from baseline is maintained beyond 3 months in line with previous modelling approaches, such as that adopted by the AG in TA445 (3), with the exception of apremilast (as per TA433; see **Section B.3.3.1.6** for further detail) and

best supportive care (BSC), whereby HAQ scores increase in a linear fashion (see Error! Reference source not found.) (2).

Figure 16: HAQ score changes over time



Abbreviations: HAQ, Health Assessment Questionnaire.

Error! Reference source not found. illustrates the progression in HAQ-DI trajectories over time for three types of patients: a patient successfully established on a bDMARD; a patient discontinuing after 3 years (and transitioning to BSC); and a patient receiving BSC. When patients discontinue treatment, it is assumed that they experience a rebound in HAQ-DI and PASI scores equal to their initial gains. These assumptions are in line with the York AG model (4) from TA445 (3).

The psoriasis component of PsA is modelled via changes in Psoriasis Area and Severity Index (PASI) scores, which are assumed to be correlated with PsARC responses. The psoriasis component of PsA is assumed to not be progressive and therefore PASI scores do not increase while patients remain on therapy (3) or BSC.

For all outcomes (PsARC response, PASI response, and HAQ-DI change conditional on PsARC response), response rates for tofacitinib 5 mg BD and its comparators were taken from the network meta-analyses (NMAs), where available, as outlined in **Section 0**. In the bDMARD-experienced population (sub-population 3), it was only possible to

estimate the model of PsARC response for tofacitinib 5 mg BD, ustekinumab and placebo due to a lack of response data available in primary and secondary publications. To include PsARC response for secukinumab in the economic model, the odds ratio for secukinumab 300 mg versus placebo was taken from the base-case analysis for the bDMARD-experienced population from TA445 (3). HAQ-DI change conditional on PsARC response was not available in either the naïve or experienced populations for secukinumab and certolizumab, therefore the values from the TA445 meta-regression NMA of HAQ scores have been incorporated into the model for these comparators in the bDMARD naïve populations. In the bDMARD experienced population the values have been taken from the TA445 bDMARD experienced NMA (3).

A half-cycle correction has not been applied as the cycle length is short (182) and, as stipulated by NICE guidance, response to treatment should be assessed at 3-monthly intervals which are reflected in the cycles of the model (2, 3, 47-49). The primary outcomes are total costs, QALYs, and the incremental cost-effectiveness ratio (ICER). A 3.5% annual discount rate is applied to costs and QALYs.

B.3.2.2.1 Comparison with models submitted in other NICE technology appraisals

There have been six previous NICE technology appraisals for psoriatic arthritis (only five are available for comparison, as one has been withdrawn). **Table G29** in **Appendix G** summarises the main inputs to the economic models accepted by appraisal committees in these five appraisals. The model structure presented here follows the approach used in TA445, with two minor alterations:

1. Mortality is modelled using England and Wales life tables directly, while previous models have fit a Gompertz distribution to life tables; and
2. PASI subgroups have been modelled together in contrast to TA445 analysis which modelled PASI subgroups separately (**Section B.3.2.2.1.1**).

B.3.2.2.1.1 Baseline levels of psoriasis

To reflect differences in baseline levels of psoriasis, each sub-population (as defined in the NICE scope) is divided into subgroups. As per TA445 (3), the population was split into 50% with no psoriasis, 25% with mild to moderate psoriasis, and 25% with moderate to severe psoriasis (**Table 41**); this assumption was based on a 2009 report by the British Association of Dermatologists (183).

Table 41: Distribution of psoriasis patients and baseline PASI scores within the economic model

	Without psoriasis	Mild to moderate psoriasis	Moderate to severe psoriasis
% of population	50%	25%	25%
Baseline PASI score	0.0	7.3	12.5

Abbreviations: PASI, Psoriasis Area and Severity Index.

PASI response was assessed separately for each subgroup defined by its baseline level of psoriasis (i.e., no psoriasis, mild to moderate psoriasis, and moderate to severe psoriasis, as in **Table 41**). A weighted average PASI score of these three subgroups was then calculated for the entire population, for each model cycle. This differs from the approach taken in TA445, where PASI responses were separately modelled for each baseline level of psoriasis. This approach was taken in TA445 because the 300 mg dose of secukinumab is only licensed for patients with severe psoriasis, which does not apply for tofacitinib 5mg BD.

B.3.2.3 Intervention technology and comparators

The intervention technology is tofacitinib 5 mg BD in combination with a csDMARD, which is expected to receive a Marketing Authorisation for the treatment of active PsA in adult patients who have had an inadequate response or have been intolerant to a prior DMARD therapy.

The comparator technologies include TNFis (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), secukinumab (an IL17A inhibitor), ustekinumab

(an IL12/IL23 inhibitor), apremilast (a PDE4 inhibitor), and BSC. These comparators are implemented within the model as per their respective Marketing Authorisations. BSC is also included as a comparator in each sub-population.

The selection of the first treatment in a sequence for each sub-population is based on previous NICE recommendations (2, 3, 47-49) and the NICE scope. The selection of second and third treatment options reflects TA445 (3) (**Table 42**). As some sub-populations are eligible for more lines of treatment (prior to moving to BSC) than others, the length of treatment sequence varies across the sub-populations.

Table 42: Treatment sequences for each patient sub-population

Patient sub-population	Treatment options as per NICE scope†		
	First in sequence	Second in sequence	Third in sequence
Disease has not responded to at least 2 nbDMARDs*	TOF	UST	BSC
	ADA		
	APR		
	CZP		
	ETN		
	GOL		
	INF		
	SEC (188mg, weighted dose)		
	BSC	-	-
Disease has not responded to nbDMARDs and at least 1 TNFi	TOF	BSC	-
	SEC (300mg)		
	UST		
	BSC	-	-
TNFi contraindicated or not tolerated	TOF	BSC	-
	SEC (188mg, weighted dose)		
	UST		
	BSC	-	-

†First treatment in sequence options are chosen in accordance with NICE guidance (2, 3, 47-49). Second- and third treatment in sequence options are aligned with those used in TA445 (3).*nbDMARDs ~ csDMARDs

Abbreviations: ADA, adalimumab; APR, apremilast; BSC, best supportive care; bDMARD, biological disease-modifying anti-rheumatic drug; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; nbDMARD, non-biological disease-modifying anti-rheumatic drug; SEC, secukinumab; TNFi, TNF inhibitor; TOF, tofacitinib; UST, ustekinumab.

The NICE scope lists certolizumab pegol as a comparator for sub-population 3, which includes people whose disease has not responded adequately to non-biological DMARDs and 1 or more TNFi. Certolizumab pegol has been excluded from sub-population 3 because the data available from the RAPID PsA trial informs only a subset of patients in this sub-population (i.e., primary responders to a prior TNFi who were secondary failures [primary non-responders were explicitly excluded from this trial]) (4).

All therapies, with the exception of BSC, are subject to a continuation rule. Patients must achieve a PsARC response at 3 months to remain on therapy. This continuation rule is in line with guidance from the BSR (184) and previous NICE appraisals (2, 3, 47-49). It is worth nothing that this does not reflect the continuation rules specified by NICE guidance for *all* comparators. Guidance for etanercept, infliximab and adalimumab (2), golimumab (47), and certolizumab (3) states that response should be assessed at week 12. By contrast, NICE guidance for apremilast (49) and secukinumab (3) states that PsARC response should be assessed at week 16; guidance for ustekinumab states that PsARC response should be assessed at week 24. However, to avoid introducing superfluous complexity into the model, the same 3-month continuation rule has been applied to all drugs, in alignment with the approach adopted in the most recent NICE MTA (3).

B.3.3 Clinical parameters and variables

B.3.3.1 Incorporation of clinical data into the model

Estimates of clinical efficacy considered in the model were derived from NMAs. The base case analysis incorporates the most plausible NMA models, which were selected on the basis of model fit and statistical plausibility (goodness of fit). Optimistic and pessimistic NMA scenario analyses (using models from the NMA in which tofacitinib 5 mg BD had the highest probability and lowest probability of response across all

outcomes relevant to the economic model), respectively) were included and presented in **Section B.3.8.3**. Details and results of base case NMAs are provided in **Section 0**; a summary of optimistic and pessimistic NMAs (explored in sensitivity analyses) is provided in **Section 0**, with the results presented in **Appendix E**.

As per TA445, it is assumed that the placebo arms of the NMAs are representative of the effectiveness of BSC and patients receiving BSC may have PsARC, HAQ-DI and PASI responses (3).

References to bDMARD-naive populations in the sections below align to sub-populations 2 and 4, and references to the bDMARD-experienced population align to sub-population 3 (as per **Section 0**). In sub-populations 2 and 4, where BSC is used at the end of a sequence including bDMARDs, tofacitinib or apremilast then efficacy is taken from the biologic experienced NMA, while for the BSC only arm efficacy is drawn from the biologic naïve NMA. Additionally, in sub-population 2, as ustekinumab is only modelled as a subsequent therapy following treatment with bDMARDs, tofacitinib or apremilast, the ustekinumab efficacy is also drawn from the biologic experienced NMA.

B.3.3.1.1 PsARC response

A PsARC treatment response is defined as an improvement in at least two of the four PsARC criteria (one of which must be the joint tenderness or swelling score) with no worsening in any of the four criteria (see also **Appendix L**). PsARC response rates for tofacitinib 5 mg BD and comparators were primarily taken from the NMA results detailed in **Section B.2.10.4.1**.

Nine alternative models have been specified for the bDMARD-naïve population (sub-populations 2 and 4). These were designed to be consistent with those generated in TA445 (3); the main differences include the use of random effects models in the current analysis, and the inclusion of data in the TA445 (3) analysis which are not publicly available (and therefore could not be included in the current analysis) (3). Of these models, Model B2 was selected as the base case, which is a random effects model with independent treatment effects, including a common interaction term with log odds of

response in the placebo arm (placebo adjusted). Results of this NMA are presented in **Table 25** (**Section B.2.10.4.1**).

In the bDMARD-experienced population (sub-population 3), a single model with an independent analysis of treatment effects was estimated. Results of this NMA are presented in **The bDMARD-experienced** population data for PSUMMIT2 were sourced from the TA445 AG report (94). As per the TA445 analysis, "the inclusion of the 24-week PsARC data for ustekinumab was based on an assumption that they fairly reflected the 12-week results (bDMARD-experienced population results for PsARC at 12 weeks in PSUMMIT2 were not available, though 12-week data for the full population were available)" (see Appendix 12.3.2 of the TA445 AG report) (4). Only one analysis was conducted examining the PsARC response in this population; base case model A1 FE (

Table 23) used data from PSUMMIT 2 (24-week data available in AG report from TA445) and OPAL Beyond.

The results of the base case model (A1 FE) showed that tofacitinib 5 mg BD [redacted] Tofacitinib 5 mg BD had a probability of PsARC response [redacted] Error! Not a valid bookmark self-reference. [redacted]

Table 27 (**Section B.2.10.4.2**). Due to the lack of data, it was only possible to estimate this model for tofacitinib 5 mg BD, ustekinumab and placebo. To include secukinumab in the economic model, the odds ratio for secukinumab 300 mg versus placebo was obtained from the base-case analysis for the bDMARD-experienced population from TA445 (3). The model used in TA445 (3) assumed independent treatment effects and fixed effects across trials. The primary difference between the model presented here and the model from TA445 (3) is the data included in the analysis. Importantly, the predicted response rates for placebo and ustekinumab are similar between the TA445 (3) analysis (PCB, 0.266; UST, 0.566) and the NMAs estimated here (PCB, 0.282; UST, 0.582), therefore the inclusion of different data is not expected to have a significant effect on results.

The probability of response for secukinumab 300mg was then calculated relative to the probability of response for placebo predicted by the NMA models relevant to this analysis, detailed in **Section B.2.10.4.2**. The odds ratio for secukinumab 300 mg compared with placebo estimated in TA445 (3) was 6.033; therefore, utilising this estimate, the estimated mean PsARC response rate for secukinumab 300 mg is [redacted][1] The confidence intervals presented in TA445 (3) were used to assess uncertainty in this odds ratio in probabilistic sensitivity analysis (PSA).

B.3.3.1.2 PASI response

PASI assesses the severity of, and the extent of body surface affected by, psoriasis. A PASI 75 response is defined as a 75% reduction in PASI from baseline, with corresponding terminology used for alternative percentage reductions (e.g., PASI 50 and PASI 90 for 50% and 90% reductions in PASI, respectively (185); see also **Appendix L**). The analysis of PASI response at the PASI 50/75/90 thresholds estimates all three probabilities at the same time using multinomial models.

[1] Calculated as $odds_{sec} = \frac{prob_{placebo}}{(1 - prob_{placebo})} \cdot odds\ ratio_{sec}$, and $prob_{sec} = \frac{odds_{sec}}{(1 + odds_{sec})}$

For the bDMARD-naïve population, Model E2 – a random effects model with independent treatment effects and no adjustment of placebo arms – was selected as the base case. Results of this NMA are presented in **Table 25** (**Section B.2.10.4.1**).

In the bDMARD-experienced population, two models were fitted for PASI response, one using 24-week data, and the other excluding these data. The model excluding the 24-week data forms the base case as it had better statistical fit, which is consistent with TA445 (3). Results of the NMA are presented in **The bDMARD-experienced** population data for PSUMMIT2 were sourced from the TA445 AG report (94). As per the TA445 analysis, "the inclusion of the 24-week PsARC data for ustekinumab was based on an assumption that they fairly reflected the 12-week results (bDMARD-experienced population results for PsARC at 12 weeks in PSUMMIT2 were not available, though 12-week data for the full population were available)" (see Appendix 12.3.2 of the TA445 AG report) (4). Only one analysis was conducted examining the PsARC response in this population; base case model A1 FE (

Table 23) used data from PSUMMIT 2 (24-week data available in AG report from TA445) and OPAL Beyond.

The results of the base case model (A1 FE) showed that tofacitinib 5 mg BD [redacted] Tofacitinib 5 mg BD had a probability of PsARC response [redacted] Error! Not a valid bookmark self-reference. [redacted]

Table 27 (**Section B.2.10.4.2**).

B.3.3.1.3 HAQ-DI change conditional on PsARC response

The HAQ-DI score measures physical function, capturing the level of disability associated with arthritis on a 0–3 scale, with higher scores indicating greater disability/functional impairment (34).

Four models were used to estimate the mean changes in HAQ-DI scores in PsARC responders and non-responders for each therapy in the bDMARD-naïve population. Model K2 – a random effects NMA using independent treatment effects where responders and non-responders are evaluated in separate analyses (non-placebo adjusted) – was selected as the base case. Results of this NMA are presented in **Model K2** RE (

Table 23) was used as a base case model because it included an adjustment for multi arm studies (alternative code to the code previously-used by Rodgers (111) and Cummins (112)) and because a RE model would take a better account of heterogeneity (vs model K1 FE; see **Appendix E**). Results for all models evaluated are presented in **Appendix E**. Placebo-adjusted models were not undertaken in line with TA445, as HAQ-DI change in the current submission was assessed based on PsARC response/non-response.

The results of the base case model (K2 RE) showed that tofacitinib 5 mg BD [redacted]

The analyses did not include Future 2 and RAPID-PsA, as the bDMARD-naïve data were redacted in TA445 and were not available in the primary publications. Therefore, our NMA had no results for certolizumab pegol and secukinumab for HAQ-DI.

Table 26 (**Section B.2.10.4.1**). This differs from the TA445 (3) base case in that it uses random effects, adjusts for trials with more than two arms, and uses separate models for responders and non-responders. The analyses using separate models for responders and non-responders predict larger changes in HAQ-DI for responders than do the combined models, including for placebo responders. As HAQ-DI data for secukinumab and certolizumab pegol were not available by PsARC responses, the values from the TA445 (3) NMA of HAQ scores have been incorporated into the model instead. For certolizumab pegol, the PsARC change for responders was -0.47 and for non-responders was -0.12. For the secukinumab 150mg and 300mg doses the changes for responders were -0.43 and -0.51, respectively. For non-responders they were -0.09 and -0.08 respectively.

Two models were fitted for the bDMARD-experienced population. Model K1 – a fixed effects model with responders and non-responders considered in separate models –

was selected as the base case. Results of these NMAs are presented in **The bDMARD-experienced** population data for PSUMMIT2 were sourced from the TA445 AG report (94). As per the TA445 AG analysis, the PSUMMIT2 bDMARD-experienced population data at 24-weeks were included in the analysis, as the AG had determined that 24-week data was equivalent to the 12-weeks outcome. Data for FUTURE2 were redacted in TA445 and were not available from the primary publication.

Analyses for two models were conducted; model G FE and model K1 FE. Model K1 FE was an alternative model to the Rodgers (111) and Cummins (112) code and included an adjustment for multi-arm studies. DICs for the two models were not comparable, but the average residual deviance for model K1 (**Table 28**) [redacted] was thus selected as the base case model. Results for the two models evaluated are presented in **Appendix E**.

The results of the base case model (K1 FE) showed that tofacitinib 5 mg BD [redacted] from baseline in HAQ-DI in PsARC non-responders (see **Table E76** in **Appendix E**). Tofacitinib 5 mg BD was [redacted] in PsARC responders of non-responders.

Table 28 (**Section B.2.10.4.2**). This differs from the TA445 (3) approach in that it uses separate models for responders and non-responders.

As HAQ-DI data for secukinumab were not available by PsARC response, the values from the TA445 (3) NMA of HAQ scores in the bDMARD-experienced population have been incorporated into the model. Thus, HAQ changes in responders and non-responders are assumed to be -0.3838 and -0.4295, respectively. As this implies a greater HAQ change for non-responders than for responders a scenario analysis has been included in **Appendix R,** using the data from the bDMARD-naïve population to populate changes in HAQ-DI for secukinumab (-0.51 for responders and -0.08 for non-responders).

It is important to note that HAQ-DI change can be measured as either the difference from baseline or the difference relative to the HAQ change in placebo non-responders. Appendix 9 of the AG report from TA199 (2) provides the rationale for the latter approach. While RCTs are accepted as the gold standard for estimating an unbiased measure of the relative effect of treatment, they may not produce an accurate estimate of the absolute effect that will be observed in clinical practice. To make the results of the NMAs more generalisable to clinical practice, the AG proposed an adjustment that assumes the HAQ-DI change in placebo non-responders is attributable to the clinical trial setting and would not be seen in clinical practice. Thus, the HAQ change observed in clinical practice is assumed to be the HAQ-DI change relative to the change in the placebo non-responder arm.

However, the NMAs used in the base case for our cost-effectiveness analyses showed an increase in HAQ-DI scores compared to baseline for placebo non-responders. Therefore, the base case presented here used the absolute change in HAQ-DI, as using the adjusted values would imply a greater change in scores than was seen in the clinical trials. The absolute change in HAQ-DI for responders and non-responders from each model is presented in **Model K2** RE (

Table 23) was used as a base case model because it included an adjustment for multi arm studies (alternative code to the code previously-used by Rodgers (111) and Cummins (112)) and because a RE model would take a better account of heterogeneity (vs model K1 FE; see **Appendix E**). Results for all models evaluated are presented in **Appendix E**. Placebo-adjusted models were not undertaken in line with TA445, as HAQ-DI change in the current submission was assessed based on PsARC response/non-response.

The results of the base case model (K2 RE) showed that tofacitinib 5 mg BD [redacted]

The analyses did not include Future 2 and RAPID-PsA, as the bDMARD-naïve data were redacted in TA445 and were not available in the primary publications. Therefore, our NMA had no results for certolizumab pegol and secukinumab for HAQ-DI.

Table 26 (**Section B.2.10.4.1**). This approach presents a more conservative estimate of absolute HAQ change.

B.3.3.1.4 ACR response

An ACR 20 response is defined as a 20% reduction in ACR, with corresponding terminology used for alternative percentage reductions (e.g., ACR 50 and ACR 70 for 50% and 70% reductions in ACR, respectively; see also **Appendix L**). ACR response is considered in scenario analyses as an alternative response criterion for remaining on treatment (**Section B.2.6.1.1** and **Section 0**). In these scenarios, PsARC, PASI and HAQ responses are assigned as previously described; however, the decision as to whether a patient remains on treatment is based on ACR 20 response, rather than PsARC response.

In the bDMARD-naïve population, the probabilities of ACR 20/50/70 responses have been estimated in a single multinomial model, as they were for PASI response. Five model specifications have been considered. Model E2 – a random effects model with independent treatment effects and no adjustment of placebo arms – was selected as the base case for the bDMARD naïve population. The probabilities determined from these NMAs are presented in **Table 25** (**Section B.2.10.4.1**).

Two models have been estimated for the bDMARD-experienced patients, one excluding 24-week data and one including it. Model E1 excluding 24-week data was selected for the base case. The probabilities determined from these NMAs are presented in **The bDMARD-experienced** population data for PSUMMIT2 were sourced from the TA445 AG report (94). As per the TA445 analysis, "the inclusion of the 24-week PsARC data for ustekinumab was based on an assumption that they fairly reflected the 12-week results (bDMARD-experienced population results for PsARC at 12 weeks in PSUMMIT2 were not available, though 12-week data for the full population were available)" (see Appendix 12.3.2 of the TA445 AG report) (4). Only one analysis was conducted examining the PsARC response in this population; base case model A1 FE (

Table 23) used data from PSUMMIT 2 (24-week data available in AG report from TA445) and OPAL Beyond.

The results of the base case model (A1 FE) showed that tofacitinib 5 mg BD [redacted] Tofacitinib 5 mg BD had a probability of PsARC response [redacted] Error! Not a valid bookmark self-reference. [redacted]

Table 27 (**Section B.2.10.4.2**).

The rationale for undertaking a scenario analysis utilising ACR response data was to assess the sensitivity of the cost-effectiveness results to the use of a response outcome often used as a primary endpoint in clinical trials of treatments for PsA. It was furthermore deemed a useful scenario on the basis that ACR response shares some component similarities with PsARC response (e.g., tender/swollen joint counts and patients/physicians global assessments) with the latter having been substantially affected by placebo creep in the OPAL Broaden clinical trial. This is discussed in more detail in **Section B.2.14.2.2**.

B.3.3.1.5 Biological DMARD withdrawal rate

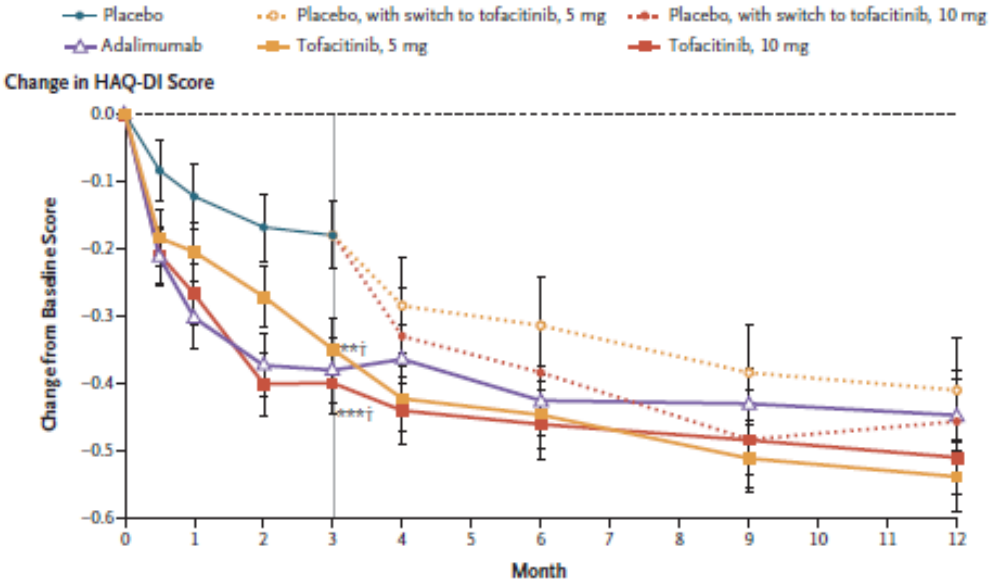
The treatment withdrawal rate, estimated from a meta-analysis of registry data from several countries, was obtained from the York model reported in TA199 (2) and resulted in a 12-week probability of withdrawal of 3.96%.

B.3.3.1.6 HAQ progression/natural history

In line with TA199 (2, 111), and subsequent NICE TAs, it is assumed that patients who respond to bDMARDs experience no HAQ progression (2, 3, 47-49). This assumption is also applied to tofacitinib 5 mg BD responders, supported by the following:

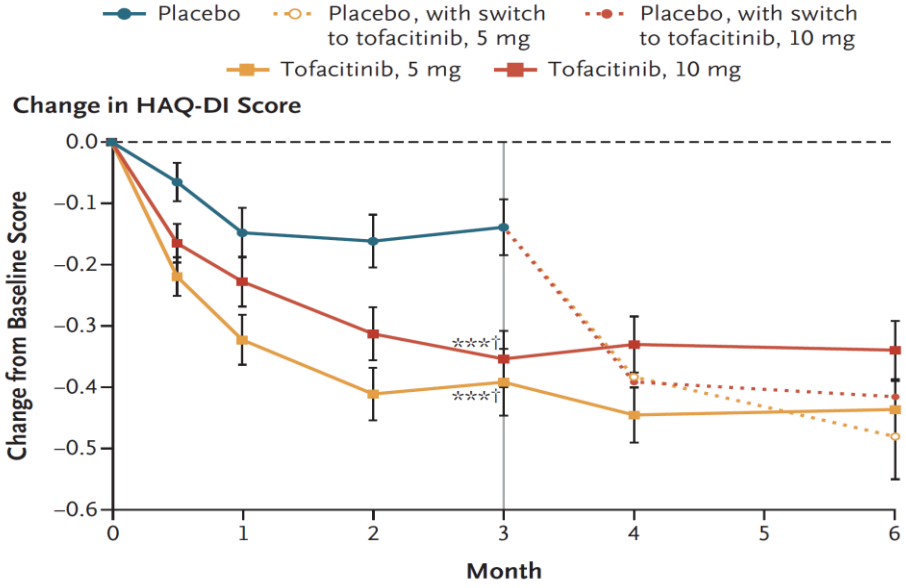
1. Evidence from OPAL Broaden and OPAL Beyond demonstrated significant improvements in HAQ-DI in patients treated with tofacitinib 5 mg BD at 3 months, which were sustained in a blinded manner for up to 12 months (OPAL Broaden) and 6 months (OPAL Beyond) (**Sections** Error! Reference source not found. and Error! Reference source not found.). The least squares mean changes at 3 months in both trials were equivalent to or greater than the minimum clinically important difference (MCID) compared with baseline (Error! Reference source not found. and Error! Reference source not found.).

Figure 17: Change in HAQ-DI score from baseline (OPAL Broaden)



Abbreviations: HAQ-DI, Health Assessment Questionnaire-Disability Index.

Figure 18: Change in HAQ-DI score from baseline (OPAL Beyond)

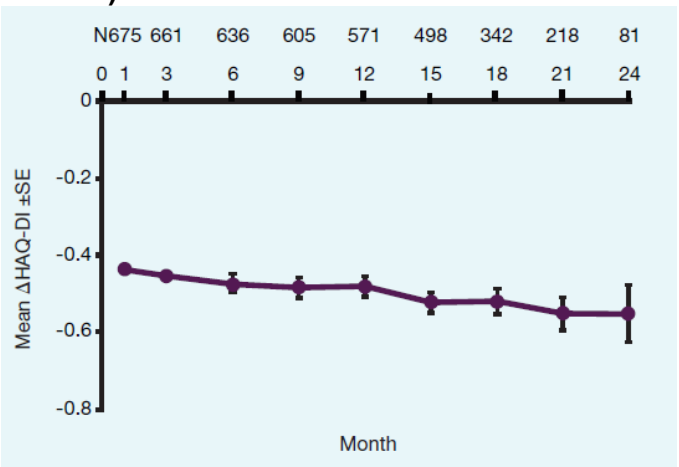


Abbreviations: HAQ-DI, Health Assessment Questionnaire-Disability Index.

2. These data are also supported by post-hoc analyses of changes in HAQ-DI for PsARC responders in OPAL Broaden and OPAL Beyond, which show that improvements in HAQ-DI are sustained up to Month 12 and Month 6 respectively (see **Table M8**, **Table M9**, **Table M17** and **Table M18** in **Appendix M**).

3. Furthermore, evidence from the LTE study OPAL Balance (Error! Reference source not found.) demonstrates that HAQ-DI changes were maintained while patients remained on treatment with tofacitinib over a 24-month period (both 5 mg BD and 10 mg BD doses). See also **Section B.2.8.7**.

Figure 19:Change in HAQ-DI score from baseline up to Month 24 (25 January 2017 data cut) - FAS.



Abbreviations: FAS, Full Analysis Set; HAQ-DI, Health Assessment Questionnaire Disability Index.

[redacted] 20[redacted]The maintained reduction in HAQ-DI from baseline scores observed in OPAL Balance is supported by data from ORAL Sequel, a LTE of n=6 phase III Rheumatoid Arthritis RCTs, which demonstrated that HAQ-DI scores were stable over 75 months of follow-up and were presented in TA480 (see **Appendix O**).

Figure 20: Change from baseline in HAQ-DI scores in OPAL Balance

[redacted]

4. Evidence from OPAL Broaden indicates a minimal rate of radiographic progression (Δ baseline in van der Heijde mTSS =0.01) for tofacitinib 5 mg BD after 12 months of treatment. The difference between tofacitinib 5 mg BD and the active control (adalimumab 40 mg Q2W) was not considered clinically significant by clinical experts (and was not statistically significant, although the study was not powered for statistical comparisons between tofacitinib and adalimumab). Ninety-six percent of patients treated with tofacitinib 5 mg BD were radiographic non-progressors (Δ van der Heijde mTSS ≤0.5).

5. [redacted]

For patients receiving BSC or csDMARDs, a HAQ progression rate of 0.077 per year is applied. This progression rate was used in the York AG model in TA199 (2, 3). The rate was estimated using data from the Norfolk Arthritis Register (NOAR) (186) on the progression of HAQ scores in patients with long-standing polyarthritis plus psoriasis who had previously used two or more csDMARDs.

The appraisal committee for TA433 concluded that there was insufficient evidence to demonstrate that apremilast halts radiographic disease progression (49), and concluded that the rate of disease progression experienced while receiving apremilast was assumed to be half of the progression rate for BSC/csDMARDs (i.e. 0.0385 per year). The same assumption was applied for this analysis.

B.3.3.1.7 Mortality

Mortality rates are derived from life tables for England and Wales 2014–2016 (187). A standardised mortality ratio (SMR) of 1.36 is applied. This ratio was obtained from a prospective study of patients with PsA (188) and was applied in TA445 (3).

B.3.3.2 Calculation of transition probabilities from clinical data

Transition probabilities for patients during the first treatment cycle on a given drug represent the probability of a response, defined in the base case as a PsARC response. These transition probabilities were primarily taken from the NMAs (**Section B.3.3.1.1**).

If a patient responded to treatment in the first cycle they were assumed to remain on treatment either until death, loss of efficacy or an adverse event. The treatment withdrawal rate was taken from the York PsA model (4) (**Section B.3.3.1.5**).

B.3.3.2.1 Correlation between PsARC response and PASI

As in previous appraisals (TA199 (2) and TA445 (3)), it was assumed that PASI 75 response rates may vary by treatment response (based on PsARC). In order to capture this, a positive correlation between PsARC and PASI 75 response was included in the model.

This economic evaluation adopts the correlation coefficient for PsARC and PASI (0.436) used in the York model in TA199 (2) and TA445 (3). The following formula was used to determine the probability of both a PsARC and a PASI 75 response:

$$\Pr(x = 1, y = 1) = \rho\, s_x s_y + \Pr(x = 1)\Pr(y = 1).$$

Here x is PsARC response, y is PASI 75 response, ρ is the correlation coefficient and s_x and s_y are the standard deviations in the probability of a PsARC and a PASI 75 response, respectively. The standard deviations are estimated as:

$$s_i = \sqrt{P(i = 1) * [1 - P(i = 1)]}, i = x, y.$$

Table P1 and **Table P2** in **Appendix P** present the jointly estimated probabilities of a PsARC and PASI 75 response for the respective bDMARD-naïve and bDMARD-experienced populations that are used in the base case. To calculate the proportion of patients achieving a PASI 50 or PASI 90 response for PsARC responders and non-responders, the proportions of PASI 75 non-responders achieving a PASI 50 response and the proportions of PASI 75 responders achieving a PASI 90 response are assumed to be constant.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life (HRQoL) data from clinical trials

HRQoL data were collected as primary and secondary endpoints in both the OPAL Broaden (87) and OPAL Beyond (88) studies. Both trials collected EQ-5D data at baseline and months 1, 3 and 6; in OPAL Broaden data, were also collected at months 9 and 12. A mapping algorithm was estimated using EQ-5D, HAQ and PASI data from OPAL Broaden and Beyond which is outlined below.

B.3.4.2 Mapping

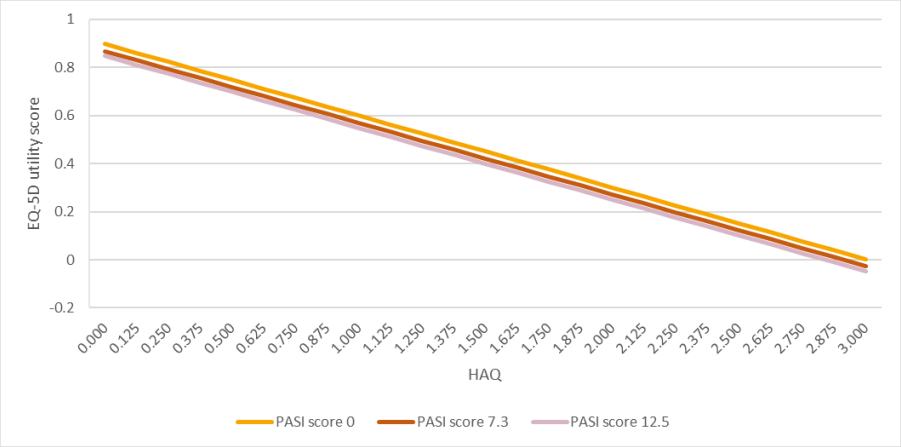
Previous appraisals have mapped EQ-5D to HAQ and PASI scores (TA199 (2) and TA445 (3)). EQ-5D data were available from OPAL Broaden and OPAL Beyond clinical trials for tofacitinib 5 mg BD, but for consistency with previous appraisals the base case uses the algorithm presented in the York model used in TA199 (2) and TA445 (3).

EQ-5D was estimated from HAQ and PASI scores. For the base case, the following formula from the York model in TA199 (2) and TA445 (3) was used:

$$EQ - 5D = 0.897 - 0.289 * HAQ - 0.004 * PASI$$

This algorithm was originally developed using ordinary least-squares regression of EQ-5D utility based on HAQ, PASI and the interaction thereof. However, the interaction term was not significant, therefore it was excluded here, as it was in TA199 (2). Details of the accuracy of the algorithm have not been identified. The effect of different levels of HAQ and PASI on EQ-5D is illustrated in **Figure 21**.

Figure 21: Utilities associated with HAQ progression



Abbreviations: EQ-5D, EuroQol 5 dimensions; HAQ, Health Assessment Questionnaire; PASI, Psoriasis Area and Severity Index.

Scenario analyses are presented in which *de novo* mapping algorithms derived using individual patient data (IPD) from OPAL Broaden and OPAL Beyond clinical data are applied to either tofacitinib 5 mg BD alone, or to tofacitinib 5 mg BD and its comparators.

Statistical models were developed using data from OPAL Broaden (sub-populations 2 and 4) and OPAL Beyond (sub-population 3) separately. Two models were estimated using each study:

- A ‘main effect’ model predicting EQ-5D in which HAQ and PASI scores were included as independent covariates

- An ‘interaction effect’ model which augmented the ‘main effect’ model by including the interaction between HAQ and PASI scores as a covariate.

All models pool all non-missing data at all time points from across all arms of the respective clinical trials. Models were implemented as mixed effects models to account for repeated measures within subjects. Results are presented in **Appendix Q**.

B.3.4.3 Health-related quality-of-life studies

A systematic review was conducted to identify HRQoL studies from the published literature relevant to the decision problem. Studies reporting health utility measured as a function of HAQ-DI and PASI were considered eligible for inclusion. As part of TA445 (3), the AG performed such a search (3). This search has been updated in this appraisal to identify more recent publications. Full details of the search are provided in **Appendix H**.

The HRQoL systematic review identified one additional paper by Mlcoch et al (189) that mapped the Disease Activity in Psoriatic Arthritis (DAPsA), clinical DAPsA (cDAPsA) and HAQ-DI to the EQ-5D using a cohort of 228 patients with PsA in the Czech Republic. However, neither the DAPsA nor the cDAPsA have been collected in the tofacitinib clinical trials, thus we were unable to include this algorithm in the economic model.

B.3.4.4 Adverse reactions

In OPAL Broaden (87), OPAL Beyond (88) and OPAL Balance, the incidence of AEs was generally similar between tofacitinib- and placebo-treated populations (see **Section B.2.11**). In line with previous models considered by NICE, e.g., TA199 (2, 111) and TA445 (3), adverse events are not explicitly included in the model. However, the treatment withdrawal rate incorporates withdrawal due to adverse events, and upon withdrawal a patients HAQ-DI and PASI score is assumed to return to baseline.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Patients' HRQoL is defined in the model in terms of HAQ and PASI scores (**Section B.3.2.2**), and these are mapped to EQ-5D (**Section B.3.4.2**).

The health states in the model are defined by the treatment received and response to treatment, or not. Patients' HAQ-DI and PASI scores change according to treatment response (Section B.3.6.2). HAQ-DI scores remain constant while patients are on treatment with bDMARDS or tofacitinib 5 mg BD, but they progress linearly while patients are on apremilast or BSC (reflecting worsening of physical function following failure to respond to treatment).

PASI scores do not progress on BSC as they are not progressive. Whilst on treatment, improvements in PASI scores are possible.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Resource identification, measurement and valuation studies

A search of the published literature was undertaken to identify alternative evidence regarding resource use and costs associated with the management of PsA in the UK. Full details of the search are provided in **Appendix I**.

One publication that specifically reported estimates of costs according to HAQ-DI and/or PASI identified in the search was eligible for inclusion (Poole et al (2010) (30)); however, it does not inform the model .

B.3.5.2 Intervention and comparators' costs and resource use

Costs for acquisition, administration and monitoring differ between the first cycle and subsequent cycles to reflect clinical management practices associated with switching a patient onto a new treatment – details are provided below.

B.3.5.2.1 Drug dosing

Drug dosing and administration route are based on NICE guidance (190) (**Table 43**). All drugs are assumed to be taken in combination with methotrexate. The average

number of vials required for infliximab has been calculated by assuming patient weight is normally distributed.

Table 43: Drug dosing

Drug	Dose (mg, unless otherwise specified)	Frequency	Vial/pill formulation (mg)	Number of vials/pills per admin	Administration
TOF	5	Twice daily	5	1	Oral
ADA	40	Every 2 weeks	40	1	SC
APR	30	Twice daily	30	1	Oral
CZP	200	Every 2 weeks	200	1	SC
ETN	25	Twice weekly	25	1	SC
GOL	50	Once per month	50	1	SC
INF	5 mg/kg	Every 8 weeks	100	4.79	IV
SEC 150 mg	150	Once per month	150	1	SC
SEC 300 mg	300	Once per month	150	2	SC
SEC wd	188	Once per month	150	1.25	SC
UST	45	Every 12 weeks	45	1	SC
MTX	7.5	Weekly	2.5	3	Oral
csDMARD	7.5	Weekly	2.5	3	Oral

Abbreviations: ADA, adalimumab; APR, apremilast; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; MTX, methotrexate; SEC, secukinumab; SC: subcutaneous injection; UST, ustekinumab; wd, weighted dose.

B.3.5.2.2 Drug acquisition costs

Acquisition costs (**Table 44**) are taken from the British National Formulary (BNF) (190) for the bDMARDs and apremilast and from the electronic market information tool (eMIT) database (191) for methotrexate. Patient access schemes (PAS) prices are listed below where information is in the public domain. No drug costs are assumed for BSC; instead, it is assumed that these drug costs are captured in the estimates of resource use associated with HAQ-DI **(Section B.3.5.3.1**).

Table 44: Drug costs

Therapy	Pack size	Pack cost	Patient access scheme?
TOF	56	£690.03	No
[redacted]	[redacted]	[redacted]	[redacted]
ADA	2	£704.28	No
APR	56	£550.00	No†
CZP	2	£715.00	The first 3 months of treatment are free
ETN (biosimilar)	4	£328.00	No (biosimilar price)
GOL	1	£762.97	100 mg dose must be same price as 50 mg
INF (biosimilar)	1	£377.00	No (biosimilar price)
SEC	2	£1,218.78	No†
UST	1	£2,147.00	90 mg dose is available at the same price as the 45 mg dose
MTX	24	£0.96	No
csDMARD	24	£0.96	No
BSC	0	£0.00	No

†PAS details are not available for APR and SEC so their list prices are used in the economic model.

Abbreviations: ADA, adalimumab; APR, apremilast; BSC, best supportive care; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; MTX, methotrexate; PAS, patient access scheme; SEC, secukinumab; UST, ustekinumab.

B.3.5.2.3 Administration costs

Administration costs are taken from NHS reference costs (192) and PSSRU (193).

An intravenous infusion cost of £241 (192) is applied in each cycle for infliximab. This value is a weighted average cost for simple parenteral chemotherapy at first attendance, taking into account day case, outpatient and other costs, taken from NHS reference costs (192) as per TA445 (3). For treatments that require administration by subcutaneous injection, the cost of one hour of hospital-based nurse specialist time is applied (£45) to reflect clinical practice for bDMARDs prescribed by rheumatologists (193). This cost is implemented in the first cycle only as it is assumed that the patient will self-administer subsequent treatment following training by the nurse.

B.3.5.2.4 Monitoring costs

Monitoring activities included in the model and their frequency of use (**Table 45**) are based on the models from TA199 (2) and TA445 (3).

In the first cycle patients undergo tests – full blood count, erythrocyte sedimentation rate, liver function test and urea and electrolytes – at the start of treatment and at month 3. In subsequent cycles, these tests are conducted every 6 months. The chest x-ray, tuberculosis Heaf test, antinuclear antibody, double-stranded DNA test and specialist visit are assumed to occur in the first cycle only.

Costs were taken from NHS reference costs (192), except for the liver function test, chest x-ray and tuberculosis Heaf test costs, which were inflated from the costs presented by the AG in TA445 (3).

Table 45: Initiation and monitoring costs

Item	Frequency – first cycle	Frequency – subsequent cycles	Unit cost
Full blood count	2	0.5	£3.06
Erythrocyte sedimentation rate	2	0.5	£3.06
Liver function test	2	0.5	£0.78
Urea and electrolytes	2	0.5	£1.13
Chest x-ray	1	0	£27.22
Tuberculosis Heaf test	1	0	£9.07
Antinuclear antibody	1	0	£6.55
Double strand DNA test	1	0	£6.55
Specialist visit	1	0	£146.77

Abbreviations: DNA, deoxyribonucleic acid.

B.3.5.2.5 Other considerations

Vial sharing is not assumed in the base case – the number of vials per administration is rounded up to the nearest whole number.

Costs for the following treatments differ between the first cycle and subsequent cycles to account for loading doses or PAS arrangements:

- Apremilast – a cost of £265.18 is included for a 14-day treatment pack for titration (194)
- Certolizumab pegol – free for the first 3 months under a PAS
- Infliximab – 3 doses in the first cycle (194)

- Secukinumab – One dose per week for the first 5 weeks plus 2 additional months of treatment (194)

- Ustekinumab – 2 doses in the first cycle (194)

Total costs for tofacitinib 5 mg BD and its comparators in the first cycle and subsequent cycles are detailed in **Table 46**. These costs include acquisition, administration and monitoring.

Table 46: Unit costs associated with the technology in the economic model

Therapy	Costs in first cycle				Costs in subsequent cycles			
	Total drug cost*	Admin	Monitoring	Total	Total drug cost*	Admin	Monitoring	Total
TOF (List price)	£2,251.86	£0.00	£212.22	£2,464.08	£2,251.86	£0.00	£4.01	£2,255.87
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	£2,298.34	£45.00	£212.22	£2,555.56	£2,298.34	£0.00	£4.01	£2,302.35
APR	£1,761.44	£0.00	£212.22	£1,973.66	£1,795.20	£0.00	£4.01	£1,799.21
CZP	£1.57	£45.00	£212.22	£258.79	£2,333.30	£0.00	£4.01	£2,337.31
ETN	£2,140.89	£45.00	£212.22	£2,398.11	£2,140.89	£0.00	£4.01	£2,144.90
GOL	£2,290.48	£45.00	£212.22	£2,547.70	£2,290.48	£0.00	£4.01	£2,294.49
INF	£5,255.06†	£241.00	£212.22	£5,708.28	£2,856.98†	£241.00	£4.01	£3,101.99
SEC 150mg	£4,267.30	£45.00	£212.22	£4,524.52	£1,829.74	£0.00	£4.01	£1,833.75
SEC 300mg	£8,533.03	£45.00	£212.22	£8,790.25	£3,657.91	£0.00	£4.01	£3,661.92
SEC wd	£5,333.73‡	£45.00	£212.22	£5,590.95	£2,286.78‡	£0.00	£4.01	£2,290.79
UST	£4,669.37	£45.00	£212.22	£4,926.59	£2,335.47	£0.00	£4.01	£2,339.48
MTX	£1.57	£0.00	£212.22	£213.79	£1.57	£0.00	£4.01	£5.58
BSC	£0.00	£0.00	£212.22	£212.22	£0.00	£0.00	£4.01	£4.01

*Includes cost of methotrexate where relevant; †dose dependent on body weight so the mean weight of the relevant population from the Broaden (87) (82.9kg) and Beyond (88) (85.7kg) Phase III clinical trials was used to determine cost; ‡the cost per cycle of the weighted dose of secukinumab is based on the proportion of patients with moderate to severe psorisasis (25%).

Abbreviations: ADA, adalimumab; admin, administration; APR, apremilast; BSC, best supportive care; CI, confidence interval; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; ref, reference in submission; SEC, secukinumab; UST, ustekinumab; wd weighted dose.

B.3.5.3 Health-state unit costs and resource use

Health state costs are based on HAQ and PASI scores, in line with TA199 (2) and TA445 (3). Most previous analyses draw on the same set of assumptions and use HAQ score to define the cost due to arthritis and PASI score to define the cost due to psoriasis.

B.3.5.3.1 Arthritis costs

Costs associated with the arthritis component were based on HAQ scores. A 2002 analysis by Kobelt et al (2002) (195) estimated the mean annual direct medical costs for people with RA, disaggregated by HAQ score (**Table 47**).

Table 47: Annual direct cost by HAQ score in Kobelt 2002

HAQ score range	Proportion of patients	Direct costs (2002 GBP)
0.0 - 0.6	0.35	£1,094
0.6 - 1.1	0.16	£2,809
1.1 - 1.6	0.15	£1,864
1.6 - 2.1	0.14	£2,751
2.1 - 2.6	0.11	£3,031
2.6 - 3.0	0.08	£2,404

Abbreviations: GBP, Great British pounds; HAQ, Health Assessment Questionnaire.

Bansback et al (178) used this data to inform a linear regression with direct costs as a function of HAQ score:

$$\text{Annual direct cost} = £358 \times \text{HAQ} + £1182$$

Kobelt et al (195) estimated that 13-15% of the total costs were drug costs, so Rodgers et al (111) reduced the total cost by 15% for use in the York PsA model in TA199 (2) giving an incremental cost per unit increase in HAQ of £103 per 3 months. These costs have since been used in TA445 (3).

The paper by Poole et al (30) identified in the systematic review also predicted cost based on HAQ score. This paper was identified during TA445 and was included by the manufacturer of certolizumab pegol in their economic evaluation (3). The presented relationship estimates total costs as a function of HAQ using a cohort of

patients with PsA and has the advantage of estimating costs in PsA patients directly However the estimates of resource use are larger than for RA, leading the authors to suggest that this may indicate an important distinction between RA and PsA. However, this could also be a consequence of methodological limitations as it was necessary to map baseline characteristics to HAQ scores in the dataset they used for resource use. This analysis uses a generalised linear model using a Poisson distribution assuming a log link to estimate the annual resource use as a function of HAQ score and age, including an interaction term between these terms:

$$Annual\ direct\ cost = \exp(3.537 + 2.048 * HAQ + 0.026 * Age - 0.012 * HAQ * Age)$$

Given the limitations of the Poole analysis and to ensure consistency across NICE TAs, the AG for TA445 (3) opted to use the same data sources as were used in the York model. As no new analyses have been identified since the publishing of TA445 (3), we use the same source to remain consistent with previous appraisals.

For the model presented in this submission the annual direct cost was calculated using the formula from Rodgers et al (178), with costs inflated to 2017 prices:

$$Annual\ direct\ cost = £466.47\ x\ HAQ + £1{,}547.04$$

With the exception of BSC, these costs incorporate a 15% reduction to account for drug costs, in accordance with the York PsA model (2, 111). This is no applied to BSC as drug costs are assumed to be captured by this analysis and so are not applied separately, as in TA445 (3) (**Section B.3.5.2.2**).

B.3.5.3.2 Psoriasis costs

The psoriasis component of resource use has previously been estimated based on PASI scores.

This analysis follows the approach taken in the York PsA model in TA199 (2) and TA445 (3). The AG estimated costs for patients receiving bDMARDs based on baseline severity of psoriasis and whether or not they had a PASI75 response (2). For patients with mild–moderate or moderate–severe psoriasis at baseline achieving a PASI 75 response, the monthly estimated cost of a patient in remission (196) was

applied. The source of this cost is a study which considered the cost-effectiveness of an intervention for patients with moderate to severe psoriasis in a Dutch setting. Costs from this analysis were similar to NHS reference costs and so it was assumed the Dutch costs were generalisable to the UK after currency conversion.

Patients with moderate to severe psoriasis not achieving a PASI75 response were assumed to undergo one course of ultraviolet B treatment (UVB) per year. This incorporated the cost of the initial course of treatment and the cost of follow-up for the year. Patients were put into three categories for response – no response, response maintained for 12 months, and response maintained for 6 months followed by relapse. The total cost for the year was weighted by the frequency of these outcomes in the Hartman analysis (2002) (196).

Patients with mild to moderate psoriasis and no PASI 75 response were also assumed to receive a course of UVB but with the cost taken from NHS reference costs. The proportion of responders was taken from an analysis by Poyner et al (1999) (197). Patients with no baseline psoriasis incurred no costs.

Costs associated with the psoriasis component based on PASI scores (**Table 48**) were taken from the AG report in TA445 (3) and inflated to 2017 prices.

Table 48: Costs associated with psoriasis in the model

Description	Without psoriasis	Mild to moderate psoriasis	Moderate to severe psoriasis
Baseline PASI	0	7.30	12.50
Uncontrolled psoriasis (no PASI 75) cost	0	£224.18	£640.83
Controlled psoriasis (PASI 75) cost	0	£18.12	£18.12

Abbreviations: PASI, Psoriasis Area and Severity Index.

B.3.5.4 Adverse reaction unit costs and resource use

Adverse event costs are not explicitly included in the cost-effectiveness analysis; however, they influence response probabilities and withdrawal rates. This is in line with the approach used in previous models (3).

B.3.5.5 Miscellaneous unit costs and resource use

No other costs are considered.

B.3.6 Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

A summary of key base case inputs is provided in **Table 49**. A full list of inputs is provided in Appendix S.

Table 49: Key variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Time horizon	40 years	-	B.3.2.2
Discount rate for costs	3.5%	-	B.3.2.2
Discount rate for outcomes	3.5%	-	B.3.2.2
Baseline age (bDMARD-naïve)	47.9	-	B.3.3.1
Baseline age (bDMARD-experienced)	50	-	B.3.3.1
Gender (% female) (bDMARD-naïve)	53%	-	B.3.3.1
Gender (% female) (bDMARD-experienced)	55%	-	B.3.3.1
Baseline HAQ (bDMARD-naïve)	1.11	-	B.3.3.1
Baseline HAQ (bDMARD-experienced)	1.30	-	B.3.3.1
Mean duration of PsA (bDMARD-naïve)	6.09 years	-	-
Mean duration of PsA (bDMARD-experienced)	9.37 years	-	-
% of population with no psoriasis	50%	-	B.3.3.1
% of population with mild to moderate psoriasis	25%	-	B.3.3.1
% of population with severe psoriasis	25%	-	B.3.3.1
Baseline PASI for no psoriasis	0	-	B.3.3.1

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Baseline PASI for mild to moderate psoriasis	7.3	-	B.3.3.1
Baseline PASI for moderate to severe psoriasis	12.5	-	B.3.3.1
Correlation coefficient for PsARC and PASI	0.435	(0.19, 0.50) Beta	B.3.3.1
Log bDMARD withdrawal rate	-1.823	(-2.16, -1.49) Normal	B.3.3.1
Tofacitinib LONG-TERM HAQ change per 3 months	0	-	B.3.3.1
Adalimumab LONG-TERM HAQ change per 3 months	0	-	B.3.3.1
Apremilast LONG-TERM HAQ change per 3 months	0.0096	-	B.3.3.1
Certolizumab LONG-TERM HAQ change per 3 months	0	-	B.3.3.1
Etanercept LONG-TERM HAQ change per 3 months	0	-	B.3.3.1
Golimumab LONG-TERM HAQ change per 3 months	0	-	B.3.3.1
Infliximab LONG-TERM HAQ change per 3 months	0	-	B.3.3.1
Secukinumab 150 mg LONG-TERM HAQ change per 3 months	0	-	B.3.3.1
Secukinumab 300 mg LONG-TERM HAQ change per 3 months	0	-	B.3.3.1
Ustekinumab LONG-TERM HAQ change per 3 months	0	-	B.3.3.1
BSC LONG-TERM HAQ change per 3 months	0.019	(0.01, 0.03) Normal	B.3.3.1
SMR for life tables	1.36	-	B.3.3.1
Mapping algorithm constant	0.897	(0.89, 0.91) Normal	B.3.4.2
Mapping algorithm HAQ coeff	-0.298	(-0.31, -0.29) Normal	B.3.4.2

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Mapping algorithm PASI coeff	-0.004	(0.00, 0.00) Normal	B.3.4.2

Abbreviations: bDMARD, biological disease-modifying anti-rheumatic drug; BSC, best supportive care; CI, confidence interval; HAQ, Health Assessment Questionnaire; PASI, Psoriasis Area and Severity Index; SD, standard deviation.

B.3.6.2 Assumptions

A list of assumptions made in the economic analysis is provided in **Table 50**.

Table 50: Key model assumptions and inputs

Model input and cross reference	Source/assumption	Justification
Continuation rules	PsARC non-responders discontinue at 3 months for all therapies	This assumption has been made to simplify the model structure. The response rates included in the NMAs for each comparator reflect the assessment time point recommended in clinical guidelines for that drug. As such, the correct proportion of responders will be modelled. This approach has been taken in previous appraisals (2, 3, 47).
Efficacy	PsARC response for secukinumab in the bDMARD-experienced population is determined using the odds ratio from the base-case NMA for the bDMARD-experienced population in TA445 (3)	Due to paucity of data, it was not possible to estimate this in our NMA for secukinumab, so data from TA445 were used to inform efficacy.
Efficacy	Values for changes in HAQ-DI by PsARC response for secukinumab and certolizumab pegol are taken from the meta-regression NMA for TA445 (3) in the bDMARD-naïve population Values for changes in HAQ-DI by PsARC response for secukinumab are taken from the NMA for TA445 (3) in the bDMARD-experienced population	These approaches were necessary due to stratified response data not being available in the primary publications and being redacted in TA445 (3).
HAQ progression	It is assumed that patients treated with tofacitinib 5 mg BD and bDMARDs do	Data from OPAL Broaden demonstrates that improvements in HAQ-DI score with tofacitinib 5 mg BD are maintained over 12 months in a blinded manner. Furthermore, evidence from a

	not experience any HAQ progression	population adjusted meta-regression analysis demonstrated that changes from baseline in mTSS with tofacitinib 5 mg BD were not significantly different compared to adalimumab. Data from OPAL Balance, the open label extension trial of tofacitinib, shows that reductions in HAQ-DI are maintained over 24 months. This assumption has also been applied to bDMARDs in line with previous appraisals (2, 3, 47, 48).
	HAQ scores progress linearly for apremilast, csDMARDs and BSC	This is consistent with previous appraisals (199, 433, 445)
HAQ change	Patients who are on treatment but who do not have a PsARC response still have a change in HAQ score in the first 3 months	This assumption is in line with previous appraisals and evidence from trial data
PASI progression	PASI scores do not progress after the initial 3 months of treatment	PASI scores are not progressive and a change from baseline is determined solely by PASI50/75/90 response. This assumption has been applied in previous appraisals (2, 3).
PASI response	PASI75 response is assumed to be correlated with PsARC response	This assumption has been applied in previous appraisals (2, 3)
Discontinuation	HAQ and PASI scores return to baseline levels upon discontinuation of treatment for all apart from apremilast and BSC	This assumption has been applied in previous appraisals (3)

Abbreviations: BSC, best supportive care; csDMARDS, conventional synthetic disease-modifying anti-rheumatic drugs; HAQ, Health Assessment Questionnaire; NMA, network meta-analysis; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria; SEC, secukinumab; UST, ustekinumab.

B.3.7 Base case results

The tables below present the base case results, which incorporate the PAS price for tofacitinib 5 mg BD and for comparators for which PAS details are in the public domain (otherwise list prices for comparators have been considered in the analysis)

B.3.7.1 People whose disease has not responded adequately to at least 2 non-biological DMARDs.

Table 51: Base case analysis (sub-population 2)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
APR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; APR, apremilast; BSC, best supportive care; CZP, certolizumab pegol; ETN, etanercept; Ext. dom, Extendedly dominated; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib.

B.3.7.2 People whose disease has not responded adequately to non-biological DMARDs and 1 or more TNFis.

Table 52: Base case analysis (sub-population 3)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; Ext. dom, Extendedly dominated; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab.

B.3.7.3 People in whom TNFis are contraindicated or not tolerated.

Table 53: Base case analysis (sub-population 4)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

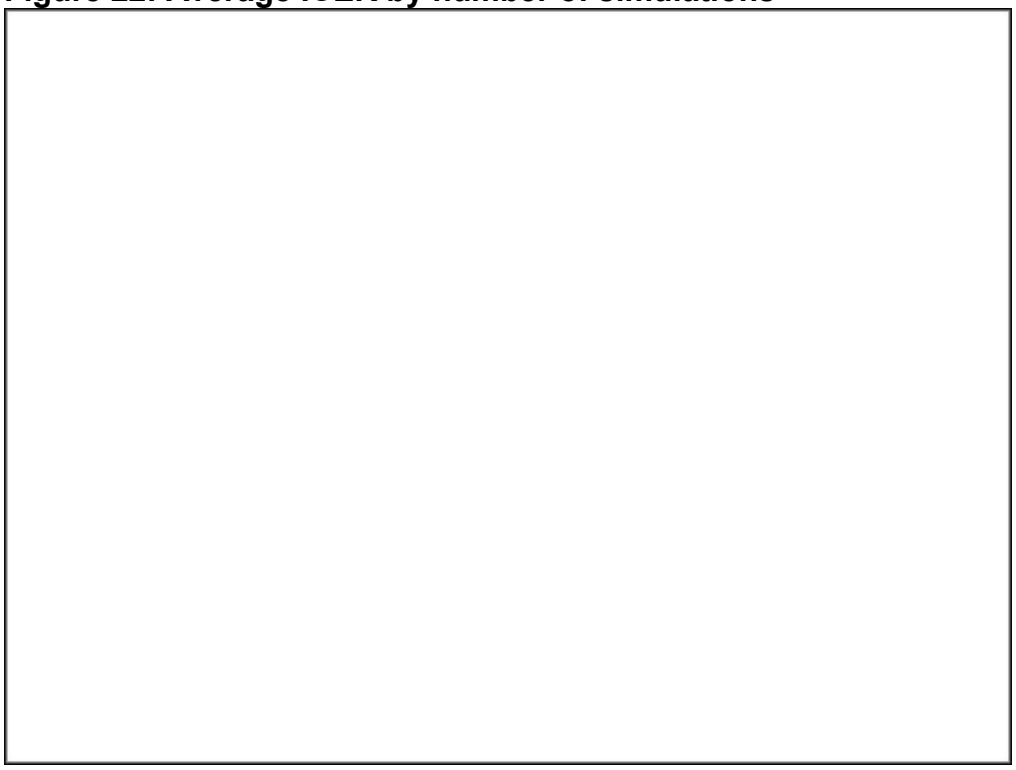
Abbreviations: BSC, best supportive care; Ext. dom, Extendedly dominated; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. Ten thousand Monte Carlo simulations were recorded. This was deemed to be appropriate, as the probabilistic analysis closely matches the deterministic analysis. **Figure 22** presents the average ICER by number of simulations in sub-population 2. This shows that by 10,000 simulations the results are stable. Where parameters have been taken from an NMA they have been varied using the CODA output. Results were plotted on the cost-effectiveness plane (CEP) and cost-effectiveness acceptability curves (CEAC) were generated.

Figure 22: Average ICER by number of simulations



B.3.8.1.1 People whose disease has not responded adequately to at least 2 non-biological DMARDs (sub-population 2)

Table 54 presents the average results of the PSA, which demonstrates that the total cost in most arms was similar to the total cost from the deterministic results, although the total QALYs were slightly higher in most arms; overall, incremental QALYs for all treatment sequences decrease relative to BSC, and ICERs increase. **Figure 23** and

Figure 24 present the cost-effectiveness plane and multiple CEACs, respectively.

Figure 24 shows that

[redacted]

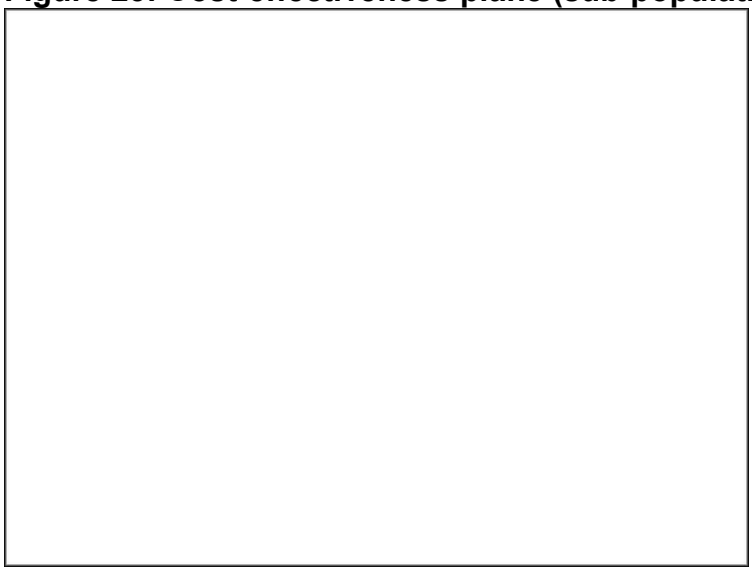
[redacted]

Table 54: Average costs and QALYs from the PSA (sub-population 2)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
APR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

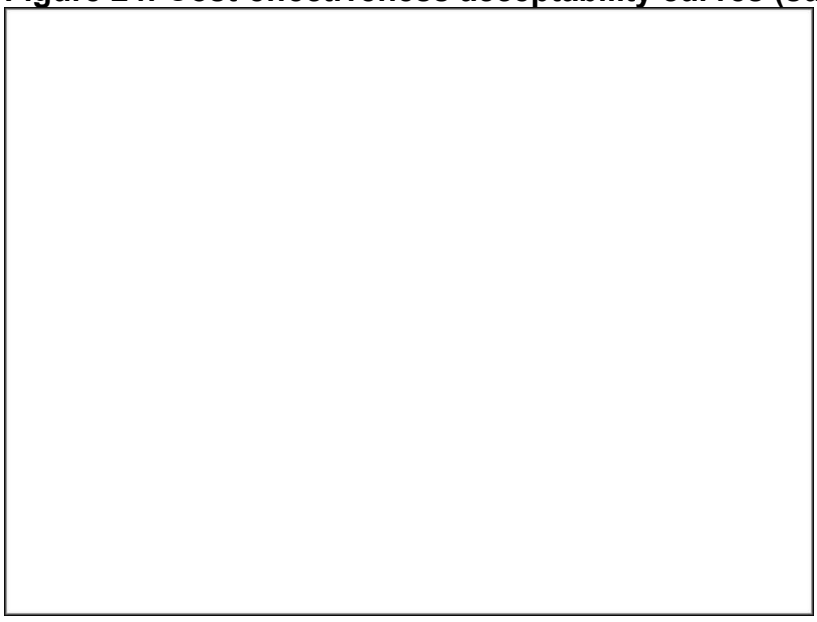
Abbreviations: ADA, adalimumab; APR, apremilast; BSC, best supportive care; CZP, certolizumab pegol; ETN, etanercept; Ext. dom, Extendedly dominated; GOL, golimumab; INF, infliximab; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib.

Figure 23: Cost-effectiveness plane (sub-population 2)



Abbreviations: ADA, adalimumab; APR, apremilast; BSC, best supportive care; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib.

Figure 24: Cost-effectiveness acceptability curves (sub-population 2)



Abbreviations: ADA, adalimumab; APR, apremilast; BSC, best supportive care; CEAC, cost-effectiveness acceptability curve; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; NMB, net monetary benefit; SEC, secukinumab; TOF, tofacitinib; WTP, willingness to pay.

B.3.8.1.2 People whose disease has not responded adequately to non-biological DMARDs and 1 or more TNFis (sub-population 3)

Table 55 presents the average results of the PSA. Results are comparable to the deterministic results; however, there is a small increase in QALYs across sequences and a slight decrease in costs, which favours BSC and increases ICERs for tofacitinib 5 mg BD and comparator bDMARDs. **Figure 25** and **Figure 26** present the cost-effectiveness plane and multiple CEACs respectively.

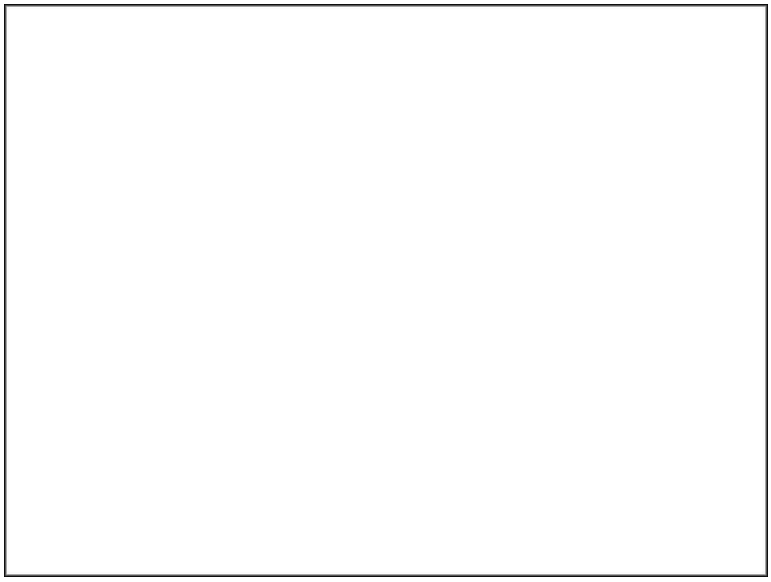
[redacted]

Table 55: Average costs and QALYs from the PSA (sub-population 3)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

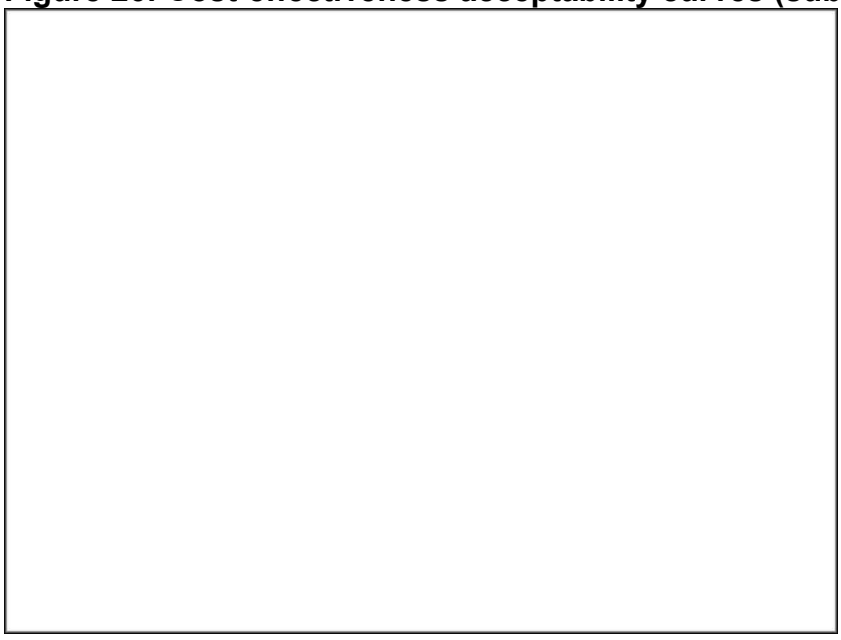
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab.

Figure 25: Cost-effectiveness plane (sub-population 3)



Abbreviations: BSC, best supportive care; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab.

Figure 26: Cost-effectiveness acceptability curves (sub-population 3)



Abbreviations: BSC, best supportive care; CEAC, cost-effectiveness acceptability curve; NMB, net monetary benefit; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab; WTP, willingness to pay.

B.3.8.1.3 People in whom TNFis are contraindicated or not tolerated (sub-population 4)

Table 56 presents the average results of the PSA. The costs in both arms are similar to those in the deterministic analysis thought they all decrease by a small amount. The total QALYs show a higher level of variation, with a small increase in QALYs across arms. Overall, the incremental ICERs are comparable to those from the deterministic analysis. **Figure 27** and **Figure 28** present the cost-effectiveness plane and multiple CEACs respectively.

[redacted]

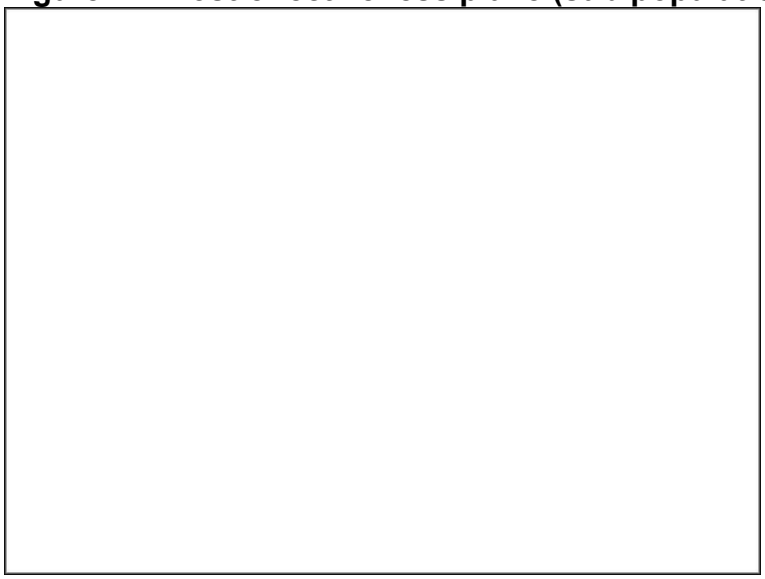
[redacted]

Table 56: Average costs and QALYs from the PSA (sub-population 4)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

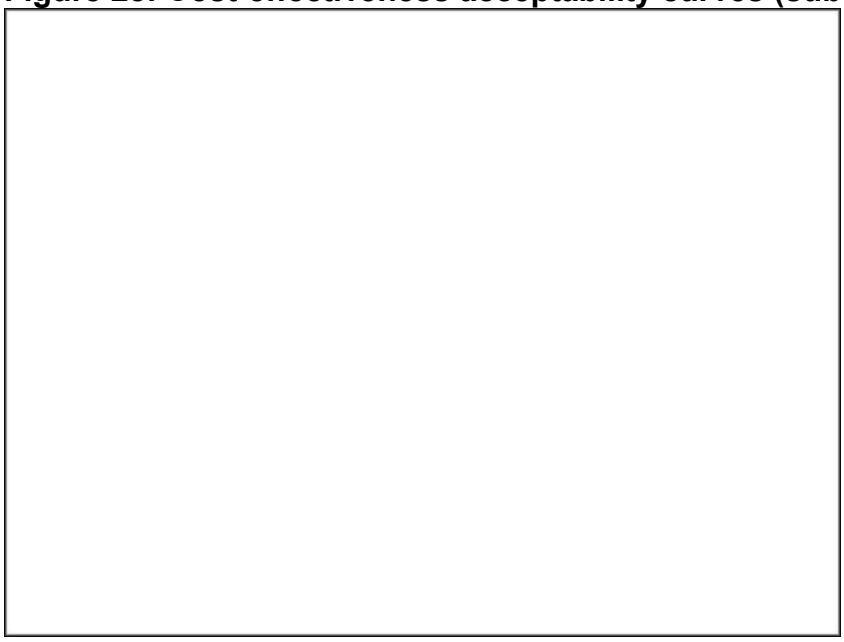
Abbreviations: BSC, best supportive care; Ext. dom, Extendedly dominated; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab.

Figure 27: Cost-effectiveness plane (sub-population 4)



Abbreviations: BSC, best supportive care; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab.

Figure 28: Cost-effectiveness acceptability curves (sub-population 4)



Abbreviations: BSC, best supportive care; CEAC, cost-effectiveness acceptability curve; NMB, net monetary benefit; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab; WTP, willingness to pay.

B.3.8.2 Deterministic sensitivity analysis

As a consequence of modelling treatment sequences, deterministic sensitivity analysis has not been performed; therefore tornado diagrams have not been presented, which is consistent with previous TAs. Alternatively, uncertainty in individual parameters has been assessed in scenario analysis.

B.3.8.3 Scenario analysis

Summaries of scenario analyses performed are presented below. Full details of scenario analyses are presented in **Appendix R**. Results of these analyses are discussed in **Section B.3.8.4**.

People whose disease has not responded adequately to at least 2 non-biological DMARDs (sub-population 2).

Table 57: Scenario analyses (sub-population 2)

Scenario	Scenario detail	Brief rationale	Tofacitinib ICER vs BSC (£/QALY)	Fully Incremental Analysis (£/QALY)
Base case			[redacted]	[redacted]
List price analysis	Using the list price for tofacitinib 5 mg BD	To present results of the list price analysis	[redacted]	[redacted]
Pessimistic NMA	Using alternate NMAs with worst outcomes for tofacitinib 5 mg BD only	To present a lower bound on the NMA analysis	[redacted]	[redacted]
Optimistic NMA	Using alternate NMAs with best outcomes for tofacitinib 5 mg BD only	To present an upper bound on the NMA analysis	[redacted]	[redacted]
ACR20 stopping rules	Response is defined by ACR20 response	To test the assumption of PsARC stopping rules	[redacted]	[redacted]
Pfizer mapping algorithm for all treatments	The Pfizer mapping algorithm is applied instead of the algorithm from TA199 (2, 111)	The Pfizer algorithm allows population-specific prediction of utility	[redacted]	[redacted]
Pfizer mapping algorithm for tofacitinib 5 mg BD only	The Pfizer mapping algorithm is applied to the tofacitinib 5 mg BD arm only	The Pfizer algorithm allows population-specific prediction of utility	[redacted]	[redacted]

Abbreviations: ACR, American College of Rheumatology BSC, best supportive care; HAQ, Health Assessment Questionnaire; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; PAS, patient access scheme; QALY, quality-adjusted life year; TOF, tofacitinib.

Two further scenarios were explored using data directly from OPAL Broaden to inform the relevant inputs in the economic model:

1. An OPAL Broaden exclusive analysis, comparing tofacitinib 5 mg BD with adalimumab and placebo (=BSC)

Table 58: OPAL Broaden Scenario 1

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	

TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, Adalimumab; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TOF, tofacitinib.

2. Data from OPAL Broaden were used to inform tofacitinib 5 mg BD and adalimumab only, and considered alongside data from the base case NMA for other comparators

Table 59: OPAL Broaden scenario 2

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
APR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, Adalimumab; APR, Apremilast; BSC, best supportive care; CTZ, Certolizumab pegol; ETN, Etanercept; GOL, Golimumab; INF, Infliximab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TOF, tofacitinib.

B.3.8.3.1 People whose disease has not responded adequately to non-biological DMARDs and 1 or more TNFis (sub-population 3)

Table 60: Scenario analyses (sub-population 3)

Scenario	Scenario detail	Brief rationale	Tofacitinib ICER vs BSC (£/QALY)	Fully Incremental Analysis (£/QALY)
Base case			[redacted]	[redacted]
List price analysis	Using the list price for tofacitinib 5 mg BD	To present results of the list price analysis	[redacted]	[redacted]
Pessimistic NMA	Using alternate NMAs with worst outcomes for tofacitinib 5 mg BD	To present a lower bound on the NMA analysis	[redacted]	[redacted]

Optimistic NMA	Using alternate NMAs with best outcomes for tofacitinib 5 mg BD	To present an upper bound on the NMA analysis	[redacted]	[redacted]
ACR20 stopping rules	Response is defined by ACR20 response	To test the assumption of PsARC stopping rules	[redacted]	[redacted]
Pfizer mapping algorithm for all treatments	The Pfizer mapping algorithm is applied instead of the algorithm from TA199 (2, 111)	The Pfizer algorithm allows population-specific prediction of utility	[redacted]	[redacted]
Pfizer mapping algorithm for TOF only	The Pfizer mapping algorithm is applied to the tofacitinib 5 mg BD arm only	The Pfizer algorithm allows population-specific prediction of utility	[redacted]	[redacted]

*The pessimistic NMAs are the same as in the base-case.
Abbreviations: ACR, American College of Rheumatology BSC, best supportive care; HAQ, Health Assessment Questionnaire; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; PAS, patient access scheme; QALY, quality-adjusted life year; TOF, tofacitinib.

B.3.8.3.2 People in whom TNFis are contraindicated or not tolerated (sub-population 4)

Table 61: Scenario analyses (sub-population 4)

Scenario	Scenario detail	Brief rationale	ICER vs BSC (£/QALY)	Fully Incremental Analysis (£/QALY)
Base case			[redacted]	[redacted]
List price analysis	Using the list price for tofacitinib 5 mg BD	To present results of the list price analysis	[redacted]	[redacted]
Pessimistic NMA	Using alternate NMAs with worst outcomes for tofacitinib 5 mg BD	To present a lower bound on the NMA analysis	[redacted]	[redacted]
Optimistic NMA	Using alternate NMAs with best outcomes for tofacitinib 5 mg BD	To present an upper bound on the NMA analysis	[redacted]	[redacted]
ACR20 stopping rules	Response is defined by ACR20 response	To test the assumption of PsARC stopping rules	[redacted]	[redacted]
Pfizer mapping algorithm for all treatments	The Pfizer mapping algorithm is applied instead of the algorithm from TA199 (2, 111)	The Pfizer algorithm allows population-specific prediction of utility	[redacted]	[redacted]

Pfizer mapping algorithm for TOF only	The Pfizer mapping algorithm is applied to the tofacitinib 5 mg BD arm only	The Pfizer algorithm allows population-specific prediction of utility	[redacted]	[redacted]

Abbreviations: ACR, American College of Rheumatology BSC, best supportive care; HAQ, Health Assessment Questionnaire; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; PAS, patient access scheme; QALY, quality-adjusted life year; TOF, tofacitinib.

B.3.8.4 Summary of sensitivity analyses results

B.3.8.4.1 Summary of probabilistic sensitivity analysis (PSA)

The average results of PSA in all three sub-populations were consistent with the deterministic analyses and demonstrate that the tofacitinib 5 mg BD sequence remains cost-effective versus BSC in all sub-populations when parameter uncertainty is explored.

In sub-population 2, the ICER versus BSC for the tofacitinib 5 mg BD sequence was [redacted], and in sub-populations 3 and 4, the tofacitinib 5 mg BD sequence was associated with the highest probability of being cost-effective at conventional willingness to pay thresholds of £20,000 and £30,000 per QALY.

B.3.8.4.2 Summary of scenario analyses

The scenario analysis shows that tofacitinib 5 mg BD remained a cost-effective therapy across a range of plausible settings for all sub-populations. In sub-population 2, the tofacitinib 5 mg BD sequence remained cost-effective under both the optimistic and pessimistic NMA scenarios vs BSC. Notably, when data from OPAL Broaden directly informed the model, tofacitinib 5 mg BD remained cost-effective compared to BSC and adalimumab (Scenario 1) and when data from OPAL Broaden were applied for tofacitinib and adalimumab only, alongside NMA data for the remaining comparators and BSC, tofacitinib remains cost-effective in versus all comparators (Scenario 2). In sub-populations 3 and 4, the tofacitinib 5 mg BD sequence remained the most cost-effective treatment sequence under all scenarios tested, which were consistent with the base case analysis.

The most influential parameter identified in the scenario analyses was the choice of mapping algorithm (**Section** Error! Reference source not found.), which was consistent across all three sub-populations. Using ACR 20 as a stopping rule in place of PsARC response reduced ICERs in all sub-populations, most markedly in sub-population 4. However, in all scenarios explored, the tofacitinib 5 mg BD sequence remained a cost-effective treatment sequence versus BSC, which is consistent with the results presented in the base case analysis.

B.3.9 Subgroup analysis

No subgroup analyses have been performed.

B.3.10 Validation

The cost-effectiveness model has been validated by the model developers and by health economists not involved in the construction of the model. The model was validated using standard procedures:

- Cell-by-cell checks of logic and consistency,
- Logical check of model outputs, and
- Comparison of outputs to those from previous economic analyses.

Model outputs were also compared with outputs from TA445 (3) and were considered to be consistent.

B.3.11 Interpretation and conclusions of economic evidence

B.3.11.1 Overall Conclusions

The cost-effectiveness of tofacitinib 5mg BD for patients with PsA has been appraised across three sub-populations outlined in the Final NICE Scope and explored under different model settings and scenarios. All analyses demonstrate that when compared to BSC, and positioned alongside current treatments recommended by NICE, tofacitinib 5mg BD is a cost-effective intervention for the treatment of PsA for:

- Sub-population 2 – People whose disease has not responded adequately to at least 2 non-biological DMARDs (Population 2);

- Sub-population 3 – People whose disease has not responded adequately to non-biological DMARDs and 1 or more TNFis; and

- Sub-population 4 – People in whom TNFis are contraindicated or not tolerated.

The conclusions of the analyses presented in this dossier are comparable to the results presented in the TA445 (3); however ICERs in this analysis tend to be lower. This is partially due to differences between the NMAs, as those used here estimated larger changes in HAQ-DI for the majority of therapies, including placebo.

The robustness of results was assessed through extensive sensitivity analysis (i.e., PSA) and multiple scenario analyses, which demonstrated that the base case ICERs for all populations were relatively insensitive to plausible changes. The greatest differences from base case results were seen in scenario analyses using results from alternative NMAs and an alternative utility mapping function (developed using data from the OPAL Broaden and OPAL Beyond RCTs); however, the conclusion that tofacitinib 5 mg BD is a cost-effective treatment across all three populations assessed here remains unchanged.

B.3.11.2 Relevance to patients with PsA

The economic analyses presented here demonstrate that tofacitinib 5mg BD is a cost-effective oral medication. Tofacitinib 5 mg BD provides an additional treatment option to patients and clinicians and meets a current unmet need for an oral medication with efficacy across multiple PsA clinical domains and an acceptable safety profile.

This analysis is relevant to all patient groups that may receive tofacitinib 5 mg BD in PsA. Population-specific data from the tofacitinib clinical trial programme are used where available, reflecting the positioning of patient groups within their respective treatment pathways. The analysis is generalisable to English clinical practice. The model is designed to imitate the treatment pathway and captures the sequenced nature of treatments used in England and Wales. Data used in the model are generalisable to the UK.

B.3.11.3 Strengths and limitations of the analyses

The main strengths of the analysis:

- The model follows the structure of previous economic evaluations used to inform current NICE recommendations in PsA, including the recent introduction of treatment sequences in TA445 (3), and is representative of clinical practice.

- The model provides flexibility to consider a wide range of treatment scenarios.

- The impact of different assumptions around the effectiveness of tofacitinib 5 mg BD has been thoroughly tested by presenting the results using a range of alternative NMA results.

The main limitations of the analysis:

- While the model is able to account for the effect of some baseline characteristics, it is not fully able to account for patient heterogeneity in the clinical trials. This weakness is a limitation of cohort models in general.

- The variation in PsARC response rates between the placebo arms of clinical trials may affect the relative efficacy of the drugs being considered. We have tried to address this limitation by presenting a variety of scenarios for the efficacy obtained from our NMAs for PsARC response. One of the approaches used in an attempt to address this issue was to remove the placebo arm from the OPAL Broaden clinical trial and link tofacitinib 5 mg BD to the NMA via the adalimumab arm. However, this approach may unfairly benefit tofacitinib 5 mg BD, as high placebo response rates are also an issue in other trials that do not have an active control/comparator to form the link (77).

  It was not possible to include all relevant comparators in all NMAs. No data were available on HAQ-DI change by PsARC response for secukinumab or certolizumab pegol. Data for inclusion in the bDMARD experienced NMAs were only available for tofacitinib 5 mg BD and ustekinumab (with the

exception of PASI and ACR data which were available for secukinumab in this population).

- The model was not able to account for all patient access schemes approved for comparator bDMARD treatment options, as many of these are not publicly available.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient Access Scheme submission template

February 2018

1 Introduction

The 2014 Pharmaceutical Price Regulation Scheme (PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the PPRS (2014) is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the functions of the PPRS (2014) is to improve patients' access to medicines at prices that better reflect their value through Patient Access Schemes.

Patient Access Schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient Access Schemes propose a discount, rebate or other variation from the list price of a medicine that may be linked to the number of patients estimated to receive the medicine, the clinical response of patients to the medicine or the collection of new evidence (outcomes) relating to the medicine. Proposed schemes should aim to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for Patient Access Schemes is provided in the PPRS (2014).

Patient Access Schemes are proposed by a pharmaceutical company and agreed with NHS England, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

The PPRS recognises the need to ensure that the cumulative burden on the NHS arising from Patient Access Schemes is manageable, and notes that these schemes should be the exception rather than the rule. Simple discount Patient Access Schemes are preferred to complex schemes because they create no significant implementation burden for the NHS. Where a more complex scheme is proposed, applicants should use the complex scheme proposal template rather than this simple discount scheme template, and will need to explain and justify their choice of scheme.

2 Instructions for companies

This document is the Patient Access Scheme submission template for technology appraisals. If companies want the National Institute for Health and Care Excellence (NICE) to consider a Patient Access Scheme as part of a technology appraisal, they should use this template. NICE can only consider a Patient Access Scheme after formal referral from NHS England.

The template contains the information NICE requires to assess the impact of a Patient Access Scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal'
- 'Company evidence submission template' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the technology appraisal process, please see NICE's 'Guide to the processes of technology appraisal April 2018. The 'User guide for company evidence submission template' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed Patient Access Scheme. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that

has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a Patient Access Scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the Patient Access Scheme incorporated, in accordance with the 'Guide to the methods of technology appraisal'

If you are submitting the Patient Access Scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the appraisal committee considered to be most plausible. No other changes should be made to the model.

3 Details of the Patient Access Scheme

3.1 Please give the name of the technology and the disease area to which the Patient Access Scheme applies.

The Patient Access Scheme (ID PAS0139) has been approved by the NHSE and PASLU for tofacitinib citrate (Xeljanz®) in respect of its expected indication for PsA:

[redacted]

3.2 Please outline the rationale for developing the Patient Access Scheme.

The Patient Access Scheme aims to provide access for patients toan innovative therapy with a novel mechanism of action (first in class Jak inhibitor for PsA), by improving the cost-effectiveness of tofacitinib for use within the above indication.

3.3 Please describe the type of Patient Access Scheme, as defined by the PPRS (2014). If it is a Simple Discount scheme, please include details of the list price and the proposed percentage discount/fixed price.

The Patient Access Scheme is a simple discount, which is conditional on the level of discount offered remaining confidential. The Scheme was first agreed with the Department of Health as part of the NICE appraisal of tofacitinib for the treatment of rheumatoid arthritis (TA480). The Department of Health considered that this Scheme does not constitute an excessive administrative burden on the NHS.

The new Scheme lowers the confidential fixed price below that which was previously agreed. This amendment to the Scheme will provide a simple discount of [redacted] (discounted price of £[redacted] per 5mg 56-tablet pack) to the list

price of tofacitinib, with the discount applied at the point of purchase or invoice.

3.4 Please provide specific details of the patient population to which the Patient Access Scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

This Scheme will apply to all licensed populations, upon tofacitinib receiving a positive NICE recommendation for the indication specified in question 3.1.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen?

The Scheme is not dependent upon any criteria and will continue to be applied as a discount at the point of purchase or invoice.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

The Scheme will apply to all NHS patients for whom tofacitinib is indicated.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The discount will continue to be applied at the point of invoice, as with the Scheme currently in operation. The new Scheme lowers the confidential fixed price below that which was previously agreed. This amendment to the Scheme will provide a simple discount of [redacted] (discounted price of £[redacted] per 5mg 56-tablet pack) to the list price of tofacitinib, with the discount applied at the point of purchase or invoice. Following positive guidance from NICE, this net price will be fixed in relation to this scheme, regardless of any subsequent changes to UK NHS list price.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

The discount will continue be applied at the point of invoice, as with the Scheme currently in operation. NHS Trusts (and relevant Commissioners requiring knowledge of the scheme for budget planning or other purposes) will receive a notification letter of the Scheme, although these organisations are not required to sign an additional agreement to receive the benefit of the scheme. No additional information collection will be required.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

The scheme will operate consistently with the current PAS associated with TA480.

Pfizer will provide a letter to all NHS Trusts (and relevant Commissioners) notifying them that a confidential simple Patient Access Scheme has been agreed with and approved by NHSE and PASLU, and the way in which the Patient Access Scheme will be administered . This letter will not require a signature.

For orders received directly from NHS Trusts/Hospitals, Pfizer receives the order and Pfizer delivers tofacitinib directly to the hospital with a confidential discount applied to the invoice. The NHS pays under the current payment terms and the terms of the letter referred to above.

In circumstances where the NHS Trust/Hospital chooses to engage the services of a third-party homecare provider to deliver tofacitinib to patients, Pfizer would need to ensure either that the homecare provider complies with Pfizer's Homecare Validation process, and executes an appropriate distribution agreement with Pfizer, or that the homecare provider is already validated and contracted to Pfizer. For the avoidance of doubt, the third party provider is free, at its discretion, to invoice its NHS customer at any price. Although we will do everything reasonably within our power to ensure that the NHS receives the benefit of the PAS, for legal reasons we cannot mandate that homecare companies pass on the discount to their customers

3.10 Please provide details of the duration of the scheme.

The Patient Access Scheme will remain in place, subject to NHSE agreement, so long as NICE positive guidance exists for tofacitinib for the indication specified in question 3.1.

It will be conditional upon:

(1) NICE positive guidance for tofacitinib in the indication specified in question 3.1; and

(2) NHS Trusts (and relevant Commissioners requiring knowledge of the scheme for budget planning or other purposes) receiving a notification letter of the Scheme, although these organisations are not required to sign an additional agreement to receive the benefit of the scheme.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equality issues relating to the scheme taking into account current legislation.

3.12 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix A.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main company submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Company evidence submission template'. You should complete those sections both with and without the Patient Access Scheme. You must also complete the rest of this template.

The population to whom the Scheme applies is the same as that covered in the main company submission and outlined in section 3.1 above.

4.2 If you are submitting the Patient Access Scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the appraisal committee considered to be most plausible. No other changes should be made to the model.

An update to the Scheme is being submitted after the original company submission, but prior to the first appraisal committee meeting. The economic model has been adjusted to incorporate feedback received in the ERG clarification questions A14 and B2, but is otherwise identical to the original economic model. The only change that affects the base-case of the economic analysis is that the NMA data inputs have been updated commensurate with ERG questions A14 (*amends HAQ-DI NMA for population 2 and 4*) and B2 (*Inconsistencies between the economic model and the company submission*), i.e., the all corrections model

4.3 Please provide details of how the Patient Access Scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the appraisal committee considered most plausible.

The Scheme is a simple discount applied at the point of invoice. To account for this, the acquisition price in the economic model has been adjusted accordingly (in line with sections 3.3 and 3.7 above).

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the Patient Access Scheme.

The Scheme is a simple discount applied at the point of invoice and therefore does not impact the clinical effectiveness data used in the evidence synthesis or in the economic model. The clinical input data used in the model, as well as the clinical output data produced by the model, remain the same with or without the Scheme.

4.5 Please list any costs associated with the implementation and operation of the Patient Access Scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 3.5 of the 'User guide for company evidence submission template'.

The Scheme is a simple discount applied at the point of invoice. The Scheme does not carry with it any implementation or operation costs to the NHS.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the Patient Access Scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the Patient Access Scheme. Please give the reference source of these costs.

The Scheme is a simple discount applied at the point of invoice. The Scheme does not carry with it any additional implementation costs.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

A suggested format is shown below (table 3).

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Note: The results presented below reflect the All Corrections model as referenced in section 4.2

Table 1 Base-case cost-effectiveness results with tofacitinib at list price – sub-population 2

	BSC	APR	TOF	ADA	CTZ	ETN	SEK	GOL	INF
Intervention cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER vs. BSC		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 2 Base-case cost-effectiveness results with confidential PAS – sub-population 2

	BSC	TOF	APR	ADA	CTZ	ETN	SEK	GOL	INF
Intervention cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs		£32,881	£40,499	£47,901	£48,839	£51,700	£52,978	£53,557	£71,190
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference		2.45	2.07	2.71	2.85	3.27	2.86	2.99	3.35
ICER vs. BSC		£13,419	£19,569	£17,687	£17,126	£15,798	£18,543	£17,904	£21,225

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life-year.

Table 3 Base-case cost-effectiveness results with tofacitinib at list price – sub-population 3

	BSC	TOF	UST	SEC
Intervention cost	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]	[redacted]	[redacted]
ICER vs. BSC	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 4 Base-case cost-effectiveness results with confidential PAS – sub-population 3

	BSC	TOF	UST	SEC
Intervention cost	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs	N/A	£11,732	£26,709	£54,206
QALYs	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference	N/A	1.30	1.42	1.60
ICER vs. BSC	£0	£9,001	£18,761	£33,914

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life-year.

Table 5 Base-case cost-effectiveness results with tofacitinib at list price – sub-population 4

	BSC	TOF	UST	SEC
Intervention cost	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]	[redacted]	[redacted]
ICER vs. BSC	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 6 Base-case cost-effectiveness results with confidential PAS – sub-population 4

	BSC	TOF	UST	SEK
Intervention cost	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs	£0	£8,930	£24,979	£30,153
QALYs	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference	-	1.14	1.33	1.62
ICER vs. BSC	£0	£7,825	£18,837	£18,557

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life-year.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 7: Incremental cost-effectiveness results with tofacitinib at list price - sub-population 2

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
[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: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 8: Incremental cost-effectiveness results using the confidential PAS - sub-population 2

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£32,881	2.45	£13,419	£13,419
APR	[redacted]	[redacted]	£40,499	2.07	£19,569	Dominated
ADA	[redacted]	[redacted]	£47,901	2.71	£17,687	Extendedly dominated
CTZ	[redacted]	[redacted]	£48,839	2.85	£17,126	Extendedly dominated
ETN	[redacted]	[redacted]	£51,700	3.27	£15,798	£22,886
SEK	[redacted]	[redacted]	£52,978	2.86	£18,543	Dominated
GOL	[redacted]	[redacted]	£53,557	2.99	£17,904	Dominated

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
INF	[redacted]	[redacted]	£71,190	3.35	£21,225	£239,101

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life-year.

Table 9: Incremental cost-effectiveness results using the tofacitinib list price- sub-population 3

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 10: Incremental cost-effectiveness results using the confidential PAS - sub-population 3

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£11,732	1.30	£9,001	£9,001
UST	[redacted]	[redacted]	£26,709	1.42	£18,761	£124,510
SEC	[redacted]	[redacted]	£54,206	1.60	£33,914	£157,429

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life-year.

Table 11: Incremental cost-effectiveness results using the tofacitinib list price - sub-population 4

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
[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: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 12: Incremental cost-effectiveness results using the confidential PAS - sub-population 4

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£8,930	1.14	£7,825	£7,825
UST	[redacted]	[redacted]	£24,979	1.33	£18,837	Extendedly dominated
SEK	[redacted]	[redacted]	£30,153	1.62	£18,557	£43,872

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life-year.

Sensitivity analyses

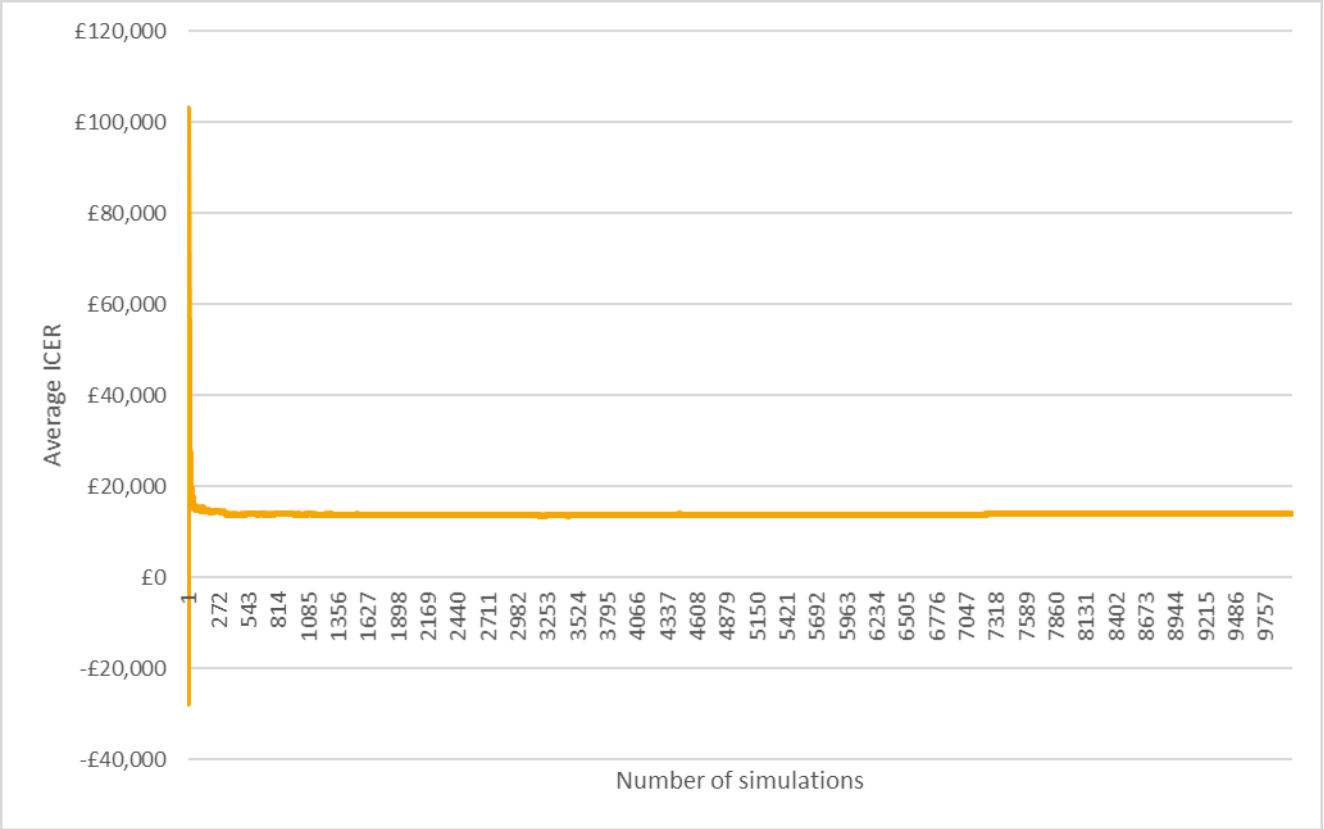
4.9 Please present deterministic sensitivity analysis results as described for the main company submission of evidence for the technology appraisal. Consider using tornado diagrams.

No deterministic sensitivity analyses were performed for the main company submission. As such, none have been provided here.

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. Ten thousand Monte Carlo simulations were recorded. This was deemed to be appropriate, as the probabilistic analysis closely matches the deterministic analysis. **Figure 1** presents the average ICER by number of simulations in sub-population 2. This shows that by 10,000 simulations the results are stable. Where parameters have been taken from an NMA they have been varied using the CODA output. Results were plotted on the cost-effectiveness plane (CEP) and cost-effectiveness acceptability curves (CEAC) were generated.

Figure 1: Average ICER by number of simulations (Sub-population 2)



People whose disease has not responded adequately to at least 2 non-biological DMARDs (sub-population 2)

Table 13 presents the average results of the PSA, which demonstrates that the total cost in most arms was similar to the total cost from the deterministic results, although the total QALYs were slightly higher in most arms; overall, incremental QALYs for all treatment sequences decrease relative to BSC, and ICERs increase. **Figure 2** and

Figure 3 present the cost-effectiveness plane and multiple CEACs, respectively.

Figure 3 shows that below an ICER of £14,000 the BSC sequence is most likely to be cost-effective, between £14,000 and £25,000 tofacitinib is most likely to be cost-effective and above this the etanercept biosimilar sequence is most cost-effective.

At thresholds of £20,000 and £30,000 per QALY, tofacitinib 5 mg BD had a 54% and 22% chance, respectively, of being the optimal treatment. At a

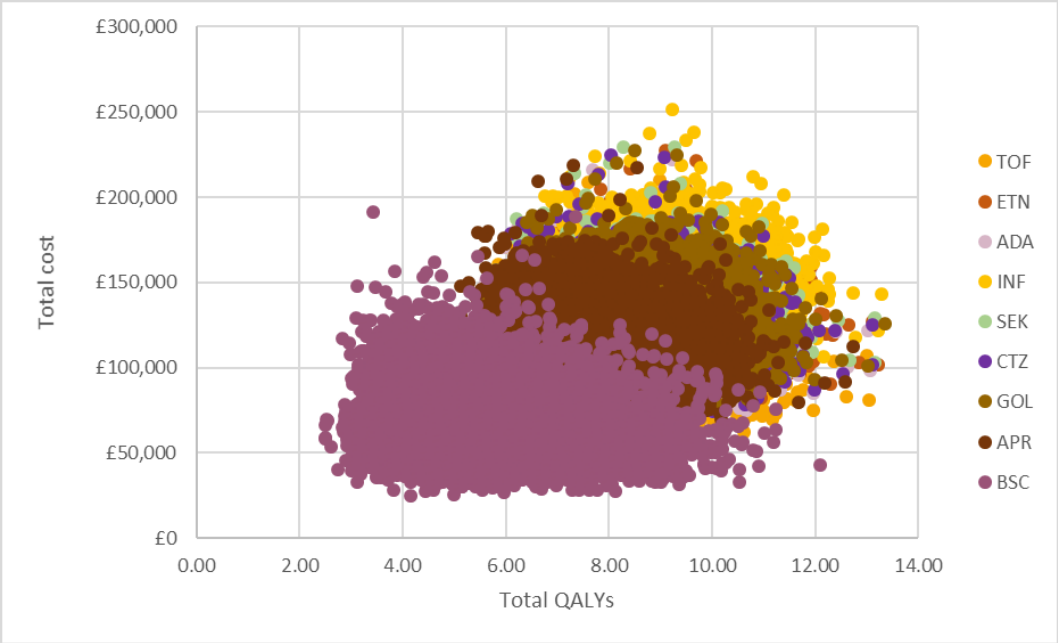
£20,000 threshold it was the most likely to be optimal. At £30,000 it was the 2nd most likely, behind etanercept biosimilar. Of the 10,000 simulations, 76% and 87% of the tofacitinib 5 mg BD compared with BSC ICERs were below £20,000 and £30,000 per QALY, respectively.

Table 13: Average costs and QALYs from the PSA (sub-population 2 using confidential PAS)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]				
TOF	[redacted]	[redacted]	**£33,231**	**2.39**	**£13,918**	**£13,918**
APR	[redacted]	[redacted]	£40,841	2.00	£20,422	Dominated
ADA	[redacted]	[redacted]	£48,350	2.64	£18,318	Extendedly dominated
CTZ	[redacted]	[redacted]	£49,313	2.77	£17,815	Dominated
ETN	[redacted]	[redacted]	£52,182	3.19	£16,371	£23,696
SEK	[redacted]	[redacted]	£53,510	2.78	£19,253	Dominated
GOL	[redacted]	[redacted]	£54,009	2.90	£18,641	Dominated
INF	[redacted]	[redacted]	£71,630	3.27	£21,900	£233,602

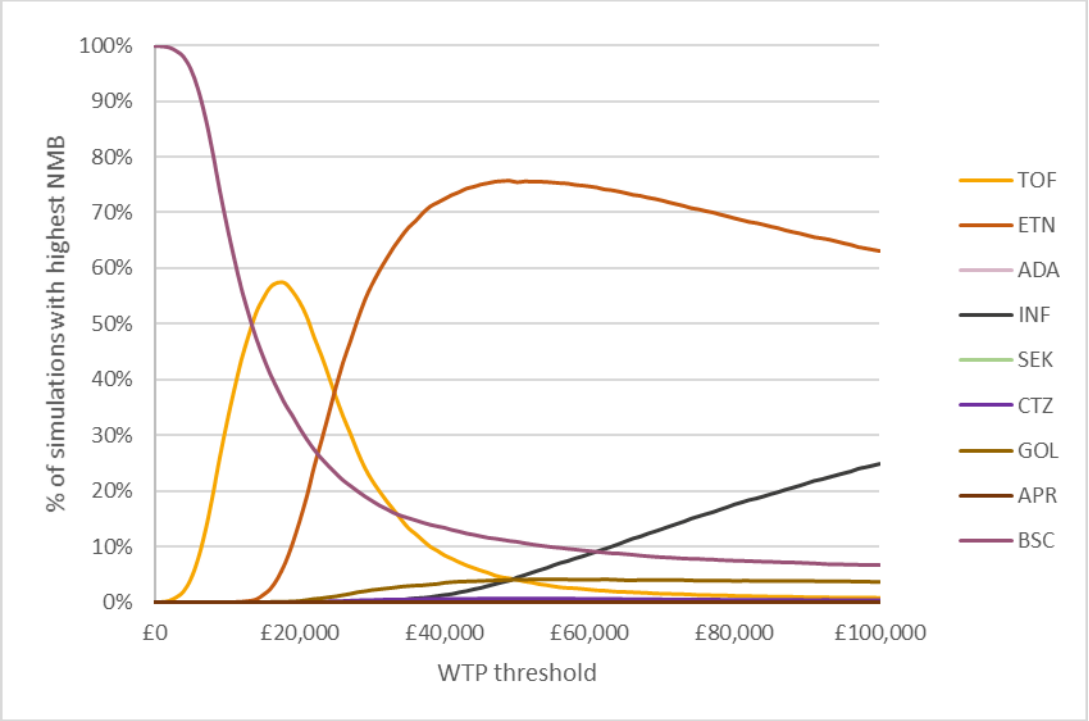
Abbreviations: ADA, adalimumab; APR, apremilast; BSC, best supportive care; CZP, certolizumab pegol; ETN, etanercept; Ext. dom, Extendedly dominated; GOL, golimumab; INF, infliximab; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib.

Figure 2: Cost-effectiveness plane (sub-population 2)



Abbreviations: ADA, adalimumab; APR, apremilast; BSC, best supportive care; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib.

Figure 3: Cost-effectiveness acceptability curves (sub-population 2)



Abbreviations: ADA, adalimumab; APR, apremilast; BSC, best supportive care; CEAC, cost-effectiveness acceptability curve; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; NMB, net monetary benefit; SEC, secukinumab; TOF, tofacitinib; WTP, willingness to pay.

People whose disease has not responded adequately to non-biological DMARDs and 1 or more TNFis (sub-population 3)

Table 14 presents the average results of the PSA. Results are comparable to the deterministic results; however, there is a small increase in QALYs across sequences and a slight decrease in costs, which favours BSC and increases ICERs for tofacitinib 5 mg BD and comparator bDMARDs. **Figure 4** and **Figure 5** present the cost-effectiveness plane and multiple CEACs respectively. The tofacitinib 5 mg BD sequence is most likely to be cost-effective beyond a threshold of £10,000 per QALY.

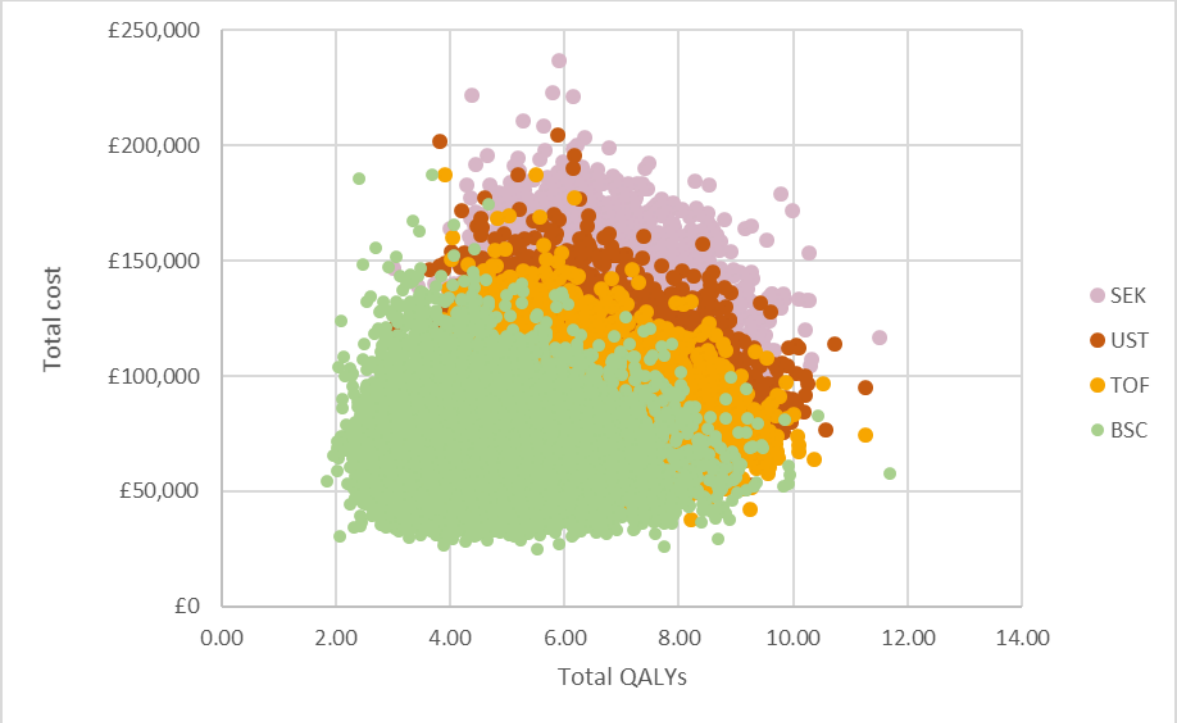
At thresholds of £20,000 and £30,000 per QALY tofacitinib 5 mg BD had a 97% and 93% chance, respectively, of being the optimal treatment. Of the 10,000 simulations, 97% and 99% of the tofacitinib 5 mg BD compared with BSC ICERs were below £20,000 and £30,000 per QALY, respectively.

Table 14: Average costs and QALYs from the PSA (sub-population 3 using confidential PAS)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]				
TOF	[redacted]	[redacted]	£11,863	1.25	£9,467	£9,467
UST	[redacted]	[redacted]	£27,004	1.38	£19,554	£118,419
SEK	[redacted]	[redacted]	£53,713	1.51	£35,549	£205,549

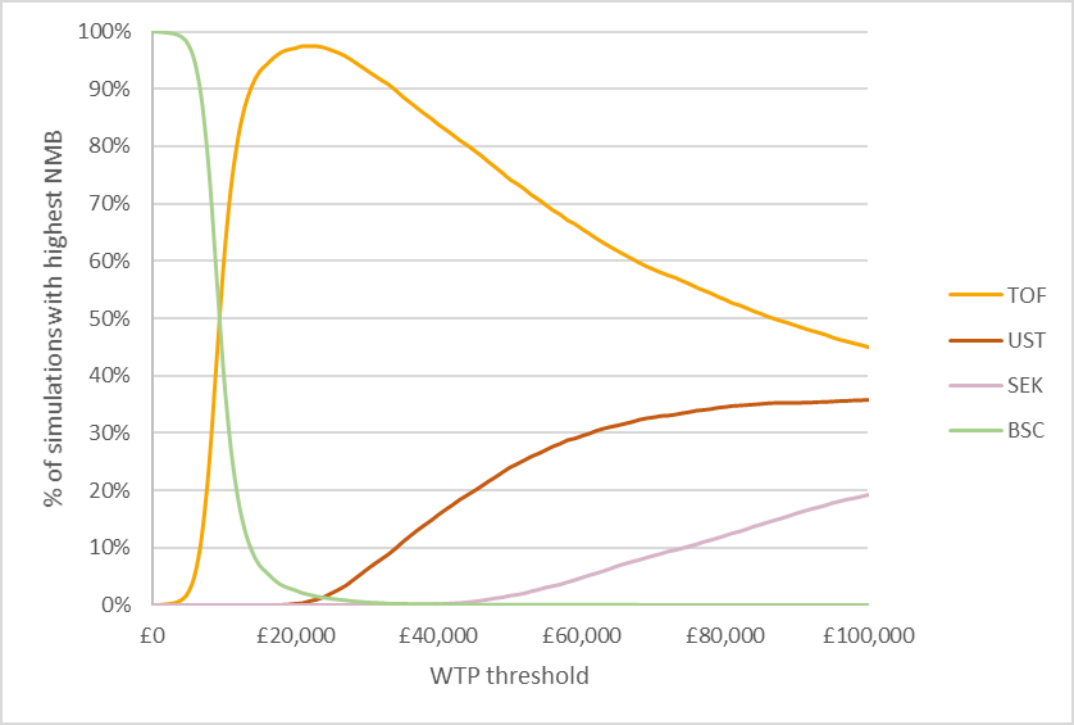
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab.

Figure 4: Cost-effectiveness plane (sub-population 3)



Abbreviations: BSC, best supportive care; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab.

Figure 5: Cost-effectiveness acceptability curves (sub-population 3)



Abbreviations: BSC, best supportive care; CEAC, cost-effectiveness acceptability curve; NMB, net monetary benefit; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab; WTP, willingness to pay.

People in whom TNFis are contraindicated or not tolerated (sub-population 4)

Table 15 presents the average results of the PSA. The costs in both arms are similar to those in the deterministic analysis thought they all decrease by a small amount. The total QALYs show a higher level of variation, with a small increase in QALYs across arms. Overall, the incremental ICERs are comparable to those from the deterministic analysis. **Figure 6** and **Figure 7** present the cost-effectiveness plane and multiple CEACs respectively. The tofacitinib 5 mg BD sequence has the highest probability of being cost-effective at thresholds greater than £8,000 per QALY gained (until the cost-effectiveness threshold exceeds £49,000 per QALY).

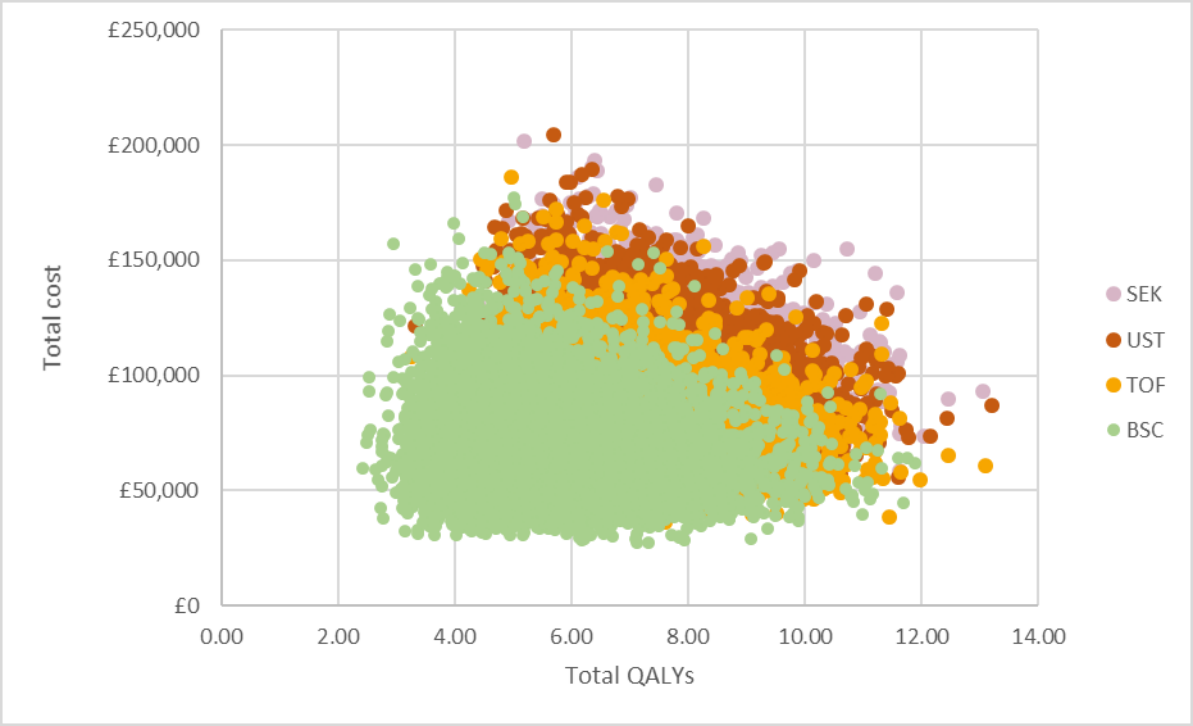
At thresholds of £20,000 and £30,000 per QALY tofacitinib 5 mg BD had a 65% and 61% chance, respectively, of being the optimal treatment. Of the 10,000 simulations, 89% and 93% of the tofacitinib 5 mg BD compared with BSC ICERs were below £20,000 and £30,000 per QALY, respectively.

Table 15: Average costs and QALYs from the PSA (sub-population 4 using confidential PAS)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]				
TOF	[redacted]	[redacted]	£9,050	1.11	£8,123	£8,123
UST	[redacted]	[redacted]	£25,167	1.29	£19,479	Extendedly dominated
SEK	[redacted]	[redacted]	£30,683	1.60	£19,228	£44,919

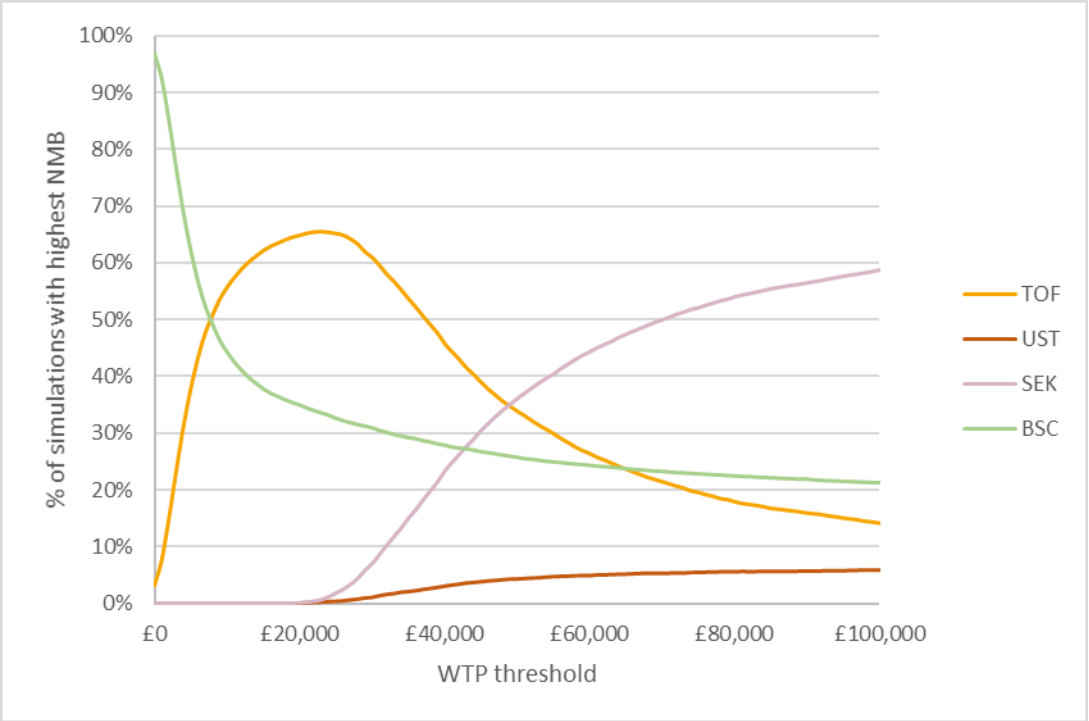
Abbreviations: BSC, best supportive care; Ext. dom, Extendedly dominated; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab.

Figure 6: Cost-effectiveness plane (sub-population 4)



Abbreviations: BSC, best supportive care; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab.

Figure 7: Cost-effectiveness acceptability curves (sub-population 4)



Abbreviations: BSC, best supportive care; CEAC, cost-effectiveness acceptability curve; NMB, net monetary benefit; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab; WTP, willingness to pay.

4.11 Please present scenario analysis results as described for the main company submission of evidence for the technology appraisal.

Scenario analyses were performed to explore the impact of using alternate clinical data, stopping rules and mapping algorithms. Table 16, Table 17 and Table 18 present the results of the scenario analysis for sub-populations 2, 3 and 4 respectively.

The most influential parameter identified in the scenario analyses was the choice of mapping algorithm, which was consistent across all three sub-populations. Using ACR 20 as a stopping rule in place of PsARC response reduced ICERs in all sub-populations. However, in all scenarios explored, the tofacitinib 5 mg BD sequence remained a cost-effective treatment sequence at PAS price, which is consistent with the results presented in the base case analysis.

Table 16: Scenario analyses using confidential PAS - sub-population 2

Scenario	Scenario detail	Brief rationale	Tofacitinib ICER vs BSC (£/QALY)	Fully Incremental Analysis (£/QALY)
Base case			£13,419	£13,419
Pessimistic NMA	Using alternate NMAs with worst outcomes for tofacitinib 5 mg BD only	To present a lower bound on the NMA analysis	£14,124	£14,124
Optimistic NMA	Using alternate NMAs with best outcomes for tofacitinib 5 mg BD only	To present an upper bound on the NMA analysis	£12,013	£12,013
ACR20 stopping rules	Response is defined by ACR20 response	To test the assumption of PsARC stopping rules	£12,996	£12,996
OPAL Broaden scenario 1	Compares BSC, tofacitinib and adalimumab using the data from OPAL Broaden	To test the effect of using OPAL Broaden data directly	£15,016	£15,016
OPAL Broaden scenario 2	Compares all treatments using the data from OPAL Broaden for tofacitinib and adalimumab and NMA data for everything else	To test the effect of using OPAL Broaden data directly	£12,913	£12,913
Pfizer mapping algorithm for all treatments	The Pfizer mapping algorithm is applied instead of the algorithm from TA199 (2, 111)	The Pfizer algorithm allows population-specific prediction of utility	£18,235	£18,235
Pfizer mapping algorithm for tofacitinib 5 mg BD only	The Pfizer mapping algorithm is applied to the tofacitinib 5 mg BD arm only	The Pfizer algorithm allows population-specific prediction of utility	£13,582	£13,582

Abbreviations: ACR, American College of Rheumatology BSC, best supportive care; HAQ, Health Assessment Questionnaire; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; PAS, patient access scheme; QALY, quality-adjusted life year; TOF, tofacitinib.

Table 17: Scenario analyses using confidential PAS - sub-population 3

Scenario	Scenario detail	Brief rationale	Tofacitinib ICER vs BSC (£/QALY)	Fully Incremental Analysis (£/QALY)
Base case			£9,001	£9,001
Pessimistic NMA	Using alternate NMAs with worst outcomes for tofacitinib 5 mg BD only	To present a lower bound on the NMA analysis	£9,001	£9,001
Optimistic NMA	Using alternate NMAs with best outcomes for tofacitinib 5 mg BD only	To present an upper bound on the NMA analysis	£7,908	£7,908
ACR20 stopping rules*	Response is defined by ACR20 response	To test the assumption of PsARC stopping rules	£8,968	£8,968
Pfizer mapping algorithm for all treatments	The Pfizer mapping algorithm is applied instead of the algorithm from TA199 (2, 111)	The Pfizer algorithm allows population-specific prediction of utility	£10,522	£10,522
Pfizer mapping algorithm for tofacitinib 5 mg BD only	The Pfizer mapping algorithm is applied to the tofacitinib 5 mg BD arm only	The Pfizer algorithm allows population-specific prediction of utility	£9,229	£9,229

*ACR20 analysis excludes secukinumab as it was not possible to include this in the NMA.

Abbreviations: ACR, American College of Rheumatology BSC, best supportive care; HAQ, Health Assessment Questionnaire; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; PAS, patient access scheme; QALY, quality-adjusted life year; TOF, tofacitinib.

Table 18: Scenario analyses using confidential PAS - sub-population 4

Scenario	Scenario detail	Brief rationale	Tofacitinib ICER vs BSC (£/QALY)	Fully Incremental Analysis (£/QALY)
Base case			£7,825	£7,825
Pessimistic NMA	Using alternate NMAs with worst outcomes for tofacitinib 5 mg BD only	To present a lower bound on the NMA analysis	£8,599	£8,599
Optimistic NMA	Using alternate NMAs with best outcomes for tofacitinib 5 mg BD only	To present an upper bound on the NMA analysis	£6,089	£6,089
ACR20 stopping rules	Response is defined by ACR20 response	To test the assumption of PsARC stopping rules	£7,516	£7,516
Pfizer mapping algorithm for all treatments	The Pfizer mapping algorithm is applied instead of the algorithm from TA199 (2, 111)	The Pfizer algorithm allows population-specific prediction of utility	£10,655	£10,655
Pfizer mapping algorithm for tofacitinib 5 mg BD only	The Pfizer mapping algorithm is applied to the tofacitinib 5 mg BD arm only	The Pfizer algorithm allows population-specific prediction of utility	£8,032	£8,032

Abbreviations: ACR, American College of Rheumatology BSC, best supportive care; HAQ, Health Assessment Questionnaire; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; PAS, patient access scheme; QALY, quality-adjusted life year; TOF, tofacitinib.

4.12 If any of the criteria on which the Patient Access Scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the appraisal committee can determine which criteria are the most appropriate to use.

Not applicable.

Impact of Patient Access Scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the Patient Access Scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the Patient Access Scheme at the end of the appraisal process, you must include the scenario with the assumptions that the appraisal committee considered to be most plausible.

Table 19, Table 20 and Table 21 present the base-case and scenario analysis results at both the list price and PAS price. In sub-populations 3 and 4 the incremental analysis shows tofacitinib to be a cost-effective treatment at list price and the effect of the PAS is to reduce the ICER further. In sub-population 2, tofacitinib is extendedly dominated at list price and the effect of the PAS is to make tofacitinib a cost-effective treatment option in all scenarios.

Table 19 Results showing the impact of Patient Access Scheme on ICERs - sub-population 2

	ICER for tofacitinib			
	Without PAS		With PAS	
	ICER vs BSC	Incremental ICER	ICER vs BSC	Incremental ICER
Base-case	[redacted]	[redacted]	£13,419	£13,419
Pessimistic NMA	[redacted]	[redacted]	£14,124	£14,124
Optimistic NMA	[redacted]	[redacted]	£12,013	£12,013
ACR20 stopping rules	[redacted]	[redacted]	£12,996	£12,996
OPAL Broaden scenario 1	[redacted]	[redacted]	£15,016	£15,016
OPAL Broaden scenario 2	[redacted]	[redacted]	£12,913	£12,913
Pfizer mapping algorithm for all treatments	[redacted]	[redacted]	£18,235	£18,235
Pfizer mapping algorithm for tofacitinib 5 mg BD only	[redacted]	[redacted]	£13,582	£13,582

PAS: Patient Access Scheme.

Table 20 Results showing the impact of Patient Access Scheme on ICERs - sub-population 3

	ICER for tofacitinib			
	Without PAS		With PAS	
	ICER vs BSC	Incremental ICER	ICER vs BSC	Incremental ICER
Base-case	[redacted]	[redacted]	£9,001	£9,001
Pessimistic NMA	[redacted]	[redacted]	£9,001	£9,001
Optimistic NMA	[redacted]	[redacted]	£7,908	£7,908
ACR20 stopping rules	[redacted]	[redacted]	£8,968	£8,968
Pfizer mapping algorithm for all treatments	[redacted]	[redacted]	£10,522	£10,522
Pfizer mapping algorithm for tofacitinib 5 mg BD only	[redacted]	[redacted]	£9,229	£9,229

PAS: Patient Access Scheme.

Table 21 Results showing the impact of Patient Access Scheme on ICERs - sub-population 4

	ICER for tofacitinib			
	Without PAS		With PAS	
	ICER vs BSC	Incremental ICER	ICER vs BSC	Incremental ICER
Base-case	[redacted]	[redacted]	£7,825	£7,825
Pessimistic NMA	[redacted]	[redacted]	£8,599	£8,599
Optimistic NMA	[redacted]	[redacted]	£6,089	£6,089
ACR20 stopping rules	[redacted]	[redacted]	£7,516	£7,516
Pfizer mapping algorithm for all treatments	[redacted]	[redacted]	£10,655	£10,655
Pfizer mapping algorithm for tofacitinib 5 mg BD only	[redacted]	[redacted]	£8,032	£8,032

PAS: Patient Access Scheme.

5 Appendix A: Details for outcome-based schemes only

5.1 If you are submitting an outcome based scheme which is expected to result in a price increase, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.2 If you are submitting an outcome based scheme which is expected to result in a price reduction or rebate, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.3 Provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection

- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable.

5.4 Please specify the period between the time points when the additional evidence will be considered.

Not applicable.

5.5 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered.

Not applicable.

5.6 Please provide the other data used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable.

5.7 Please present the cost-effectiveness results as follows.

- For a scheme that is expected to result in a price increase, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For a scheme that is expected to result in a price reduction or rebate, please summarise in separate tables:

- the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
- the results based on the current evidence and the lower price (if the new evidence is not forthcoming).

A suggested format is shown in table 3, section 4.7.

5.8 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

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Single technology appraisal

Tofacitinib for treating active psoriatic arthritis after DMARDs [ID1220]

Dear Jo,

The Evidence Review Group, Centre for Reviews and Dissemination and Centre for Health Economics – York, and the technical team at NICE have looked at the submission received on 6 April 2018 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 **Thursday 17 May**. 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 attached checklist for confidential information.

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 Ross Dent, Technical Lead (Ross.Dent@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

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Section A: Clarification on effectiveness data

Literature searching

A1. Please confirm that the correct search strategy for MEDLINE been provided in Table D2, page 13, Appendix D. Lines 4, 12, 20, 22, 24 are searches for MeSH terms which do not exist in MEDLINE and when entered into Ovid MEDLINE retrieve O hits. Are these lines searches of another field rather than MeSH searches?

A2. The search strategy for EconLit is missing from Appendix G. Please provide the strategy along with the date of the search.

Methods

A3. **Priority question:** Please provide the study protocols for OPAL Broaden, OPAL Beyond and OPAL Balance.

A4. **Priority question:** Please provide a breakdown of the previous anti-TNFs taken by patients in OPAL Beyond (i.e. the proportion of patients that had 1, 2, 3 or more than 3 anti-TNFs). Please also provide the proportion of patients that had each individual anti-TNF (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), ustekinumab, secukinumab, apremilast or abatacept.

A5. **Priority question:** Please clarify the number of patients from each arm of OPAL Broaden and OPAL Beyond that entered OPAL Balance.

A6. **Priority question:** In Table M22 (appendix M) it states that a key inclusion criterion for OPAL Balance is: “Subjects who have completed at least 24 months of treatment with tofacitinib in the extension study.” Please clarify whether patients who entered OPAL Balance did so directly from OPAL Broaden and OPAL Beyond or if there was an interim extension open label period in each of these trials.

A7. Table 8 of the company submission states that the type I error rate was adjusted for multiple comparisons for ACR20 and change in HAQ-DI at 3 months. Please provide more details of the methods used to adjust for multiple comparisons.

A8. Please provide the number of patients who switch from tofacitinib to another treatment in OPAL Beyond and OPAL Broaden and whether the next treatment was a csDMARD or bDMARD.

A9. Please clarify how best supportive care is defined (i.e. proportion of patients assumed to be taking a DMARD, which DMARDs etc.)

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Effectiveness data

A10. **Priority question:** Please provide the results of any efficacy analyses using the post-3 month data for patients who switched from placebo to 5mg or 10mg tofacitinib. Please also confirm if these data were included in the safety analysis.

A11. **Priority question:** In Table M22, (appendix M) PsARC is listed as a key secondary outcomes in OPAL Balance but results for PsARC are not included in Table 21 of the company submission. Please provide these results

A12. In Table 21 and Figure 6 of the company submission, the number of patients in OPAL Balance falls over time but the percentage of patients whose disease achieves an ACR 20, 50 or 70 response stays the same. Please clarify why at these later follow-up assessments there are any patients whose disease does not achieve an ACR 20 response.

Evidence synthesis

A13. **Priority question:** Please provide a full description of specifications for each of the network meta-analysis (NMA) models, alongside all files required to run the models in WinBUGS (including data, model, and initial values for every chain).

A14. **Priority question:** Please justify the new specification introduced with NMA model K (HAQ), commenting on the advantages and disadvantages and justify and explain the differences in the results between models G and K.

A15. **Priority question:** Please compare the results of models in the company submission that have the same specification as those in NICE Technology Appraisal guidance 445 (TA445) and justify any differences. In particular, please explain differences in the outcomes for placebo (PASI and PsARC outcomes); please justify any differences and explore the reasons for such differences.

A16. **Priority question:** For the no prior bDMARD subgroup, please consider any differences/similarities between the results in the company submission and those in TA445 for model selection undertaken using goodness of fit measures (such as DIC and residual deviance) for all outcomes (PsARC, PASI, HAQ and ACR).

A17. **Priority question:** Please provide complete results for the NMA models reported in the company submission as some information is missing (e.g. the z-scores for PASI models, treatment effect in HAQ models in Table E45, appendix E).

A18. **Priority question:** Please explore the reasons for the placebo arm of the OPAL Broaden trial not having a good fit to the NMA model with placebo adjustment for

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PsARC. Consider alternative model specifications that better reflect the results of this trial.

Withdrawals

A19. **Priority question:** For OPAL Broaden and OPAL Beyond, please provide the numbers of patient withdrawals (total for each arm broken down by reason and at 3, 6 and 12 month time points).

A20. **Priority question:** For OPAL Broaden and OPAL Beyond, please provide details of patients who discontinued concomitant csDMARDs (total for each arm, broken down by methotrexate or other csDMARD and at 3, 6 and 12 month time points)

A21. **Priority question:** For OPAL Balance please give the numbers and reason for withdrawals by dose of tofacitinib at each assessment time point (months 6, 12, 18 and 24). Please provide details of the patient withdrawals (number of withdrawals with reason (e.g. lack of efficacy, adverse effects or other)).

A22. **Priority question:** For the patients randomised to tofacitinib 5mg in OPAL Broaden and OPAL Beyond, please provide separately for each trial, the mean (and standard deviation) and median (and range) persistence (drug survival) calculated from the longest follow-up available, including any data from open label extension studies or OPAL Balance.

Tofacitinib 10mg

A23. **Priority question:** In OPAL Balance please provide details of the proportion of patients receiving tofacitinib 10mg and the duration of treatment with this dose.

A24. Please comment on whether the 10mg dose is expected to be used in clinical practice. If not, what impact does the inclusion of patients taking the 10mg dose in OPAL Balance have on the generalisability of these data to clinical practice?

Radiographic progression

A25. **Priority question:** Please clarify the source of the estimates of difference in mTSS and rate of progression for adalimumab vs baseline in the ADEPT study at 48 weeks reported in tables D36 and D38 in appendix D. The citation for the study in table D38 (34) does not match that in the reference list.

A26. **Priority question:** Please clarify how the non-inferiority (NI) margins for difference in mTSS and rate of progression were calculated. p188 of appendix D states that the same approach as the FDA Arthritis Advisory Committee was used, however the NI margins for both difference in mTSS and rate of progression appear to differ from the

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25-75% upper bound criteria used to determine the NI margin in the FDA Arthritis Advisory Committee review.

Immunogenicity

A27. Please explain in more detail and provide greater justification for the statement that tofacitinib will be less likely to be associated with immunogenicity. (page 25 of the company submission)

Section B: Clarification on cost-effectiveness data

Withdrawal

B1. **Priority question**: The model assumes the same rate of withdrawal for tofacitinib as used in previous appraisals of biological DMARDs. Please provide additional evidence and justification to support this assumption given the different mechanism of action and mode of delivery. Specifically:

a) In addition to the withdrawal data requested in Question A19, please provide withdrawal data for patients whose disease initially responds to treatment (as assessed by PsARC) and subsequently withdraw due to loss of efficacy or adverse events.

b) Please provide a revised version of the model that allows a separate withdrawal rate to be specified for tofacitinib

c) Please present an additional scenario which uses the rate of withdrawal based on the data from the OPAL trials for tofacitinib

Quality of Life

B2. **Priority question:** Please provide appendix Q, referred to in the company submission.

B3. **Priority question**: The published protocol for OPAL Beyond states that EQ-5D data were collected. Please provide the results of any EQ-5D assessments in OPAL Broaden, OPAL Beyond and OPAL Balance including sample sizes, missing data, follow up points, EQ-5D scores at baseline and follow up for each treatment and details and results of any statistical tests performed.

B4. **Priority question**: Please provide the utility algorithm, derived from the data collected in the OPAL trials, used in the scenario analysis reported in appendix R. Please justify the specific covariates and regression function used.

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Probabilistic Sensitivity Analyses

B1. **Priority question**: The code for the probabilistic sensitivity analyses (PSA) is complex and difficult to validate. Please provide the following information:

- A step by step description of how the VBA code implements the PSA, including how the Monte Carlo sampling is implemented/
- Confirmation of whether the simulations are done simultaneously for all comparators or separately for each individual comparator.
- Detailed annotations within the VBA code for each step.

Inconsistencies between the economic model and the company submission

B2. **Priority question**: There are a number of inconsistencies between the data used in the economic model and that reported in the company submission (listed below). Please clarify which values are correct and if necessary provide a version of the model using corrected values.

- In populations 2 and 3, the probability of PsARC, PASI and ARC response for Ustekinumab is inconsistent between the company submission (Tables 25 and 27) and Appendices (Table E62) compared to the NMA data used in the model (Sheet 'NMA Data'; Rows A10:AL10, A28:AL28, A49:AL49, A70:AI70, A120:AL120, A138:AL138, A156:AL156).

- The results of the base case model for ACR response in subpopulation 3 (Sheet 'NMA Data'; Rows J115:M166) are not consistent with what is reported in the company submission (Table 25).

- For populations 2-4, (Sheet 'NMA Data'; (Rows Y23:AL33, Y44:AL44, Y51:AL51 and Y65:AL75), the probability of PASI response is not consistent with what is reported in the company submission (Table 27 in submission or Tables E67 and E69 in Appendix E). On the same sheet (Rows Y115:AB125) the probability of ARC 20 response does not match the values in Table 27 of the company submission.

- Table 24 in the company submission states that model E1 FE with 24-wk data was selected as the 'pessimistic' case for the ACR endpoint and model E1 FE without 24-wk data was selected as both the optimistic and base case for the ACR response. For populations 2-4 (Sheet 'NMA Data; Rows Y115;AL165), it seems that model E1 FE without 24-wk data was selected for the base case and 'pessimistic' case while model E1 FE with 24-week data was used for the 'optimistic' case data.

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- In population 2-4, the company submission and appendices do not report ARC response for secukinumab 300mg when presenting the summary results for the biologic experienced NMA data. This data is reported in Sheet 'NMA Data' (Rows Y125:AL125, Y143:AL143, Y161:AL161). The source of this data is not detailed; please provide these details.

Baseline characteristics

B3. Baseline characteristics data in the model are taken from the OPAL trials. Please justify why the baseline patient characteristics from the trials included in the NMA were not used. Please provide a scenario using the baseline patient characteristics from the NMA.

Section C: Textual clarifications and additional points

C1. The results from MEDLINE in figure D1 PRISMA on page 27, Appendix D are reported as 1404. However the search strategy for MEDLINE in Table D2, page 16, Appendix D shows that 1415 records were retrieved. Please clarify the number of records that were retrieved from MEDLINE.

C2. In figure G1: Economic PRISMA flow diagram, page 23, Appendix G, the number of hits from Embase are reported as 3837 and from MEDLINE 1677. These numbers differ from those found in the search strategies for Embase (1672 hits – line 71, table G1, page 9) and from MEDLINE (557 hits – line 71, table G2, page 14). Please explain these differences.

Section A: Clarification on effectiveness data

Literature searching

A1. Please confirm that the correct search strategy for MEDLINE been provided in Table D2, page 13, Appendix D. Lines 4, 12, 20, 22, 24 are searches for MeSH terms which do not exist in MEDLINE and when entered into Ovid MEDLINE retrieve O hits. Are these lines searches of another field rather than MeSH searches?

Pfizer Response: The correct MEDLINE strategy is presented in the table below. The terms in lines 4, 12, 20, 22 and 24 are controlled vocabulary in Embase, as opposed to MEDLINE. The MEDLINE search strategy therefore contained '.mp,kw.' at the end of these search terms instead of '/' originally indicated in the submission presented to NICE on 6 April 2018. Please see corrected search terms in the table below. No changes were required to lines 8, 10, 14, 16, and 18.

Correction to **Table D2: Search strategy for MEDLINE®**

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>		
Last searched: October 20, 2017		
1	arthritis, psoriatic/	5496
2	(psoria$ adj3 (arthrit$ or arthropath$ or axial or peripheral or oligoart$ or "mixed disease")).ti,ab,kw.	9317
3	or/1-2	10275
4	tofacitinib.mp,kw.	768
5	(tofacitinib or xeljanz or tasocitinib or cp-690550$ or cp690550$ or cp690,550$ or cp 690550$ or 477600-75-2).ti,ab,rn.	760
6	abatacept.mp,kw.	3409
7	(abatacept or belatacept or nulojix or orencia or 332348-12-6 or "bms 188667" or bms188667 or bms-188667 or "bms 224818" or bms224818 or bms-224818 or "CTLA4 Ig" or CTLA4Ig or CTLA4-Ig or CTLA-4-Ig or CTLA4-Fc or "Cytotoxic T Lymphocyte associated Antigen 4 immunoglobulin" or "Cytotoxic T Lymphocyte-associated Antigen 4-immunoglobulin" or D03203 or LEA29Y).ti,ab,rn.	3983
8	adalimumab/	4382
9	(adalimumab or trudexa or humira or amgevita or D2E7 or "D2 E7" or LS-186588).ti,ab,rn.	6701
10	etanercept/	5510
11	(etanercept or enbrel or benepali or embrel or "tnr 001" or "tnr001 tumor necrosis factor receptor Fc fusion protein" or 185243-69-0 or 200013-86-1 or erelzi or etanercept or etanercept-szzs or "HSDB 7849" or OP401G7OJC or "Recombinant human TNF" or "Recombinant human dimeric TNF receptor type II-IgG fusion protein" or "TNF receptor type II-IgG fusion protein" or "TNFR-Fc"	8369

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Last searched: October 20, 2017		
	or "TNFR-Fc fusion protein" or "TNFR:Fc" or "TNR 001" or UNII-OP401G7OJC).ti,ab,rn.	
12	golimumab.mp,kw.	904
13	(golimumab or "cnto 148" or cnto148 or simponi or 476181-74-5 or ACN-040096).ti,ab,rn.	882
14	infliximab/	9326
15	(infliximab or avakine or flixabi or inflectra or remicade or revellex or LS-183368 or LS183368).ti,ab,rn.	13085
16	certolizumab pegol/	494
17	(certolizumab pegol or CZP or Cimzia or "cdp 870" or cdp870 or cimzia or "necrosis factor alpha antibody Fab fragment" or "pha 738144" or pha738144 or pha-738144 or 1132819-27-2 or 339184-10-0 or 428863-50-7 or G6ADW90R16 or HSDB 7848 or UMD07X179E or UNII-G6ADW90R16 or UNII-UMD07X179E).ti,ab,rn.	1010
18	ustekinumab/	643
19	(ustekinumab or "cnto 1275" or cnto1275 or stelara or GTPL6885 or L04AC05 or TT-20).ti,ab,rn.	1220
20	secukinumab.mp,kw.	447
21	(secukinumab or "ain 457" or ain457 or cosentyx or 1229022-83-6 or 875356-43-7 or 875356-44-8).ti,ab,rn.	440
22	ixekizumab.mp,kw.	214
23	(ixekizumab or taltz or GTPL7541 or "ly 2439821" or ly2439821 or ly-2439821).ti,ab,rn.	208
24	apremilast.mp,kw.	332
25	(apremilast or "cc 10004" or cc10004 or otezla or "608141-41-9" or "666854-78-0" or "AB0093139" or "AC-27650" or "AJ-84147" or "AK151389" or "AKOS016339660" or "AOB87775" or "apremilast" or "apremilastum" or "BC600507" or "BCP0726000109" or "BCP9000311" or "BDBM50248919" or "C22H24N2O7S" or "CC 10004" or "CC10004" or "CC-10004" or "CHEMBL514800" or "CS-0671" or "D08860" or "DB05676" or "EX-A336" or "FK-0727" or "GTPL7372" or "HE224053" or "HSDB 8221" or "HY-12085" or "KB-74720" or "MFCD18782607" or "MolPort-023-219-158" or "Otezla" or "QCR-202" or "S-7765" or "SC-95443" or "SCHEMBL302992" or "UNII-UP7QBP99PN" or "UP7QBP99PN" or "Y0437" or "ZINC30691736").ti,ab,rn.	320
26	or/4-25	26914
27	3 and 26 [Disease & Drug]	2079
28	Case Study/ or case report.tw. or letter/ or abstract report/	2861564
29	(catalogs or comment or conference proceeding or conference abstract or editorial or essays or guidebooks or handbooks or historical article or interview or journal correspondence or	2230034

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	lectures or letter or meeting abstracts or news or newspaper article or note or posters or short survey).pt.	
30	(exp animal experiment/ or exp animal model/ or exp experimental animal/ or exp transgenic animal/ or exp male animal/ or exp female animal/ or exp juvenile animal/ or animal/ or chordata/ or vertebrate/ or tetrapod/ or exp fish/ or amniote/ or exp amphibia/ or mammal/ or exp reptile/ or exp sauropsid/ or therian/ or exp monotremate/ or placental mammals/ or exp marsupial/ or Euarchontoglires/ or exp Afrotheria/ or exp Boreoeutheria/ or exp Laurasiatheria/ or exp Xenarthra/ or primate/ or exp Dermoptera/ or exp Glires/ or exp Scandentia/ or Haplorhini/ or exp prosimian/ or simian/ or exp tarsiiform/ or Catarrhini/ or exp Platyrrhini/ or ape/ or exp Cercopithecidae/ or hominid/ or exp hylobatidae/ or exp chimpanzee/ or exp gorilla/ or exp orang utan/ or (animal or animals or pisces or fish or fishes or catfish or catfishes or sheatfish or silurus or arius or heteropneustes or clarias or gariepinus or fathead minnow or fathead minnows or pimephales or promelas or cichlidae or trout or trouts or char or chars or salvelinus or salmo or oncorhynchus or guppy or guppies or millionfish or poecilia or goldfish or goldfishes or carassius or auratus or mullet or mullets or mugil or curema or shark or sharks or cod or cods or gadus or morhua or carp or carps or cyprinus or carpio or killifish or eel or eels or anguilla or zander or sander or lucioperca or stizostedion or turbot or turbots or psetta or flatfish or flatfishes or plaice or pleuronectes or platessa or tilapia or tilapias or oreochromis or sarotherodon or common sole or dover sole or solea or zebrafish or zebrafishes or danio or rerio or seabass or dicentrarchus or labrax or morone or lamprey or lampreys or petromyzon or pumpkinseed or pumpkinseeds or lepomis or gibbosus or herring or clupea or harengus or amphibia or amphibian or amphibians or anura or salientia or frog or frogs or rana or toad or toads or bufo or xenopus or laevis or bombina or epidalea or calamita or salamander or salamanders or newt or newts or triturus or reptilia or reptile or reptiles or bearded dragon or pogona or vitticeps or iguana or iguanas or lizard or lizards or anguis fragilis or turtle or turtles or snakes or snake or aves or bird or birds or quail or quails or coturnix or bobwhite or colinus or virginianus or poultry or poultries or fowl or fowls or chicken or chickens or gallus or zebra finch or taeniopygia or guttata or canary or canaries or serinus or canaria or parakeet or parakeets or grasskeet or parrot or parrots or psittacine or psittacines or shelduck or tadorna or goose or geese or branta or leucopsis or woodlark or lullula or flycatcher or ficedula or hypoleuca or dove or doves or geopelia	4665527

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	or cuneata or duck or ducks or greylag or graylag or anser or harrier or circus pygargus or red knot or great knot or calidris or canutus or godwit or limosa or lapponica or meleagris or gallopavo or jackdaw or corvus or monedula or ruff or philomachus or pugnax or lapwing or peewit or plover or vanellus or swan or cygnus or columbianus or bewickii or gull or chroicocephalus or ridibundus or albifrons or great tit or parus or aythya or fuligula or streptopelia or risoria or spoonbill or platalea or leucorodia or blackbird or turdus or merula or blue tit or cyanistes or pigeon or pigeons or columba or pintail or anas or starling or sturnus or owl or athene noctua or pochard or ferina or cockatiel or nymphicus or hollandicus or skylark or alauda or tern or sterna or teal or crecca or oystercatcher or haematopus or ostralegus or shrew or shrews or sorex or araneus or crocidura or russula or european mole or talpa or chiroptera or bat or bats or eptesicus or serotinus or myotis or dasycneme or daubentonii or pipistrelle or pipistrellus or cat or cats or felis or catus or feline or dog or dogs or canis or canine or canines or otter or otters or lutra or badger or badgers or meles or fitchew or fitch or foumart or foulmart or ferrets or ferret or polecat or polecats or mustela or putorius or weasel or weasels or fox or foxes or vulpes or common seal or phoca or vitulina or grey seal or halichoerus or horse or horses or equus or equine or equidae or donkey or donkeys or mule or mules or pig or pigs or swine or swines or hog or hogs or boar or boars or porcine or piglet or piglets or sus or scrofa or llama or llamas or lama or glama or deer or deers or cervus or elaphus or cow or cows or bos taurus or bos indicus or bovine or bull or bulls or cattle or bison or bisons or sheep or sheeps or ovis aries or ovine or lamb or lambs or mouflon or mouflons or goat or goats or capra or caprine or chamois or rupicapra or leporidae or lagomorpha or lagomorph or rabbit or rabbits or oryctolagus or cuniculus or laprine or hares or lepus or rodentia or rodent or rodents or murinae or mouse or mice or mus or musculus or murine or woodmouse or apodemus or rat or rats or rattus or norvegicus or guinea pig or guinea pigs or cavia or porcellus or hamster or hamsters or mesocricetus or cricetulus or cricetus or gerbil or gerbils or jird or jirds or meriones or unguiculatus or jerboa or jerboas or jaculus or chinchilla or chinchillas or beaver or beavers or castor fiber or castor canadensis or sciuridae or squirrel or squirrels or sciurus or chipmunk or chipmunks or marmot or marmots or marmota or suslik or susliks or spermophilus or cynomys or cottonrat or cottonrats or sigmodon or vole or voles or microtus or myodes or glareolus or primate or primates or prosimian or prosimians or	

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	lemur or lemurs or lemuridae or loris or bush baby or bush babies or bushbaby or bushbabies or galago or galagos or anthropoidea or anthropoids or simian or simians or monkey or monkeys or marmoset or marmosets or callithrix or cebuella or tamarin or tamarins or saguinus or leontopithecus or squirrel monkey or squirrel monkeys or saimiri or night monkey or night monkeys or owl monkey or owl monkeys or douroucoulis or aotus or spider monkey or spider monkeys or ateles or baboon or baboons or papio or rhesus monkey or macaque or macaca or mulatta or cynomolgus or fascicularis or green monkey or green monkeys or chlorocebus or vervet or vervets or pygerythrus or hominoidea or ape or apes or hylobatidae or gibbon or gibbons or siamang or siamangs or nomascus or symphalangus or hominidae or orangutan or orangutans or pongo or chimpanzee or chimpanzees or pan troglodytes or bonobo or bonobos or pan paniscus or gorilla or gorillas or troglodytes).ti,ab,kw.) not (human/ or (human$ or man or men or woman or women or patient$).ti,ab,kw.)	
31	or/28-30	8610861
32	27 not 31	1531
33	limit 32 to english language	1404

A2. The search strategy for EconLit is missing from Appendix G. Please provide the strategy along with the date of the search.

Pfizer Response: The search strategy for EconLit is presented in the table below. The EconLit search was performed on 20 October 2017.

EconLit		
Last searched: 20 October 2017		
S1	(TI psoria* AND (TI arthrit* OR TI arthropath* OR TI axial OR TI peripheral OR TI oligoart* OR TI "mixed disease")) OR (AB psoria* AND (AB arthrit* OR AB arthropath* OR AB axial OR AB peripheral OR AB oligoart* OR AB "mixed disease"))	12
S2	(TI tofacitinib) OR (TI xeljanz) OR (TI tasocitinib) OR (TI cp-690550*) OR (TI cp690550*) OR (TI cp690,550*) OR (TI cp 690550*) OR (TI 477600-75-2) OR (AB tofacitinib) OR (AB xeljanz) OR (AB tasocitinib) OR (AB cp-690550*) OR (AB cp690550*) OR (AB cp690,550*) OR (AB cp 690550*) OR (AB 477600-75-2)	0
S3	(TI etanercept) OR (AB etanercept) OR (TI enbrel) OR (AB enbrel) OR (TI etanercept) OR (AB etanercept) OR (TI enbrel) OR (AB enbrel) OR (TI benepali) OR (AB benepali) OR (TI embrel) OR (AB embrel) OR (TI "tnr 001") OR (AB "tnr 001") OR (TI "tnr001 tumor necrosis factor	12

EconLit		
Last searched: 20 October 2017		
	receptor Fc fusion protein") OR (AB "tnr001 tumor necrosis factor receptor Fc fusion protein") OR (TI 185243-69-0) OR (AB 185243-69-0) OR (TI 200013-86-1) OR (AB 200013-86-1) OR (TI erelzi) OR (AB erelzi) OR (TI etanercept) OR (AB etanercept) OR (TI etanercept-szzs) OR (AB etanercept-szzs) OR (TI "HSDB 7849") OR (AB "HSDB 7849") OR (TI OP401G7OJC) OR (AB OP401G7OJC) OR (TI "Recombinant human TNF") OR (AB "Recombinant human TNF") OR (TI "Recombinant human dimeric TNF receptor type II-IgG fusion protein") OR (AB "Recombinant human dimeric TNF receptor type II-IgG fusion protein") OR (TI "TNF receptor type II-IgG fusion protein") OR (AB "TNF receptor type II-IgG fusion protein") OR (TI "TNFR-Fc") OR (AB "TNFR-Fc") OR (TI "TNFR-Fc fusion protein") OR (AB "TNFR-Fc fusion protein") OR (TI "TNFR:Fc") OR (AB "TNFR:Fc")	
S4	(TI golimumab) OR (AB golimumab) OR (TI "cnto 148") OR (AB "cnto 148") OR (TI golimumab) OR (AB golimumab) OR (TI "cnto 148") OR (AB "cnto 148") OR (TI cnto148) OR (AB cnto148) OR (TI simponi) OR (AB simponi)	4
S5	(TI infliximab) OR (AB infliximab) OR (TI ACN-040096) OR (AB ACN-040096) OR (TI infliximab) OR (AB infliximab) OR (TI avakine) OR (AB avakine) OR (TI flixabi) OR (AB flixabi) OR (TI inflectra) OR (AB inflectra) OR (TI remicade) OR (AB remicade) OR (TI revellex) OR (AB revellex)	16
S6	(TI certolizumab pegol) OR (AB certolizumab pegol) OR (TI LS183368) OR (AB LS183368) OR (TI certolizumab pegol) OR (AB certolizumab pegol) OR (TI CZP) OR (AB CZP) OR (TI Cimzia) OR (AB Cimzia) OR (TI "cdp 870") OR (AB "cdp 870") OR (TI cdp870) OR (AB cdp870) OR (TI cimzia) OR (AB cimzia) OR (TI "necrosis factor alpha antibody Fab fragment") OR (AB "necrosis factor alpha antibody Fab fragment") OR (TI "pha 738144") OR (AB "pha 738144") OR (TI pha738144) OR (AB pha738144) OR (TI pha-738144) OR (AB pha-738144) OR (TI 1132819-27-2) OR (AB 1132819-27-2) OR (TI 339184-10-0) OR (AB 339184-10-0) OR (TI 428863-50-7) OR (AB 428863-50-7) OR (TI G6ADW90R16) OR (AB G6ADW90R16) OR (TI HSDB 7848) OR (AB HSDB 7848) OR (TI UMD07X179E) OR (AB UMD07X179E)	0
S7	(TI ustekinumab) OR (AB ustekinumab) OR (TI "cnto 1275") OR (AB "cnto 1275") OR (TI cnto1275) OR (AB cnto1275) OR (TI stelara) OR (AB stelara) OR (TI GTPL6885) OR (AB GTPL6885)	1
S8	(TI secukinumab) OR (AB secukinumab) OR (TI TT-20) OR (AB TT-20) OR (TI secukinumab) OR (AB secukinumab) OR (TI "ain 457") OR (AB "ain 457") OR (TI ain457) OR (AB ain457) OR (TI cosentyx) OR (AB cosentyx) OR (TI 1229022-83-6) OR (AB 1229022-83-6)	0
S9	(TI ixekizumab) OR (AB ixekizumab) OR (TI 875356-44-8) OR (AB 875356-44-8) OR (TI ixekizumab) OR (AB ixekizumab) OR (TI taltz) OR (AB taltz) OR (TI GTPL7541) OR (AB GTPL7541) OR (TI "ly 2439821") OR (AB "ly 2439821")	0

EconLit		
Last searched: 20 October 2017		
S10	(TI brodalumab) OR (AB brodalumab) OR (TI ly-2439821) OR (AB ly-2439821) OR (TI brodalumab) OR (AB brodalumab) OR (TI lumicef) OR (AB lumicef) OR (TI siliq) OR (AB siliq) OR (TI "amg 827") OR (AB "amg 827") OR (TI amg827) OR (AB amg827) OR (TI amg-827) OR (AB amg-827) OR (TI GTPL7540) OR (AB GTPL7540) OR (TI apremilast) OR (AB apremilast) OR (TI "cc 10004") OR (AB "cc 10004") OR (TI cc10004) OR (AB cc10004) OR (TI otezla) OR (AB otezla) OR (TI "608141-41-9") OR (AB "608141-41-9") OR (TI "666854-78-0") OR (AB "666854-78-0") OR (TI "AB0093139") OR (AB "AB0093139") OR (TI "AC-27650") OR (AB "AC-27650") OR (TI "AJ-84147") OR (AB "AJ-84147") OR (TI "AK151389") OR (AB "AK151389")	0
S11	(TI "apremilast") OR (AB "apremilast") OR (TI "AOB87775") OR (AB "AOB87775") OR (TI "apremilast") OR (AB "apremilast") OR (TI "apremilastum") OR (AB "apremilastum") OR (TI "BC600507") OR (AB "BC600507") OR (TI "BCP0726000109") OR (AB "BCP0726000109") OR (TI "BCP9000311") OR (AB "BCP9000311") OR (TI "BDBM50248919") OR (AB "BDBM50248919") OR (TI "C22H24N2O7S") OR (AB "C22H24N2O7S") OR (TI "CC 10004") OR (AB "CC 10004") OR (TI "CC10004") OR (AB "CC10004") OR (TI "CC-10004") OR (AB "CC-10004") OR (TI "CHEMBL514800") OR (AB "CHEMBL514800") OR (TI "CS-0671") OR (AB "CS-0671") OR (TI "D08860") OR (AB "D08860") OR (TI "DB05676") OR (AB "DB05676") OR (TI "EX-A336") OR (AB "EX-A336") OR (TI "FK-0727") OR (AB "FK-0727") OR (TI "GTPL7372") OR (AB "GTPL7372") OR (TI "HE224053") OR (AB "HE224053") OR (TI "HSDB 8221") OR (AB "HSDB 8221") OR (TI "HY-12085") OR (AB "HY-12085") OR (TI "KB-74720") OR (AB "KB-74720") OR (TI "MFCD18782607") OR (AB "MFCD18782607") OR (TI "MolPort-023-219-158") OR (AB "MolPort-023-219-158") OR (TI "Otezla") OR (AB "Otezla") OR (TI "QCR-202") OR (AB "QCR-202") OR (TI "S-7765") OR (AB "S-7765") OR (TI "SC-95443") OR (AB "SC-95443") OR (TI "SCHEMBL302992") OR (AB "SCHEMBL302992") OR (TI "UNII-UP7QBP99PN") OR (AB "UNII-UP7QBP99PN") OR (TI "UP7QBP99PN") OR (AB "UP7QBP99PN")	0
S12	S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11	26
S13	S1 AND S12	3

Methods

A3. **Priority question:** Please provide the study protocols for OPAL Broaden, OPAL Beyond and OPAL Balance.

Pfizer Response: The study protocols for the OPAL Broaden, OPAL Beyond and OPAL Balance trials accompany this response. Any information contained therein not otherwise contained in the respective trial publications should be considered commercial-in-confidence.

A4. **Priority question:** Please provide a breakdown of the previous anti-TNFs taken by patients in OPAL Beyond (i.e. the proportion of patients that had 1, 2, 3 or more than 3 anti-TNFs). Please also provide the proportion of patients that had each individual anti-TNF (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), ustekinumab, secukinumab, apremilast or abatacept.

Pfizer Response: The information regarding the number of prior treatments is available in the OPAL Beyond CSR Table 9 (p.93) and is reproduced below.

[redacted]OPAL Beyond CSR Table 9: Prior drug treatments for PsA by treatment group (safety analysis set)

	[redacted]	[redacted]
Prior oral corticosteroid use (oral only)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Prior NSAID use		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Number of prior bDMARDs		
1 TNFi bDMARD	[redacted]	[redacted]
2 TNFi bDMARDs	[redacted]	[redacted]
≥3 TNFi bDMARDs	[redacted]	[redacted]
≥1 non-TNFi bDMARDs[a]	[redacted]	[redacted]
Prior TNFi bDMARDs only experience		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

Abbreviations: BD, twice daily; bDMARDs, biologic DMARD; DMARD, disease-modifying antirheumatic drugs; mg, miligram; N, number of subjects in the analysis set; n, number of subjects that met the criteria; NSAID, nonsteroidal anti-inflammatory; PBO, placebo; TNFi, tumour necrosis factor inhibitor; TOF, tofacitinib
Prior drug treatment was defined as a drug taken on or before Day 0.
[a.] Subjects who were treated with any non-TNFi bDMARD or both TNFi bDMARD and non-TNFi bDMARDs were counted in the ≥1 non-TNFi bDMARDs category.

Additional information regarding the number of previous TNFi medications per subject in OPAL Beyond is available in the OPAL Beyond CSR Table 14.4.2.1.3.1 (p.1973) and is reproduced below. The number of prior treatments in the table below is higher than those in the table above because subjects in the table below are counted and grouped regardless of whether they have received non-TNFi bDMARDs.

.

OPAL Beyond CSR Table 14.4.2.1.3.1: Number of previous TNFi medications per subject (safety analysis set)

Statistic	[redacted]	[redacted]
Categories		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
>4	[redacted]	[redacted]
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min-Max	[redacted]	[redacted]

Abbreviations: BD, twice daily; TNFi, tumour necrosis factor inhibitor; max, maximum; mg, miligram; min, minimum; N, number of subjects in the analysis set; n, number of subjects that met the criteria; PBO, placebo; sd, standard deviation; TOF, tofacitinib
Previous drug treatment is defined as a drug taken on or before Day 0.
Each subject is counted with the number of unique TNFi medications. ie. If there is more than one record per drug for a subject, count as one medication.
Categories are summarized as number (%) of subjects in each category.

Information regarding the proportion of patients that had each individual drug (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, ustekinumab, secukinumab, apremilast or abatacept) can be found in the OPAL Beyond CSR Table 14.4.2.1.1.2 (p.1939-1940) and is reproduced below:

OPAL Beyond CSR Table 14.4.2.1.1.2: Prior drug treatments for PsA by medication type and treatment sequence (safety analysis set)

	[redacted]	[redacted]	[redacted]
Number of Subjects with Any Medication/Drug Treatment (DMARDs, Non-DMARDs, Oral Steroids, Joint Injections)	[redacted]	[redacted]	[redacted]
Number of Subjects with DMARDs Drug Treatment	[redacted]	[redacted]	[redacted]
bDMARD (all)	[redacted]	[redacted]	[redacted]
bDMARD (received TNFi only)	[redacted]	[redacted]	[redacted]
bDMARD (received both TNFi and 'other' bDMARDs)	[redacted]	[redacted]	[redacted]
bDMARD (received 'other' bDMARDs only)	[redacted]	[redacted]	[redacted]
Non-biologic DMARD	[redacted]	[redacted]	[redacted]
Number of Subjects with Non-DMARDs Drug Treatment	[redacted]	[redacted]	[redacted]
Number of Subjects with Oral Steroids Drug Treatment	[redacted]	[redacted]	[redacted]

Number of Subjects with Joint Injections Drug Treatment	[redacted]	[redacted]	[redacted]
DMARDs Drug Treatment			
Abatacept	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]
Certolizumab	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]

Abbreviations: BD, twice daily; bDMARDs, biologic DMARD; DMARD, disease-modifying antirheumatic drugs; mg, miligram; N, number of subjects in the analysis set; n, number of subjects that met the criteria; PBO, placebo; TNFi, tumour necrosis factor inhibitor; TOF, tofacitinib
Biologic DMARD (received both TNFi and 'other' bDMARDs)=Biologic DMARD (received both TNFi and non-TNFi bDMARDs).
Biologic DMARD (received 'other' bDMARDs only)=Biologic DMARD (received non-TNFi bDMARDs only).
WHO-Drug (vJUN2014) coding dictionary applied.
Prior medication is defined as a drug taken on or before Day 0.
Percentages are based on number of subjects in Safety Analysis Set.

A5. **Priority question:** Please clarify the number of patients from each arm of OPAL Broaden and OPAL Beyond that entered OPAL Balance.

Pfizer Response: Available interim data from the ongoing open-label long-term extension (LTE) study (OPAL Balance) were presented in a poster by Nash *et al.* (2017) at the 2017 ACR/ARHP Annual Meeting (see reference 93 in the Pfizer submission).

At the time of this second interim analysis (25 January 2017; database not locked, data may change), there were 686 patients enrolled in OPAL Balance:

- Of the 422 patients treated in OPAL Broaden, 363 patients enrolled in OPAL Balance.
- Of the 394 patients treated in OPAL Beyond, 323 patients enrolled in OPAL Balance.

A breakdown of patients from each arm of OPAL Broaden and OPAL Beyond that entered OPAL Balance is presented in the two tables below, taken from the OPAL Balance CSR.

Excerpt from **OPAL Balance CSR Table 14.1.1.2: Subject evaluation groups by qualifying study and overall (Subjects from OPAL Broaden)**

	Qualifying Study OPAL Broaden					
	TOF5 BD	**TOF10 BD**	**PBO→TOF 5 BD**	**PBO→TOF 10 BD**	**ADA 40mg SC Q2W**	**All**
Randomised	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Randomised and treated, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Randomised but not treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enrolled in OPAL Balance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enrolled and treated in OPAL Balance, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enrolled but not treated in OPAL Balance, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At Month 3 in OPAL Balance						
In Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At Month 6 in OPAL Balance						
In Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At Month 9 in OPAL Balance						
In Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At Month 12 in OPAL Balance						
In Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At Month 18 in OPAL Balance						
In Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At Month 24 in OPAL Balance						

In Study, n (%)	[redacted]					
Discontinued from Study, n (%)	[redacted]					
At Month 36 in OPAL Balance						
In Study, n (%)	[redacted]					
Discontinued from Study, n (%)	[redacted]					

[redacted]

Excerpt from **OPAL Balance CSR Table 14.1.1.2: Subject evaluation groups by qualifying study and overall (Subjects from OPAL Beyond)**

	Qualifying Study OPAL Beyond				
	TOF5 BD	**TOF10 BD**	**PBO→TOF5 BD**	**PBO→TOF10 BD**	**All**
Randomised	[redacted]				
Randomised and treated, n (%)	[redacted]				
Randomised but not treated	[redacted]				
Enrolled in OPAL Balance	[redacted]				
Enrolled and treated in OPAL Balance, n (%)	[redacted]				
Enrolled but not treated in OPAL Balance, n (%)	[redacted]				
At Month 3 in OPAL Balance					
In Study, n (%)	[redacted]				
Discontinued from Study, n (%)	[redacted]				
At Month 6 in OPAL Balance					
In Study, n (%)	[redacted]				
Discontinued from Study, n (%)	[redacted]				
At Month 9 in OPAL Balance					
In Study, n (%)	[redacted]				

Discontinued from Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At Month 12 in OPAL Balance					
In Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At Month 18 in OPAL Balance					
In Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At Month 24 in OPAL Balance					
In Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
At Month 36 in OPAL Balance					
In Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from Study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

A6. **Priority question:** In Table M22 (appendix M), it states that a key inclusion criterion for OPAL Balance is: "Subjects who have completed at least 24 months of treatment with tofacitinib in the extension study." Please clarify whether patients who entered OPAL Balance did so directly from OPAL Broaden and OPAL Beyond or if there was an interim extension open label period in each of these trials.

Pfizer Response: The summary in Table M22 (Appendix M) regarding inclusion criteria (specifically the statement "Subjects who have completed at least 24 months of treatment with tofacitinib in the extension study") is confusing and we thank NICE for bringing this to our attention.

The OPAL Balance study is a long-term, open-label extension study designed to evaluate the safety, tolerability and efficacy of tofacitinib in subjects with active PsA who have previously participated in randomised PsA clinical studies with tofacitinib (Nash et al., 2017; see reference 93 in the Pfizer submission).

All eligible subjects from the qualifying studies, OPAL Broaden and OPAL Beyond, received open-label tofacitinib 5 mg BD upon entry into OPAL Balance. [redacted].

Patients from OPAL Broaden received the first dose of study medication ≥1 week after their final injection of study medication (placebo or adalimumab; Nash et al., 2017; see reference 93 in the Pfizer submission). Patients were eligible to enter OPAL Balance ≤3 months after completing or discontinuing the qualifying study for non-study-drug-related reasons (Nash et al., 2017; see reference 93 in the Pfizer submission).

The statement regarding the completion of at least 24 months of treatment with tofacitinib in the extension study refers to an inclusion criterion for the sub-study within OPAL Balance that compares tofacitinib 5 mg BD administered as monotherapy after methotrexate with tofacitinib 5 mg BD continued in combination with methotrexate (clinicaltrials.gov; see reference 3 in Appendix M of the Pfizer submission). However, please note that an application for a marketing authorisation for tofacitinib 5 mg BD as monotherapy has not been filed with the EMA.

A7. Table 8 of the company submission states that the type I error rate was adjusted for multiple comparisons for ACR20 and change in HAQ-DI at 3 months. Please provide more details of the methods used to adjust for multiple comparisons.

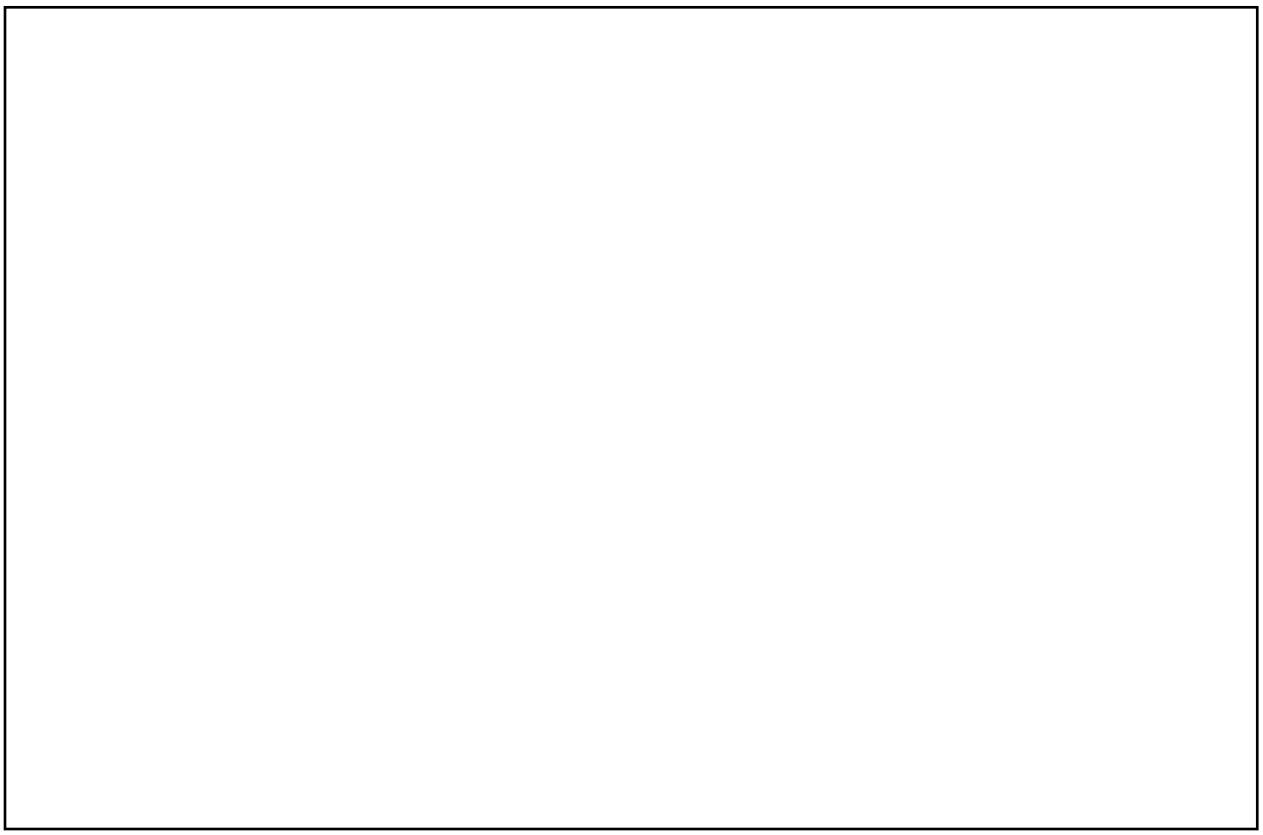
Pfizer Response: Table 8 of the Pfizer submission states that:

> *"In order to control for Type I error rate at the 5% level in the primary analysis, a step-wise testing procedure was used to adjust for multiple comparisons of two TOF doses (5 mg BD and 10 mg BD) against PBO for the co-primary endpoints of ACR20 and ΔHAQ-DI at Month 3.*
>
> *A similar step-down procedure was also applied to certain secondary endpoints in the following order (after ACR20 and HAQ-DI): PASI75, ΔLEI, ΔDSS, ΔSF-36 Physical Functioning Domain and ΔFACIT-F total score at Month 3.*
>
> *Because the endpoints ACR50 and ACR70 can be viewed as extensions of the ACR20, and all belong to the ACR family of endpoints, a step-down approach to testing the ACR20, ACR50 and ACR70 at Month 3 was used for each endpoint and doses within each endpoint. In order to be more rigorous about establishing the onset of efficacy, a step-down approach with the ACR20 from 3 months to earlier time points was also utilised.*
>
> *No preservation of the type I error rate was applied for the remainder of secondary endpoints or other endpoints."*

Further details regarding the methods used to adjust for multiple comparisons are provided below.

- [redacted] (Pfizer data on file).
- [redacted] (Pfizer data on file).

- [redacted] (Pfizer data on file).
- Three families of hierarchical testing procedures were used (Mease et al., 2017 and Gladman et al., 2017; see references 87 and 88 in the Pfizer submission):
    - Primary and key secondary endpoints at Month 3 (Global type I error)
    - The ACR family responses (ACR20/50/70) at Month 3
    - ACR20 time course (Month 3, Month 2, Month 1, Week 2)
- [redacted] (Pfizer data on file).
- [redacted] (Pfizer data on file):

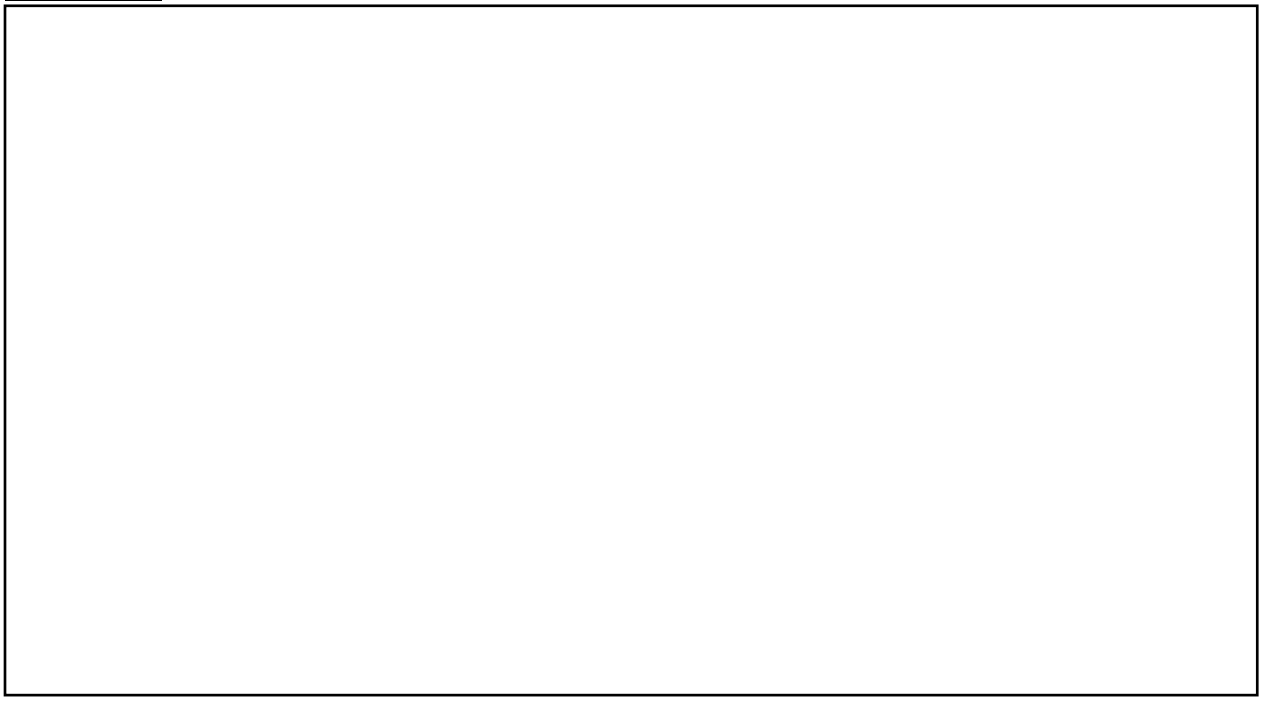


- [redacted]

[redacted] (Pfizer data on file).

- [redacted] (Pfizer data on file).
  - [redacted]

[redacted] (Pfizer data on file):



[redacted]ACR20=20% improvement in American College of Rheumatology response; HAQ-DI=Health Assessment Questionnaire–Disability Index; OPAL=Oral Psoriatic Arthritis Trial; PASI75=75% improvement in Psoriasis Area and Severity Index.
[redacted]

A8. Please provide the number of patients who switch from tofacitinib to another treatment in OPAL Beyond and OPAL Broaden and whether the next treatment was a csDMARD or bDMARD.

Pfizer Response: Neither OPAL Beyond nor OPAL Broaden were designed to assess subsequent treatments after discontinuation of tofacitinib.

In OPAL Beyond, 395 patients were randomised in a 2:2:1:1 ratio to 5 mg tofacitinib BD (131 patients); 10 mg tofacitinib BD (132 patients), placebo, with a switch at 3 months to either 5 mg or 10 mg tofacitinib BD (66 and 65 patients, respectively). Overall, 345 (87.6%) subjects completed the study and 49 (12.4%) subjects discontinued from the study up to Month 6. The percentage of

discontinuations was lowest for the relevant dose in the submission (tofacitinib 5 mg BD), at 6.9%, with numerically higher discontinuation rates for the other 3 treatment sequences (15.9%, for tofacitinib 10 mg BD, with 15.2% and 13.8% for the placebo groups switching at 3 months to tofacitinib 5 mg and 10 mg BD, respectively) at Month 6 (Gladman et al., 2017; see reference 88 in the Pfizer submission).

In OPAL Broaden, 422 patients were randomised in a 2:2:2:1:1 ratio to tofacitinib 5 mg BD (107 patients), tofacitinib 10 mg BD (104), adalimumab 40 mg s/c every 2 weeks (106), placebo with a blinded switch at 3 months to either tofacitinib 5 mg or 10 mg BD (52 and 53 patients, respectively). The tofacitinib 5 and 10 mg BD groups achieved the highest numerical rates for study completion, with 90% in the 5 mg BD group, 92% in the 10 mg BD, 89% in the adalimumab group, and 85% and 81% in the placebo groups switching at 3 months to 5 mg and 10 mg of tofacitinib, respectively (Mease et al., reference 87 in the Pfizer submission). Due to the very high drug survival rates for the relevant dose of 5 mg BD tofacitinib (93% in OPAL Beyond at 6 months, and 90% in OPAL Broaden at 12 months), only a total of 20 patients would have required an alternative line of treatment following tofacitinib within the study duration.

The American College of Rheumatology (ACR)/National Psoriasis Foundation (NPF) recently presented their draft recommendations for the management of PsA, in lieu of publication of the full guidelines, at the 2017 ACR/ARHP Annual Meeting. Although the draft recommendations were presented prior to the approval of tofacitinib for PsA in any market, tofacitinib already featured in the draft recommendations. Recommendations varied according to different treatment domains, but overall, following failure of tofacitinib or another ‘oral small molecule’, the panel appeared to recommend a sequencing strategy of a TNFi, IL17i biologic, and then IL12/23i (Ogdie et al., 2017).

It is also of note that the EULAR recommendations for rheumatoid arthritis (RA) recommend that, in the event of failure with a bDMARD or tsDMARD, treatment with another bDMARD or a tsDMARD should be considered; and that if one TNFi therapy has failed, patients may receive another TNFi, or an agent (bDMARD or tsDMARD) with a different mode of action. Although these recommendations are provided for patients with RA, the flexibility of tofacitinib recommended at multiple lines of therapy by EULAR is based on mechanistic rationale, as the RA trial programme also did not assess subsequent lines of therapy after tofacitinib failure (Smolen et al., 2017). NICE TA480 provided a similar degree of flexibility in the choice of subsequent therapies, should there be an inadequate response to tofacitinib.

References:

Ogdie A, Singh JA, Siegel E, Gladman DD, Husni ME. Treatment of psoriatic arthritis: a new ACR/NPF clinical guideline. Presented at: 2017 ACR/ARHP Annual Meeting; November 3-8, 2017; San Diego, CA. Scientific Session 5T064

Smolen JS, Landewé 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. Annals of the Rheumatic Diseases. 2017;76(6):960-77.

A9. Please clarify how best supportive care is defined (i.e. proportion of patients assumed to be taking a DMARD, which DMARDs etc.)

Pfizer Response: In the context of our economic analysis, Best Supportive Care (BSC) includes a mixture of csDMARDs and/or usual care (e.g., NSAIDs, corticosteroids). BSC reflects the clinical effectiveness estimates of the placebo groups in the trials of tofacitinib and the relevant comparators included in the NMAs. This definition is consistent with the definition used by the Assessment Group (AG) for TA445 (Corbett et al., 2017; see reference 3 in the Pfizer submission).

It is important to note that study protocols did not always mandate that the placebo groups received csDMARDs. By way of example, in the PALACE trials (Kavanaugh *et al*., 2014, Cutolo *et al*., 2016, and Edwards *et al*., 2016; see references 69, 70, and 71 in the Pfizer submission) of apremilast, use of any DMARD at baseline ranged from 60-71.1% in the placebo groups. Similarly, in the ADEPT study of adalimumab (Mease *et al*., 2005; see reference 157 in the Pfizer submission), 50% of the placebo group were using methotrexate at baseline (other DMARDs were prohibited if used ≤4 weeks of the baseline visit).

In contrast, the trial designs of OPAL Broaden and Beyond required patients to be receiving a stable background dose of a single csDMARD throughout the trial (see Table 5 on p.32 of the Pfizer submission), primarily methotrexate, sulfasalazine or leflunomide (Mease et al., 2017 and Gladman et al., 2017; see references 87 and 88 in the Pfizer submission), [redacted]

Information on the proportions of patients taking csDMARDs, along with which csDMARDs at baseline, in the placebo groups across the trials included in the NMA networks are reported in the table below.

Table 1: Proportion of patients taking baseline csDMARDs across trials in the NMA

Main Author, Year [TRIAL ID]; sponsor	**Baseline csDMARD, % patients taking csDMARDs***
Gladman et al., 2017 [OPAL Beyond]; Pfizer	**MTX,** PBO=77% **LEF,** PBO=7% **SSZ,** PBO=15% **Other csDMARDs,** PBO=1%
Mease et al., 2017 [OPAL Broaden]; Pfizer	**MTX,** PBO=88% **LEF,** PBO=4% **SSZ,** PBO=9% **HCQ,** PBO=0%

Main Author, Year [TRIAL ID]; sponsor	Baseline csDMARD, % patients taking csDMARDs*
Mease et al., 2017 [ASTRAEA]	**MTX,** PBO=60.2%
Mease et al. 2017 [SPIRIT P1]	**MTX,** PBO=55.7%
Nash et al., 2017 [SPIRIT-P2]	**MTX,** PBO=34% **Other csDMARD,** PBO=44%
Cutolo et al., 2016 [PALACE 2]	**MTX,** PBO=59.1% **LEF,** PBO=10.7% **SSZ,** PBO=10.7%
Edwards et al., 2016 [PALACE 3]	**MTX,** PBO=54% **LEF,** PBO=3% **SSZ,** PBO=6%
McInnes 2015 [FUTURE 2]	**MTX,** PBO=51%
McInnes et al., 2014‡	**MTX,** PBO=46% **LEF,** PBO=8% **CLQ,** PBO=0% **SSZ,** PBO=0%
Kavanaugh et al., 2014 [PALACE 1]	**MTX,** PBO=53.6% **LEF,** PBO=6.5% **SSZ,** PBO=7.1%
Mease et al., 2014 [RAPID-PsA]	**MTX,** PBO=61.8%
Ritchlin et al., 2014 [PSUMMIT2]	**MTX,** PBO=47.1%
McInnes et al., 2013 [PSUMMIT 1]	**MTX,** PBO=46.6%
Mease et al., 2011	**MTX,** PBO= 55% **Other DMARDs**, PBO= 5%
Kavanaugh et al., 2009 [GO-REVEAL]	**MTX,** PBO=48%
Genovese et al., 2007	**MTX,** PBO=46.9% **Other DMARDs,** PBO=67.3%

Main Author, Year [TRIAL ID]; sponsor	Baseline csDMARD, % patients taking csDMARDs*
Antoni et al., 2005 [IMPACT]	**MTX,** Proportions NR **LEF,** Proportions NR **SSZ,** Proportions NR **HCQ,** Proportions NR **Intramuscular gold,** Proportions NR **Penicillamine,** Proportions NR **Azathioprine,** Proportions NR
Antoni et al., 2005 [IMPACT 2]	**MTX,** PBO=45%
Mease et al., 2005 [ADEPT]	**MTX,** PBO=50%
Mease et al., 2004	**MTX,** PBO=41%
Mease et al., 2000	**MTX,** PBO=47%

‡ study dropped out of the NMA because secukinumab IV is not licensed as a treatment in PsA;
CLQ, chloroquine; csDMARD, conventional synthetic disease modifying anti-rheumatic drugs; DMARD, disease modifying anti-rheumatic drug; HLQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; NR, not reported; PBO, placebo; SSZ, sulfasalazine
*Patients may have been taking more than 1 csDMARD at baseline

As indicated in section B.3.5.2.2 (p.134) and B.3.5.3.1 (p.139) of the Pfizer submission, no drug acquisition costs are assumed for BSC; instead, this cost was captured in the estimates of resource use associated with HAQ-DI (undiscounted for prescribing costs) and uncontrolled psoriasis costs (section B.3.5.3.2), consistent with TA445 (Corbett et al., 2017; see reference 3 in the Pfizer submission).

Effectiveness data

A10. **Priority question:** Please provide the results of any efficacy analyses using the post-3-month data for patients who switched from placebo to 5mg or 10mg tofacitinib. Please also confirm if these data were included in the safety analysis.

Efficacy results for the 'placebo switched to tofacitinib 5 mg BD at 3 months' groups for OPAL Broaden and OPAL Beyond are presented in the tables below. These results (in the rightmost column of each table) have been added to the respective outcomes tables from the original submission.

Data for the patients who switched from placebo to tofacitinib 5mg BD group were included in the safety analysis. Though summarised in the tables below, these data are also presented in the safety section of the submission (section B.2.11 in the main document, with additional information reported in section M.3 of appendix M).

Data for the 'placebo switched to tofacitinib 10 mg BD at month 3' groups are not presented, as this dose was not filed for marketing authorisation with the EMA.

OPAL Broaden

Data for the patients initially in the placebo group that switched to tofacitinib 5 mg BD at month 3 are reported in columns labelled as 'PBO→TOF' in the tables below.

Secondary and other efficacy outcomes

Amendment to **Table 10: ACR20, ACR50, and ACR70 response rates for OPAL Broaden (FAS)**

Outcome	TOF 5mg	ADA	PBO*	PBO→TOF5
ACR20 response rate, n/N (%)				
Week 2	[redacted]	[redacted]	[redacted]	--
Difference from placebo	[redacted]	[redacted]	--	--
95% CI for difference	[redacted]	[redacted]	--	--
p-value	<0.001	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	73/107 (68)	64/106 (60)	--	35/52 (67)
ACR50 response rate, n/N (%)				
Month 3	30/107 (28)	35/106 (33)	10/105 (10)	--
Difference from placebo	18.5	23.5	--	--
95% CI for difference	8.3, 28.7	12.9, 34.1	--	--
p-value	0.001	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	48/107 (45)	43/106 (41)	--	21/52 (40)
ACR70 response rate, n/N (%)				
Month 3	18/107 (17)	20/106 (19)	5/105 (5)	--
Difference from placebo	12.1	14.1	--	--
95% CI for difference	3.9, 20.2	5.6, 22.6	--	--
p-value	0.004	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	25/107 (23)	31/106 (29)	--	12/52 (23)

Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; FAS, full analysis set; n, number of responders; N, number of subjects in FAS; PBO, placebo; TOF, tofacitinib

[§]nominal p-value ≤0.05 for comparison of tofacitinib 5 mg BD with adalimumab; [†]nominal p-value for the comparison between adalimumab and placebo; [redacted]*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

[redacted]

Amendment to **Table 11: Change in HAQ-DI from baseline for OPAL Broaden (FAS)**

Outcome	TOF 5mg	ADA	PBO→TOF5
HAQ-DI score, LS Mean (SE) [n/N]			
Month 6	[redacted]	[redacted]	[redacted]
Month 12	-0.54 (0.05) [96/107]	-0.45 (0.05) [94/106]	-0.41 (0.08) [44/52]

Abbreviations: ADA, adalimumab; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; LS, Least Squares; mg, milligram; N, total number of unique subjects in the longitudinal model; n, number of subjects evaluable at each visit; SE, standard error; TOF, tofacitinib

[redacted]

Amendment to **Table 12: Change in van der Heijde-mTSS from baseline and progressor rate for OPAL Broaden (FAS)**

Outcome	TOF 5mg	ADA	PBO→TOF5
mTSS, LS Mean (SE) [N*]			
Month 12	0.01 (0.07) [98]	-0.07 (0.07) [95]	0.00 (0.09) [48]
Difference from ADA	[redacted]	--	--
95% CI for difference	[redacted]	--	--
p-value	[redacted]	--	--
mTSS progressor rate, n/N (%)			
Month 12	[redacted]	[redacted]	[redacted]
Difference from ADA	[redacted]	--	--
95% CI for difference	[redacted]	--	--
p-value	[redacted]	--	--

Abbreviations: ADA, adalimumab; LS, least squares; mg, milligram; mTSS, modified Total Sharp Score; N, number of subjects evaluable at Month 12 after linear extrapolation; N*, total number of unique subjects in ANCOVA analysis; n, number of progressors; SE, standard error; TOF, tofacitinib

[redacted]

The proportion of subjects with radiographic non-progression (defined as ≤0.5 increase in van der Heijde mTSS from baseline) at Month 12 was 96% in the PBO→TOF5 group. As noted in the original submission, the proportion of subjects with radiographic non-progression at Month 12 was 96% in the tofacitinib 5 mg BD groups and 98% in the adalimumab group.

Amendment to **Table 13: PsARC response rates for OPAL Broaden (FAS)**

Outcome	TOF 5mg	ADA	PBO*	PBO→TOF5
PsARC response rate, n/N* (%)				
Month 3	55/107 (51.4)	65/106 (61.3)	47/105 (44.8)	--
Difference from placebo	6.6	16.6	--	--
95% CI for difference	-6.8, 20.1	3.3, 29.8	--	--
p-value	[redacted]	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	69/107 (64.5)	69/106 (65.1)	--	39/52 (75.0)

Abbreviations: ADA, adalimumab; FAS, full analysis set; n, number of responders; N*, number of subjects in FAS; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; TOF, tofacitinib
*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period
†nominal p-value
[redacted]

Amendment to Table 14: PASI75 response rates for OPAL Broaden (FAS)

Outcome	TOF 5mg	ADA	PBO*	PBO→TOF5
PASI75 response rate, n/N (%)				
Month 3	35/82 (43)	30/77 (39)	12/82 (15)	--
Difference from placebo	28.1	24.3	--	--
95% CI for difference	14.9, 41.2	11.0, 37.6	--	--
p-value	<0.001	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	46/82 (56)	43/77 (56)	--	15/42 (36)

Abbreviations: ADA, adalimumab; FAS, full analysis set; n, number of responders; N*, number of subjects in FAS; N, number of subjects in FAS with baseline BSA≥3% and baseline PASI>0; PASI, Psoriatic Area and Severity Index; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; TOF, tofacitinib
*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period
†nominal p-value
[redacted]

Amendment to **Table M4: Change in ACR components from baseline in OPAL Broaden (FAS)**

Outcome	TOF 5mg	ADA	PBO*	PBO→TOF5
Tender/Painful Joint Count, LS Mean (SE) [n/N]				
Month 3	[redacted]	[redacted]	[redacted]	--
Difference from placebo	-1.9	-0.7	--	--
95% CI for difference	-4.6, 0.9	-3.5, 2.0	--	--
p-value	[redacted]	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	[redacted]	[redacted]	--	[redacted]
Swollen Joint Count, LS Mean (SE) [n/N]				
Month 3	[redacted]	[redacted]	[redacted]	--
Difference from placebo	-1.7	-1.8	--	--
95% CI for difference	-3.3, -0.2	-3.3, -0.2	--	--
p-value	[redacted]	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	[redacted]	[redacted]	--	[redacted]
C-Reactive Protein, LS Mean (SE) [n/N]				
Month 3	[redacted]	[redacted]	[redacted]	--
Difference from placebo	-4.7	-7.0	--	--
95% CI for difference	-6.8, -2.6	-9.1, -4.9	--	--
p-value	[redacted]	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	[redacted]	[redacted]	--	[redacted]
Patient's Assessment of Arthritis Pain, LS Mean (SE) [n/N]				
Month 3	[redacted]	[redacted]	[redacted]	--
Difference from placebo	-11.3	-11.7	--	--
95% CI for difference	-17.3, -5.2	-17.7, -5.6	--	--
p-value	[redacted]	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]

Amendment to **Table M4: Change in ACR components from baseline in OPAL Broaden (FAS)**

Outcome	TOF 5mg	ADA	PBO*	PBO→TOF5
Month 12	[redacted]	[redacted]	--	[redacted]
Patient's Global Assessment of Arthritis, LS Mean (SE) [n/N]				
Month 3	[redacted]	[redacted]	[redacted]	--
Difference from placebo	-8.7	-10.1	--	--
95% CI for difference	-14.6, -2.7	-16.0, -4.1	--	--
p-value	[redacted]	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	[redacted]	[redacted]	--	[redacted]
Physician's Global Assessment of Arthritis, LS Mean (SE) [n/N]				
Month 3	[redacted]	[redacted]	[redacted]	--
Difference from placebo	-5.2	-6.8	--	--
95% CI for difference	-10.5, 0.1	-12.1, -1.5	--	--
p-value	[redacted]	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	[redacted]	[redacted]	--	[redacted]

Abbreviations: ADA, adalimumab; FAS, full analysis set; LS, least squares; N, total number of unique subjects in the longitudinal model; n, number of subjects evaluable at each visit; PBO, placebo; SE, standard error; TOF, tofacitinib

[§]Nominal p-value ≤0.05 for comparison with adalimumab; [redacted]

[†]nominal p-value for the comparison between adalimumab and placebo; [redacted] *Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

Amendment to **Table M5: Change in enthesitis and dactylitis scores from baseline for OPAL Broaden (FAS)**

Outcome	TOF 5mg	ADA	PBO*	PBO→TOF5
LEI score, LS Mean (SE) [n/N]				
Month 3	-0.8 (0.2) [70/[redacted]]	-1.1 (0.2) [73/[redacted]]	-0.4 (0.2) [63/[redacted]]	--
Difference from placebo	-0.4	-0.7	--	--
95% CI for difference	-0.9, 0.2	-1.2, -0.1	--	--
p-value	[redacted]	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	-1.7 (0.2) [67/[redacted]]	-1.6 (0.2) [67/[redacted]]	--	-1.4 (0.3) [24/[redacted]]
SPARCC score, LS Mean (SE) [n/N]				
Month 3	-1.8 (0.4) [77/[redacted]]	-1.9 (0.4) [79/[redacted]]	-1.2 (0.4) [78/[redacted]]	--
Difference from placebo	-0.7	-0.7	--	--
95% CI for difference	-1.6, 0.2	-1.6, 0.2	--	--
p-value	[redacted]	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	-3.2 (0.3) [72/[redacted]]	-2.8 (0.4) [72/[redacted]]	--	-2.5 (0.5) [31/[redacted]]
DSS score, LS Mean (SE) [n/N]				
Month 3	-3.5 (1.0) [58/[redacted]]	-4.0 (1.0) [56/[redacted]]	-2.0 (1.1) [55/[redacted]]	--
Difference from placebo	-1.5	-2.0	--	--
95% CI for difference	-3.9, 0.9	-4.4, 0.4	--	--
p-value	[redacted]	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	-7.4 (0.7) [54/[redacted]]	-6.1 (0.7) [52/[redacted]]	--	-6.7 (0.9) [26/[redacted]]

Abbreviations: ADA, adalimumab; DSS, Dactylitis Severity Score; FAS, full analysis set; LEI, Leeds Enthesitis Index; LS, least squares; mg, milligram; N, total number of unique subjects in the longitudinal model; n, number of subjects with data; PBO, placebo; SE, standard error; SPARCC, Spondyloarthritis Research Consortium of Canada; TOF, tofacitinib

†nominal p-value for the comparison between adalimumab and placebo;

‖nominal p-value for the comparison between tofacitinib 5 mg BD and placebo

*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

Amendment to **Table M6: MDA response rates for OPAL Broaden (FAS)**

Outcome	TOF 5mg	ADA	PBO*	PBO→TOF5
MDA response rate, n/N (%)				
Month 3	28/107 (26)	27/106 (25)	7/105 (7)	--
Difference from placebo	19.5	18.8	--	--
95% CI for difference	9.9, 29.1	9.2, 28.4	--	--
p-value	[redacted]	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	40/107 (37)	42/106 (40)	--	16/52 (31)

Abbreviations: ADA, adalimumab; FAS, full analysis set; MDA, Minimal Disease Activity; mg, milligram; n, number of responders; N, number of subjects in the FAS; PBO, placebo; TOF, tofacitinib

*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

†nominal p-value for the comparison between adalimumab and placebo.

Amendment to **Table M7: Change from baseline in SF-36, FACIT-F, DLQI, and ISI for OPAL Broaden (FAS)**

Outcome	TOF 5mg	ADA	PBO*	PBO→TOF5
SF-36 physical functioning domain score, LS Mean (SE) [n/N]				
Month 3	5.2 (0.8) [102/[redacted]]	5.2 (0.9) [101/[redacted]]	2.1 (0.9) [102/[redacted]]	--
Difference from placebo	3.1	3.2	--	--
95% CI for difference	0.9, 5.3	1.0, 5.3	--	--
p-value	[redacted]	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	7.7 (0.9) [96/[redacted]]	6.8 (0.9) [94/[redacted]]	--	6.5 (1.3) [44/[redacted]]
FACIT-F total score, LS Mean (SE) [n/N]				
Month 3	7.0 (0.9) [102/[redacted]]	6.0 (0.9) [101/[redacted]]	3.3 (0.9) [102/[redacted]]	--
Difference from placebo	3.7	2.6	--	--
95% CI for difference	1.5, 5.9	0.5, 4.8	--	--
p-value	[redacted]	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	8.5 (1.0) [96/[redacted]]	6.9 (1.0) [94/[redacted]]	--	5.7 (1.4) [44/52]
DLQI score, LS Mean (SE) [n/N]				
Month 3	[redacted]	[redacted]	[redacted]	--
Difference from placebo	[redacted]	[redacted]	--	--
95% CI for difference	[redacted]	[redacted]	--	--
p-value	[redacted]	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	[redacted]	[redacted]	--	[redacted]
ISI score, LS Mean (SE) [n/N]				
Month 3	[redacted]	[redacted]	[redacted]	--
Difference from placebo	[redacted]	[redacted]	--	--

Amendment to **Table M7: Change from baseline in SF-36, FACIT-F, DLQI, and ISI for OPAL Broaden (FAS)**

Outcome	TOF 5mg	ADA	PBO*	PBO→TOF5
95% CI for difference	[redacted]	[redacted]	--	--
p-value	[redacted]	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	[redacted]	[redacted]	--	[redacted]

Abbreviations: ADA, adalimumab; DLQI, Dermatology Life Quality Index; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; ISI, Itch Severity Item; LS, least squares; N, total number of unique subjects in the longitudinal model; n, number of subjects evaluable at each visit; PBO, placebo; SE, standard error; SF-36, 36-Item Short-Form Health Survey; TOF, tofacitinib.
†nominal p-value for the comparison between adalimumab and placebo;
‖nominal p-value for the comparison between tofacitinib 5 mg BD and placebo; [redacted]*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

Post-hoc outcomes

Amendment to **Table M8: Descriptive Statistics of Mean Change from Baseline HAQ-DI by PsARC in OPAL Broaden (FAS, No Imputation)**

Outcome	TOF 5mg	ADA	PBO*	PBO→TOF5
HAQ-DI at Month 3, [N] M (SD)				
PsARC responders	[redacted]	[redacted]	[redacted]	[redacted]
PsARC non-responders	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI at Month 6, [N] M (SD)				
PsARC responders	[redacted]	[redacted]	--	[redacted]
PsARC non-responders	[redacted]	[redacted]	--	[redacted]
HAQ-DI at Month 12, [N] M (SD)				
PsARC responders	[redacted]	[redacted]	--	[redacted]
PsARC non-responders	[redacted]	[redacted]	--	[redacted]
[redacted]				

Amendment to **Table M9: Descriptive Statistics of Median Change from Baseline HAQ-DI by PsARC in OPAL Broaden (FAS, No Imputation)**

Outcome	TOF 5mg	ADA	PBO*	PBO→TOF5
HAQ-DI at Month 3, [N] Median (IQR)				
PsARC responders	[redacted]	[redacted]	[redacted]	[redacted]
PsARC non-responders	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI at Month 6, [N] Median (IQR)				
PsARC responders	[redacted]	[redacted]	--	[redacted]
PsARC non-responders	[redacted]	[redacted]	--	[redacted]
HAQ-DI at Month 12, [N] Median (IQR)				
PsARC responders	[redacted]	[redacted]	--	[redacted]
PsARC non-responders	[redacted]	[redacted]	--	[redacted]

[redacted]

Amendment to **Table M10: PASI50 and PASI90 response rates for OPAL Broaden (FAS)**

Outcome	TOF 5mg	ADA	PBO*	PBO→TOF5
PASI50 response rate, n/N (%)				
Month 3	[redacted]	[redacted]	[redacted]	[redacted]
Difference from placebo	[redacted]	[redacted]	--	--
95% CI for difference	[redacted]	[redacted]	--	--
p-value	[redacted]	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	[redacted]	[redacted]	--	[redacted]
PASI90 response rate, n/N (%)				
Month 3	[redacted]	[redacted]	[redacted]	[redacted]
Difference from placebo	[redacted]	[redacted]	--	--
95% CI for difference	[redacted]	[redacted]	--	--
p-value	[redacted]	[redacted]	--	--
Month 6	[redacted]	[redacted]	--	[redacted]
Month 12	[redacted]	[redacted]	--	[redacted]

[redacted]

OPAL Beyond

Data for the patients initially in the placebo group that switched to tofacitinib 5 mg BD at month 3 are reported in columns labelled as 'PBO→TOF' in the tables below.

Secondary and other efficacy outcomes

Amendment to **Table 16: ACR20, ACR50, and ACR70 response rates for OPAL Beyond (FAS)**

Outcome	TOF 5mg	PBO*	PBO→TOF5
ACR20 response rate, n/N (%)			
Week 2	[redacted]	[redacted]	--
Difference from placebo	[redacted]	--	--
95% CI for difference	[redacted]	--	--
p-value	0.005	--	--
Month 6	78/131 (60)	--	33/66 (50)
ACR50 response rate, n/N (%)			
Month 3	39/131 (30)	19/131 (15)	--
Difference from placebo	15.3	--	--
95% CI for difference	5.4, 25.2	--	--
p-value	0.003	--	--
Month 6	50/131 (38)	--	21/66 (32)
ACR70 response rate, n/N (%)			
Month 3	22/131 (17)	13/131 (10)	--
Difference from placebo	6.9	--	--
95% CI for difference	-1.3, 15.1	--	--
p-value	[redacted]	--	--
Month 6	28/131 (21)	--	10/66 (15)

Abbreviations: ACR, American College of Rheumatology; FAS, full analysis set; mg, milligram; N, number of subjects in FAS; n, number of responders; PBO, placebo; TOF, tofacitinib
†nominal p-value; [redacted]*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

Amendment to **Table 17: Change in HAQ-DI from baseline for OPAL Beyond (FAS)**

Outcome	TOF 5mg	PBO*	PBO→TOF5
HAQ-DI score, LS Mean (SE) [n/N]			
Month 6	-0.44 (0.05) [122/131]	--	-0.48 (0.07) [56/66]

Abbreviations: FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; LS, least squares; N, total number of unique subjects in the longitudinal model; n, number of subjects evaluable at each visit; PBO, placebo; SE, standard error; TOF, tofacitinib
*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

Amendment to **Table 18: PsARC response rates for OPAL Beyond (FAS)**

Outcome	TOF 5mg	PBO*	PBO→TOF5
PsARC response rate, n/N* (%)			
Month 3	77/131 (58.8)	38/131 (29.0)	--
Difference from placebo	29.8	--	--
95% CI for difference	18.3, 41.2	--	--
p-value	[redacted]	--	--
Month 6	77/131 (58.8)	--	34/66 (51.5)

Abbreviations: FAS, full analysis set; n, number of responders; N*, number of subjects in FAS; mg, milligram; PBO, placebo; PsARC, Psoriatic Arthritis Response Criteria; TOF, tofacitinib
*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

Amendment to **Table 19: PASI75 and PsARC response rates for OPAL Beyond (FAS)**

Outcome	TOF 5mg	PBO*	PBO→TOF5
PASI75 response rate, n/N (%)			
Month 3	17/80 (21)	12/86 (14)	--
Difference from placebo	7.3	--	--
95% CI for difference	-4.3, 18.9	--	--
p-value	[redacted]	--	--
Month 6	27/80 (34)	--	11/42 (26)

Abbreviations: FAS, full analysis set; n, number of responders; N*, number of subjects in FAS; N, number of subjects in FAS with baseline BSA≥3% and baseline PASI>0; mg, milligram; PASI, Psoriatic Area and Severity Index; PBO, placebo; TOF, tofacitinib
*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

Amendment to **Table M13: Change in ACR components from baseline for OPAL Beyond (FAS)**

Outcome	TOF 5mg	PBO*	PBO→TOF5
Tender/Painful Joint Count, LS Mean (SE) [n/N]			
Month 3	[redacted]	[redacted]	--
Difference from placebo	-5.4	--	--
95% CI for difference	-8.1, -2.7	--	--
p-value	[redacted]	--	--
Month 6	[redacted]	--	[redacted]
Swollen Joint Count, LS Mean (SE) [n/N]			
Month 3	[redacted]	[redacted]	--
Difference from placebo	-4.9	--	--
95% CI for difference	-6.5, -3.2	--	--
p-value	[redacted]	--	--
Month 6	[redacted]	--	[redacted]
C-Reactive Protein, LS Mean (SE) [n/N]			
Month 3	[redacted]	[redacted]	--
Difference from placebo	-6.5	--	--
95% CI for difference	-11.5, -1.4	--	--
p-value	[redacted]	--	--
Month 6	[redacted]	--	[redacted]
Patient's Assessment of Arthritis Pain, LS Mean (SE) [n/N]			
Month 3	[redacted]	[redacted]	--
Difference from placebo	-13.9	--	--
95% CI for difference	-20.0, -7.9	--	--
p-value	[redacted]	--	--
Month 6	[redacted]	--	[redacted]
Patient's Global Assessment of Arthritis, LS Mean (SE) [n/N]			
Month 3	[redacted]	[redacted]	--
Difference from placebo	-14.5	--	--
95% CI for difference	-20.7, -8.3	--	--
p-value	[redacted]	--	--
Month 6	[redacted]	--	[redacted]

Amendment to **Table M13: Change in ACR components from baseline for OPAL Beyond (FAS)**

Outcome	TOF 5mg	PBO*	PBO→TOF5
Physician's Global Assessment of Arthritis, LS Mean (SE) [n/N]			
Month 3	[redacted]	[redacted]	--
Difference from placebo	-11.4	--	--
95% CI for difference	-16.7, -6.1	--	--
p-value	[redacted]	--	--
Month 6	[redacted]	--	[redacted]

Abbreviations: FAS, full analysis set; LS, least squares; N, total number of unique subjects in the longitudinal model; n, number of subjects evaluable at each visit; PBO, placebo; SE, standard error; TOF, tofacitinib
†p-value <0.001 for comparison with placebo. ‡p-value ≤0.05 for comparison with placebo.
*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

Amendment to **Table M14: Change in enthesitis and dactylitis scores from baseline for OPAL Beyond (FAS)**

Outcome	TOF 5mg	PBO*	PBO→TOF5
LEI score, LS Mean (SE) [n/N]			
Month 3	-1.3 (0.2) [79/[redacted]]	-0.5 (0.2) [82/[redacted]]	--
Difference from placebo	-0.9	--	--
95% CI for difference	-1.4, -0.3	--	--
p-value	[redacted]	--	--
Month 6	-1.5 (0.2) [77/[redacted]]	--	-1.4 (0.3) [38/[redacted]
SPARCC score, LS Mean (SE) [n/N]			
Month 3	-2.5 (0.3) [92[redacted]	-1.3 (0.3) [87/[redacted]	--
Difference from placebo	-1.2	--	--
95% CI for difference	-2.2, -0.3	--	--
p-value	[redacted]	--	--
Month 6	-2.6 (0.4) [91[redacted]	--	-2.6 (0.5) [40/[redacted]]
DSS score, LS Mean (SE) [n/N]			
Month 3	-5.2 (0.7) [64/[redacted]]	-1.9 (0.8) [55/[redacted]]	--
Difference from placebo	-3.3	--	--
95% CI for difference	-5.4, -1.2	--	--
p-value	[redacted]	--	--
Month 6	-6.0 (0.8) [61/[redacted]]	--	-5.4 (1.3) [25/[redacted]]

Abbreviations: DSS, Dactylitis Severity Score; FAS, full analysis set; LEI, Leeds Enthesitis Index; LS, least squares; mg, milligram; N, total number of unique subjects in the longitudinal model; n, number of subjects evaluable at each visit; PBO, placebo; SE, standard error; SPARCC, Spondyloarthritis Research Consortium of Canada; TOF, tofacitinib
†nominal p-value for the comparison between tofacitinib 5 mg BD and placebo
*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

Amendment to **Table M15: MDA response rates for OPAL Beyond (FAS)**

Outcome	TOF 5mg	PBO*	PBO→TOF5
MDA response rate, n/N (%)			
Month 3	30/131 (23)	19/131 (15)	--
Difference from placebo	8.4	--	--
95% CI for difference	-1.0, 17.8	--	--
p-value	[redacted]	--	--
Month 6	31/131 (23.7)	--	12/66 (18.2)

Abbreviations: FAS, full analysis set; MDA, Minimal Disease Activity; mg, milligram; n, number of responders; N, number of subjects in FAS; PBO, placebo; TOF, tofacitinib
*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

Amendment to **Table M16: Change from baseline in SF-36, FACIT-F, DLQI, and ISI for OPAL Beyond (FAS)**

Outcome	TOF 5mg	PBO*	PBO→TOF5
SF-36 physical functioning domain score, LS Mean (SE) [n/N]			
Month 3	5.0 (0.7) [124/[redacted]]	1.7 (0.7) [117/[redacted]]	--
Difference from placebo	3.3	--	--
95% CI for difference	1.3, 5.3	--	--
p-value	[redacted]	--	--
Month 6	5.4 (0.8) [121/[redacted]]	--	5.9 (1.2) [56/[redacted]]
FACIT-F total score, LS Mean (SE) [n/N]			
Month 3	7.0 (0.8) [124/[redacted]]	3.0 (0.8) [117/[redacted]]	--
Difference from placebo	3.9	--	--
95% CI for difference	1.6, 6.2	--	--
p-value	[redacted]	--	--
Month 6	7.1 (0.87) [122[redacted]	--	7.6 (1.3) [56/[redacted]
DLQI score, LS Mean (SE) [n/N]			
Month 3	[redacted]	[redacted]	--
Difference from placebo	[redacted]	--	--
95% CI for difference	[redacted]	--	--
p-value	[redacted]	--	--
Month 6	[redacted]	--	[redacted]
ISI score, LS Mean (SE) [n/N]			
Month 3	[redacted]	[redacted]	--

Difference from placebo	[redacted]	--	--
95% CI for difference	[redacted]	--	--
p-value	[redacted]	--	--
Month 6	[redacted]	--	[redacted]

Abbreviations: ADA, adalimumab; DLQI, Dermatology Life Quality Index; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; ISI, Itch severity Item; LS, least squares; N, total number of unique subjects in the longitudinal model; n, number of subjects evaluable at each visit; PBO, placebo; SE, standard error; SF-36, 36-Item Short-Form Health Survey; TOF, tofacitinib.
†nominal p-value for the comparison between tofacitinib 5 mg BD and placebo
*Results for the placebo group are presented up to Month 3, as that was the end of the placebo-controlled period

Post-hoc outcomes

Amendment to **Table M17: Descriptive Statistics of Mean Change from Baseline HAQ-DI by PsARC in OPAL Beyond (FAS, No Imputation)**

Outcome	TOF 5mg	PBO*	PBO→TOF5
HAQ-DI at Month 3, [N] M (SD)			
PsARC responders	[redacted]	[redacted]	[redacted]
PsARC non-responders	[redacted]	[redacted]	[redacted]
HAQ-DI at Month 6, [N] M (SD)			
PsARC responders	[redacted]	--	[redacted]
PsARC non-responders	[redacted]	--	[redacted]

[redacted]

Amendment to **Table M18: Descriptive Statistics of Median Change from Baseline HAQ-DI by PsARC in OPAL Beyond (FAS, No Imputation)**

Outcome	TOF 5mg	PBO*	PBO→TOF5
HAQ-DI at Month 3, [N] Median (IQR)			
PsARC responders	[redacted]	[redacted]	[redacted]
PsARC non-responders	[redacted]	[redacted]	[redacted]
HAQ-DI at Month 6, [N] Median (IQR)			
PsARC responders	[redacted]	--	[redacted]
PsARC non-responders	[redacted]	--	[redacted]

[redacted]

Amendment to **Table M19: PASI50 and PASI90 response rates for OPAL Beyond (FAS)**

Outcome	TOF 5mg	PBO*	PBO→TOF5
PASI50 response rate, n/N (%)			
Month 3	[redacted]	[redacted]	[redacted]
Difference from placebo	[redacted]	--	--
95% CI for difference	[redacted]	--	--
p-value	[redacted]	--	--
Month 6	[redacted]	--	[redacted]
PASI90 response rate, n/N (%)			
Month 3	[redacted]	[redacted]	[redacted]
Difference from placebo	[redacted]	--	--
95% CI for difference	[redacted]	--	--
p-value	[redacted]	--	--
Month 6	[redacted]	--	[redacted]

[redacted]

A11. **Priority question:** In Table M22, (appendix M) PsARC is listed as a key secondary outcome in OPAL Balance but results for PsARC are not included in Table 21 of the company submission. Please provide these results

Pfizer Response: The results for PsARC response rates in OPAL Balance (25th January 2017 data cut off) are provided below from Table 14.2.2.3.1 of the interim CSR. [redacted]. It should be noted that sample sizes were too small beyond 24 months for meaningful efficacy analyses (Nash et al., 2017, see reference 93 in the Pfizer submission).

[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]

A12. In Table 21 and Figure 6 of the company submission, the number of patients in OPAL Balance falls over time but the percentage of patients whose disease achieves an ACR 20, 50 or 70 response stays the same. Please clarify why at these later follow-up assessments there are any patients whose disease does not achieve an ACR 20 response.

Pfizer Response: OPAL Balance is a Phase III, long-term, open-label extension study designed to evaluate the safety, tolerability and efficacy of tofacitinib in subjects with active PsA. Current data cuts for OPAL Balance demonstrate that tofacitinib sustains efficacy across various PsA disease domains over time.

We acknowledge the ERG’s query as to why some patients in the long-term extension (LTE) study remain on tofacitinib at 24 months, despite having not achieved an ACR 20 response. As the decision to discontinue a treatment is multi-factorial, and not determined by a single efficacy endpoint (e.g., ACR 20), we would make the assumption that, in these cases, the treating physician and patient have determined that the net benefit of continuing with tofacitinib was justified. This would have been informed by a number of factors, including patient-preference, safety, and alternative measures of efficacy by the clinician.

Also, given that patients completing OPAL Beyond fed into the LTE, it is of note that TNF-IR patients have traditionally had poorer outcomes, and so the overall efficacy of tofacitinib in this line of therapy at 24 months may have been deemed acceptable and the best available option, relative to anticipated outcomes with other DMARDs.

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Please note that lack of efficacy, as measured by ACR, is not a reason for discontinuation.

Evidence synthesis

A13. **Priority question:** Please provide a full description of specifications for each of the network meta-analysis (NMA) models, alongside all files required to run the models in WinBUGS (including data, model, and initial values for every chain).

Pfizer Response: Files required to run the models in WinBUGS accompany this response. The file named “WinBUGS Files” includes the log files with the necessary scripts to help the ERG re-run the models. The ERG will need to edit the folders to match their folder structure.

A14. **Priority question:** Please justify the new specification introduced with NMA model K (HAQ), commenting on the advantages and disadvantages and justify and explain the differences in the results between models G and K.

Erratum:
Pfizer have identified a data entry error for Models K1 and K2 in the bDMARD-naïve NMA. As a result, the 06 April submission overestimated the common baseline for placebo responders, which consequently overestimated the absolute change in HAQ-DI for PsARC responders treated with tofacitinib and all comparators.

We have rectified the data entry error and the tables below update those NMA results in our 06 April submission, using table numbering which aligns to the submission. These corrections are provided prior to the response specifically addressing the clarification question concerning models G and K. The response to the clarification question takes account of these corrections.

Table E41: HAQ-DI | PsARC summary results for bDMARD naïve population: Model K1 | PsARC responders

	06 April Results			Corrected Results		
Comparator	WMD for TOF 5 versus Comparator	WMD for TOF 10 versus Comparator	**Absolute change from baseline**	WMD for TOF 5 versus Comparator	WMD for TOF 10 versus Comparator	**Absolute change from baseline**
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

Table E43: HAQ-DI | PsARC summary results for bDMARD naïve population: Model K2 | PsARC responders random-effects

	06 April Results			Corrected Results		
Comparator	WMD for TOF 5 versus Comparator	WMD for TOF 10 versus Comparator	**Absolute change from baseline**	WMD for TOF 5 versus Comparator	WMD for TOF 10 versus Comparator	**Absolute change from baseline**
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

Table E46: HAQ-DI | PsARC summary results for bDMARD naïve population: Absolute change from baseline data for the economic model (best case, worst case and recommended data)

Comparator	Model G (FE, Rodgers (18) and Cummins (19))	Model K1 (FE, alternative code	Model K2 (RE, alternative code)
	TOF 5 worst case	TOF 5 best case	Recommended model
PsARC responders			
[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]

Table 26: HAQ-DI | PsARC summary results for bDMARD-naïve population: Absolute change from baseline (base case model data)

Comparator	Model K2 (RE, alternative code)	Model K2 (RE, alternative code)
	PsARC responders	PsARC non-responders
[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]	-	-

On the basis of these corrections, text relating to the base case model in the bDMARD-naïve population on page 75 (including Table 26) of the Pfizer submission should read as follows:

- [redacted]

Similarly, text in Section A.7.1 of the summary document should read:

- [redacted]

When comparing the results of model K1 (FE) and K2 (RE) from the 06 April submission with those of the updated model K1 (FE) and K2 (RE), the results are broadly similar, with similar relative effects of tofacitinib 5mg BD vs its comparators.

Pfizer Response (commenting on model K vs model G; question A14): The analysis for Model K is a normal model with identity link, code as per TSD 2. This is the standard model used for continuous outcomes (see DSU TSD 2, section 3.4). Model G in TA445 is a fixed effect model, based on the model by Rodgers (Rodgers et al., 2011; see reference 111 in the Pfizer submission). Note that the code for Model G does not take account of trials with three or more study arms at randomisation; OPAL Broaden is, at randomisation, a four-armed trial.

The Rodgers model (Model G) assumes changes in HAQ-DI given placebo non-responders as common baseline. Treatment response and non-response for HAQ-DI change are assumed to be treatment specific and additive to the placebo probability of non-response.

In contrast, Model K assumes that in the PsARC responders group, the common baseline is change in HAQ-DI for placebo responders; for PsARC non-responders, the common baseline is change in HAQ-DI for placebo non-responders. In Model K, data from the PsARC responder subgroup are analysed separately from the data for the PsARC non-responders, allowing for treatment effects in responders to be independent of the treatment effects in non-responders. An Excel workbook accompanies this clarification response. Please see Sheet A14 for a comparison of the results from Model G with those from Model K. Please note that the results for Model K contain the corrections described in the above erratum.

With regards to the relative effects of tofacitinib 5mg BD versus other treatments for change in HAQ-DI score from baseline, Model G and Model K (FE) generally produce similar relative effects in PsARC responders. It is, however, noteworthy that for PsARC responders, the change in HAQ-DI from baseline (median) significantly favoured etanercept and infliximab in model G, with no significant differences for tofacitinib 5mg BD versus any comparator in model K (FE). In PsARC non-responders, there is a small difference in the relative effects (median) produced by Model K (FE) compared with Model G. The results from Model K (FE) slightly favoured

tofacitinib 5mg BD, but there were no significant differences in change in HAQ-DI for tofacitinib 5mg BD versus other treatments.

A15. **Priority question:** Please compare the results of models in the company submission that have the same specification as those in NICE Technology Appraisal guidance 445 (TA445) and justify any differences. In particular, please explain differences in the outcomes for placebo (PASI and PsARC outcomes); please justify any differences and explore the reasons for such differences.

Pfizer Response: Please see tabs marked A15 in the accompanying Excel workbook, which presents a tabulated comparison of: (1) the data used in TA445 against those used in the Pfizer submission; and (2) the results from TA445 against the equivalent model results from the Pfizer submission.

In all cases, the differences between the results can be explained by differences in the input data. For the PsARC response, subgroup data for bDMARD-naïve and experienced populations were available to the Assessment Group (AG) for TA445; some of these data were redacted in the AG report and were not available in the primary publications. For our submission, data for FUTURE 2 and RAPID-PsA were substituted with the nearest equivalent data for the bDMARD-naïve network. That is to say, we used PsARC response data from the primary publications of FUTURE 2 (secukinimab) and RAPID-PsA (certolizumab pegol) from the mixed populations in those studies (i.e., bDMARD-naive/experienced patients). Similarly, for PASI 75/90 in the bDMARD-naïve network, we used 16-week response data for secukinumab (as the 12-week response data were redacted in TA445) and data from SPIRIT-P1 contributed evidence to the network for placebo, ixekizumab, and adalimumab (the ixekizumab arm from this study was not included in the evidence networks in TA445). In the bDMARD-naïve network, OPAL Broaden contributed evidence for tofacitinib, placebo, and adalimumab (which was not available for TA445).

In the bDMARD-experienced network, the PSUMMIT 2 trial contributed evidence across clinical outcomes. Additionally, SPIRIT-P2 contributed evidence for PASI75/90 and ACR20/50/70 for ixekizumab and placebo (which was not incorporated in TA445). The OPAL Beyond clinical trial contributed evidence for tofacitinib and placebo (which was not available for TA445). Data were redacted in the AG report for FUTURE 2 and were therefore substituted with the nearest equivalent data; for ACR20/50/70, data at 24 weeks were used, and for PASI75/90, the data at 16 weeks were used. No data were available for FUTURE 2 for the PsARC and HAQ outcomes, which was different from TA445, which included FUTURE 2 data for all outcomes.

A16. **Priority question:** For the no prior bDMARD subgroup, please consider any differences/similarities between the results in the company submission and those in TA445 for model selection undertaken using goodness of fit measures (such as DIC and residual deviance) for all outcomes (PsARC, PASI, HAQ and ACR).

Pfizer Response: Please see Sheet A16 of the accompanying Excel workbook, which includes a table comparing the base models in TA445 with the base model in the Pfizer submission, along with the rationale for the model choice. Where the models are equivalent, DIC and resdev have been tabulated for comparison.

Please see section D2.3 in Appendix D of the Pfizer submission for clinical opinion on class effect models. Clinical expert opinion favoured the model in which all drugs are included separately, as opposed to one which assumed a class effect.

A17. **Priority question:** Please provide complete results for the NMA models reported in the company submission as some information is missing (e.g. the z-scores for PASI models, treatment effect in HAQ models in Table E45, appendix E).

Pfizer Response: Please see tabs marked A15 in the accompanying Excel workbook, which tabulate the z scores for the model presented in the Pfizer submission for the PASI and ACR outcomes. The log files described in the response to question A13 (which accompany this response) also have all NMA outputs.

A18. **Priority question:** Please explore the reasons for the placebo arm of the OPAL Broaden trial not having a good fit to the NMA model with placebo adjustment for PsARC. Consider alternative model specifications that better reflect the results of this trial.

Pfizer Response: Section B.2.14.2.2 (p.106) of the Pfizer submission provides a discussion on "placebo creep". As indicated in the Pfizer submission, elevated placebo PsARC response rates in bDMARD PsA clinical trials have previously been noted by the NICE Assessment Group for TA445 (Corbett 2017; see reference 4 in the Pfizer submission).

This placebo creep effect has been most evident since 2013, commencing with the PSUMMIT trials (Corbett 2017; see reference 4 in the Pfizer submission). Variation in placebo PsARC responses was therefore observed in the clinical trials that informed this review: clinical trials that informed our NMAs spanned from the years 2000-2017, during which time placebo PsARC response rates ranged from 21-45%, with a general trend of more recent trials yielding higher placebo response rates (see below and Sheet A18 'Alt PsARC analysis' from the accompanying Excel workbook).

We therefore explored placebo-adjusted and class effects models in our NMAs, similar to the approach taken in TA445. The notable placebo PsARC responses observed in our review (and in TA445) are not unexpected, given that PsARC has been reported to be relatively more prone to placebo effects compared to other composite outcome measures for PsA (Kavanaugh & Cassell, 2005).

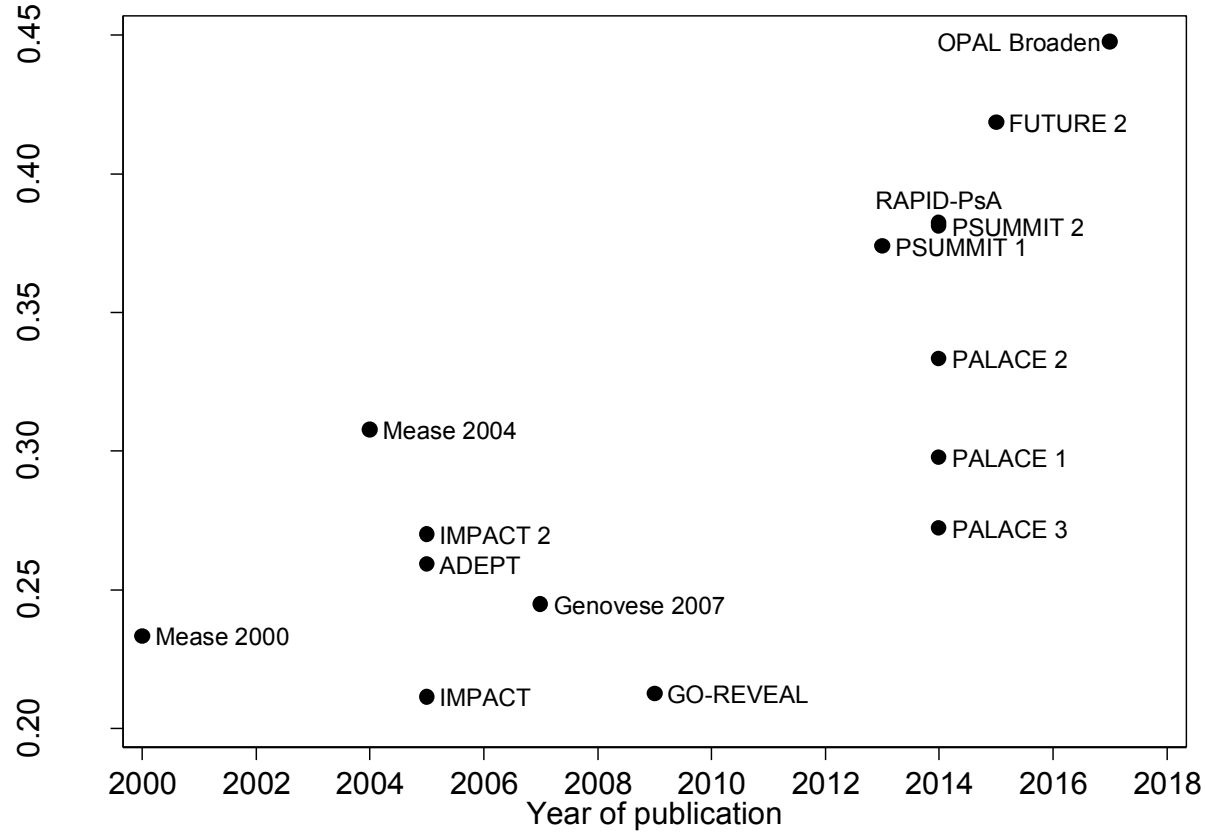
Placebo creep is a phenomenon that has been observed over time in other therapy areas, with plausible explanations linked to changes in trial populations and background treatment (Julious & Wang, 2008). It has been suggested that advancements in medical practice/improvements in

concomitant therapy over time may increase placebo responses and that this rate of improvement may be relatively greater than that observed in an active treatment group (Julious & Wang, 2008). Furthermore, it has also been suggested that differences in demographics in geographical regions from which trial populations originate may influence placebo response, particularly if these differences affect treatment administration (Julious & Wang, 2008). For example, a 10% difference in placebo response has been reported in arthritis pain studies comparing North American populations with those of the rest of the world (Julious & Wang, 2008)

Our review included the OPAL Broaden clinical trial of tofacitinib 5 mg BD and 10 mg BD (Mease et al., 2017; see reference 87 in the Pfizer submission), which yielded the highest placebo PsARC response (45%) among the included trials. By contrast, the IMPACT (Antoni et al., 2005; see reference 156 in the Pfizer submission) and GO-REVEAL (Kavanaugh et al., 2009) studies reported the lowest placebo PsARC responses (21%); these older studies were conducted in 2005 and 2009, respectively. Similarly, the ADEPT (2005; see reference 157 in the Pfizer submission) and Genovese *et al.*, 2007 (see reference 116 in the Pfizer submission) clinical trials of adalimumab reported placebo PsARC response rates of 26 and 27%, respectively. It is noteworthy that these studies were conducted many years prior to OPAL Broaden, and that the respective baseline DMARD or methotrexate (MTX) use in these trials was 79% (DMARDs), 48% (MTX), 50% (MTX) and 67.3%, respectively, compared to 100% baseline csDMARD use in OPAL Broaden. Given that the OPAL Broaden trial design required csDMARD use in all placebo-treated patients, this may have resulted in the elevated placebo PsARC response relative to the older trials, with the placebo group effectively comprising a csDMARD active comparator arm.

The placebo creep effect in trials of b/tsDMARDs for PsA over time is reported in the figure below.

Figure 1: Placebo creep effect in trials of b/tsDMARDs for PsA over time



There were also some observed differences in the distribution of patients from different geographical locations when comparing the tofacitinib 5 mg BD and placebo groups in OPAL Broaden (see table below). [redacted]. The differences in the geographical location of patients and any potential differences in standard clinical practice may have influenced the relative PsARC responses in the OPAL Broaden trial.

[redacted]

It is also possible that the placebo creep observed in recent trials may be attributed to differences in inclusion/exclusion criteria for the older PsA trials when compared with the newer trials. As illustrated in the table below, unlike the newer trials, some of the older trials did not require patients to have failed DMARDs (e.g., GO-REVEAL and IMPACT2 [inadequate response to NSAIDs or DMARDs], ADEPT [NSAID failure or intolerance], Mease 2000 and Mease 2004 [inadequate response to NSAID therapy]).

Table 1: Number of previous treatments allowed/required across trials included in the NMA

Main Author, Year [TRIAL ID]; sponsor	Previous treatments allowed/required
Gladman et al., 2017 [OPAL Beyond]; Pfizer	Inadequate response to at least one TNFi
Mease et al., 2017 [OPAL Broaden]; Pfizer	Inadequate response to ≥ 1 csDMARD and no previous TNFi treatment
Mease et al., 2017 [ASTRAEA]	Inadequate response or intolerance to ≥ 1 csDMARD
Mease et al. 2017 [SPIRIT P1]	No previous treatment with bDMARDs
Nash et al., 2017 [SPIRIT-P2]	Previous treatment with TNFi's and had an inadequate response to one or two TNFi's or were intolerant to TNFi's. Previous treatment with one or more csDMARDs
Cutolo et al., 2016 [PALACE 2]	Prior treatment with csDMARD and/or bDMARD or concurrent treatment with csDMARD

Main Author, Year [TRIAL ID]; sponsor	Previous treatments allowed/required
Edwards et al., 2016 [PALACE 3]	Prior treatment with csDMARDs and/or bDMARDs
McInnes 2015 [FUTURE 2]	Previous treatment with NSAIDs, csDMARDs, or anti-TNFi's
McInnes et al., 2014‡	Inadequate response on ≥1 DMARD given for ≥3 months at the maximum tolerated dose
Kavanaugh et al., 2014 [PALACE 1]	Inadequate response to prior csDMARDs, and/or biologic treatment or concurrent treatment with csDMARDs
Mease et al., 2014 [RAPID-PsA]	Previous failure on ≥1 DMARD
Ritchlin et al., 2014 [PSUMMIT2]	≥3 months of DMARD therapy, ≥4 weeks of NSAID therapy and/or ≥8 (ETA, ADA, GOL, CZP) or 14(INF) continuous weeks (or less if patient was intolerant) of TNFi therapy
McInnes et al., 2013 [PSUMMIT 1]	Inadequate response to 3 months or more of treatment with DMARDs or 4 weeks or more of treatment with NSAIDS, or both, or with intolerance to these treatments
Mease et al., 2011	Inadequate response to DMARDs, including by not limited to, MTX or anti-TNF agents
Kavanaugh et al., 2009 [GO-REVEAL]	Inadequate response to treatment with DMARDs or NSAIDs
Genovese et al., 2007	All patients were receiving concomitant DMARD therapy OR had a history of DMARD therapy with an inadequate response
Antoni et al., 2005 [IMPACT]	Previous failure with ≥1 DMARDs
Antoni et al., 2005 [IMPACT 2]	Inadequate response to current or previous DMARDs or NSAIDs
Mease et al., 2005 [ADEPT]	Inadequate response or intolerance to NSAID therapy
Mease et al., 2004	Inadequate response to NSAID therapy
Mease et al., 2000	Inadequate response to NSAID therapy

In the 06 April submission, we considered eight different NMA models for the PsARC outcome in the bDMARD-naïve network. We noted that the residual deviance for the OPAL Broaden placebo arm was high in most of these models [redacted] indicating a poor fit (see Excel workbook [Sheet A18] for a comparison of model fit across all of these models). The model with the lowest residual deviance for the OPAL Broaden placebo arm was the unadjusted model A with random-effects [redacted] While the placebo-adjusted models may have accounted for the placebo effect in some of the studies, the OPAL Broaden placebo arm did not fit these models well.

We considered two alternative model specifications that may better reflect the placebo arm of OPAL Broaden. [redacted]

[redacted]

Table 2: PsARC Odds ratio for the new NMA splitting the network into PBO 2 (placebo from PSUMMIT1 and 2, RAPID-PsA, Future 2, OPAL Broaden) and PBO 1 (all other trials)

Treatment	Control	FE NMA	RE NMA
ADA	[redacted]	[redacted]	[redacted]
APR	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]
IFX	[redacted]	[redacted]	[redacted]
USK	[redacted]	[redacted]	[redacted]
GOL	[redacted]	[redacted]	[redacted]
TOF 5	[redacted]	[redacted]	[redacted]
TOF 10	[redacted]	[redacted]	[redacted]
SEC 150	[redacted]	[redacted]	[redacted]
SEC 300	[redacted]	[redacted]	[redacted]
CZP	[redacted]	[redacted]	[redacted]
PBO 2	[redacted]	[redacted]	[redacted]
PBO 1	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]
APR	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]
IFX	[redacted]	[redacted]	[redacted]
USK	[redacted]	[redacted]	[redacted]
GOL	[redacted]	[redacted]	[redacted]
TOF 5	[redacted]	[redacted]	[redacted]
TOF 10	[redacted]	[redacted]	[redacted]
SEC 150	[redacted]	[redacted]	[redacted]
SEC 300	[redacted]	[redacted]	[redacted]
CZP	[redacted]	[redacted]	[redacted]

† significant base on 95% CrI

We considered a second alternative model [redacted]. Please Sheet A18 in the Excel workbook which accompanies this response for the results of the new analysis compared with Model A.
The workbook also shows the residual deviance for the OPAL Broaden trial arms and overall model fit across all models used for the analysis of PsARC.

[redacted]

References:

Julious SA, Wang S-J. How Biased are Indirect Comparisons, Particularly When Comparisons are Made over Time in Controlled Trials? Drug Information Journal. 2008;42(6):625-33.

Kavanaugh A, Cassell S. The assessment of disease activity and outcomes in psoriatic arthritis. Clinical and experimental rheumatology. 2005;23(5 Suppl 39):S142-7.

Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis and rheumatism. 2009;60(4):976-86.

Withdrawals

A19. **Priority question:** For OPAL Broaden and OPAL Beyond, please provide the numbers of patient withdrawals (total for each arm broken down by reason and at 3-, 6- and 12-month time points).

Pfizer Response: Information on patient withdrawals is presented below, first for OPAL Broaden, followed by OPAL Beyond.

<u>OPAL Broaden</u>

- *Discontinuations up to 3-months*

The table below shows the number of patients who completed or did not complete each arm of OPAL Broaden at 3-months (Table 14.1.1.2.1, p.341 in OPAL Broaden CSR). The reasons for non-completion are stated.

OPAL Broaden CSR Table 14.1.1.2.1: Subject Discontinuation by Treatment Group and Treatment Sequence Month 3 (Safety Analysis Set)

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

- *Discontinuations up to 6-months*

Table 00099.1 (accompanying this response) shows the number of patients who completed or did not complete each arm of OPAL Broaden at 6-months from a post hoc analysis. The reasons for non-completion are stated. Please note that the contents of this table are commercial-in-confidence.

- *Discontinuations up to 12-months*

The table below shows the number of patients who completed or did not complete each arm of OPAL Broaden at 12-months (Table 14.1.1.2.2, p.342 in OPAL Broaden CSR). The reasons for non-completion are stated.

OPAL Broaden Table 14.1.1.2.2: Subject Discontinuation by Treatment Group and Treatment Sequence Month 12 (Safety Analysis Set)

[redacted]

[redacted]

The figure below shows the number of patients who completed or did not complete each arm of OPAL Broaden at 12-months (from p.1542 in Mease *et al.,* 2017; reference 87 in the Pfizer submission). The reasons for non-completion are stated.

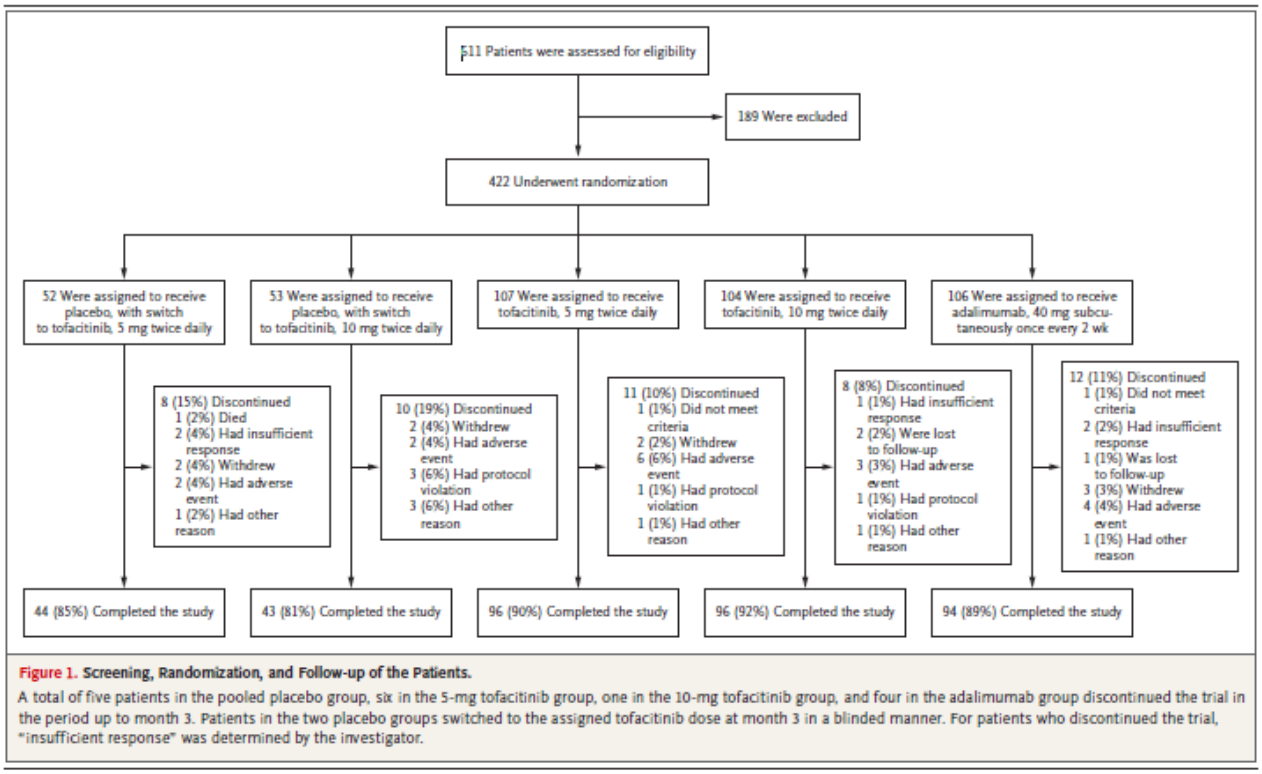


Figure 1. Screening, Randomization, and Follow-up of the Patients.
A total of five patients in the pooled placebo group, six in the 5-mg tofacitinib group, one in the 10-mg tofacitinib group, and four in the adalimumab group discontinued the trial in the period up to month 3. Patients in the two placebo groups switched to the assigned tofacitinib dose at month 3 in a blinded manner. For patients who discontinued the trial, "insufficient response" was determined by the investigator.

<u>OPAL Beyond</u>

- *Discontinuations up to 3-months*

The table below shows the number of patients who completed or did not complete each arm of OPAL Beyond at 3-months (Table 6, p.87 in OPAL Beyond CSR). The reasons for non-completion are stated.

OPAL Beyond CSR Table 6: Subject Discontinuation by Treatment Group and Treatment Sequence Month 3 (Safety Analysis Set)

[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]

- *Discontinuations up to 6-months*

The table below shows the number of patients who completed or did not complete each arm of OPAL Beyond at 6-months (Table 6, p.87 in OPAL Beyond CSR). The reasons for non-completion are stated.

OPAL Beyond CSR Table 6: Subject Discontinuation by Treatment Group and Treatment Sequence Month 6 (Safety Analysis Set)

[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]

The figure below shows the number of patients who completed or did not complete each arm of OPAL Beyond at 6-months (from p.1529 in Gladman *et al.,* 2017; reference 88 in the Pfizer submission). The reasons for non-completion are stated.

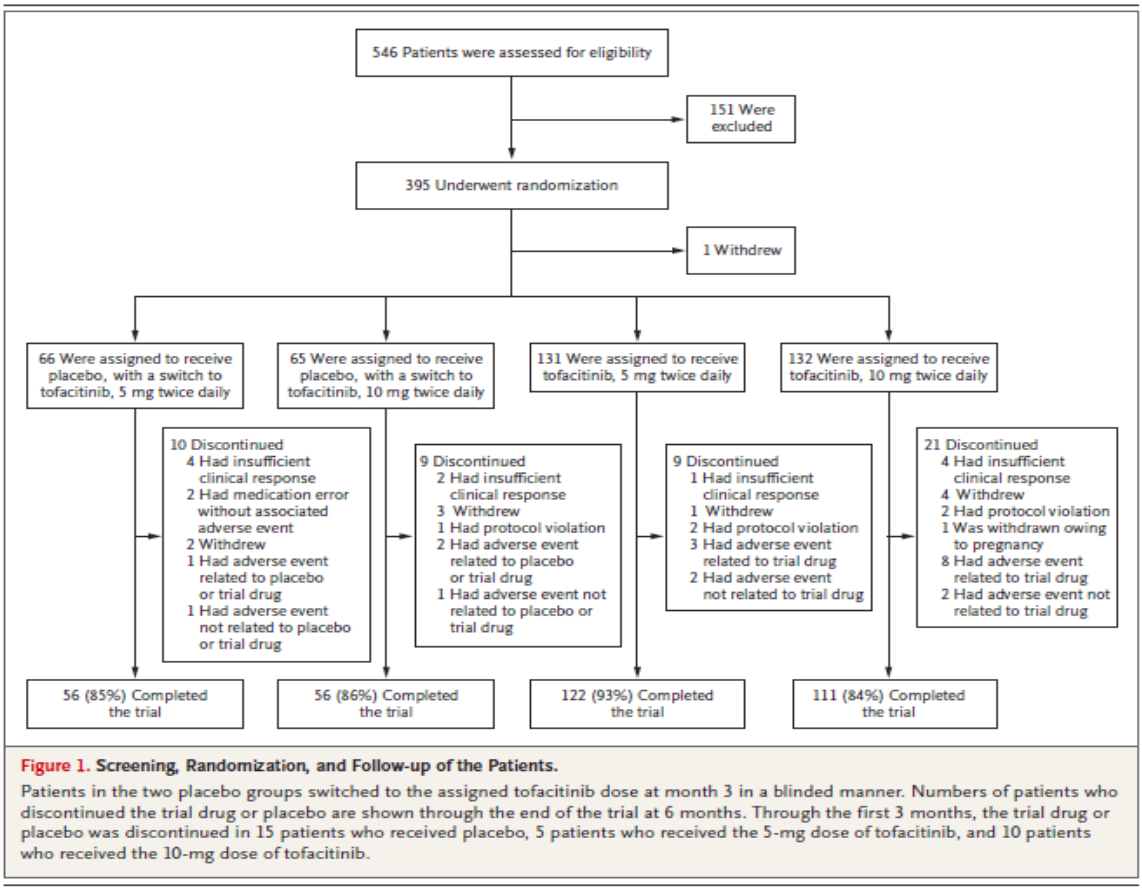


Figure 1. Screening, Randomization, and Follow-up of the Patients.

Patients in the two placebo groups switched to the assigned tofacitinib dose at month 3 in a blinded manner. Numbers of patients who discontinued the trial drug or placebo are shown through the end of the trial at 6 months. Through the first 3 months, the trial drug or placebo was discontinued in 15 patients who received placebo, 5 patients who received the 5-mg dose of tofacitinib, and 10 patients who received the 10-mg dose of tofacitinib.

- *Discontinuations up to 12-months*

Data at this time point are not available from OPAL Beyond because the trial ended at month 6.

A20. **Priority question:** For OPAL Broaden and OPAL Beyond, please provide details of patients who discontinued concomitant csDMARDs (total for each arm, broken down by methotrexate or other csDMARD and at 3-, 6- and 12-month time points)

Pfizer Response: [redacted]

[redacted]. For the 25 January 2017 data-cut of OPAL Balance, only 8.3% (56) of those (676 [98.5%]) originally receiving concomitant csDMARDs on Day 1 later discontinued and did not restart csDMARD treatment (Nash et al., 2017; see reference 92 in the Pfizer submission).

OPAL Broaden

[redacted]

[redacted]

[redacted]

The additional clarifying information presented below is from the OPAL Broaden CSR and is therefore commercial in-confidence.

OPAL Broaden baseline data on concomitant DMARDs – Safety Analysis Set

OPAL Broaden CSR Table 13. Concomitant Drug Treatments for Psoriatic Arthritis (Taken on Day 1) by Medication Type, Safety Analysis Set

	Tofacitinib 5 mg BD (N = 107)	Tofacitinib 10 mg BD (N = 104)	Adalimumab 40 mg SC Q2W (N = 106)	Placebo → Tofacitinib 5 mg BD (N = 52)	Placebo → Tofacitinib 10 mg BD (N = 53)
Number of subjects with any medication/drug treatment (DMARDs, Non-DMARDs, oral steroids, joint injections, rescue medication)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with DMARDs drug treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with non-DMARDs drug treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with oral steroids drug treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with joint injections drug treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with rescue medication drug treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

OPAL Broaden CSR Table 7. Summary of Key Protocol Deviations by Treatment Sequence, Month 12 (Safety Analysis Set)

Category of Deviations Subcategory of Deviation	TOF 5 mg BD (N = 107)	TOF 10 mg BD (N = 104)	ADA 40 mg SC Q2W (N = 106)	PBO → TOF 5 mg BD (N = 52)	PBO → TOF 10 mg BD (N = 53)	Total (N=422) n (%)
Any protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CCMEDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Took prohibited med during treatment[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Specify in comments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclusion/exclusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Specify in comments[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subject didn't have study condition[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subject on excluded medication(s)[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Laboratory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Labs not done	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Specify in comments[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Procedures/tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Performed outside window	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Procedure not done[f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Specify in comments[g]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dosing incompliant due to manual assignment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dosing noncompliance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incorrect medication/ randomisation[h]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lack of IP[i]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Specify in comments[j]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit schedule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit not done[k]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Change in concomitant DMARDs at Month 3 in OPAL Broaden (SAS)

OPAL Broaden CSR Table 12. Concomitant Drug Treatments for Psoriatic Arthritis (Taken on or After Day 2, Which Was Not the Same Drug Taken on Day 1) by Medication Type up to Month 3, Safety Analysis Set

	Tofacitinib 5 mg BD (N = 107)	**Tofacitinib 10 mg BD (N = 104)**	**Adalimumab 40 mg SC Q2W (N = 106)**	**Placebo (N = 105)**
	New n (%)	New n (%)	New n (%)	New n (%)
Number of subjects with any medication/drug treatment (DMARDs, Non-DMARDs, oral	[redacted]	[redacted]	[redacted]	[redacted]

steroids, joint injections, rescue medications)				
Number of subjects with DMARDs drug treatment	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with non-DMARDs drug treatment	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with oral steroids drug treatment	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with joint injections drug treatment	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with rescue drug treatment	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Change in concomitant DMARDs at Month 12 in OPAL Broaden (SAS)

OPAL Broaden CSR Table 14. Concomitant Drug Treatments for Psoriatic Arthritis (Taken On or After Day 2, Which Was Not the Same Drug Taken on Day 1) by Medication Type Up to Month 12, Safety Analysis Set

	TOF 5 mg BD (N = 107)	TOF 10 mg BD (N = 104)	ADA 40 mg SC Q2W (N = 106)	PBO → TOF 5 mg BID (N = 52)	PBO → TOF 10 mg BID (N = 53)
	New n (%)	New n (%)	New n (%)	New n (%)	New n (%)
Number of subjects with any medication/drug treatment (DMARDs, Non-DMARDs, oral steroids, joint injections, rescue medication)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with DMARDs drug treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with non-DMARDs drug treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with oral steroids drug treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with joint injections drug treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with rescue medication drug treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

<u>OPAL Beyond</u>

The additional clarifying information presented below is from the OPAL Beyond CSR and is therefore commercial in-confidence.

OPAL Beyond Summary of key protocol deviations at Month 6

OPAL Beyond CSR Table 7. Summary of Key Protocol Deviations by Treatment Sequence, Month 6 (Safety Analysis Set)

Category of Deviations Subcategory of Deviation	Tofacitinib 5 mg BD (N = 131) n (%)	Tofacitinib 10 mg BD (N = 132) n (%)	Placebo → Tofacitinib 5 mg BD (N = 66) n (%)	Placebo → Tofacitinib 10 mg BD (N = 65) n (%)	Total (N = 394) n (%)
Any protocol deviation					
Key					
CCMEDS					
Specify in comments[a]					
Took prohibited med during treatment[b]					
ICF issues					
Specify in comments[c]					
Study procedure prior to consent[d]					
Inclusion/exclusion					
Specify in comments[e]					
Subject on excluded medication(s)[e]					
Laboratory					
Labs not done					
Specify in comments[f]					
Other					
Protocol specific					

Category of Deviations Subcategory of Deviation	Tofacitinib 5 mg BD (N = 131) n (%)	Tofacitinib 10 mg BD (N = 132) n (%)	Placebo → Tofacitinib 5 mg BD (N = 66) n (%)	Placebo → Tofacitinib 10 mg BD (N = 65) n (%)	Total (N = 394) n (%)
discontinuation criteria[g]					
Specify in comments[h]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Procedures/tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Procedure not done[i]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Specify in comments[j]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dosing non-compliance[k]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incorrect medication/ randomisation[l]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lack of IP[m]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Specify in comments[n]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subject took incorrect dose[o]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit schedule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit not done[p]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit outside protocol window[q]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

OPAL Beyond overall discontinuations at month 6

OPAL Beyond CSR Table 14.1.1.1.1. Subject evaluation groups by treatment sequence, Month 6

	Tofacitinib 5 mg BD	**Tofacitinib 10 mg BD**	**Placebo → Tofacitinib 5 mg BD**	**Placebo → Tofacitinib 10 mg BD**	**Total**
	Number (%) of subjects	Number (%) of subjects	Number (%) of subjects	Number (%) of subjects	Number (%) of subjects
Screened					
Assigned to Study Treatment					
Not treated					
Treated					
Completed					
Discontinued					
Analysed for Efficacy					
Per-Protocol Analysis Set (PP)					
Full Analysis Set (FAS)					

Analysed for Safety					
Adverse Events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Laboratory Data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Safety Analysis Set (SAFETY)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

OPAL Beyond Safety analysis at month 3

[redacted]OPAL Beyond CSR Table 14.1.1.2.1. Subject discontinuations by treatment group, Month 3

	Tofacitinib 5 mg BD (N=131)	Tofacitinib 10 mg BD (N=132)	Placebo (N=131)	Total (N=394)
Discontinuations at or before Month 3				
Relation to study drug not Defined[a]	[redacted]	[redacted]	[redacted]	[redacted]
Insufficient clinical response	[redacted]	[redacted]	[redacted]	[redacted]
Medication error without associated adverse event	[redacted]	[redacted]	[redacted]	[redacted]
No longer willing to participate in study	[redacted]	[redacted]	[redacted]	[redacted]
Protocol violation	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawn due to pregnancy	[redacted]	[redacted]	[redacted]	[redacted]
Related to study drug[b]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Not related to study drug[b]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

OPAL Beyond Safety analysis at month 6

OPAL Beyond CSR Table 14.1.1.2.2. Subject discontinuation by treatment sequence, Month 6

Number (%) of Subjects	TOF 5 mg BD (N=131)	TOF 10 mg BD (N=132)	PBO→TOF 5 mg BD (N=66)	PBO→TOF 10 mg BD (N=65)	Total (N=394)
Discontinuations	N (%)	N (%)	N (%)	N (%)	N (%)
Relation to study drug not defined (a)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insufficient clinical response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Medication error without associated adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No longer willing to participate in study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol violation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawn due to pregnancy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Related to study drug (b)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not related to study drug (b)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Concomitant DMARDs at Month 3 in OPAL Beyond (SAS)

OPAL Beyond CSR Table 14.4.2.4.1.1. Concomitant drug treatments for psoriatic arthritis up to month 3

Number (%) of Subjects	TOF 5 mg ID (N=131)		TOF 10 mg BD (N=132)		Placebo (N=131)	
	Day 1 n, (%)	New n, (%)	Day 1 n, (%)	New n, (%)	Day 1 n, (%)	New n, (%)
Number of Subjects with Any Medication/Drug Treatment (DMARDs, Oral Steroids, Joint Injections, Rescue Medication)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with DMARDs drug treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with Non-DMARDs Drug Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with Oral Steroids Drug Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with Joint Injections Drug Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with rescue drug treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DMARDs drug treatment						
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chloroquine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number (%) of Subjects	TOF 5 mg ID (N=131)	TOF 10 mg BD (N=132)	Placebo (N=131)
Hydroxychloroquine	[redacted]	[redacted]	[redacted]
Leflunnomide	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]
Sulfasalazine	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Concomitant DMARDs at Month 6 in OPAL Beyond (SAS)

OPAL Beyond CSR Table 14.4.2.4.1.2. Concomitant drug treatments for psoriatic arthritis up to month 6

Number (%) of Subjects	TOF 5 mg BD (N=131)		TOF 10 mg BD (N=132)		PBO→5 mg BD (N=66)		PBO→10 mg BD (N=65)	
	Day 1 n, (%)	New n, (%)	Day 1 n, (%)	New n, (%)	Day 1 n, (%)	New n, (%)	Day 1 n, (%)	New n, (%)
Number of Subjects with Any Medication/Drug Treatment (DMARDs, Oral Steroids, Joint Injections, Rescue Medication)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with DMARDs drug treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with Non-DMARDs Drug Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with Oral Steroids Drug Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with Joint Injections Drug Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of subjects with rescue drug treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DMARDs drug treatment								
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chloroquine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number (%) of Subjects	TOF 5 mg BD (N=131)	TOF 10 mg BD (N=132)	PBO→5 mg BD (N=66)	PBO→10 mg BD (N=65)
Hydroxychloroquine	[redacted]	[redacted]	[redacted]	[redacted]
Leflunnomide	[redacted]	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]	[redacted]
Sulfasalazine	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

A21. **Priority question:** For OPAL Balance please give the numbers and reason for withdrawals by dose of tofacitinib at each assessment time point (months 6, 12, 18 and 24). Please provide details of the patient withdrawals (number of withdrawals with reason (e.g. lack of efficacy, adverse effects or other)).

Pfizer Response: Table 00099.4 (accompanying this response) shows the numbers and reason for withdrawals by dose of tofacitinib at each assessment time point. Please note that the contents of this table are commercial-in-confidence.

[redacted]

A22. **Priority question:** For the patients randomised to tofacitinib 5mg in OPAL Broaden and OPAL Beyond, please provide separately for each trial, the mean (and standard deviation) and median (and range) persistence (drug survival) calculated from the longest follow-up available, including any data from open label extension studies or OPAL Balance.

Pfizer Response: As agreed with NICE, the response to this question will be provided separately on 21 May 2018.

Tofacitinib 10mg

A23. **Priority question:** In OPAL Balance please provide details of the proportion of patients receiving tofacitinib 10mg and the duration of treatment with this dose.

Pfizer Response: Table 00099.5 (accompanying this response) reports data from a post hoc analysis of available data from OPAL Balance which addresses this question. Please note that the contents of this table are commercial-in-confidence.

[redacted]

Notes for interpretation of this table:

[redacted]

A24. Please comment on whether the 10mg dose is expected to be used in clinical practice. If not, what impact does the inclusion of patients taking the 10mg dose in OPAL Balance have on the generalisability of these data to clinical practice?

Pfizer Response: Pfizer has not submitted a marketing authorisation application to the EMA for the tofacitinib 10 mg dose in PsA. We are therefore not seeking reimbursement approval from NICE for this dose, as this would be considered outside of licence (off label). See draft tofacitinib SmPC, 2017; reference 16 in the Pfizer submission.

The inclusion of the 10 mg dose in the presentation of results from OPAL Balance in our submission reflects the trial design and the results presented at the American College of Rheumatology (ACR) 2017 conference (Nash et al 2017; see references 92 and 93 in the Pfizer submission).

In section B.2.8.7.1 and Figure 7 (p.59) of the Pfizer submission, we presented results of an interim analysis (data cut 4th April 2016) comparing changes in HAQ-DI for the tofacitinib 5 mg BD constant dose cohort with the FAS (full analysis set: [redacted] (OPAL Balance CSR, Pfizer data on file 2018).

The results from the interim analysis speak to the generalisability of the OPAL Balance data to UK clinical practice, particularly with regard to the importance of changes in HAQ-DI. [redacted] (as indicated in the draft SmPC, [redacted]. See draft tofacitinib SmPC, 2017; reference 16 in the Pfizer submission). [redacted] the changes in HAQ-DI (through time) for the tofacitinib 5 mg BD constant dose are of relevance to UK clinical practice.

Radiographic progression

A25. **Priority question:** Please clarify the source of the estimates of difference in mTSS and rate of progression for adalimumab vs baseline in the ADEPT study at 48 weeks reported in tables D36 and D38 in appendix D. The citation for the study in table D38 (34) does not match that in the reference list.

Pfizer Response: The reference for these estimates reported in the submission was incorrect and should have been reported in the submission as:

Mease PJ, Ory P, Sharp JT, et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). Ann Rheum Dis. 2009; 68: 702-9.

The data used are on page 703 from Table 1 (number with increase in mTSS score from baseline to week 48, 13 out of 115 [11.3%]) and Table 2 (mean change in mTSS from baseline to week 48: All adalimumab 0.1 [SD 1.95]).

A26. **Priority question:** Please clarify how the non-inferiority (NI) margins for difference in mTSS and rate of progression were calculated. p188 of appendix D states that the same approach as the FDA Arthritis Advisory Committee was used, however the NI margins for both difference in mTSS and rate of progression appear to differ from the 25-75% upper bound criteria used to determine the NI margin in the FDA Arthritis Advisory Committee review.

Pfizer Response: We used the same approach as the FDA-ACC review, but at a different follow-up point, therefore the data and NI margins for difference in mTSS will differ from data and NI margins reported in the FDA-ACC review.

Please note the FDA published an Errata August 3, 2017. This notes that the text in the FDA report in page 40, first paragraph should read:

> "Using 25-75% of the upper confidence interval bound leads to NI margins in the range of approximately 0.125 to 0.375 utilizing historical data across TNF inhibitors, or approximately 0.10 to 0.30 utilizing only historical data for adalimumab."

These NI margins agree with the NI margins reported in Appendix D Table D35: Non-inferiority Margins used in the FDA-AAC Review using 24-week Data. In Table D36, the difference in mTSS compared to placebo also agrees with FDA Table 17 (page 41), though the 95% CI for ADEPT is not reported in the FDA table. The FDA-ACC review does not report NI margins for rate of progression.

The FDA NI margins were based on 6-month data, whereas the progression analysis in the Pfizer submission used 48- to 52-week data for NI margins, because OPAL Broaden captured progression data at 52 weeks. The difference in mTSS from baseline and rate of progression from ADEPT at 48 weeks is reported in table D36 Appendix D. As per response to A25, these data agree with the ADEPT publication (*Mease 2009. Ann Rheum Dis; 68: 702-9)*. The NI margins in Table D36 are calculated using the same approach as the FDA, which is to take 25% and 75% of the upper part of the CI as the NI margins. Note that difference in mTSS versus placebo is not reported as all patients crossed over after 24 weeks therefore difference from baseline is used instead. For this reason, the upper part of the CI is measured from the mean.

The difference from baseline in mTSS at 48 weeks is 0.1 (95% -0.26, 0.46) which is 0.1 +/- 0.36. Therefore, the NI margins are 0.1 +25% *0.36=0.1 + 0.09 = 0.19 and 0.1 + 75% *0.36= 0.1+ 0.27 = 0.37.

The rate of progression at 48 weeks is 11.3% (13 /115) with a 95% CI of 6.2% to 18.6%. The upper bound can be written as 11.3% + 7.3%. Therefore, the NI margins are 11.3% + 7.3%. *25% = 11.3% + 1.8% = 13.1% and 11.3% + 7.3% * 75% = 11.3% + 5.5% = 16.8%.

Immunogenicity

A27. Please explain in more detail and provide greater justification for the statement that tofacitinib will be less likely to be associated with immunogenicity. (page 25 of the company submission)

Pfizer Response: Immunogenicity describes the phenomenon specific to protein-based therapeutics, where recombinant proteins or monoclonal antibodies are recognized as antigens, stimulating a humoral or cell-mediated immune response. In vaccines, this response confers the associated therapeutic benefit, but with biologic DMARDs used in the management of systemic inflammatory disorders, this is an undesirable consequence, which can impact the therapeutic efficacy of these agents. The resulting anti-drug antibodies produced can work through neutralisation or can reduce drug efficiency by hastening clearance or preventing access to target tissue. This can translate to secondary failure of therapies, and thus therapeutic drug-monitoring (TDM) can be adopted, to detect and mitigate this complication by ensuring plasma concentrations are at therapeutic levels.

Tofacitinib is a synthetic small molecule with a molecular weight of ~ 500Da, in contrast to biologic protein molecules, which are typically >1kDA. Tofacitinib would not therefore be expected to be associated with immunogenicity. This view has been widely accepted by the clinical and scientific community and cited in multiple independent expert review articles (De Vries et al., 2017; Danese et al., 2016; Pouillon L et al., 2016), including in relation to PsA (Yiu et al., 2016). This has been corroborated by PK/PD data for tofacitinib studied in patients with ulcerative colitis, where the plasma concentration of tofacitinib reaches steady state within 24 hours of the start of therapy and remains stable over the course of maintenance treatment (Mukherjee et al., 2017). Within dosing groups, small variations in plasma concentration at 52 weeks did not correlate with changes in remission status, supporting the view that tofacitinib does not provoke an immunogenic response, and that TDM is unnecessary in patients treated with tofacitinib. To our knowledge, no case studies have been published reporting immunogenicity associated with tofacitinib in any of its indications, which includes 22,390 patient years' experience in rheumatoid arthritis.

Regulatory authorities have also accepted this position: the US FDA and EMA developed specific guidance in 2014 and 2015, respectively, to mandate assessment of immunogenicity as a condition of approval of a therapeutic protein, defined by the FDA as polypeptides (greater than 40 amino acids) whose active components are derived from a biological source by being produced in microorganisms and cells (humans and animals) using biotechnology. As synthetic small molecules, JAK inhibitors that have been filed with the FDA and EMA since the introduction of this guidance were not required to be assessed for immunogenicity as part of their development programme (FDA Briefing Document, 2018). The recent cross-discipline team review taken as part of the FDA Arthritis Advisory Committee Meeting (April 2018) for baricitinib explicitly stated "as an orally administered small molecule, baricitinib is not expected to be associated with immunogenicity" (FDA Briefing Document, 2018).

There is mounting evidence that synthetic DMARDs and immunomodulators such as methotrexate and azathioprine may confer properties to actually reduce the immunogenicity associated with biologics (Jani et al., 2014). Mechanistic data specific to tofacitinib suggests that tsDMARDs may also benefit from similar properties (Onda et al., 2014).

References

Danese S, Grisham M, Hodge J, Telliez JB. JAK inhibition using tofacitinib for inflammatory bowel disease treatment: a hub for multiple inflammatory cytokines. American journal of physiology Gastrointestinal and liver physiology. 2016;310(3):G155-62.

De Vries LCS, Wildenberg ME, De Jonge WJ, D'Haens GR. The Future of Janus Kinase Inhibitors in Inflammatory Bowel Disease. Journal of Crohn's & colitis. 2017;11(7):885-93.

Jani M, Barton A, Warren RB, Griffiths CE, Chinoy H. The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. Rheumatology (Oxford, England). 2014;53(2):213-22.

Mukherjee A, Deng C, Xie R, Martin SW, Chan G, Moscariello M, et al. Mo1780 Tofacitinib Pharmacokinetics and Durability of Drug Exposure in Moderate to Severe Crohn's Disease Patients in Phase 2 Induction and Maintenance Studies. Gastroenterology. 2016;150(4):S774.

Onda M, Ghoreschi K, Steward-Tharp S, Thomas C, O'Shea JJ, Pastan IH, et al. Tofacitinib suppresses antibody responses to protein therapeutics in murine hosts. Journal of immunology (Baltimore, Md : 1950). 2014;193(1):48-55.

Pouillon L, Bossuyt P, Peyrin-Biroulet L. Tofacitinib Is the Right OCTAVE for Ulcerative Colitis. Gastroenterology. 2017;153(3):862-4.

US Food and Drug Administration. FDA Briefing Document. Arthritis Advisory Committee Meeting. NDA 207924. Baricitinib Janus Kinase (JAK) inhibitor for RA 2018 [Available from: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM605061.pdf.

Yiu ZZ, Warren RB. Novel Oral Therapies for Psoriasis and Psoriatic Arthritis. American journal of clinical dermatology. 2016;17(3):191-200.

Section B: Clarification on cost-effectiveness data

Withdrawal

B1. **Priority question**: The model assumes the same rate of withdrawal for tofacitinib as used in previous appraisals of biological DMARDs. Please provide additional evidence and justification to support this assumption given the different mechanism of action and mode of delivery.

Pfizer response: Overall, tofacitinib 5 mg BD has been shown to be an effective treatment for patients with active PsA who previously had an inadequate response to csDMARDs and were TNFi-naïve, and for patients who previously had an inadequate response to a TNFi.

Among those patients who had previously had an inadequate response to at least one csDMARD and were TNFi naïve, OPAL Broaden revealed efficacy of tofacitinib 5 mg BD that was similar in a numerical sense to adalimumab for the primary outcomes and radiographic progressor/non-progressor rates (although it is important to note that the study was not powered to formally compare tofacitinib with adalimumab).

Results from the LTE study, OPAL Balance, demonstrated that the efficacy of tofacitinib was generally sustained over 24 months (January 2017 data cut, FAS) with respect to signs and symptoms of PsA and physical functioning. An earlier interim data-set from OPAL Balance [redacted] Tofacitinib 5mg BD is also well tolerated in patients with active PsA and has a safety profile which is broadly consistent with other NICE-approved bDMARDs (see **Section B.2.11** of the Pfizer submission).

The results of OPAL Broaden (Mease et al., 2017; see reference 87 in the Pfizer submission) indicated that the total rate of withdrawal for tofacitinib 5mg BD over the 12-month trial period (10%) was consistent with that observed for adalimumab (11%; the most commonly prescribed bDMARD for PsA in the UK; see section 5.1, Table 7 of Budget Impact Analysis). Similarly, the total withdrawal rate in OPAL Beyond (Gladman et al., 2017; see reference 89 in the Pfizer submission) for tofacitinib 5mg BD was 7% over the 6-month trial period. These data would indicate that the assumptions regarding withdrawal rates for tofacitinib in our economic analyses were justified.

a) In addition to the withdrawal data requested in Question A19, please provide withdrawal data for patients whose disease initially responds to treatment (as assessed by PsARC) and subsequently withdraw due to loss of efficacy or adverse events.

Pfizer Response: Tables reporting the discontinuation rates and reasons for discontinuation among those patients whose disease initially responds to treatment (as assessed by PsARC response at 3 months) from OPAL Broaden and OPAL Beyond accompany this response. These are provided by treatment group (see tables 00099.2.1; 00099.2.2.1; 00099.2.2.2 for OPAL Broaden, and 00099.3.1; 00099.3.2 for OPAL Beyond). Please note that the contents of these tables are commercial-in-confidence.

b) Please provide a revised version of the model that allows a separate withdrawal rate to be specified for tofacitinib

Pfizer Response: A revised version of the models that allow a separate withdrawal rate to be specified for tofacitinib accompanies this response. These models incorporate the corrections to the NMA data.

c) Please present an additional scenario which uses the rate of withdrawal based on the data from the OPAL trials for tofacitinib

Model results using tofacitinib 5mg BD-specific withdrawal rates estimated from data presented in the publications and CSRs for OPAL Broaden and OPAL Beyond are presented at the end of this document. (using methodology reported in Briggs et al 2011) In OPAL Broaden, [redacted] discontinued treatment with tofacitinib 5mg BD over 12 months. Assuming a constant rate with respect to time, we have estimated a 3-monthly probability of discontinuation of [redacted]. Similarly, a 3-month probability of discontinuation has been estimated for adalimumab of [redacted] indicating a probability of withdrawal that was numerically similar to that of tofacitinib 5mg BD.

In OPAL Beyond [redacted] discontinued treatment with tofacitinib 5mg BID over 6 months. This gives a 3-month probability of discontinuation of [redacted]

Please note, these probabilities are based on discontinuation rates including the first 3 months of the OPAL Broaden and OPAL Beyond clinical trials and converted to time constant probabilities. The approach used in TA445 utilised an estimated probability of discontinuation after the first 3 months of treatment (see Rodgers et al 2011; reference 111 in the Pfizer submission). Thus, the approach in our response to this question may have elevated (relatively) the time constant probabilities for tofacitinib 5mg BD.
In sub-populations 2 and 4 the OPAL Broaden discontinuation rate is applied to tofacitinib 5mg BD. In sub-population 3 the OPAL Beyond rate is applied to tofacitinib 5mg BD. These scenarios have been generated using a version of the model which has been updated to incorporate the correct NMA data, as per question B1.

Please see the end of the document for a section on 'Updated Cost-Effectiveness results'.

Briggs A, Claxton K and Sculpher M. Decision modelling for health economic evaluation, Oxford: Oxford University Press 2011; p51

Quality of Life

B2. **Priority question:** Please provide appendix Q, referred to in the company submission.

Pfizer Response: Appendix Q accompanies this clarification response. Please accept our apologies for the unintentional exclusion of this appendix from the submission package.

B3. **Priority question**: The published protocol for OPAL Beyond states that EQ-5D data were collected. Please provide the results of any EQ-5D assessments in OPAL Broaden, OPAL Beyond and OPAL Balance including sample sizes, missing data, follow up points, EQ-5D scores at baseline and follow up for each treatment and details and results of any statistical tests performed.

Pfizer Response: Tables reporting the EQ-5D assessments in OPAL Broaden, OPAL Beyond and OPAL Balance accompany this response. See tables 00098.1; 00098.2; 00098.3; 00098.4; 00082.1; 00082.2; 00082.3; 00082.4; 00082.5; 00082.6; 00082.7; 00082.8. These tables are commercial in confidence

B4. **Priority question**: Please provide the utility algorithm, derived from the data collected in the OPAL trials, used in the scenario analysis reported in appendix R. Please justify the specific covariates and regression function used.

Pfizer Response: A main effects model and an interaction effects model have been separately estimated for OPAL Broaden and OPAL Beyond (producing four utility algorithms in total). In the main effects models, HAQ-DI and PASI scores are included as covariates, while in the interaction effects models, an interaction term for HAQ-DI and PASI is also included. A mixed effects regression function was used to account for repeated measures in the data.

These analyses were designed to match the analysis requested by the Assessment Group during TA199 (NICE TA199; see reference 2 in the Pfizer submission). Statistical models with and without the interaction term were estimated, as an interaction term had been included in previous analyses. The inclusion of these terms was not found to improve goodness-of-fit. We therefore used the main effects model in our scenario analyses

Information regarding these algorithms is detailed in the previously-missing Appendix Q, which now accompanies this clarification response.

Probabilistic Sensitivity Analyses

B1. **Priority question**: The code for the probabilistic sensitivity analyses (PSA) is complex and difficult to validate. Please provide the following information:

- A step by step description of how the VBA code implements the PSA, including how the Monte Carlo sampling is implemented
- Confirmation of whether the simulations are done simultaneously for all comparators or separately for each individual comparator.
- Detailed annotations within the VBA code for each step.

Pfizer Response: Simulations are performed simultaneously for all comparators. Each of the multiple engines are recalculated simultaneously for each Monte Carlo sample. The results of each iteration are drawn from all engines and recorded in the 'Simulations' sheet. Where possible, correlation between parameters is preserved. For example, a single 'row' of CODA output is sampled for all therapies in a given iteration of the model during simulation.

Description of how the VBA code implements PSA:

In sheet calculations

- The PSA is implemented through the VBA code and through the 'Control sheet' (Sheet13) where all inputs and their distributions are listed.
    - Columns B, C, D and F of the control sheet list the name, current value, default value, and location of each input in the model, respectively.
    - Column G allows a statistical distribution to be assigned to each parameter for the PSA. The possible distributions include: 'not varied', 'CODA', 'normal', 'log-normal', 'beta', 'gamma', 'multivariate normal', and 'dirichlet'.
    - Column T is where the probabilistic values for each parameter are calculated. The formula in this column uses IF statements to read which distribution is listed in column G and randomly generate a probabilistic value for each parameter.
        - For parameters which are sampled from CODA, the random sampling is performed on the 'CODA' tab.

Description of VBA procedure

- The first part of the VBA code, up to line 57, sets up the variables and ranges, and then checks if the model inputs (currentArray) are set to the default values (defaultArray). The VBA includes code for a message box to notify the user if there are values not set to default, as these will be overwritten if they proceed. This means that the PSA cannot be run with non-varied values not set to their default value.
- The 'restoreAll' macro is called, and this replaces all model inputs with the default values listed in the control sheet (line 64).

- The range ‘PSA_flag’ is set to true (line 67). This ensures that the NMA data is taken from the CODA.
- The start time is recorded on the simulations sheet (Sheet12) to check the run time of the PSA (line 70-71).
- Any previously recorded PSA results are cleared from the simulations sheet (line 74-77).
- Each model input is then replaced with a link to the probabilistic values in column T of the control sheet (line 80 to 82). Column T calculates a probabilistic value for each input, with a formula that uses the distribution chosen for each input. Each time the model is recalculated a new set of probabilistic inputs are generated and passed through the model.
- The Monte Carlo sampling occurs in the ‘for’ loop from sim=1 to numSim, which runs from lines 85 to 94.
    - numSim is the number of simulations stated on the Sensitivity analysis sheet.
    - The status bar is set up to show the progress of the PSA (how many simulations are completed).
    - The calculate function is called, which samples a new set of random variables to populate the model for each simulation.
    - The results from each simulation are printed on the simulations sheet in columns AA to AT. Each simulation result is printed in the next free row in this range.
- The following section of the VBA code, lines 96 to 102, hides unused columns in the range since the number of comparators can vary so all columns may not be used.
- The macro ‘runCEAC’ is called to generate the CEAC (line 105).
    - This macro runs through a number of threshold values and prints out the probabilities of cost effectiveness for each treatment at each threshold into columns C to L of the simulations sheet.
- The end time is recorded on the simulations sheet indicating how long the PSA takes to run (line 108-109).
- The number of simulations is recorded on the simulations sheet (line 112).
- The range ‘PSA_flag’ is set to false. This restores the NMA data choice to the selected values (line 118).
- ‘restoreDefaults’ is called to restore the ‘currentArray’ to the values in the ‘defaultArray’, returning the model to the deterministic base-case (line 121).

Additional annotation of the VBA code has also been provided in the updated versions of the electronic model submitted alongside these responses.

Inconsistencies between the economic model and the company submission

B2. **Priority question**: There are a number of inconsistencies between the data used in the economic model and that reported in the company submission (listed below). Please clarify which values are correct and if necessary provide a version of the model using corrected values.

- In populations 2 and 3, the probability of PsARC, PASI and ARC response for Ustekinumab is inconsistent between the company submission (Tables 25 and 27) and Appendices (Table E62) compared to the NMA data used in the model (Sheet 'NMA Data'; Rows A10:AL10, A28:AL28, A49:AL49, A70:AI70, A120:AL120, A138:AL138, A156:AL156).

- The results of the base case model for ACR response in subpopulation 3 (Sheet 'NMA Data'; Rows J115:M166) are not consistent with what is reported in the company submission (Table 25).

- For populations 2-4, (Sheet 'NMA Data'; (Rows Y23:AL33, Y44:AL44, Y51:AL51 and Y65:AL75), the probability of PASI response is not consistent with what is reported in the company submission (Table 27 in submission or Tables E67 and E69 in Appendix E). On the same sheet (Rows Y115:AB125) the probability of ARC 20 response does not match the values in Table 27 of the company submission.

- Table 24 in the company submission states that model E1 FE with 24-wk data was selected as the 'pessimistic' case for the ACR endpoint and model E1 FE without 24-wk data was selected as both the optimistic and base case for the ACR response. For populations 2-4 (Sheet 'NMA Data; Rows Y115;AL165), it seems that model E1 FE without 24-wk data was selected for the base case and 'pessimistic' case while model E1 FE with 24-week data was used for the 'optimistic' case data.

- In population 2-4, the company submission and appendices do not report ARC response for secukinumab 300mg when presenting the summary results for the biologic experienced NMA data. This data is reported in Sheet 'NMA Data' (Rows Y125:AL125, Y143:AL143, Y161:AL161). The source of this data is not detailed; please provide these details.

Pfizer Response: The response below incorporates the corrections to the NMA noted in the response to question A14. Please note, to assist interpretation of the impact on the model results from changes to the economic model, this response presents results incorporating the PAS submitted as part of the 06 April submission. An update to this PAS has been approved by

NHSE and PASLU; results incorporating this new PAS are presented in the PAS Template, which accompanies this response.

The differences in the NMA data between the economic model and company submission are caused primarily by differences in the outcomes reported. In the company submission, the median values have been presented (as per TA445), while the economic model uses the mean values, as these are deemed more appropriate for economic modelling (as per TA445; see reference 3 in the Pfizer submission). For the bDMARD naïve analysis, the median values were mistakenly copied into the model in some instances (instead of the mean values from the NMA). However, the values presented in the economic model for ustekinumab for the bDMARD naïve analysis were mean values from the bDMARD experienced NMA (which was deemed the appropriate NMA as ustekinumab was second option in the treatment sequence, usually post bDMARD) These factors resulted in inconsistencies between data in the model and those in the main company submission.

Additionally, the economic model used the incorrect version of the ACR NMAs for the pessimistic and optimistic scenarios in the bDMARD-experienced population; those reported in the company submission are correct. As ACR response rates for secukinumab 300mg (bDMARD-experienced network) were only available from the AG report for TA445 (24-week ACR response data; see appendix E, Table E8) and the base model NMA to inform the economic model was model E1 FE excluding 24-week data, these results were only used in scenario analyses, and do not affect the base-case results.

These errors have been rectified and updated versions of the model provided. The updated versions of the models contain both the mean and median NMA results.

Please see the end of the document for a section on 'Updated Cost-Effectiveness results'.

Baseline characteristics

B3. Baseline characteristics data in the model are taken from the OPAL trials. Please justify why the baseline patient characteristics from the trials included in the NMA were not used. Please provide a scenario using the baseline patient characteristics from the NMA.

Pfizer Response: The baseline characteristics from the OPAL trials were believed to represent the populations under consideration most accurately. The characteristics of PsA populations may be expected to change over time. For example, many of the earlier trials, including Mease (2000; see reference 158 in the Pfizer submission) and ADEPT (2005; see reference 157 in the Pfizer submission), do not include inadequate response to a previous DMARD in their inclusion criteria. In contrast, inadequate response to a previous DMARD does form part of the inclusion criteria for the OPAL trials (which reported in 2017); this difference reflects how standard of care has changed over time, particularly in the use of prior treatments.

The average baseline characteristics from the NMA are presented in **Error! Reference source not found.**. For the biologic naïve and experienced populations, data have been taken from trials included in Figure 8 and Figure 9 of the main company submission respectively, where they have reported the mean value of the relevant outcome.

Table 1: Comparison of patient baseline characteristics in the OPAL clinical trials and NMAs

Characteristic	OPAL Broaden	OPAL Beyond	bDMARD-naïve NMA	bDMARD - experienced NMA
Baseline age	47.90	50.00	48.71	50.03
% female	53.30%	55.30%	49.94%	54.66%
Baseline HAQ-DI	1.11	1.30	1.15	1.27
Weight	82.9	85.7	85.5	87.1
Weight (SD)	17.6	19.9	19.6	20.2

Abbreviations: HAQ-DI, health assessment questionnaire – disability index; NMA, network meta-analysis; SD, standard deviation.

Overall, the trial populations in the OPAL phase III trials and the corresponding NMAs were similar. Patients in the bDMARD-naïve NMA were older, more likely to be male, had higher HAQ-DI scores at baseline, and were heavier than patients in OPAL Broaden. In the bDMARD-experienced NMA, the difference in age was negligible, with patients more likely to be male, have lower HAQ scores, and be slightly heavier. The differences in weight may be explained by the higher proportion of men in the NMA populations.

Please see the end of the document for a section on 'Updated Cost-Effectiveness results'.

Section C: Textual clarifications and additional points

C1. The results from MEDLINE in figure D1 PRISMA on page 27, Appendix D are reported as 1404. However, the search strategy for MEDLINE in Table D2, page 16, Appendix D shows that 1415 records were retrieved. Please clarify the number of records that were retrieved from MEDLINE.

Pfizer Response: The number of records retrieved from MEDLINE was 1404, as indicated in the PRISMA. Table D2 (provided in response to question A1) has been corrected.

C2. In figure G1: Economic PRISMA flow diagram, page 23, Appendix G, the number of hits from Embase are reported as 3837 and from MEDLINE 1677. These numbers differ from those found in the search strategies for Embase (1672 hits – line 71, table G1, page 9) and from MEDLINE (557 hits – line 71, table G2, page 14). Please explain these differences.

Pfizer Response: Appendix G states that in addition to the search strategy designed for the identification of relevant economic evaluations, publications that were identified during the clinical literature search as meeting the inclusion criteria for the economic evaluation review

were also included. Appendix I states something similar with respect to cost/healthcare resource use studies. These statements should be expanded upon for greater clarity.

All citations retrieved from the main clinical search (shown search strategy tables D1 and D2) were also screened at the title/abstract stage for inclusion in the literature reviews concerned with economic evaluations (as presented in Appendix G) and cost/healthcare resource use studies (as presented in Appendix I).

A separate search strategy regarding economic evaluations and cost/healthcare resource use studies was designed to identify additional citations potentially missed in the clinical search. It is this specific search that is reflected in the search strategy tables G1 and G2 (presented in Appendix G and cross-referenced in Appendix I).

The PRISMA diagrams presented in Appendix G (Figure G1) and Appendix I (Figure I1) list only the numbers of unique citations identified within each database. In other words, these diagrams show the combined number of citations retrieved from Embase (reported in Tables D1 and G1) and the combined number of citations retrieved from MEDLINE (reported in Tables D2 and G2), but only after the exclusion of duplicate citations identified by both searches.
By way of explicit example, the citations retrieved from the Embase searches shown in the PRISMAs (=3837) is the combination of citations retrieved from the Embase clinical search (=2765) and any unique citations from the Embase economic/cost search (1072 = 1672 total - 600 duplicate citations from what was identified in the clinical search). This total is 3837 (=2765+1072), as shown in the PRISMAs.

Similarly, the citations retrieved from the MEDLINE search shown in the PRISMAs (=1677) is the combination of citations retrieved from the MEDLINE clinical search (1404) and any unique citations from the Embase economic/cost specific search (273 = 557 total - 284 duplicate citations from what was identified in the clinical search). This total is 1677 (=1404+273), as shown in the PRISMAs.

The “Duplicates removed” row of each diagram reflects the removal of duplicate citations following the combination of the searches from the different databases. It does not reflect the removal of “within database” duplicates discussed above.

Updated cost-effectiveness results

Please note, the results presented below incorporate the PAS submitted as part of the 06 April submission. An update to this PAS has been approved by NHSE and PASLU; results incorporating the new PAS are presented in the PAS Template, which accompanies this response.

This section presents the cost-effectiveness results using the corrected version of the economic model:

1. Corrections to the HAQ-DI NMA results, as presented in the response to A14; and

2. Corrections to the economic model, as presented in the response to Question B2.

For each sub-population we present the base-case results from the original model; the results using the updated HAQ-DI NMA data detailed in question A14; and the results using the updated HAQ-DI NMA and the correct versions of the NMA data, as discussed in question B2. Following this we present the results of the scenarios requested in questions B1 and B3 (i.e., accounting for differing withdrawal rates for tofacitinib 5mg BD and different baseline characteristics). These scenarios have been estimated using the updated version of the model with all corrections (updated HAQ-DI NMA [QA14] and updated NMA results [QB2]). For ease of reference the results presented here use the same PAS price as was presented in the base-case of the company submission.

People whose disease has not responded adequately to at least 2 non-biological DMARDs (sub-population 2).

Table 2: Original base-case analysis (sub-population 2)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
APR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CZP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; APR, apremilast; BSC, best supportive care; CZP, certolizumab pegol; ETN, etanercept; Ext. dom, Extendedly dominated; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib.

Table 3: Base-case analysis using the updated HAQ-DI NMA data only (sub-population 2)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
APR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; APR, apremilast; BSC, best supportive care; CZP, certolizumab pegol; ETN, etanercept; Ext. dom, Extendedly dominated; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib.

Table 4: Base-case analysis with all corrections (sub-population 2)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
APR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; APR, apremilast; BSC, best supportive care; CZP, certolizumab pegol; ETN, etanercept; Ext. dom, Extendedly dominated; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib.

Table 2, Table 3 and Table 4 present the original base-case results, the results using the updated HAQ-DI NMA and the results using the new HAQ-DI NMA and correcting errors in the NMA results in the original model.

[redacted]

People whose disease has not responded adequately to non-biological DMARDs and 1 or more TNFis (sub-population 3).

Table 5: Original base-case analysis (sub-population 3)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; Ext. dom, Extendedly dominated; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab.

Table 6: Base-case analysis using the updated HAQ-DI NMA data (sub-population 3)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; Ext. dom, Extendedly dominated; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab.

Table 7: Base-case analysis with all corrections (sub-population 3)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; Ext. dom, Extendedly dominated; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab.

Table 5, Table 6 and

Table 7 present the original base-case results, the results using the updated HAQ-DI NMA and the results using the new HAQ-DI NMA and correcting errors in the NMA results in the original model. As the update to the HAQ-DI NMA only affects the biologic naïve analysis, there are no changes to the results for sub-population 3. Similarly, the data in the biologic experienced populations already used the mean values, thus there is no change to the sub-population 3 results.

People in whom TNFis are contraindicated or not tolerated (sub-population 4).

Table 8: Original base-case analysis (sub-population 4)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; Ext. dom, Extendedly dominated; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab.

Table 9: Base-case analysis using the updated HAQ-DI NMA data (sub-population 4)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; Ext. dom, Extendedly dominated; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab.

Table 10: Base-case analysis with all corrections (sub-population 4)

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; Ext. dom, Extendedly dominated; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib; UST, ustekinumab.

Table 8,

Table 9 and Table 10 present the original base-case results, the results using the updated HAQ-DI NMA and the results using the new HAQ-DI NMA and correcting errors in the NMA results in the original model. Updating the HAQ-DI NMA reduces the ICERs vs BSC, but does not change the conclusions of the incremental analysis. Correcting the errors in the NMA data does not lead to any significant changes in results.

Withdrawal rates analysis

Table 11: Results using a tofacitinib specific discontinuation rate (OPAL Broaden) - sub-population 2

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
APR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 12: Results using a tofacitinib specific discontinuation rate (OPAL Beyond) - sub-population 3

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SEK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 13: Results using a tofacitinib specific discontinuation rate (OPAL Broaden) - sub-population 4

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 11, Table 12 and Table 13 present the results of the scenario analysis using a tofacitinib-specific withdrawal rate for sub-populations 2,3, and 4, respectively. In all 3 cases the tofacitinib strategy is associated with higher costs and more QALYs than in the base-case analysis. For sub-population 2 this results in a small decrease in the ICER and for sub-populations 3 and 4 there is a slight increase in the ICERs.

Baseline characteristics scenarios

Table 14: Results using the baseline characteristics from the NMAs – sub-population 2

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
APR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CTZ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; APR, apremilast; BSC, best supportive care; CZP, certolizumab pegol; ETN, etanercept; Ext. dom, Extendedly dominated; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib.

Table 15: Results using the baseline characteristics from the NMAs – sub-population 3

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; APR, apremilast; BSC, best supportive care; CZP, certolizumab pegol; ETN, etanercept; Ext. dom, Extendedly dominated; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib.

Table 16: Results using the baseline characteristics taken the NMAs – sub-population 4

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
BSC	[redacted]	[redacted]	-	-	-	-

Sequence	Total costs	Total QALYs	Incremental costs vs BSC	Incremental QALYs vs BSC	ICER vs BSC (£/QALY)	Fully incremental analysis (£/QALY)
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SEK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; APR, apremilast; BSC, best supportive care; CZP, certolizumab pegol; ETN, etanercept; Ext. dom, Extendedly dominated; GOL, golimumab; ICER, incremental cost-effectiveness ratio; INF, infliximab; QALYs, quality-adjusted life years; SEC, secukinumab; TOF, tofacitinib.

Table 14, Table 15 and Table 16 present the results in sub-populations 2-4 respectively using the baseline data from the NMAs. The changes in results are small, with slight increases in ICERs for sub-populations 2 and 4 and a decrease for sub-population 3. Total costs vary very little from the base-case. In populations 2 and 4 there are reductions in the total QALYs across the arms, driven by increases in baseline age and HAQ-DI. In population 3 there are increases in the total QALYs between arms, due to the decrease in baseline HAQ-DI. In sub-populations 3 and 4 there are no changes to the conclusions of the incremental analysis, however in sub-population 2 [redacted]

NICE National Institute for Health and Care Excellence

Patient organisation submission

Tofacitinib for treating active psoriatic arthritis after DMARDs [ID1220]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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 submission

- 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 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Psoriasis and Psoriatic Arthritis Alliance (PAPAA)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	PAPAA is a national charity, which provides information and support to people affected by psoriasis and psoriatic arthritis. The current incarnation followed the merger of two separate organisations, with the oldest dating back to 1992. Although the charity has no formal membership, it has a supporter register of >13,000 people which includes both patients and healthcare professionals. In a changing 21st century, activity and support has evolved with more taking place online, with most interaction via that medium. The main charity website had >850,000 page views during the past year. Regular use of feedback forms and online surveys help to direct the charity's work and how it represents its constituent group. Funding is via donations, subscriptions and from the sale of promotional items. Financial support is not accepted from the pharmaceutical industry, either as direct payment or in-kind, this includes third-party work via PR or research agencies. The organisation values its independence and feels this provides an agenda which is patient-centred and not driven by marketing or promotional activities that may be behind such support, however arms-length or segmented.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	Data for this submission has been gathered via our online surveys and direct feedback. We compile ongoing views and opinions of those who interact with us to provide a broad consensus that we think reflects the general psoriatic arthritis population that is likely to be those who would potentially qualify for tofacitinib.

carers to include in your submission?	We receive many calls via our information line and questions are often about treatments and in particular the use of biological therapies, therefore we get a lot of feedback about how these are being offered and prescribed to patients. The online quality of life survey has been running since 2014 with 261 responses to-date. Average mean age is 44 (19-69). The submissions primarily are from females (207). The survey is completed anonymously from a self-selecting group.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Given the age group affected a common theme is related to work: The following are free text entries from our survey: *"I had to retire on ill health and have had to give up nursing and now do admin work, also had to reduce hours."* *"I had to give up work aged fifty"* *"Working but exhausted end of day and particularly weak."* *"Inability to walk far affects mobility at work."* *"Off on long term sick. Constant and chronic pain"* *"Struggling to stand in front of classes for long periods of time stopped working - pain, fatigue, (1 - 1.5 hours to recoup after shower) and now brain fog"* *"I have to reconsider career choices as a result of flare up and long term joint damage."* *"I work on my feet, and sometimes it's just too painful to walk, I limp everywhere and have to take time off a lot"* *"I have had to give up working due to fingers swollen and stiff."*

	"I can no longer do any clinical GP work; this has a huge effect on my work life as my management work depends on being a GP." *"Took retirement at 52 because exhausted, affected fingers make it difficult to use a keyboard, and I have to ask for help when opening things (not doors)"* *"Can only work part time due to fatigue and flares"* *"Only been diagnosed a few months but the ability to work normally is starting to be tested."* *"My sickness rate is not good, so now redundant and looking for work, which appears to be hopeless when employers see sick record"* *"Unpredictable pain & stiffness makes working difficult to plan."* *"I'm a flight attendant and when I'm in pain it's really hard to work."* Relationships and socialising also are affected significantly, as can been seen in the following submissions: *"Fatigue causes me to sleep at weekends, so not spending time with husband & friends."* *"My family & friends have been very supportive but I'm not seeing my friends as much because I'm not socialising as much."* *"Because of the pain, intimacy is sometimes affected. Also, it is hard for others to understand the pain and fatigue that I have."* *"I am fortunate to a have very caring husband, but our lives are affected by my pain."* *"Husband has had to become my carer in many aspects and friends often do not understand how much it limits me."* *"My family have had to miss out on a lot because of me being in too much pain/ unable to do things."*

	"Fatigue and general feelings of malaise make me unable to go out and even be with friends let alone socialise." *"I'm reliant on others which I hate, unable to do some things and having to change plans at last minute if unwell."* *"I depend on my husband so much and I dislike asking for help all the time. I was the one who always helped everyone."* *"I have mood swings, and I believe my husband thinks I am lazy as I am often too tired to do anything."* *"My wife and I have struggled with coming to terms with the illness although I hope we'll stay together."* *"Can't look after my children in the same way when remitting. Feel my husband is sometimes my carer. Sex sometimes impossible"* *"My husband and I have a strained relationship as he tries to understand the fatigue, but can't."* *"My husband left me shortly after I was diagnosed. I haven't the energy to have a social life any more."*
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Dependent on the severity, psoriatic arthritis is managed with a number of treatments, singularly or in combination these include non-steroidal anti-inflammatory medicines (NSAIDs), corticosteroids (injection, orally), disease-modifying anti-rheumatic drugs (DMARDs) and targeted biologic agents. The use of physiotherapy for mobility is common as is pain management techniques. The treatments all provide differing results and are dependent upon patient preference, fears and prejudice. The use of NSAIDs often lead to gastric problems, or with targeted NSAIDs increased cardiovascular risk. Corticosteroids are associated with weight gain and risks to bone health. The use of DMARDs such as methotrexate worry patients with side-effect profiles being of concern and for younger men the limiting or abstinence from alcohol can be a reason for not wanting to start methotrexate. Biologic agents are increasingly becoming of interest to patients, as the convenient less frequent dosage helps to alleviate the burden of more regular medication, although there is concern about the long-term

	effects of these drugs from the younger population. There is also concern about failure of these agents and what happens when a drug doesn't work adequately or stops working after initial benefit. Current guidance limits use, therefore patients become anxious about what options will be available once those therapies have been exhausted.
8. Is there an unmet need for patients with this condition?	For those where therapies fail or lose efficacy, there is a need for more options. Tackling the issue of fatigue and relief from those symptoms would be welcomed as would a therapy that also provides benefit to the aspects of psoriasis such as nail disease which is very common in people with psoriatic arthritis.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	As tofacitinib is not currently routinely available within the NHS for psoriatic arthritis, we have no information on the patients and carers views of the advantages of the technology. Although a twice-day oral therapy may be seen as advantageous to some, generally patients are more interested in the benefits on symptoms with low adverse reactions.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As tofacitinib is not currently routinely available within the NHS for psoriatic arthritis, we have no information on the patients and carers views of the disadvantages of the technology.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	People who also have elements of skin psoriasis, such as nail involvement too, if tofacitinib provides benefit.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We don't believe there are issues which are considered under equality legislation that need to be taken in to account.

Other issues	
13. Are there any other issues that you would like the committee to consider?	No

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Reduction in pain, inflammation and fatigue.
- Avoid disabling consequences of psoriatic arthritis by maintaining mobility, stopping further deterioration and joint destruction.
- Symptom improvement without adverse events.
- Access and choice to a wide range of therapies
- Improve psoriasis including nails.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Tofactinib for treating active psoriatic arthritis after DMARDs [ID1220]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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 submission

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Psoriasis Association
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Patient Support Organisation and Charity. The Psoriasis Association currently has around 2000 members who help to fund the organisation via an annual fee. Other sources of income include fundraising (individuals, legacies and trusts), investments and unrestricted educational grants from the Pharmaceutical Industry for projects (there is a policy that no more than 15% of the total income of the Psoriasis Association can come from the Pharmaceutical Industry). In addition to traditional members, the Psoriasis Association regularly communicates with, or offers a platform enabling people whose lives are affected by the condition to communicate with one another via online forums on their own websites (8,400 registered users), and Social Media (16,000 people). The main Psoriasis Association website received almost 600,000 visits in 2017, and over 850 enquiries were answered via telephone or email.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	This submission has been informed by informal, anecdotal information that we hear from patients and carers themselves, through the following channels provided by the Psoriasis Association:- the Psoriasis Association website (600,000 visitors in 2017) telephone and email helpline (850 enquiries in 2017)

carers to include in your submission?	online forums (8,400 registered users in 2017) social media channels (including Facebook Group, Twitter and Instagram, 16,000 people in 2017) online surveys carried out by the Psoriasis Association questions submitted to the Psoriasis Priority Setting Parnership
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Psoriatic Arthritis is a destructive form of arthritis with a peak onset in people between 30 and 40 years of age. Owing to the age of onset of the condition (and the joints affected often being the fingers and toes right through to larger joints) impact on work, social life and relationships can be marked. Being unable to do top buttons up on a shirt can be frustrating, but being unable to change your babies nappy due to the pain and destruction of your finger joints can be utterly devastating. Many jobs now have an element of computer work associated with them, but if you have PsA in the finger joints it can be extremely difficult to do any dexterous work. For those for whom PsA affects the joints in the toes, walking can be extremely painful and therefore impacts again on the types of job an individual can do, if they can work at all. PsA, unlike other more common forms of arthritis is often worse after a period of rest, and so early morning tasks may not be possible, or would take a longer amount of time compared to someone without PsA. Symptoms of PsA vary from mild to very severe, and can include swollen fingers and toes, tendonitis (particularly in the Achilles) and joints in the back. It is a destructive form of arthritis and so without timely, suitable treatment, joints can be destroyed quickly owing to the quick onset of inflammation. Patients therefore experience pain associated with the inflammation and current destruction of their joints, but also once the flare-up has subsided are left with pain due to the damage caused by the flare. It is key then that patients should have access to the relevant therapies to prevent the destruction (hence avoiding the need for joint replacement operations) and to continue to lead a full and active life. Nail psoriasis is common in people with psoriatic arthritis, and this too can be extremely disabling, painful, and limits the tasks that a person can perform. Nail psoriasis affecting the toenails can make it difficult to wear shoes, which in turn can affect employment eligibility not to mention negatively impacting someone's quality of life. Fingernail psoriasis is painful and unsightly, limiting a person's day-to-day activities.

	One Psoriasis Association member in her 20's who has both psoriasis and psoriatic arthritis recently told us that the burden of living with pain and discomfort from both conditions, contributed to the breakdown of her relationship. "My relationship with my partner suffered as we had always been active. I was too exhausted to do anything outside of work…eventually we split, I lost the house I had bought with him and had to start again". The same young woman went on to inform us that despite training to be a paramedic, she is now physically unable to perform this role and has had to seek an office role instead.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Treatments for Psoriatic Arthritis are extremely limited and so an addition to the treatment armamentarium is most welcome. Peak onset for psoriatic arthritis is amongst those of studying / working age and so appropriate, timely access to efficacious treatments is vital in order to prevent unnecessary negative life impact. Current treatments available on the NHS can also cause restrictions on people's careers, essentially preventing them from leading a fulfilling life - a response in a recent survey carried out by the Psoriasis Association stated "I have a degree in microbiology but due to medication I now take for psoriatic arthritis I can no longer work in the field I was building my career in".
8. Is there an unmet need for patients with this condition?	Yes

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The treatment is taken orally – an online survey carried out by the Psoriasis Association found that two thirds of respondents would prefer oral medication to injection medication. The oral medication is less intrusive and restrictive on lifestyle as some of the biologic injection treatments which can impact on travelling etc. An oral treatment with good efficacy can lead to a patient being able to return to a good standard of living that reflects people who do not live with the condition. As tablets are easier to store and transport, we would hope to avoid situations such as the one a respondent to a recent Psoriasis Association survey reported:- "I couldn't go to university as I got psoriasis and psoriatic arthritis in the summer before I was due to go. As it was all new to me I needed help from my mum to manage it so I didn't accept my university place". As you can see in this case, the psoriatic arthritis is affecting both the patient and family members' lives, making the patient feel dependent at a time in life when they would otherwise be embracing independence.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients for whom other DMARDS and also biologics have failed may benefit more from the technology. However, the decision on which therapy may be most appropriate must be left to the clinician who can assess both psoriatic arthritis and psoriasis and prescribe accordingly if both conditions require treatment. Those who may also find the administering of biologics difficult owing to psoriatic arthritis effecting the hand and finger joints may find tablets to be preferable.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Tablet rather than an injection is often more preferable to patients
- Psoriatic arthritis can not only destroy the joints affected, but also the lives of those affected
- Having a treatment that can work on both the skin and joints affected by psoriasis is of importance to patient choice
- There are currently few treatments available for psoriatic arthritis, and so an extension to the treatment armoury is most welcomed.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Tofacitinib for treating active psoriatic arthritis after DMARDs [ID1220]

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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**James Galloway**
2. Name of organisation	**King's College London**

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):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The intention of therapy is to improve quality of life, prevention progression of disease and subsequent disability.
8. 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.)	Responses in psoriatic arthritis are typically described in terms of ACR20 response – which implies at least a 20% improvement across a series of domains including how many joints are actively inflamed. Existing targeted therapies that we use typically demonstrated ACR20 responses between 40 and 60%. There are limitations to ACR20 use in PsA, and several other scoring systems exist, although these are less frequently used as a primary endpoint in RCTs.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. I typically start 2-3 patients a month on a targeted therapy for PsA. Despite a growing number of available drugs, there remain patients who fail to respond adequately. In addition, the majority of our current options are parenteral preparations – which can be challenging for some individuals.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	For active PsA, we typically treat first with oral DMARDs (e.g. methotrexate, leflunomide). Inadequate response may lead to either combination therapy or switching across agents. Persistent active disease (>3 active joints/active enthesitis/dactylitis) would then prompt escalation to targeted therapy. The existing options in the NHS include anti-TNF, anti-IL-17, anti-IL12/23 and apremilast (phosphodiesterase inhibitor). If one of these agents fails, we usually switch across to an alternative targeted therapy strategy.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE
• 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 pathways are clear, although local variation exists, driven largely by funding agreements with CCGs with respect to the costs of targeted therapy.

• What impact would the technology have on the current pathway of care?	The proposed technology would offer a further therapeutic option to patients with active PsA.
11. 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?	It is orally administered. Otherwise, conceptually – it is much the same as other strategies.
• 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.)	None. Rheumatologists are already familiar with this agent because it is licensed in rheumatoid arthritis.
12. Do you expect the technology to provide clinically	Yes

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
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I think the answer to this is addressed in the scope document accurately.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare	Easier (oral versus subcut)

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.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Testing is comparable to other targeted therapies.
16. 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	No.

quality-adjusted life year (QALY) calculation?	
17. 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. The mode of action is entirely distinct to any other licensed option for PsA. This is a significant step in our goal or personalised medicine. As we evolve the platform of drugs available, we will move closer to the model of right drug, right patient, first time. It is clear that PsA is a heterogeneous disease, and as the available treatment options grow, we will see the strengths of each agent become clear. For example, the skin / enthesitis / dactylitis responses vary across agents. Although in recent years we have seen several non-TNF options arrive on the market, none have quite had the same success with treating the articular manifestations of PsA. The two NEJM trials of Tofacitinib have shown impressive articular response data.
• Is the technology a 'step-change' in the management of the condition?	Yes.
• Does the use of the technology address any particular unmet need of the patient population?	Yes.

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Infection risk is an important side effect of all our targeted therapies. The data are now consistent that Shingles is a specific problem with JAK inhibition. The event rates in the PsA population are if anything slightly lower than the RA trials (perhaps less concurrent steroid). However, what has been clear with the RA experience is that for patients with active joint disease, the risk benefit balance remains firmly in favour of treatment. In both the RA trials and also my clinical experience, patients on JAK inhibitor therapy who develop shingles elect to continue on therapy once the shingles resolves. It is also relevant to note that the cases of shingles are no more likely to be 'serious' in people on JAKs. Having said all this, it will be crucial that adequate post marketing surveillance is undertaken (as with all targeted therapies).
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trials recruited carefully selected patients, with mean swollen joint counts of >10. This is typical of all the PsA trials that we base are existing practice on. The two NEJM trials are particularly valuable – as these include patients who were (1) DMARD failures and (2) anti-TNF failures.
• 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?	These are fairly self explanatory I think. The primary and secondary endpoints are clearly defined and appropriate to the disease.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology	No.

appraisal guidance TA340 (ustekinumab), TA433 (apremilast), TA445 (certolizumab pegol and secukinumab), TA199 (etanercept, infliximab and adalimumab) or TA220 (golimumab)?	
22. How do data on real-world experience compare with the trial data?	Hard to say – given the recent license. However, in the RA field, the real world experience is emerging in the published literature and is supports the clinical trial programme findings in that disease.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No.

23b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- I agree that there remains unmet need in PsA
- Pfizer have provided robust RCT data supporting the efficacy of Xeljanz
- Xeljanz is effective in both DMARD and anti-TNF failure settings, and has ACR20 responses comparable to other targeted therapies
- The safety profile, based on existing evidence, of Xeljanz is acceptable
-

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 active psoriatic arthritis after DMARDs [ID1220]

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Jon Packham**
2. Name of organisation	**Staffordshire and Stoke on Trent Partnership NHS Trust**

3. Job title or position	**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):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. 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 control disease activity (across all the domains of psoriatic arthritis (joints, entheses (where tendons attach to bone), spine, skin psoriasis) and thus control pain, prevent progression to irreversible damage and ensuing disability. PsA is also associated with a variety of comorbidities which increase morbidity and mortality. Treating the condition appropriately can reduce these associated comorbidities. Overall the aim of treatment is to improve quality of life.
8. 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.)	Accepted treatment response for previously approved TAs have largely been based around achievement of PsARC (PsA response Criteria) which is an adequate outcome measure and the most widely used outcome across the UK for PsA. This requires a 30% improvement in either the tender or swollen joint count (based on a 66/68 joint count) and an improvement of at least 1 point out of a 5 point Likert score in either the patient or physician global score, with no worsening of any criteria. Newer outcome measures such as MDA (minimal Disease activity) require multiple measures to be taken in the clinic which is too complicated and time consuming for the majority of centres assessing patients for response but does represent outcomes in different modalities such as skin and enthuses rather than just joints. The skin response should be measured as recommended in previous TAs such that a dramatic skin response and an acceptable joint response could allow continuation of treatment. Many clinical trials use ACR20 / 50 / 70 but this is less acceptable in the UK clinics as an outcome than PsARC

9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes There is a relative paucity of agents available to treat PsA. Non-biologic treatments eg methotrexate, sulphasalazine and leflunomide have a very poor evidence base. Although there are now 5 NICE approved TNFi, there is only one approved IL17 inhibitor (sekukinumab), one IL12/23 inhibitor (ustekinumab) and apremilast. There are now an increasing number of patients who have quite simply run out of options and are left with unremitting symptoms, a very poor quality of life and disease progression.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	DMARDs (methotrexate, sulfasalazine en, leflunomide and occasionally ciclosporin) Corticosteroids (predominantly intramuscular / intraarticular) Anti TNF therapy (etanercept, adalumimab, etc) Apremilast Ustekinumab Secukinumab
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BSR Guidelines EULAR Guidelines GRAPPA Guidelines NICE TAs NICE Clinical guideline for Spondyloarthritis
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Yes although many non-specialist clinicians continue to treat PsA like RA eg only measuring DAS scores (Disease activity scores) based on a 28 joint count rather than 66/68 joint count. Many centres will not have expertise or knowledge to adequately assess skin psoriasis.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	It will give patients more chance of achieving successful treatment of their condition. Many patients will either not respond to or develop a side effect to other agents and therefore having more agents available is vital. Additional (post DMARD) agents to anti-TNF, apemilast, anti-IL12 and anti-IL17 would be extremely useful for patients who have tried and failed these or have contraindications to these. The oral administration route of tofacitinib is currently only available for DMARDs and apremilast – so for needle phobic patients, or those allergic to parenteral preservatives, this new option becomes more important.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is likely to be used post DMARD and anti-TNF (similar to secukinumab, ustekinumab)
• How does healthcare resource use differ between the technology and current care?	Oral medication reduces need for training patients to self inject (although many will have learnt to do this with alternative biologics) Otherwise an additional choice but no other differences
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care Rheumatology centres
• What investment is needed to introduce the	None

technology? (For example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – for patients unresponsive to DMARDs, anti-TNF other biologics.
• Do you expect the technology to increase length of life more than current care?	Yes – additional ability to control the disease will lead to fewer complications related to comorbidities, cardiovascular disease, less use of steroids / NSAIDs and associated morbidity.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – further agent to choose from will offer more patients a chance of disease control
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Likely to be especially helpful in patients who are needle phobic.

The use of the technology	
14. 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.)	The same as other biologics
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Same as other biologics / TAs

16. 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?	If tofacitinib improves skin psoriasis and its impact (social, psychological, comorbidities eg depression / anxiety,) this is not particularly well reflected in QALY Other aspects of PsA such as fatigue, anxiety / depression not adequately reflected
17. 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?	Tofacitinib is a new class of agent directed at treating psoriatic arthritis and as such represents a beneficial and innovative treatment for patients who have been challenging to treat with currently available therapies.
• Is the technology a 'step-change' in the management of the condition?	Yes - as this is a treatment that is a new class of agent
• Does the use of the technology address any	This is only the second post DMARD oral medication

particular unmet need of the patient population?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects unlikely to be any more apparent than current biologics. Patients are fully consented on the potential risks and data on adverse effects should be reported by the yellow card system and hopefully soon be collected on a registry.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	yes
• 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?	Yes – PsARC, 66/68 joint score, HAQ, PASI, enthesitis and dactylitis scores
• If surrogate outcome measures were used, do they adequately predict	Many of the trials were of sufficient duration to provide some data on long term outcome (1-2 years)

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA340 (ustekinumab), TA433 (apremilast), TA445 (certolizumab pegol and secukinumab), TA199 (etanercept, infliximab and	Some ongoing trials with other JAK inhibitors (which are possibly all different from each other as the JAK/TYK pathways are more complex than 'simple' blockade of a single cytokine) and targeted IL23 inhibitor.

adalimumab) or TA220 (golimumab)?	
22. How do data on real-world experience compare with the trial data?	Little real world experience with tofacitinib in PsA in the UK (other than within trials). Tofacitinib is now used routinely in rheumatoid arthritis as a NICE approved medication, but it is not certain how responses seen in 'real world' rheumatoid arthritis will translate to psoriatic arthritis
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	None apparent (unless tofacitinib reduces axial inflammation, in which case there is a female preponderance of non-radiographic axial inflammation) With other therapies non-radiographic inflammation may not be NICE approved, whereas radiographic inflammation is approved (this probably falls outside the remit of this TA)
23b. Consider whether these issues are different from issues with current care and why.	Could be potentially similar to issues with IL-17 inhibitors (but only if helpful in axial disease)
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- PsA is a progressive, significant disease which has a major impact on a patients quality of life across all modalities including pain, disability, depression, anxiety, fatigue, inability to work and any agent which has the potential to improve this represents a major breakthrough in the treatment of this chronic disease.
- Tofacitinib would require no new assessments or resources and could be easily integrated into the pathway alongside other biologics
- Many patients with PsA are now running out of all the available biologic agents (failed due to inefficacy, loss of response or adverse events) and represent a definite unmet need.
- Tofacitinib offers an additional choice to post DMARD therapies for psoriatic arthritis

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.

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Evidence Review Group's Report
Tofacitinib for treating active psoriatic arthritis following disease modifying anti-rheumatic drugs

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Rider on responsibility for report

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Contributions of authors

Ruth Walker, Nerys Woolacott, and Nick Meader wrote the clinical effectiveness section. Aimee Fox, Marta Soares and Laura Bojke wrote the cost-effectiveness sections of the report and conducted the economic analyses. Melissa Harden wrote the sections on the search strategies. Stephen Palmer provided advice and commented on drafts of the report. Laura Bojke took overall responsibility for the cost-effectiveness sections. Nerys Woolacott took overall responsibility for the clinical effectiveness sections of the report.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all adademic-in-confidence (AIC) data are highlighted in yellow and underlined

Copyright statement

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ACR	American College of Rheumatology
ACR20/50/70	20%/50%/70% improvement in the ACR response criteria
AE	Adverse event
bDMARD	Biological disease-modifying anti-rheumatic drug
BSC	Best supportive care
CEA	Cost-effectiveness analysis
CHE	Centre for Health Economics
CHMP	Committee for Medicinal Products for Human Use
CrI	Credible interval
CSR	Clinical study report
csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug
DMARD	Disease-modifying anti-rheumatic drug
EMA	European Medicines Agency
EQ-5D	5-dimension European Quality of Life questionnaire
ERG	Evidence Review Group
HAQ-DI	Health Assessment Questionnaire-Disability Index
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
JAK	Janus Kinase
LOCF	Last observation carried forward
MCID	Minimum clinically important difference
MS	Manufacturer's submission
MXT	Methotrexate
NIHR	National Institute for Health Research
NMA	Network meta analysis

NR	Not reported
NRI	Non-responder imputation
PALACE	Psoriatic Arthritis Long-term Assessment of Clinical Efficacy
PASI	Psoriasis Area and Severity Index
PASI-50/75/90	50%/75%/90% or greater improvement in PASI score
PsA	Psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SF36	36-item Short-Form Health Survey
SJC	Swollen joint count
STA	Single Technology Appraisal
TNF	Tumour necrosis factor
tsDMARD	disease-modifying anti-rheumatic drugs targeting a particular molecular structure
WTP	Willingness to pay

1 Summary

1.1 Critique of the decision problem in the company's submission

Tofacitinib is an oral, small molecule, targeted Janus Kinase (JAK) inhibitor. A positive opinion from the Committee for Medicinal Products for Human Use (CHMP) was adopted in April 2018 for the use of tofacitinib 5mg BD, twice daily,

''in combination with methotrexate (MTX) for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy''.

The NICE scope differed from the licence in that tofacitinib could be used alone or in combination with non-biological DMARD. The CS assessed tofacitinib in combination with any csDMARD and did not restrict to the use of MTX.

The CS addressed three sub-populations, those who had not adequately responded to at least two non-biologic DMARDS, those who had not adequately responded to non-biologic DMARDS and one or more tumour necrosis factor inhibitors (TNFis), and those for whom TNFis are contradicted or not tolerated. The CS did not include a fourth sub-population that had been included in the NICE scope (those who had failed one non-biological DMARD) as there were insufficient data.

The comparators addressed in the company's decision problem matched those in the NICE scope for (1) those who had not adequately responded to at least two non-biologic DMARDS and (2) those for whom TNFis are contradicted or not tolerated. For the subpopulation, those who had not adequately responded to csDMARDS, certolizumab pegol was not addressed. The ERG agreed with the exclusion of this comparator as the RAPID PsA trial did not include all TNFi experienced patients, but only those who had initially responded to a TNFi and then lost their response [1].

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidence for the use of tofacitinib in active PsA consisted of two placebo-controlled RCT's; one for TNFi naïve (OPAL Broaden) and one for TNFi experienced patients (OPAL Beyond). Patients from these trials who received tocacitinib 10mg BD doses did not contribute to the clinical effectiveness evidence submitted by the company, as the use of tofacitinib is licenced for dose 5mg BD. Supporting evidence from a non-RCT open-label follow-up study of tofacitinib, OPAL Balance, was also presented.

OPAL Broaden and OPAL Beyond were well conducted Phase III randomised, multicentre trials. OPAL Broaden also included a comparison with adalimumab and after 3-months, patients receiving placebo were followed up on tofactinib or adalimumab to 12 months. OPAL Beyond did not include a comparison with adalimumab and after the 3 months, patients receiving placebo were followed up on tofactinib to 6 months.

Baseline characteristics were similar across both trials. The primary efficacy outcomes were ARC20 response rate at 3 months and ΔHAQ-DI at 3 months. Modified PsARC response and PASI-75 response were also included as outcomes. Radiographic assessment of joint damage was also assessed at 12 months within OPAL Broaden.

TNFi naive population

For TNFi naïve patients, OPAL Broaden demonstrated that tofacitinib 5mg BD (N= 107) was statistically significantly more effective than placebo (N=105) for the key efficacy outcomes; ARC 20/50/70, PASI70 response rate and mean ΔHAQ-DI at 3 months, but not PSARC response rate. Comparisons of tofacitinib with adalimumab show that numerically for most key efficacy outcomes adalimumab was very slightly better than tofacitinib, however the trial was not powered to test for a statistically significant difference or non-inferiority. For radiographic assessment of joint damage the proportion of progressors (change in mTSS of >0.5) was low in both treatment arms but the upper confidence interval in the population adjusted analyses (to be comparable with the ADEPT trial for adalimumab) crossed the non-inferiority margin +ndicating it was inconclusive whether tofacitinib 5mg was non-inferior to adalimumab. The ERG agreed with the FDA conclusion that there is insufficient evidence to support the assumption that tofacitinib is associated with halting radiographic progression.

Network meta-analyses across outcomes (e.g. PsARC, ACR, PASI, and HAQ changes conditional on PsARC response) found that golimumab, infliximab, and etanercept were generally the most effective treatments; followed by certolizumab, secukinumab 150, adalimumab, and secukinumab 300. Apremilast, ustekinumab and tofacitinib 5mg were consistently ranked among the lowest in effectiveness. The company found that the placebo arm of OPAL Broaden fitted poorly in their NMA models, and attributed this to the high placebo response observed in their trial. They therefore presented alternative analyses including one where the placebo arm of OPAL Broaden was excluded which also resulted in increased effectiveness estimates for tofacitinib 5mg.

TNFi experienced population

For TNFi experienced patients, OPAL Beyond demonstrated that tofacitinib 5mg BD (N= 131) was statistically significantly more effective than placebo (N=131) for the key efficacy outcomes

outcomes; ACR 20/50, PsARC response rate and mean ΔHAQ-DI at 3 months but not ACR 70 or PASI 75.

Network meta-analyses for PsARC and HAQ changes conditional on PsARC response only included ustekinumab and tofacitinib and were found to be of similar effectiveness. Tofacitinib was associated with only slightly higher HAQ changes than placebo. More treatments were included for PASI response, the results of which found that tofacitinib 5mg was among the least effective in the network meta-analysis: ustekinumab, secukinumab, ixekizumab were ranked higher and only abatacept was ranked less effective.

Adverse effects

The adverse events profile of tofacitnib in PsA patients appears similar to, and no worse than that of adalimumab. The tolerability of tofacitinib is reflected in the low rate of withdrawals due to AEs. An increased risk of herpes zoster appears to be a specific AE of tofacitinib.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The evidence for the clinical effectiveness of tofacitinib is based on good quality randomised trials and the results are likely to be reliable.

The ERG identified limitations in the generalisability of the RCT evidence to clinical practice. These were owing to a significant proportion of patients in each RCT (18% and 24%) treated in combination with sulfasalazine and leflunomide, when the marketing authorisation is for tofacitinib in combination with methotrexate (MTX) only. Furthermore, in both OPAL Broaden and OPAL Beyond the placebo-controlled phase was limited to 3 months: treatment with tofacitinib in clinical practice is long-term. Additional issues relating to generalisability included:

(1) The use of adalimumab in OPAL Broaden in combination with a csDMARD not being reflective of adalimumab in clinical practice or in other trials.
(2) The number of previous TNFis (and the specific previous TNFis) in OPAL Beyond not being reflective of the patient population in which tofacitnib will be used in current practice.
(3) [redacted], whereas the licenced dose for tofacitinib in 5mg BD.

The ERG identified errors in the implementation of the company's placebo-adjusted NMAs. Models corrected by the ERG found a more meaningful interaction between baseline risk and treatment effect than the company analyses.

1.4 Summary of cost effectiveness submitted evidence by the company

The CS submitted a decision model, which allows the comparison of multiple treatment sequences to evaluate the cost-effectiveness of tofacitinib.

The population included people whose disease has not responded adequately to two non-biological DMARDs, people whose disease has not responded adequately to non-biological DMARDs and one or more TNFis and people in whom TNFi are contraindicated or not tolerated.

For all outcomes (PsARC response, PASI response, and HAQ-DI change conditional on PsARC response), response rates for tofacitinib 5 mg BD and its comparators were taken from the network meta-analyses (NMAs), where available. Patients in the model were assumed to continue with therapy after 12 weeks if they achieve PsARC response and HAQ and PASI were assumed constant (no disease progression) for those that have a PsARC response. Withdrawal from therapy at any point after primary response was assumed to be the same for tofacitinib and all comparators. HRQoL and costs were a function of HAQ and PASI score, in addition to the costs of medication, administration and monitoring. The acquisition costs of treatments were estimated from the British National Formulary.

The original model was revised following requests for clarifications from the ERG. In their response to clarification, the company identified a data entry error for Models K1 and K2 in the bDMARD-naïve NMA. They rectified the error in the revised and corrected version. The revised version also included an updated PAS price for tofacitinib that had been approved since the original CS.

The revised results from the CS suggest that the tofacitinib 5 mg BD sequence may be a cost-effective option (at conventional willingness to pay thresholds) vs BSC for each sub-population. In each of the three sub-populations assessed, the deterministic ICER for tofacitinib 5 mg BD vs BSC was below £20,000 per QALY.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG had a number of concerns regarding assumptions and data used in the CS and economic model. In particular, the assumption that tofacitinib halts HAQ-DI progression while patients remain on treatment. The ERG is cautious of this assumption given that no long-term clinical evidence is available to support this, such as data assessing radiographic disease progression.

The ERG also had concerns about assumptions made regarding effect degradation for subsequent lines of therapy. Subsequent treatments are assumed to be as efficacious as first line, i.e. no effect

degradation is assumed. Due to the lack of flexibility in the company model, the ERG is unable to explore the sensitivity of the cost-effectiveness results to this assumption.

The ERG found errors in the NMA placebo-response adjusted models and concluded that these were incorrectly implemented. The ERG corrected the company base-case model and revisited model selection to select the ERG's preferred base-case.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Clinical Effectiveness

The CS included a systematic review of the evidence for tofacitinib and all relevant comparators and also built on a previous NICE MTA (TA445). The evidence for clincial effectiveness was derived from two well conducted RCTs, one each for TNFi naïve and –experienced patients. The trial in TNFi- naïve patients also included a comparison with adalimumab, which was very informative: in studies of bDMARDS for PsA direct comparisons with active treatments are infrequently made. To compare tofacitinib with the long list of relevant comparators appropriate NMA were conducted.

Cost effectiveness

A de novo model based on previous NICE technology appraisals was developed. This uses a model structure similar to that developed for TA445 and utilises much of the same data and assumptions. The CS presented a de novo NMA which incorporates all relevant clinical evidence for all comparators.

1.7 Weaknesses and areas of uncertainty

Clinical Effectiveness

As outlined in Section 1.3 above, the included trials had some limitations in their generalisability to clinical practice. Longer term data are required to confirm the efficacy of tofacitinib, particularly for the outcome of progression of joint disease. The trial was not powered to test whether tofacitinib was non-inferior to adalimumab and was therefore inconclusive.

Cost effectiveness

There are a number of parameter uncertainties within the company's model. The most critical of these is the assumption of zero HAQ-DI progression for PsARC responders to tofacitinib remaining on treatment, without radiographic or randomised trial data sufficient to support this assumption. The ERG also had concerns on assumptions regarding: no effect degradation, the psoriasis sub-groups and the impact of other approved PAS prices.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a range of exploratory analyses to assess the uncertainties raised in the review and critique of the manufacturer's clinical and cost-effectiveness evidence. The ERG's exploratory analyses focused on, severity of psoriasis, tofacitinib progression rates and drug costs for comparator drugs that are approved but not available publicly. The additional analyses undertaken by the ERG suggested that whilst the ICERs for all subpopulations changed in each of the scenarios, they remained within the acceptable willingness to pay threshold, compared to BSC (typically below £20,000 per QALY). The fully incremental ICERs for tofacitinib and etanercept are also within conventional willingness to pay thresholds.

2 Background

2.1 Critique of company's description of underlying health problem

The description of the underlying health problem in the company's submission was appropriate and relevant to the decision problem under consideration. Psoriatic arthritis (PsA) is an inflammatory condition with onset usually occurring between 30 and 50 years of age. Clinical manifestations are heterogeneous and may include both articular (joint) and non-articular disease features. The CS states patients have an onset of psoriasis occurring 7 to15 years prior their PsA diagnosis [2]. PsA is a chronic, progressive condition leading to irreversible joint damage and is additionally associated with a range of comorbidities including hypertension, hyperlipidaemia, depression, fibromyalgia and type II diabetes [3]. The five health domains of pain (in the joints and spine), skin problems (including itching), fatigue (both physical and mental), ability to pursue work and leisure activities, and functional capacity are identified as the most important from the patients' perspective [4].

2.2 Critique of company's overview of current service provision

The manufacturers' overview of current service provision is broadly appropriate and relevant to the decision problem under consideration. NICE clinical guidance (NG65) is outlined in the CS and in full in CS Appendix L; in addition guidance from the European League Against Rheumatism (EULAR), the British Society for Rheumatology (BSR) and the Group for Research and Assessment for Psoriasis and Psoriatic Arthritis (GRAPPA) is also detailed in the CS. Clinical guidelines for PsA emphasise the control of symptoms, prevention of structural damage, and normalisation of functional and social participation and propose disease remission or low/ minimal disease activity as the therapeutic treatment goal.

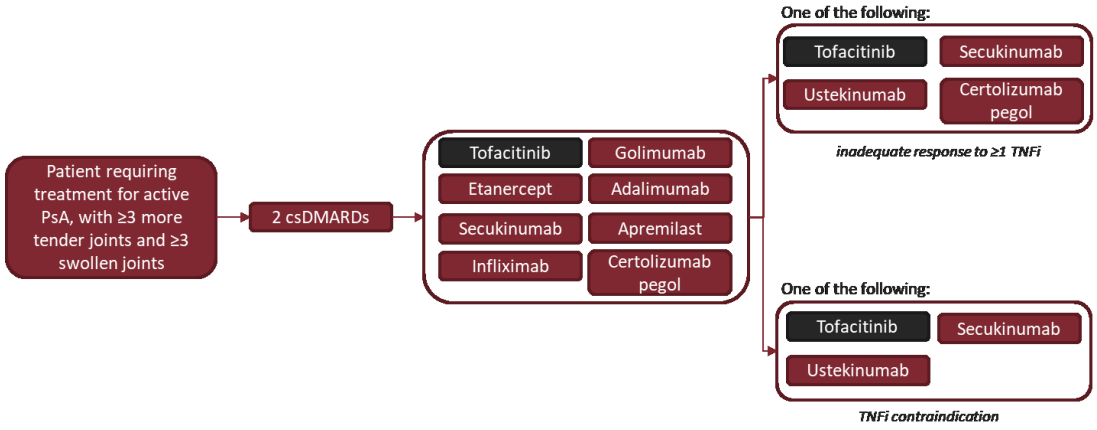
The CS states the proposed positioning of tofacitinib (Figure 1) is after conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) as an alternative to other currently recommended biologic disease-modifying anti-rheumatic drugs (bDMARD/tsDMARDs), after treatment failure or for those intolerance or contraindication to tumour necrosis factor alpha inhibitors (TNFi).

The rationale in the CS for the position of tofacitinib as an alternative to other currently recommended treatment options, for patients with active PsA who have had an inadequate response to previous treatments (csDMARDS and TNFis), was made on the basis of providing a treatment with the following characteristics:

- Oral route of administration
- A novel mechanism of action

- A proven efficacy profile across multiple PsA domains
- An acceptable safety profile

Figure 1 : Proposed Positioning of Tofacitinib in the Treatment Pathway (CS Figure 1)



The CS includes a section on problems associated with current use of bDMARDs in clinical practice (p23-24 CS). The problems highlighted are: patients' dissatisfaction, limitations associated with administration by injection or infusion, and sub-optimal treatment persistence associated with current therapies. The CS states there is a need for an (additional) oral treatment option for TNFi-naïve and TNFi-experienced patients.

The evidence in CS Section B.1.3.3 was largely taken from the Multinational Assessment of Psoriasis or Psoriatic Arthritis (MAPP) survey of patients. It is cited in the CS that bDMARDs were burdensome primarily due to the fear and anxiety associated with injections and the physical preparation for self-injection (26%), inconvenience (15%), adverse events (15%), pain/discomfort (7%), and a lack/loss of effectiveness (2%), and that 85% of patients report a need for better therapies for the treatment of PsA. The ERG notes that in the MAPP survey, only 21% of participants contributing to the 'treatment burden' outcome had PsA. Furthermore, the ERG notes that on the whole, the evidence from this survey does not fully support the suggestion that oral therapies are any better tolerated than other biologic therapies, or that injection site reaction, needle fatigue or injection anxiety played a major role in the discontinuation of treatments administered subcutaneously or via infusion. The ERG also notes that in the MAPP study, overall discontinuation rates were higher with

traditional oral therapies compared to biologic therapies (57% to 45%), with reasons for discontinuation between the two being similar: safety, tolerability or a lack or loss of effectiveness.[5] In a previous ERG report for the oral therapy apremlist for PsA, the ERG also noted that as the MAPP study was a based on a community cohort, rather than a pure hospital cohort where more severe disease is likely, the direct applicability of these findings is questionable: patients with milder symptoms are unlikely to tolerate the adverse effects of treatment as well as patients with more severe symptoms or disease. Furthermore, the number of UK patients in the survey was small (around 12%).

The CS also cites evidence from a U.S based survey of 468 patients. This choice-based conjoint survey determined patient preferences for treatment modalities for PsA and was mailed to 2,800 randomly selected patients enrolled in Humana Inc. Medicare and commercial plans (response rate 16.7%). Across both types of health plan, oral formulation was preferred relative to self-injection and intravenous routes of administration, and lower cost formulations were preferred. Results from this survey are available only in abstract form and average importance scores are presented, where the average score for 'route of administration' is highest for Medicare patients and average score for 'cost to you' is highest for commercial patients. The extent to which these findings are generalizable to UK patients is unknown.[6]

The clinical advisor to the ERG thought that oral treatment was not likely to be an important advantage from a patient's perspective. Whilst treatment requiring infusion such as infliximab, has the potential to be more burdensome to PsA patients, biological therapies requiring self-administered weekly or bi-weekly subcutaneous injection (etanercept administered once weekly and adalimumab administered once every two weeks),[7] may be less so. Furthermore, adherence and compliance with twice-daily tablets may well be poorer than to less frequent injections, and the clinical monitoring of adherence to tablets likely to more difficult than that of adherence to biologic therapies. Considering this, the need for an (additional) oral medication option for the treatment of PsA may not be as pressing as the CS suggests. In addition, the ERG notes that due to the requirment for tofacitinib to be given concomitantly with MTX (which many patients self-administer as a subcutaneous injection), treatment will not necessarily avoid an injection-based administration.

The CS states that among patients treated with TNFis, treatment persistence is low owing to a lack of response and, or tolerance to TNFis, implying the need for interventions with alternative mechanisms of action in TNFi-IR patients. The CS states that 30-50% of patients discontinue their index TNFi during the first treatment year. The CS cites evidence from a Danish cohort (2000-2009); stating 44% of patients discontinued their index TNFi therapy during the first year. The ERG notes that the cited figure of 44% of patients refers to those who discontinued TNFi therapy over the whole course of the study (median follow-up 2.9 years). One-year drug survival was in fact 70%, with two-year survival

57% [8]. The CS also states that the British Society of Rheumatology Biologics Register (BSRBR) indicates that only 59% of patients remain on their first TNFi for PsA after three years of treatment.[9]The ERG identified a recently published analysis of the UK based BSRBR data (625 PsA patients), which reported long-term persistence of etanercept, infliximab and adalimumab at 3, 5 and 8 years. Etanercept and adalimumab rather than infliximab were associated with better five-year persistence. At five years 46.7% were still on their initial TNFi treatment. Furthermore, at eight years, 33% remained on the first TNFi, 16% on the second and 12% on the third, and only 5% of patients were on a non-TNFi biologic and 10% not on a biologic treatment [10]. This suggests that within the UK, whilst patients may switch treatments, discontinuation from all biologic therapy is low at 8 years. In TNFi-IR patients, the extent to which issues with drug survival translate into the requirement for additional treatments options may be less than the CS suggests.

The CS also states that tofacitinib, as a small molecule JAK inhibitor would not be expected to induce any immunogenicity, as is associated with infliximab and adalimumab. Additional justification for this was provided in the company's response to points for clarification. This stated that the lack of association with immunogenicity was due to the lower molecular weight of tofacitinib compared to bDMARD's. The clinical advisor to the ERG advised that in clinical practice immunogenicity is not a significant issue.

Overall, the ERG acknowledges the novel mode of action of tofacitinib, but suggests that the company may have overstated the need for an oral treatment option for PsA. The efficacy relative to existing therapies is probably the key factor when deciding whether or not to use tofacitinib.

The clinical advisor to the ERG suggested that given there is limited knowledge of the use of ofacitinib in clinical practice, it would likely be reserved for an end of line treatment or possibly for specific individuals with certain clinical characteristics, for whom TNFis are contraindicated or not tolerated.

3 Critique of company's definition of decision problem

3.1 Population

The population stated in the CS was:

'Adults with active PsA whose disease has not responded adequately to previous DMARD therapy or for whom DMARDs are not tolerated or contradicted'.

This matches the NICE scope and accurately reflects the marketing authorisation.

3.2 Intervention

The intervention stated in the CS was:

'Tofacitinib (in combination with a csDMARD)'

This differs from the NICE scope that states 'tofacitinib (alone or in combination with an csDMARD)'. The marketing authorisation is for tofacitinib in combination with methotrexate (MTX) only. The clinical effectiveness of tofacitinib was informed by trials some including patients who were treated in combination with sulfasalazine and leflunomide. The licenced dose of tofacitinib is 5mg BD twice daily.

3.3 Comparators

The comparators stated in the CS are for three sub –populations (sub –populations 2, 3 and 4):

2 – For people whose disease has not responded adequately to at least 2 non-biological DMARDs: bDMARDs; apremilast; best supportive care.

3 – For people whose disease has not responded adequately to non-biological DMARDs and 1 or more TNFis: ustekinumab; secukinumab; best supportive care.

4 – For people in whom TNFis are contraindicated or not tolerated: ustekinumab; secukinumab; best supportive care.

This differs from the final scope issued by NICE that included comparators separately for one additional sub –population (sub –population 1):

1 – For people whose disease has not responded adequately to 1 non-biological DMARD

- Non-biological DMARDs

The CS states there was insufficient data to subdivide data from patients who had failed 1 non-biological DMARD and those who had failed 2 non-biological DMARDs (sub –population 1 and sub-population 2 in the NICE scope). Therefore, the company has not included this population in the submission. The ERG agrees with this and thinks it is reasonable.

Comparators for sub-populations 2, 3 and 4 in the decision problem addressed in the CS match those stated in the final NICE scope, expect for certolizumab pegol, which has been excluded from sub-population 3. The CS states this is because the data available from the RAPID PsA trial informs only a subset of patients in this sub-population. The ERG agrees with this: RAPID PsA did not include all

TNFi experienced patients, but only those who had initially responded to a TNFi and then lost their response.[1]

3.4 Outcomes

The outcome measures included in the decision problem addressed by the company were:

- Disease activity: ACR20, ACR50, ACR70, ACR response criteria components, PASI50/75/90, PsARC, MDA
- Functional capacity: HAQ-DI, HAQ-DI conditional on PsARC response status
- Disease progression: van der Heijde-mTSS
- Periarticular disease (for example, enthesitis, tendonitis, dactylitis): DSS, LEI, SPARCC
- Health-related quality of life: SF-36 (physical functioning component), FACIT-F (total score), DLQI, ISI
- Mortality
- Adverse effects of treatment
- EQ-5D: provided in the company's clarification response

These are consistent with those in the final scope issued by NICE.

3.5 Other relevant factors

No equity issues are anticipated should tofacitinib be recommended for used in England and Wales.

The patient access scheme (PAS) will provided a simple discount of [redacted] (discounted price of £[redacted] per 5mg 56-tablet pack) to the list price of tofacitinib, with the discount applied at the point of purchase or invoice.

4 Clinical Effectiveness

This section contains a critique of the methods of the review(s) of clinical effectiveness data, followed by a description and critique of the trials included in the review, including a summary of their quality and results and the results of any synthesis of studies.

4.1 Critique of the methods of review(s)

The CS included a systematic review across the intervention of interest (tofacitinib 5 mg) and all relevant comparators. The methods of the review are discussed in the sections below.

4.1.1 Searches

The search strategy used by the company to identify 1) relevant clinical data on the use of tofactinib for the treatment of PsA and 2) relevant clinical data regarding the clinical effectiveness of other existing treatments for PsA to be used in a network meta-analysis (NMA), were described in full detail in Appendix D.

The electronic databases MEDLINE, MEDLINE Daily, MEDLINE In Process, EMBASE and the Cochrane Library (including the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Cochrane Central Register of Controlled Trials (CENTRAL), NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment Database (HTA)) were searched on 20th October 2017. The database searches were restricted to publications in English. The search in EMBASE was restricted to 1996 onwards, however MEDLINE was searched back to 1946.

Manual searches of sixteen conference proceedings were conducted for the years of 2015-2017 and publicly available information from the following HTA bodies were searched: National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), Common Drug Review (CADTH CDR) and Pharmaceutical Benefits Advisory Committee (PBAC). In addition, the company searched the reference lists of identified systematic reviews and recent NICE Technology Appraisals for treatments of PsA.

The searches were mostly appropriate, however some weaknesses were identified by the ERG, which may have affected the comprehensiveness of the search. Appropriate electronic databases were searched to identify relevant published literature and a selection of resources were searched to find unpublished literature. However, the company did not search any trials registers to identify relevant reports of unpublished trials (ongoing and completed) of treatments for PsA. It is therefore a

possibility that any unpublished trials, particularly of comparator studies, could have been missed by the searches presented in the company submission.

The structure of the database search strategies was appropriate, consisting of terms for PsA combined with terms for the drugs used to treat PsA: tofacitinib, abatacept, adalimumab, etanercept, golimumab, infliximab, certolizumab pegol, ustekinumab, secukinumab, ixekizumab, and apremilast. The ERG notes that abatacept and ixekizumab are not relevant comparators in this appraisal. However, the ERG agrees it is appropriate to search for trials studying these treatments in PsA to be included in the systematic review and network meta-analyses. Also, the ERG noted that the biosimilar Resima (also known as CT-P13) was missing from the search strategies. The search strategy for the Cochrane Library in Table D3 was found to have missed searches for one of the comparator drugs abtacept. Therefore, any unique studies on abtacept for PsA contained in the Cochrane Library, but not present in EMBASE or MEDLINE, would not have been identified.

The search strategy for MEDLINE (Table D2) provided in the company submission was found to contain reporting errors at lines 4, 12, 20, 22, 24. These search lines were for medical subject headings that do not exist in MEDLINE. However the company provided a corrected MEDLINE strategy (in their responses to the points for clarification) to show that these search lines were searches of the "multi-purpose" (mp) field and author keywords (kw) field and not medical subject heading searches. In addition, the company clarified that the actual number of hits retrieved from the MEDLINE search was 1404 and not 1415 as originally reported at line 33 of the MEDLINE strategy (Table D2). These types of reporting errors could have been avoided by copying and pasting the search strategies from each database at the time of running the search and presenting these strategies without editing in the report. This is recommended in CRD's guidance for undertaking reviews in health care and helps increase transparency of the searches.

The EMBASE search strategy contained a line to remove conference abstracts from the search results. Although manual searches of relevant conference proceedings were carried out by the company, these were limited to those from 2015-2017. EMBASE could have provided results of relevant conference abstracts prior to this date. It was also noted that the EMBASE strategy did not include searches of the drug trade name field (tn). Searching in this field could have improved the comprehensiveness of the EMBASE search.

4.1.2 Inclusion criteria

The inclusion criteria for the systematic review specified randomised control trials (with parallel design) of tofactinib, bDMARDs and the PDE-4 inhibitor apremilast, for the treatment of active PsA

in adults with a previous inadequate response to csDMARD therapy, which reported relevant clinical and health-related quality of life, including adverse event outcomes. The inclusion criteria were further refined to include studies of the licensed formulation of tofactinib (5mg, BD). Studies that recruited patients who suffered from other rheumatic or dermatological conditions and DMARD naïve patients were excluded. Case reports, commentaries and editorials, observational studies, and cross-sectional studies were also excluded. Only studies reported in English were eligible for inclusion. Comparators included bDMARDs, the PDE-4 inhibitor apremilast and controls including placebo, best supportive care, and any csDMARD. Studies were screened by title and abstract according to pre-defined PICOS criteria. Those that met the criteria were screened at full text. Appropriate methods were used to reduce reviewer error and bias with two blinded reviewers conducted screening of literature and any discrepancies resolved with assistance from a third reviewer.

Appropriate methods were used to extract data from the included studies. Two reviewers, blinded to each other's decisions, conducted data extraction independently, with a third reviewer involved in resolving discrepancies. Relevant data extracted from included studies are detailed in Appendix D, section D.1.6.

4.1.3 Quality assessment

Randomised control trials were assessed using the NICE Quality Appraisal checklist for quantitative interventions that assesses RCT's based on seven domains. The results of this quality assessment are presented in CS Appendix D, section D.1.7. A risk of bias assessment was also conducted assessing sequence generation, allocation concealment, baseline imbalances, blinding of participants and researchers, incomplete outcome data and selective reporting. These results are also presented in CS Appendix D; section D.1.7, along with support for judgement. The results of these assessments are given in Section 4.2.2 and Section 4.2.3 of this report.

4.1.4 Evidence synthesis

The CS focuses on two studies with distinct populations, OPAL Broaden for TNFi-naïve and OPAL Beyond for TNFi-experienced patients. The company presents the effectiveness of tofactitinib compared with the comparator treatments in forest plots in CS Appendix E. Pooled direct estimates of treatment vs placebo were presented for tofacitinib (in combination with a csDMARD) (for which results remained the same given there was only one trial per population), and the comparator treatments: adalimumab, apremilast, etanercept, infliximab, ustekinumab, golimumab, secukinumab, certolizumab pegol and ixekizumab. These analyses were conducted for the outcomes, ARC 20, 50 and 70, PASI 50, 75 and 90, PsARC and HAQ for PsARC responders and non-responders. Direct estimates pooled by drug class are also presented for the outcome PsARC.

A network meta-analysis was performed, using indirect comparisons to compare the efficacy of tofactitinib and the comparator treatments. The network meta-analysis is described in Sections 4.3 and 4.4 of this report.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Relevant trials - OPAL Broaden and OPAL Beyond

Two RCTs of tofacitinib in combination with a csDMARD were included in the CS: OPAL Broaden and OPAL Beyond. Both trials are Phase III randomised, multicentre, double-blind placebo controlled, parallel group trials, but included different populations, comparators and duration of longer term follow-up. OPAL Broaden included only TNF-inhibitor naïve patients and included a comparison with adalimumab; after the 3-month placebo-controlled phase patients were followed up on tofactinib or adalimumab to 12 months. OPAL Beyond included only TNF-experienced or intolerant patients, and did not include a comparison with adalimumab; after the 3 month placebo-controlled phase patients were followed up on tofactinib to 6 months. Details of both trials are presented in the CS – Tables 4, 5 and 6 and summarised in Table 1. After completion of these trials patients could enter a non-RCT open-label follow-up study of tofacitinib, OPAL Balance. Further details of OPAL Balance are given in Section 4.2.4.

Table 1 Summary of efficacy trials OPAL Broaden and OPAL Beyond (Adapted from CS Tables 4, 5 and 6)

Study	OPAL Broaden (2017)	OPAL Beyond (2017)
Study design	Phase 3 randomised, multicentre, 12-month, double-blind, double-dummy, active-controlled and placebo-controlled, parallel treatment group	Phase 3 randomised, multicentre, 6-month, double-blind, placebo-controlled, parallel-group
Population	Subjects with active PsA who had an IR to at least one csDMARD due to lack of efficacy or toxicity/lack of toleration and had not previously received any TNFi treatment	Subjects with active PsA who had an IR to at least one TNFi, as determined by a lack of efficacy or the occurrence of an AE that was considered by the treating physician to be related to treatment
Intervention(s)	Tofacitinib 5 mg BD (N=107) Tofacitinib 10 mg BD (N=104) Patients were required to receive a stable background dose of a single csDMARD throughout the trial	Tofacitinib 5 mg BD (N=131) Tofacitinib 10 mg BD (N=132) Patients were required to receive a stable background dose of a single csDMARD throughout the trial
Comparator(s)	Adalimumab 40 mg SC q 2 weeks (N=106) Placebo (for 3 months; N=105) At the end of the 3-month placebo-controlled period, the PBO group switched either to TOF 5 mg BD (N=52) or TOF 10 mg BD (N=53)	Placebo (for 3 months; N=131) At the end of the 3-month placebo-controlled period, the placebo group switched either to TOF 5 mg BD (N=66) or TOF 10 mg BD (N=65)
Outcomes assessed in the trials and	Primary outcomes • **ACR20 response rate at Month 3**	

relevant to the decision problem	• **ΔHAQ-DI at Month 3** Supportive analysis of primary outcomes • HAQ-DI responder analysis (≥0.35 as the cutpoint for response) at Month 3 Secondary outcomes • ACR20 response rate: Week 2, Month 6, 12 • Δ van der Heijde-mTSS, progressor rates, and non-progressor rates: Month 12 (OPAL Broaden only) • ΔACR components: Month 3 • ACR50/70 response ratea: Month 3, 6, (and 12 OPAL Broaden only) • **PASI75 response rate: Month 3,** 6, (and 12 OPAL Broaden only) • **PsARC response rate: Month 3**, 6, (and 12 OPAL Broaden only) • ΔLEI, ΔSPARCC, ΔDSS: Month 3, 6, (and 12 OPAL Broaden only) • ΔSF-36 (PF component), FACIT-F (total score): Month 3, 6, (and 12 OPAL Broaden only) (EQ-5D) Other outcomes • MDA response rate: Month 3, 6, (and 12 OPAL Broaden only) • ΔDLQI, ΔISI: Month 3, 6, (and 12 OPAL Broaden only) • ΔHAQ-DI: Month 6, (and 12 OPAL Broaden only) • ΔACR components: Month 6, (and 12 OPAL Broaden only) Post-hoc analyses used in the economic model • PASI50/90 response rate: Months 3, 6, (and 12 OPAL Broaden only) • ΔHAQ-DI conditional on PSARC response status: Month 3, 6, (and 12 OPAL Broaden only)

The inclusion criteria for both trials were: adults aged ≥18 years; diagnosis of PsA for ≥6 months; meeting the CASPAR[11] criteria at screening; active arthritis (≥3 tender/painful and ≥3 swollen joints); and active plaque psoriasis at screening and baseline. For OPAL Broaden, patients had to have demonstrated an inadequate response (lack of efficacy and/or tolerability) to ≥1 csDMARD and to have received no previous TNFi treatment; prior use of non-TNFi bDMARDs for treatment of psoriasis must have been discontinued for ≥6 months prior to the first dose of study drug. For OPAL Beyond, patients had to have demonstrated an inadequate response to ≥1 TNFi. Details of exclusion criteria, which were the same for both trials, are given in CS Table 6.

Analysis sets and statistical methods

In both trials the analysis of efficacy was based on the full analysis set (FAS) which comprised all randomized patients who received at least one dose of the randomised study drug. In OPAL Broaden this comprised all randomized patients (tofacitinib 5 mg n=107, adalimumab n=106, and placebo n=105); in OPAL Beyond it comprised all but one patient randomized to tofacitinib 5 mg (tofacitinib 5 mg n=131 and placebo n=131). It should be noted that [redacted]

[redacted]

The statistical methods used in OPAL Broaden and Beyond were similar and are summarised in Section B2.4.2 of the CS. The methods are appropriate with both trials having over 90% power to detect a 20% treatment difference and OPAL Beyond having 84% to detect a 15% treatment difference, though the treatment difference for many outcomes is much smaller than this.

Type I error was adjusted for multiple comparisons for ARC 20, change in HAQ-DI at three months and the secondary end-points PASI75, ΔLEI, ΔDSS, ΔSF-36 Physical Functioning Domain and ΔFACIT-F total score at Month 3. As requested by the ERG, the company provided additional detail of the methods used to adjust for multiple comparisons. The response stated that a gate-keeping or step-down strategy was used to protect the global type one error; specifically which step-down method was used was not clear. Three families of hierarchical testing procedure were used:

- Primary and key secondary endpoints at Month 3 (Global type I error)
- The ACR family responses (ACR20/50/70) at Month 3
- ACR20 time course (Month 3, Month 2, Month 1, Week 2)

For secondary analyses whereby steps were not taken to control for type I error, the CS states the p-values are nominal. The ERG considers the methods used to be broadly appropriate.

Missing data and withdrawals were dealt with as follows: non-responder imputation was applied to response-type/binary endpoints: ACR20, ACR50, ACR70, ΔHAQ-DI (decrease) ≥0.35, PsARC, PASI75, and MDA. No imputation was applied to missing HAQ-DI data. Missing mTSS values at Month 12 (OPAL Broaden only) were imputed via linear extrapolation.

ERG comments on design and generalisability of the trials

The ERG notes that the design of the two OPAL RCTs is appropriate to address the questions of the efficacy of tofacitinib for the treatment of active psoriatic arthritis. The study design and inclusion criteria are similar to the RCTs of already approved TNF inhibitors and other biologic DMARDs and apremilast, and the outcomes assessed are appropriate. Although the duration of the trials is 12 and 6 months respectively, unfortunately the length of the placebo-controlled period in each trial is only 3 months. However, this assessment duration, whilst limited, is in line with that used in efficacy trials of other agents in active psoriatic arthritis.

It is important to note that in all arms of the trials patients receive a csDMARD in addition to the trial therapy. Therefore the tofacitinib arm is not fully reflective of clinical practice as the licence for tofacitinib in PsA specifies concomitant therapy with MTX. This is discussed further in Section 4.2.2.2. Also of particular interest in OPAL Broaden is the comparison with adalimumab: this randomised, double-blind comparison had a 12-month follow-up, providing clear evidence for the comparison with an established TNFi. It should be noted again however, that the concomitant use of a csDMARD means the results in the adalimumab arm are not fully reflective of clinical practice, nor comparable with those from other adalimumab trials: in both contexts only a proportion of patients would take concomitant csDMARD. In addition, it should be noted that the trial was not powered to test the comparison between tofacitinib and adalimumab; this needs to be taken into consideration when interpreting any noteworthy treatment differences that do not reach statistical significance.

4.2.2 Results of OPAL Broaden

4.2.2.1 Participant flow in OPAL Broaden

Participant flow in OPAL Broaden is presented in Appendix Figure D13. In summary, 422 patients were randomised and 373 (88.4%) completed the trial (Placebo 87/105 (82.9%), tofacitinib 5 mg 96/107 (89.7); tofacitinib 10 mg 96/104 (92.3%); and adalimumab 94/106 (88.7%). Percentage discontinuations were higher in the placebo arms, though somewhat surprisingly none of the discontinuations from the 10mg placebo group were for insufficient response. Adverse events were roughly equal across all treatment arms. In their clarification response the company clarified that in the group randomised to tofacitinib 5 mg, [redacted] patients withdrew by 3 months, [redacted] month 12. [redacted].

4.2.2.2 Patient characteristics of OPAL Broaden

As the tofacitinib 10 mg dose is not licensed and is therefore not relevant to the present appraisal, results for this treatment arm were not included in the CS nor in this report. The main baseline patient characteristics are presented in CS Table 7. These were similar across the tofacitinib 5 mg, adalimumab, and placebo groups, with the exception of significant differences between groups in the mean swollen-joint count (unadjusted p=0.03 for the comparison among all four trial groups), mean Leeds Enthesitis Index (LEI) score (unadjusted p=0.02 for the comparison among all four groups), and the rate (%) of MTX use at baseline (unadjusted p=0.02 for the comparison among all four groups), which were all lower in the adalimumab group, and significant differences among trial

groups in the rate of glucocorticoid use at day 1 (unadjusted p=0.02 for the comparison of the 10 mg tofacitinib BD group with other groups), which was 27% for tofacitinib 5 mg BD, 22% for adalimumab, 17% for placebo, and 11% for tofacitinib 10 mg BD. These differences would favour adalimumab slightly.

The majority of the subjects were white (97 to 99%); the mean age ranged from 47.4 to 49.4 years and the mean duration of PsA ranged from 5.3 to 7.3 years. Out of the 318 patients, 216 (67.92%) had enthesitis and 177 (55.66%) had dactylitis. Importantly only 262 (82.39%) patients were receiving concomitant MTX. The ERG notes that almost 18% of patients were therefore not receiving tofacitinib in accordance with the product licence. An analysis of the data relating to the concomitant MTX subgroup was not presented in the CS (or the CSR).

4.2.2.3 Summary of the quality of OPAL Broaden

Table 2 Quality assessment and Risk of bias assessment (Adapted from CS Tables D16 and D17

OPAL Broaden	ERG comment	Quality Assessment (NICE checklist)	Risk of Bias
	Support		Judgement
Appropriate randomization / Sequence generation	"Randomly assigned in a 2:2:2:1:1 ratio, by means of an automated Web-based randomization system"	Yes	Low
Treatment allocation concealment	"Randomly assigned in a 2:2:2:1:1 ratio, by means of an automated Web-based randomization system"	Yes	Low
Prognostic factors balanced at study outset	"The demographic and disease characteristics of the patients at baseline were similar across groups"	No	Low
Blinded to treatment		Yes	
Blinding of participants and researchers	"Placebo was provided as oral tablets and prefilled syringes matching those of tofacitinib and adalimumab, respectively. All patients received both tablets and injections to maintain the blind."		Low
Blinding of Outcome assessment	All rheumatological and dermatological assessments were performed by qualified, trained assessors who were blinded to the patient's safety data, previous efficacy data, and treatment randomization		Low
Unexpected imbalances in dropouts		no	
Incomplete outcome data	10-30% drop-outs in all groups except one, Reasons reported. No ITT. "Efficacy analyses included all the patients who underwent randomization and received at least one dose of tofacitinib,adalimumab, or placebo"		High
Measured more outcomes than reported/selective reporting	Results reported for all key outcomes	No	Low
Appropriate analysis performed		Yes	
Overall judgement			High

The ERG agrees with the quality/risk of bias assessment results reported except for the high risk of bias assigned due to incomplete outcome data. This should not apply to those outcomes where non-response imputations were applied (response-type/binary endpoints: ACR20, ACR50, ACR70, ΔHAQ-DI (decrease) ≥0.35, PsARC, PASI75, and MDA) No imputation was applied to missing HAQ-DI data, and therefore a high risk of bias might apply, but at 3-months data were almost complete (95 to 97%) and at 6 and 12 months (tofacitinib vs adalimumab) they were 93% and 89% to 90% respectively. Modified TSS values at Month 12 were available for [redacted]; values for 6 patients were imputed via linear extrapolation, but the impact on the results was small and the risk of bias appears to be low for this outcome.

4.2.2.4 Summary of efficacy results for OPAL Broaden

The results for the key efficacy outcomes are summarised in Table 3.

Table 3 Efficacy results for OPAL Broaden (FAS) ACR 20, 50 and 90, PSARC, PASI 75 and HAQ-DI.

	Month	PBO	TOF 5 mg	ADA	TOF 5 mg vs placebo (% Difference and 95% CI) p value	ADA vs placebo (% Difference and 95% CI Nominal p value	TOF 5 mg vs ADA Nominal p value
ACR 20 Response rate, n (%)	3	35/105 (33)	54/107 (50)	55/106 (52)	17.1 (4.1, 30.2), 0.01§	18.6% (5.5, 31.7), [redacted]†	[redacted]
	6	[redacted]	[redacted]	[redacted]	_	_	[redacted]
	12		73 (68)	64 (60)	_	_	[redacted]
ACR 50 Response rate, n (%)	3	10/105 (10)	30/107 (28)	35/106 (33)	18.5% (8.3, 28.7) 0.001	23.5% (12.9, 34.1) [redacted]†	[redacted]
	6		[redacted]	[redacted]			[redacted]
	12		48/107 (45)	43/106 (41)			[redacted]
ACR 70 Response rate, n (%)	3	5/105 (5)	18/107 (17)	20/106 (19)	12.1% (3.9, 20.2) 0.004	14.1% (5.6, 22.6) [redacted]†	[redacted]
	6		[redacted]	[redacted]			[redacted]
	12		25/107 (23)	31/106 (29)			[redacted]
PSARC response rate, n (%)	3	47/105 (44.8)	55/107 (51.4)	65/106 (61.3)	6.6 -6.8, 20.1 [redacted]	16.6 3.3, 29.8 [redacted]†	[redacted]
	6		[redacted]	[redacted]			[redacted]

	12		69/107 (64.5)	69/106 (65.1)			[redacted]
PASI75 response rate, n (%)	3	12/82 (15)	35/82 (43)	30/77 (39)	28.1 14.9, 41.2 <0.001	24.3 11.0, 37.6 [redacted]†	[redacted]
	6		[redacted]	[redacted]			[redacted]
	12		46/82 (56)	43/77 (56)			[redacted]
HAQ-DI score	3						
N*		102[a]	103	101			
LS mean change from baseline		-0.18	-0.35	-0.38	-0.2 (-0.3, -0.05) 0.006§	-0.2 (-0.3, -0.1) [redacted]†	[redacted]
	6						
N*			[redacted]	[redacted]			
LS mean change from baseline			[redacted]	[redacted]			[redacted]
	12						
N*			96	94			
LS mean change from baseline (SE)			-0.54 (0.05)	-0.45 (0.05)			[redacted]

§p-value is subject to the step-down approach; †nominal p-value for comparison between adalimumab and placebo; [a]One placebo subject was excluded from the analysis (no post-baseline assessments)

PASI50 and PASI90 response at month 3 were additional outcomes examined in a post-hoc analysis conducted to inform the economic model for the UK NICE submission and are presented in CS Appendix M.

The joint primary outcomes were ACR 20 response rate and HAQ-DI score, both at 3 months. For these and all of the other outcomes in these tables, with the exception of PsARC, tofacitinib was statistically significantly more effective than placebo. It should be noted that the PSARC response in the tofacitinib 5 mg arm was similar to that for ACR 20 (51.4% and 50% respectively), but the placebo rate for PsARC was much higher than for ACR 20 (44.8% versus 33%).

Although not a primary analysis, the data and results are also presented for a comparison with adalimumab. At the 3 months for all outcomes in these tables, adalimumab was statistically significantly more effective than placebo. Comparison of tofacitinib with adalimumab at 3, 6 and 12 months shows that numerically for most outcomes adalimumab was very slightly better than tofacitinib, but for no outcome was the difference statistically significant; the trial was not powered to test such a small difference.

Results were similar for other secondary measures of disease activity at Month 3, Month 6, and Month 12 and were reported and presented in CS Appendix M.

- The MDA response rate (CS Table M6) at Month 3 in the tofacitinib 5 mg BD, adalimumab and placebo groups was 26%, 25% and 7% respectively, with [redacted] for both comparisons with placebo. For tofacitinib 5 mg vs adalimumab, [redacted] The rates were sustained up to Month 12.
- Across measures of enthesitis (LEI, SPARCC) and dactylitis (DSS) (CS Table M5) at month 3 tofacitinib 5 mg BD was numerically but not statistically superior to placebo, with responses sustained up to month 6 and month 12. The results for adalimumab were similar to those for tofacitinib except for the LEI score, for which adalimumab was statistically significantly greater than placebo and the difference for adalimumab from placebo (-0.7 (95% CI -1.2, -0.1) was numerically superior to tofacitinib from placebo (-0.4 (95% CI -0.9, 0.2).
- The results for quality of life measures were presented in CS Table M7. Although most differences were nominally statistically significant, statistical significance could not be claimed due to the hierarchical testing scheme (tofacitinib was not statistically significantly superior for LEI score). Tofacitinib 5 mg BD was numerically (SF-36 PF, FACIT-F total score) and significantly (DLQI, ISI) superior to placebo at Month 3, with responses sustained up to Month 6 and Month 12. Results were similar for adalimumab, though the difference from placebo for adalimumab was numerically lower for FACIT-F and ISI score [redacted]). It should be noted that although EQ-5D data were collected in the trial these data were not included in the CS. The ERG requested these data and they were provided in the company's clarification response. The results suggest [redacted]; no formal testing was presented.

Radiographic assessment of disease progression at 12 months is summarised in Table 4. There is no placebo comparison as the placebo controlled phase of the study stopped at 3 months. At 12 months, there was evidence of a reduction in progression in the adalimumab but not the tofactinib arm, though the treatment difference was not statistically significant; again, the trial was not powered to test such a small difference. The proportion of progressors (defined as patients with an increase in mTSS of >0.5) was low in both treatment arms.

Table 4 Radiographic progression results for OPAL Broaden (FAS)

	Month	TOF 5 mg	ADA	TOF 5 mg vs ADA Nominal p value
Change in van der Heide-mTSS (LS mean) (SE)	12	0.01 (0.07) [98]	-0.07 (0.07) [95]	[redacted]
mTSS progressor rate, n/N (%)	12	[redacted]	[redacted]	[redacted]

;[§]p-value is subject to the step-down approach; [†]nominal p-value for comparison between adalimumab and placebo; [a]One placebo subject was excluded from the analysis (no post-baseline assessments)

The ERG enquired about the data, if any collected on those patients who were randomised to placebo and then switched to active treatment at the 3-month time point. In their clarification response the company provided the results at 6 and 12 months for these patients. Overall, the results reflect those for patients randomised to tofacitinib 5 mg group and are supportive of the main analysis data, though the results for PASI75 were lower than those at 3 and 6 months in the main analysis tofacitinib group.

4.2.3 Results of OPAL Beyond

4.2.3.1 Participant flow in OPAL Beyond

Participant flow in OPAL Beyond is presented in Appendix figure D15 of the CS. In summary, 395 randomised and 345(87.3%) completed the trial (Placebo 112/131 (85.5%), Tof 5 mg 122/132 (92.4); tofacitinib 10 mg 111/132 (84.1%). Percentage discontinuations and withdrawals due to adverse events were roughly equal across all relevant treatment arms (were higher in the tofacitinib 10 mg arms). In their clarification response, the company clarified that in the group randomised to tofacitinib 5 mg, five patients withdrew by 3 months, two due to AEs, one due to inadequate response and two due to other reasons. Nine discontinued by 6 months (a further four patients (three due to AEs and one for other reasons). None of the adverse events were considered to be treatment related.

4.2.3.2 Patient characteristics of OPAL Beyond

As for OPAL Broaden, the tofacitinib 10 mg dose is not included in the CS or in this report. The main baseline patient characteristics are presented in CS Table 7 were similar across the tofacitinib 5 mg and placebo groups except that there were more female subjects in the placebo group (61%) than the tofacitinib 5 mg BD group (49%). The majority of the subjects were white (90 to 92%); the mean age ranged from 49.0 to 49.5 years; and the mean duration of PsA ranged from 9.4 to 9.6 years. Out of the 262 subjects, 176 (67.18%) had enthesitis and 129 (49.24%) had dactylitis; 199 (75.95%) of subjects were receiving concomitant MTX. This is similar to the OPAL Broaden population except that the mean duration of PsA is longer. The ERG notes that almost 24% of patients in OPAL Beyond were

not receiving tofacitinib in accordance with the product licence. An analysis of the data relating to the MTX subgroup was not presented in the CS (or the CSR).

Additional information regarding previous PsA therapies was available in the CSR and was provided in the company's clarification; these are summarized in Table 5. It should be noted that these counts of previous TNFis are irrespective of whether the patient had or had not also taken a non-TNFi biologic.

Table 5 <u>OPAL Beyond prior drug treatments for PsA by treatment group (safety analysis set)(adapted from the Company's clarification response tables)</u>

	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

The ERG notes that whilst all patients had been exposed to one or more TNFi, [redacted] (no patient had received just a non-TNFi b DMARD). The proportion of patients who had received just one prior TNFi was slightly lower in the tofactinib than in the placebo group [redacted] These differences would tend to favour placebo. The ERG notes that these data reveal that the majority of patients in the trial (around [redacted]) had received only one TNFi. In clinical practice, it might be expected that this figure would be lower, with tofacitinib reserved for later in the treatment pathway, raising a question over the generalisability of the results as efficacy would likely be lower in a more treatment refractory population. These data also reveal that in the trial adalimumab, etanercept and infliximab were by far the most commonly received prior bDMARDS. In clinical practice a higher proportion of ustekinumab and secukinumab might be expected given their recent approvals by NICE for PsA.

4.2.3.3 Summary of the quality of OPAL Beyond

Table 6 Quality / Risk of Bias assessment results for OPAL Beyond

OPAL Beyond	ERG comment	Quality Assessment (NICE checklist)	Risk of Bias
	Support		Judgement
Appropriate randomization / Sequence generation	"A centralized automated randomization system was used to assign patients, in a 2:2:1:1 ratio"	Yes	Low
Treatment allocation concealment	""A centralized automated randomization system was used to assign patients, in a 2:2:1:1 ratio"	Yes	Low
Prognostic factors balanced at study outset	"The demographic and disease characteristics of the patients at baseline were similar across the groups, with the exception of the mean number of tender or painful joints, for which a significant difference was seen across trial groups"	No	Unclear
Blinded to treatment		Yes	
Blinding of participants and researchers	Stated as double blinded. " The investigators, patients, and sponsor were unaware of the trial-group assignments for the duration of the trial". "Matching placebo tablets were used to maintain the blinding"		Low
Blinding of Outcome assessment	"cardiovascular events, and hepatic events were adjudicated by independent expert committees whose members were unaware of the trial-group assignments" "The investigators, patients, and sponsor were unaware of the trial-group assignments for the duration of the trial"		Low
Unexpected imbalances in dropouts		no	
Incomplete outcome data	3 groups out of 4 had 10-30% drop-outs. One group had <10% drop-outs, Reasons reported. No ITT. "Efficacy analyses included all the patients who underwent randomization and received at least one dose of tofacitinib, adalimumab, or placebo"		High
Measured more outcomes than reported/selective reporting	Results reported for all key outcomes	No	Low
Appropriate analysis performed		Yes	
Overall judgement			High

The ERG agrees with the quality / Risk of Bias assessment results reported in the CS except for the high risk of bias assigned due to incomplete outcome data. This should not apply to those outcomes where non-response imputations were applied (response-type/binary endpoints: ACR20, ACR50, ACR70, ΔHAQ-DI (decrease) ≥0.35, PsARC, PASI75, and MDA). No imputation was applied to missing HAQ-DI data, and therefore a high risk of bias might apply but at 3 months, data were available for 95% tofacitinib patients and 89% placebo.

4.2.3.4 Summary of efficacy results for OPAL Beyond

Table 7 Efficacy results for OPAL Beyond (FAS) ACR 20, 50 and 90, PSARC, PASI 75 and HAQ-DI (adapted from CS Tables 15 to19).

	Month	TOF 5 mg	PBO	TOF 5 mg vs placebo (% Difference and 95% CI) p value
ACR 20 Response rate, n (%)	3	65/131(50)	31/131 (24)	26.0 (14.7, 37.2) <0.001§
	6	78/131 (60)		
ACR 50 Response rate, n (%)	3	39/131 (30)	19/131 (15)	15.3(5.4, 25.2), 0.003
	6	50/131 (38)		
ACR 70 Response rate, n (%)	3	22/131 (17)	13/131 (10)	6.9 (-1.3, 15.1), [redacted]
	6	28/131 (21)		
PSARC response rate, n (%)	3	[redacted]	[redacted]	29.8 (18.3, 41.2), [redacted]
	6	[redacted]		
PASI75 response rate, n (%)	3	17/80 (21)	12/86 (14)	7.3 (-4.3, 18.9), [redacted]
	6	27/80 (34)		
HAQ-DI score LS mean change from baseline	3	-0.39 (N=124)	-0.14 (N=117)	-0.3 (-0.4, -0.1), <0.001§
	6	-0.44 (SE 0.05) (N=122)		

§p-value is subject to the step-down approach;

PASI50 and PASI90 response at month 3 were additional outcomes examined in a post-hoc analysis conducted to inform the economic model for the UK NICE submission and are presented in CS Appendix M.

The results in Table 7 above show that there was a statistically significant benefit of tofacitinib 5 mg over placebo for the primary outcomes (ACR 20 and HAQ-DI), and also for ACR 50 and PSARC, but not for ACR 70 or PASI 75.

Results for other secondary measures of disease activity are presented in Appendix M of the CS (Tables M14 and M16). The MDA response rate at month 3 in the tofacitinib 5 mg BD group was 23% vs 15% in the placebo group, though the difference was not statistically significant ([redacted]) . The response rate in the tofactiinib group was sustained up to Month 6. For all other of these outcomes the p values for the improvements seen with tofacitinib 5 mg BD compared with placebo were all ≤0.01, although for LEI score, DSS, SF-36 physical functioning score, and FACIT-F total score statistical significance could not be claimed because they were subject to a hierarchical testing scheme (because the PASI75 response rate was not significant). Responses were sustained up to

Month 6. It should be noted that, as for OPAL Broaden, although EQ-5D data were collected in the trial these data were not included in the CS but were provided in the company's clarification response. The results suggest [redacted].no formal testing presented.

The ERG also enquired about the data, if any, collected on those patients who were randomised to placebo and then switched to active treatment at the 3-month time point. In their clarification response the company provided the results at 6 months for these patients. Overall, the results reflect those of those patients randomised to tofacitinib 5 mg group and are supportive of the main analysis data.

Comparison of results from OPAL Broaden and OPAL Beyond

A comparison of the results from these two trials does not reveal a consistent pattern, i.e. there is no clear indication from the results that the Beyond population is the more refractory to treatment. Compared with OPAL Broaden the placebo response was lower in Beyond for ACR 20, but it was higher for ACR 50 and 70, and also PSARC. For PASI75 the placebo response rates in the two trials were very similar; the lack of a statistically significant effect of tofacitininb in Beyond was due to a much lower tofacitinib 5 mg arm response rate compared with that seen in Broaden 21% vs 43%). The HAQ-DI results were similar across the two trials.

Regarding withdrawals from trial therapy, the ERG requested information on the number of withdrawals and whether from OPAL Beyond or OPAL Broaden, and whether the next treatment was a csDMARD or bDMARD. This information could have indicated the position of tofacitinib in the treatment pathway. However, in their clarification response the Company confirmed that neither OPAL Beyond nor OPAL Broaden were designed to assess subsequent treatments after discontinuation of tofacitinib; the requested information was not available.

The Company stated that the drug survival rates for the relevant dose of 5 mg BD tofacitinib were very high: 90% in OPAL Broaden at 12 months, and 93% in OPAL Beyond at 6 months, and only 20 patients would have required an alternative line of treatment following tofacitinib within the study duration.

4.2.4 Relevant non-randomised evidence – OPAL Balance

One relevant non-randomised study of tofacitinib in PsA was included in the CS: OPAL Balance. OPAL Balance is an open-label extension study of the long-term safety and efficacy of patients who had previously participated in OPAL Broaden and OPAL Beyond. OPAL Balance is ongoing, with an anticipated completion date of January 2020. Details are presented in CS Appendix M 2.1. In summary, all patients in OPAL Balance received tofacitinib upon entry into the study: patients were

to receive TOF 5 mg BD for one month, after which, the dose could be increased to 10 mg BD for efficacy reasons at the investigator's discretion. Doses could be reduced back to 5 mg BD for safety reasons at the investigator's discretion. The primary outcome of OPAL Balance was incidence and severity of adverse events; and change from baseline in laboratory values. Key secondary outcomes were ACR20/50/70, HAQ-DI, PsARC, PASI75, LEI, DSS.

Clarification from the company provided indirect information on the dose of tofactinib patients entering OPAL Balance had been treated with: the trial arms are summarised in Table 8 . This information revealed that of the [redacted] patients enrolled and treated in OPAL Balance from OPAL Broaden [redacted] had been treated with TOF 5 mg, [redacted] TOF 10mg and [redacted] adalimumab. Of the [redacted] patients enrolled and treated in OPAL Balance from OPAL Beyond, [redacted] had been treated with TOF 5 mg, and [redacted] TOF 10mg.

Table 8 OPAL Balance CSR Table 14.1.1.2: Subject evaluation groups by qualifying study and overall (Subjects from OPAL Broaden)

	TOF5 BD	PBO→TOF5 BD	TOF10 BD	PBO→TOF10 BD	ADA 40mg SC Q2W	All
From OPAL Broaden						
Enrolled and treated in OPAL Balance, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
From OPAL Beyond						
Enrolled and treated in OPAL Balance, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TOF5 BD		TOF10 BD		ADA	
	[redacted]		[redacted]		[redacted]	[redacted]

This information is not particularly useful as all patients, irrespective of the treatment in the source trial, on entering Balance initially received 5 mg dose, but increasing the dose to 10 mg was permitted. Whilst the information in Table 8 tells us that only [redacted] did not have a treatment / dose alteration at the start of this study, it does not tell us how many patients were on the 10 mg dose and therefore how representative of the licensed dose (5 mg) these data are. Further information provided in the company's clarification response [redacted]. As the 10 mg dose of tofacitnib is not licensed, there is a question over the generalisability to clinical practice of the OPAL Balance data.

Table 9 OPAL Balance Patient discontinuations by month (data from second interim analysis (25 January 2017) Information taken from Company clarification response (CCR))

OPAL Balance n=686				
	Discontinuations from CCR question A5	Table 00099.4	Table 00099.4	Table 00099.4
Assessment month	Total	Total	Due to Lack of efficacy	Due to AE
3	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]

For the January 25, 2017 data cut, safety and efficacy data from all patients in OPAL Balance were pooled, regardless of dose, due to flexible dosing between 5 mg BD and 10 mg BD. [redacted]

Baseline values for efficacy endpoints were the same baseline values used for patients in their previous clinical trial of tofacitinib.

Results

Withdrawals from OPAL Balance are presented in **Table 9**. Withdrawals at 2 years (2.5 to 3 years since start of tofacitinib) were roughly [redacted] remained on their first TNFi. This compares with 61% remaining on first anti TNFi reported for the BSBR Register.[10]The results for the change from baseline up to Month 24 (interim data analysis up to 25 January 2017) in the pooled tofacitinib group (5 mg and 10 mg BD doses) are shown in**Table 10**. These results demonstrated that improvements in signs and symptoms of the disease and physical functioning achieved by tofacitinib treatment are generally sustained long term for those patients who remain on tofacitinib therapy. The ERG notes that the number of patients in the study reduce dramatically over the 18-month period, from 634 at month 6 to 82 at month 24, presumably due to limited follow-up in a significant number of patients. This doesn't necessarily reflect drop-outs from the study, but rather the fact that the study is ongoing. Similar improvements were demonstrated for other measures of signs and symptoms of the disease (ACR50, ACR70, and PASI75), as well as measures of enthesitis (LEI), dactylitis (DSS), and pain. The ERG noted that, even though a high proportion of patients remain on tofacitinib therapy, not all achieved an ACR 20 response. In their clarification, the company confirmed that in

OPAL Balance a lack of efficacy determined by an ACR 20 response was not a criterion for withdrawal from the study.

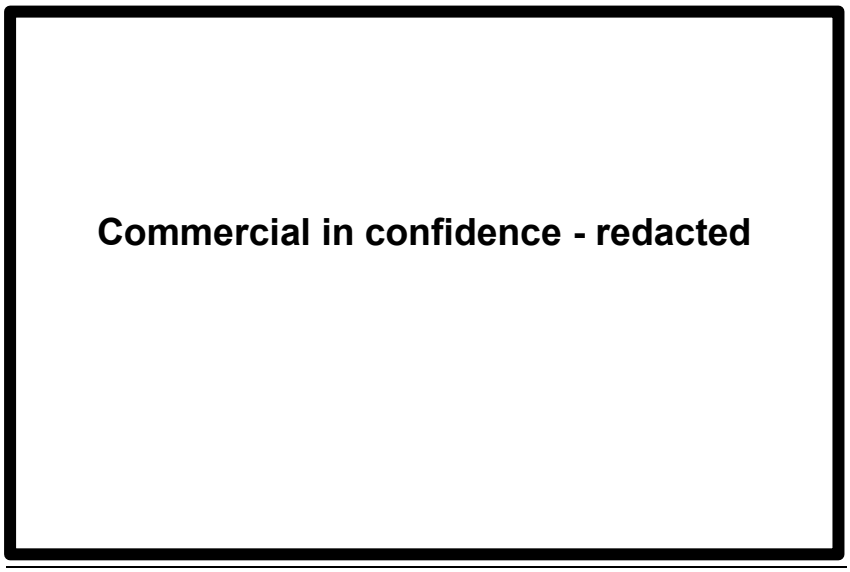
Table 10 Summary of efficacy through to Month 24 in OPAL Balance interim data analysis up to 25 January 2017 – includes TOF 5 mg and TOF 10 mg)- Includes PsARC results provided in the Company's Clarification response.

Outcome	TOF (all patients, N=686)			
Timepoint	Month 6	Month 12	Month 18	Month 24
ACR20, n/N (%)	448/634 (70.7)	422/570 (74.0)	264/341 (77.4)	55/82 (67.1)
ACR50, n/N (%)	298/633 (47.1)	284/570 (49.8)	183/342 (53.5)	41/82 (50.0)
ACR70, n/N (%)	194/636 (30.5)	183/570 (32.1)	123/341 (36.1)	22/82 (26.8)
ΔHAQ-DI, mean (SD) [N]	-0.5 (0.6) [636]	-0.5 (0.6) [571]	-0.5 (0.6) [342]	-0.6 (0.7) [81]
PSARC n/N	464/632 (73.42%)	431/566 (76.2)	271/339 (79.9)	61/82 (74.4)
PASI75 response rate, n/N1 (%)	263/433 (60.7)	250/396 (63.1)	148/242 (61.2)	40/58 (69.0)
ΔLEI, mean (SD) [N1]	-1.7 (1.8) [418]	-1.7 (1.8) [371]	-1.8 (1.8) [220]	-1.8 (1.9) [56]
ΔDSS, mean (SD) [N1]	-7.2 (7.9) [336]	-7.7 (7.8) [300]	-7.1 (7.2) [186]	-7.3 (6.6) [48]
ΔPain, mean (SD) [N1]	-26.0 (28.0) [634]	-26.8 (27.6) [570]	-29.4 (29.4) [342]	-32.6 (30.2) [81]

1= number of evaluable patients at visit. No imputation.

[redacted]

Figure 2: Change in HAQ-DI score from baseline up to Month 27 (4 April 2016 data cut) – FAS and constant tofacitinib 5 mg BD subjects only (CS Figure 7)



4.3 Evidence for impact of tofacitinib on radiographic disease progression

4.3.1 FDA Assessment – non inferiority analyses

To assess the non-inferiority (NI) of tofacitinib compared with adalimumab on radiographic outcomes the FDA developed NI margins based on two sets of data. Firstly, they conducted fixed effect (-0.63, 95% CI -0.77 to -0.48) and random-effects meta-analyses (-0.75, 95% CI -1.09 to -0.42) comparing TNFi with placebo on mean change from baseline in mTSS (modified total Sharp score) at 6 month follow up. Secondly, they used the data from the ADEPT trial on adalimumab (-1.0, 95% CI -1.60 to -0.40). Based on these data they proposed two NI margins:

- Historical data from meta-analyses of TNFi's: 0.125 to 0.375
- Historical data from adalimumab trial: 0.10 to 0.30

The upper CI for radiographic progression on tofacitinib (0.25) in OPAL Broaden is within these NI margins. However, the FDA only considered this 'borderline evidence at best' since the comparison with adalimumab was based on only one trial, and the methods used to handle missing data in the trial underestimated the standard error and therefore the width of the confidence interval (CI). In addition, there were also uncertainties regarding the constancy assumption (that the effect for the comparator observed in the OPAL Broaden reflects that of previous trials) in terms of comparability of placebo progression rates and differences in baseline characteristics.

Comparability of placebo progression rates

The FDA reviewed data on radiographic progression in psoriatic arthritis (PsA) trials. They found that placebo mean changes at 6 months ranged from 0.18 to 1.0 with mean progression greater than 0.5 in five of seven studies.

Since patients received placebo for only 3 months in OPAL Broaden, to make this comparison the FDA assumed progression at a constant rate from 3 months to 6 months. FDA concluded that the progression rates in the placebo arm of the OPAL Broaden trial were half those seen in other PsA trials historically. Similarly, mean change in erosion score for the placebo arm in OPAL Broaden was low compared with earlier studies.

Comparability of baseline characteristics in OPAL broaden with earlier trials

The FDA also compared baseline characteristics on prognostic factors such as mean baseline CRP values, baseline mTSS, erosion scores, and joint space narrowing (JSN) scores. They concluded that at baseline these values were lower in OPAL Broaden than earlier trials, potentially confounding comparisons with previous trials.

They also identified several aspects of the trial design, which further limited comparability of OPAL Broaden with previous studies. Firstly, OPAL Broaden required patients to receive a stable dose of csDMARDs. Although concomitant use of csDMARDs was not excluded in earlier trials this was not a requirement for trial inclusion (therefore some patients on placebo would have received no active treatment). Secondly, whereas in earlier trials only those who experienced an inadequate response to placebo switched to active therapy, in OPAL Broaden all patients on placebo switched to active treatment after 3 months.

FDA conclusion

The FDA concluded there is a potential effect of tofacitinib on halting radiographic progression however there is currently insufficient evidence to support this conclusion.

- Firstly, there is no evidence of difference between tofacitinib and placebo on mTSS.
- Secondly, radiographic outcomes are based on a single trial.
- Thirdly, lack of progression in the placebo arm of the OPAL Broaden is much lower than that observed in previous trials, which potentially may be explained by differences in baseline characteristics and trial design.

4.3.2 Company's analysis - Population adjusted analyses

In response to the uncertainties raised by the FDA, the company conducted population adjusted analyses based on the ADEPT trial. Differences with the FDA analyses include:

- Instead of mean difference in mTSS score for adalimumab vs placebo at 6 months, mean change from baseline mTSS score at 48 weeks was used to determine the NI margin. In addition, an NI margin was determined for rate of progression (see Table 11).

Table 11 Non-inferiority margins proposed by the FDA and the company for radiographic progression

Outcome	Source of NI margin	NI margin for upper confidence interval
mTSS	FDA: meta-analysis of TNFIs vs placebo at 6 months	0.125 to 0.375
mTSS	FDA: ADEPT trial of adalimumab vs placebo at 6 months	0.1 to 0.3
mTSS	CS: ADEPT trial of adalimumab vs placebo at 48 weeks	[redacted]
Rate of progression (change in mTSS)	CS: ADEPT trial of adalimumab vs placebo at 48 weeks	[redacted]

- The findings from OPAL Broaden were mapped to the population of the ADEPT trial adjusting for imbalances between the trial populations for potential effect modifiers and prognostic factors. Covariates assessed for inclusion in multivariable regression analyses were: baseline CRP, baseline mTSS, absence of radiographic progression at baseline, baseline erosion, baseline JSN, swollen joint count, tender joint count, use of methotrexate, RF-positive status, age in years, weight (Kg), duration of psoriatic arthritis, gender.

- In addition, covariates were centred on mean values for the ADEPT trial so that treatment differences could be interpreted within the context of the ADEPT trial population.

The population-adjusted analyses are an attempt to address the concerns raised by the FDA regarding comparability of baseline characteristics in the OPAL Broaden trial in relation to the ADEPT trial. The potential prognostic factors included in the regression model are well justified in relation to the literature.

However, there are additional potential explanations of why radiographic progression was slower in the OPAL Broaden trial other than baseline characteristics (for example, the requirement of concomitant csDMARDs for tofacitinib). Therefore, although it is possible to adjust for MTX use in

the regression models there is still potential for residual confounding due to important differences in trial design that cannot fully be adjusted for in the analyses.

Secondly, the concerns raised by the FDA regarding uncertainty associated with the non-inferiority comparisons based on a single trial remain an issue that cannot be addressed other than by further trials.

Thirdly, another source of uncertainty is length of follow up. The data for tofacitinib is based on one year follow up which is substantially shorter than data observed for TNFis. For example, the ADEPT trial provides evidence on radiographic progression up to 2.75 years and registry data provides data on radiographic progression for patients on TNFis for up to 4 years.[12]

Model selection

In univariable analyses, none of the proposed baseline covariates were associated with the treatment effect for either tofacitinib 5mg or adalimumab on mTSS at 52 weeks in the OPAL Broaden trial. Elevated CRP at baseline was associated with slightly higher odds for radiographic progression in patients receiving tofacitinib 5mg. Weight was associated with increased odds of progression in patients receiving adalimumab.

Table 12 Change in mTSS for tofacitinib 5mg vs adalimumab (adapted from table D41 in CS)

Model	Difference	p-value	95% Lower CI	95% CI Upper	AIC	Deviance
Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A1:tof*(MTX)+CRP+mTSS+weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A2:tof*(MTX)+CRP+mTSS+weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A3: tof*(MTX+mTSS) + weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

tof= tofacitinib 5mg MTX=methotrexate mTSS=modified Total Sharp Score CRP=C-reactive protein

The company selected the three best fitting multivariable models for difference in mTSS for tofacitinib 5mg vs adalimumab based on the lowest AIC and deviance statistics. There were negligible differences in goodness of fit for the multivariable models compared with the unadjusted analyses (see Table 12).

Table 13 Odds of progression for tofacitinib 5mg vs adalimumab (adapted from table D42 in CS)

Model	OR	p-value	95% Lower CI	95% CI Upper	AIC	Deviance
Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B1:tof*(MTX)+CRP+PSA duration+ weight+male+region	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B2:tof*(MTX)+CRP+weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B3: tof*(MTX+CRP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The company also selected the three best fitting multivariable models for odds of progression in tofacitinib 5mg vs adalimumab (see Table 13). As with the previous outcome, there were minor differences in goodness of fit between the multivariable and unadjusted analyses.

Comparisons with non-inferiority margins

As acknowledged in the CS the population-adjusted analyses were inconclusive as to whether reduction in radiographic progression with tofacitinib was non-inferior to adalimumab. The upper CI for the difference in mTSS and risk of progression for tofacitinib crossed both the upper and lower NI margins in unadjusted and multivariable models (see Table 14 and Table 15).

Table 14 Tofactinib 5mg on mTSS using data from ADEPT as baseline

Model	Difference	p-value	95% Lower CI	95% Upper CI
Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]
Multivariable model A1:tof*(MTX)+CRP+mTSS+weight	[redacted]	[redacted]	[redacted]	[redacted]
Additional multivariable models				
A2:tof*(MTX)+mTSS+weight	[redacted]	[redacted]	[redacted]	[redacted]
A3: tof*(MTX+mTSS) + weight	[redacted]	[redacted]	[redacted]	[redacted]

tof= tofacitinib 5mg MTX=methotrexate mTSS=modified Total Sharp Score CRP=C-reactive protein

Table 15 Tofacitinib 5mg on risk of progression using date from ADEPT as baseline

Model	Risk	95% Lower CI	95% Upper CI
Unadjusted	[redacted]	[redacted]	[redacted]
Multivariable model B2	[redacted]	[redacted]	[redacted]
Multivariable model B1	[redacted]	[redacted]	[redacted]
Multivariable model B3	[redacted]	[redacted]	[redacted]

Summary

The company attempted to reduce uncertainty raised by differences in baseline characteristics between OPAL Broaden and the ADEPT trial of adalimumab in terms of population-adjusted analyses. However, there was limited evidence to show that multivariable models substantially impacted on goodness of fit. In addition, it appears there may still be differences in trial design that cannot be fully adjusted for in the analyses.

The key finding of the non-inferiority analyses is that comparisons between tofacitinib and adalimumab are currently inconclusive as upper CI's observed for tofacitinib crossed the upper and lower NI margins for both difference in mTSS and risk of progression. It cannot therefore be concluded that tofacitinib is non-inferior to adalimumab on radiographic progression outcomes.

4.4 Adverse effects of tofacitinib

Data on the adverse events associated with tofacitinib in the PsA trials (OAL Broaden, Beyond, and Balance are presented in Sections B2.11.1 to B2.11.3. The safety overview refers also to the clinical programme for tofacitinib in rheumatoid arthritis (RA).

The CS stated that over eight years of observation through the tofacitinib RA clinical programme of studies and more than 19,400 patient-years of experience have demonstrated that the rates of AEs are stable over time and are similar to bDMARDS for RA, with the exception of herpes zoster. The CS reports that in the PsA trials programme (OPAL Broaden and OPAL Beyond) tofacitinib 5 mg BD demonstrated an acceptable safety profile that is well characterised, stable, and clinically manageable. The most frequent AEs reported in the Phase III trials were nasopharyngitis, upper respiratory infection, and headache. The rate of SAEs was low across OPAL Broaden and OPAL Beyond. The types and rates of common AEs (including infections and malignancies) were generally comparable to those seen in the RA clinical programme.

[redacted]

In OPAL Broaden, where comparison with adalimumab was possible, AEs were slightly more common in the adalimumab group (see **Table 16**)

Table 16 Summary of AEs Reported up to Month 3 and Month 12 (Safety Analysis Set, All Causalities) for OPAL Broaden (adapted from CS Tables 31 and 33)

Number (%) of Subjects:	TOF 5mg, n (%)	ADA, n (%)	PBO, n (%)
To 3 months			
Subjects evaluable for AEs	107	106	105
[redacted]	[redacted]	[redacted]	[redacted]
Subjects with AEs	42 (39)	49 (46)	37 (35)
Subjects with SAEs	3 (3)	1 (1)	1 (1)
[redacted]	[redacted]	[redacted]	[redacted]
To 12 months			
Subjects evaluable for AEs	107	106	52
[redacted]	[redacted]	[redacted]	[redacted]
Subjects with AEs	71 (66)	76 (72)	36 (69)
Subjects with SAEs	8 (7)	9 (8)	3 (6)
[redacted]	[redacted]	[redacted]	[redacted]

Withdrawals due to AEs were not reported in the adverse effects section of the CS. From the trial CONSORT diagrams (CS Appendix D) and the clarification response the ERG calculated that in [redacted] and [redacted] of patients withdrew due to an adverse event in OPAL Broaden and Beyond respectively, though none of the events were considered to be treatment related. In the longer-term OPAL Balance the rate was 5.8% at 24 months.

Adverse events of special interest are summarised in the CS. These are gastrointestinal perforation and inflammatory bowel disease: tuberculosis, serious infection/herpes zoster; opportunistic infection; interstitial lung disease; cardiovascular events; and cancer. These were summarised by trial (OPAL Broaden, Beyond and Balance) but not overall; the overall totals as calculated by the ERG from the information provided are given in Table 17.

Table 17 Adverse events of special interest reported across all OPAL studies up to 36 months (ERG calculated from text in CS Appendix M)

Adverse events of special interest	N
gastrointestinal perforation and inflammatory bowel disease:	1
tuberculosis,	4 latent
serious infection	15
herpes zoster;	22
opportunistic infection;	2+ (No information from OPAL Balance)
interstitial lung disease;	0+ (No information from OPAL Balance)
cardiovascular events;	[redacted]
cancer	13

To provide long-term safety information, interim data from the long-term extension study OPAL Balance were analysed. As of January 25, 2017, no new risks or safety signals were identified in the long-term extension data from the tofacitinib PsA 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. Recommendations on how to appropriately manage the risks associated with tofacitinib (including vaccinations and risks of serious infection) are outlined within the SmPC.

The CS also referred to a health claims database study conducted in an American cohort of PsA patients, in which the incidence of most AEs reported in tofacitinib PsA phase III studies was generally comparable with that observed in a general PsA population, with the exception of the rates of herpes zoster, which were somewhat higher in the tofacitinib cohort than in the real-world comparison cohort (Truven Marketscan Comparison Cohort).[13]

In summary, the adverse events profile of tofacitnib in PsA patients appears similar to, and no worse than that of adalimumab. The tolerability of tofacitinib is reflected in the low rate of withdrawals due to AEs. An increased risk of herpes zoster appears to be a specific AE of tofacitinib.

4.5 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The CS included a systematic review across the intervention of interest (tofacitinib 5 mg) and identified data on all relevant comparators (i.e. adalimumab, secukinumab, golimumab, infliximab, etanercept, apremilast, ustekinumab, certolizumab pegol). In addition, RCTs in the same populations but of interventions not included in the scope for this appraisal (abatacept and ixekizumab) were also included in the network meta-analyses this was judged to be appropriate by the ERG and discussed in

more detail below in sections 4.5.1 and 4.5.2. The methods of the review were also judged to be appropriate and are discussed in more detail above in section 4.1 and in Appendix D of the CS.

The company presented network meta-analyses (NMA) largely based on TA445, a multiple technology assessment of certolizumab pegol and secukinumab for psoriatic arthritis. The ERG compared the data included in the company analyses and the TA445 analyses and confirmed that these data overlapped in most instances.

However, as noted by the company, some inputs in the company NMA differed from TA445 where data used in TA445 were redacted in the report and unavailable in other publications. In addition, some data from other treatments were considered out of scope for TA445, but were included in the company analyses. These new inputs and their impact on findings are summarised below, for further details on studies and data included in the company NMA (see Appendix E in the CS). In addition, in response to clarifications the company provided a spreadsheet comparing findings reported in TA445 with the new data included in the company analyses.

4.5.1 bDMARD naïve population

The ixekizumab arm of the SPIRIT-P1 trial was excluded from TA445 but was included in the company's NMA (only for PASI response). Data from OPAL Broaden also contributed new data on adalimumab and tofacitinib 5mg and 10mg. While inferences obtained for the unlicenced treatments (ixekizumab and tofacitinib 10 mg) were not considered in the economic analyses, the data these studies provide may usefully inform other parameters in the NMA such as class effects, and hence the inclusions of these studies were judged to be appropriate.

Data used at 12 weeks in the FUTURE 2 (secukinumab) and RAPID-PsA (certolizumab pegol) trials were redacted in TA445. For PsARC response the company, instead used data from the mixed populations (i.e. included both bDMARD naïve and experienced patients). These new data did not make a substantial impact on the findings, although in some models this may have led to an underestimate of the effectiveness of secukinumab and certolizumab pegol (placebo adjusted and class-effect models). For PASI 75/90 16 week response data was used for secukinumab as the 12 week data was redacted in TA445. The logs odds ratios using these new data did not differ substantially from those found in TA445

4.5.2 bDMARD experienced population

New data on ixekizumab versus placebo from the SPIRIT-P2 trial and tofacitinib versus placebo from the OPAL Beyond trial were included in the company NMA analyses and these inclusions were judged to be appropriate.

Data from FUTURE 2 on secukinumab 300mg at 12 weeks were redacted in TA445. Therefore, the company's analyses included data at 16 weeks for PASI 75/90 and at 24 weeks for ACR 20/50/70. The secukinumab 300mg estimates were substantially lower for PASI 75 using the new data (TA445: 59.8% (23% to 89%); Model E1 company analyses [redacted]) but similar for PASI 90 (TA445: 36.5% (8% to 75%); Model E1 company analyses [redacted]).

4.5.3 Placebo arm of OPAL Broaden

The CS noted that the placebo response rate in the OPAL Broaden trial was the highest observed (45%) of all the included studies (

Figure 3). This is consistent with TA445, which found that placebo response rates have increased over time. Therefore, the high placebo response rate is not unexpected or unique to trials of tofacitinib.

Figure 3 Placebo rates in PsA trials over time (see Figure 1 in company response to ERG question A18)

In the company response to question A18 of the ERG's points for clarification, the company suggested several potential explanations for the elevated placebo response in OPAL Broaden.

Firstly, unlike many recent trials, some of the older trials did not require patients to have failed DMARDs. This may lead to change over time in patient characteristics for those included in trials.

Secondly, it was a requirement of OPAL Broaden that all participants received a single csDMARD throughout the trial (CS, Table 5). Therefore, concomitant treatment is higher in OPAL Broaden compared with other trials (see Table 1 in response to A9 of the points for clarification letter), as although csDMARDs or methotrexate (MTX) were not excluded in previous trials, none of these previous trials required their use.

However, the ERG considered that the importance of the higher rate of concomitant csDMARDs on placebo response rates was uncertain. Most trials examined the impact of concomitant treatment but there was insufficient evidence to confirm this was an important predictor of placebo response rates. In addition, other trials with high placebo response rates such as FUTURE 2 (51% MTX), RAPID PsA (61.8%), PSUMMIT 1 (46.6% MTX), PSUMMIT2 (47.1% MTX) reported relatively low concomitant treatment in participants receiving placebo. These concomitant medication rates were

similar to trials with the lowest placebo response such as GO-REVEAL (48% MTX), Mease et al 2000 (47% MTX), Genovese et al 2007 (46.9% MTX, 67.3%, other DMARDs).

Thirdly, the company observed [redacted] group as another potential explanation. As above, it is unclear to what extent this explains the higher placebo response rates in OPAL Broaden, particularly as the company did not provide estimates adjusted for geographical location.

4.5.4 Categorising placebo arms

The company's response to A18 of the ERG's points for clarification letter suggested an alternative scenario with placebo arms classified into two categories: PBO1 (older trials and apremilast trials) and PBO2 (newer trials, PSUMMIT1, RAPID-PSA, FUTURE2 and OPAL Broaden).

This categorisation partly reflects the observation in TA445 of a 'placebo creep' over time with the more recent trials reporting higher placebo response rates. However, the ERG considered there to be insufficient justification provided by the company for why apremilast trials should be categorised with the older trials, rather than those conducted from 2013 onwards.

4.6 Critique of the indirect comparison and/or multiple treatment comparison

The company submitted a number of network meta-analyses (NMA) on the effectiveness of tofacitinib (in combination with a csDMARD) compared to up to eight alternative drugs, including anti-ILs and anti-TNFs. The company presents independent analyses of 4 outcomes -- PsARC response, PASI response, HAQ conditional on PsARC response, ACR response – in 2 subpopulations -- bDMARD-naïve (of which OPAL Broaden is assumed representative), and bDMARD-experienced (of which the OPAL Beyond trial is assumed representative). OPAL Broaden evaluates two doses of tofacitinib (10mg BD and 5mg BD) and both were included in the NMA for bDMARD-naïve. The company, however, only presented cost-effectiveness results for tofacitinib 5mg BD and hence we here omit NMA results on tofacitinib 10mg BD. This critique section will focus on the most relevant outcomes for the economic analyses (PsARC response, PASI response, HAQ conditional on PsARC response). The company presents more detailed information relevant to the NMA analyses in the appendices of the main submission:

- The results of the pivotal trials are presented in the main submission and in Appendix M.
- A description of the evidence included in the NMA, of its methods, and of the opinion of the clinical expert on the assumptions of the NMA is in Appendix D,

- The results of the NMA are presented in Appendix E.

Section 4.6 is structured as follows: We will first focus on bDMARD-naïve (section 4.6.1) and only after on bDMARD-experienced (section 4.6.2). Within each subsection, a summary of the main analyses in company's submission (including methods and results) is initially presented separately for each outcome. Note that methods of analyses differ by outcome but are similar across the two subpopulations. Hence, the general approach to modelling each outcome will be described only for the bDMARD-naïve. After summarising the company's submission, we briefly critique it. The critique will be based on comparisons with the recent TA445 that focussed on the same decision problem, and on comparison with the OPAL trials results. Finally, further detail presented in the company's submission, relevant to issues deemed important in the critique are discussed in Section 4.6.3.

4.6.1 bDMARD-naïve

This subsection summarises methods and results of the synthesis of relative treatment effects, but the company has not reported how evidence on placebo-response was considered.

4.6.1.1 Summary of main analyses in company's submission

Summary of main analyses on PsARC

The company identified 14 studies that report PsARC and organised these in a network (Figure 4, PsARC). The company only had access to the published results of Future 2 and RAPID-PsA study results (secukinumab and certolizumab pegol), which included a combination of bDMARD-naïve and bDMARD-experienced patients. In TA445 subgroup specific outcome data was used. The data on PsARC response was modelled using a standard logit model with Binomial likelihood (in line with TA445) which expresses relative treatment effect as log odds ratios. A number of different model specifications were implemented, exploring:

- Independent treatment effects including all trial evidence (models A).
- Adjustment for differing placebo responses across trials (models B), and
- 'Class effects' alongside placebo response adjustment (models C and D). Model C considers the following classes tofacitinib 5mg BD, apremilast, TNFi, anti-IL and model D collapses TNFi and anti-IL into the same class.

All specifications were implemented using fixed and random effects across studies, respectively being identified with the numbers 1 or 2.

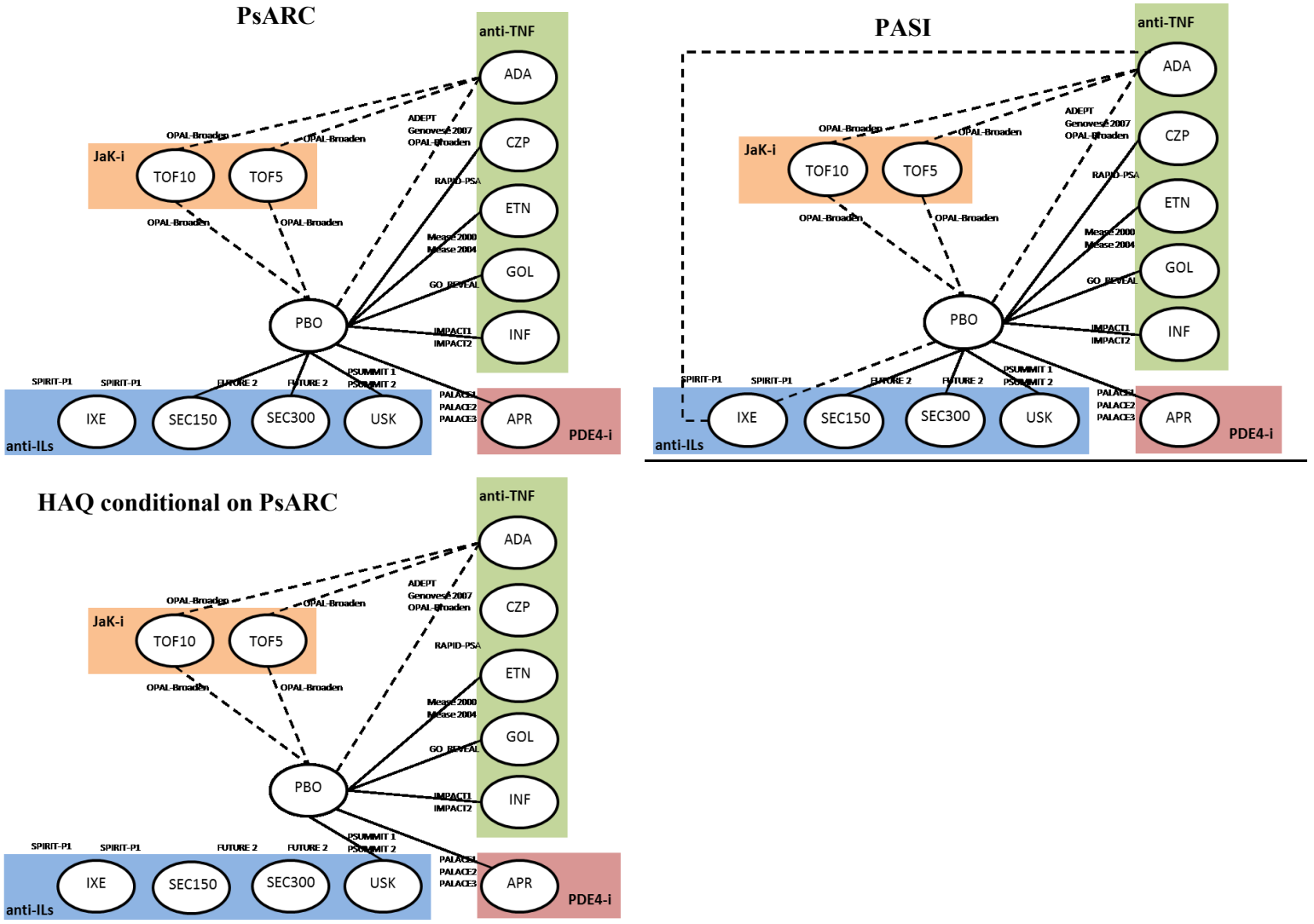
The results show that some interventions have comparable effect estimates. For ease of interpretation, in summarising results we have grouped interventions into three effectiveness levels – higher, intermediate, lower. A summary of the results across model specifications is provided below (see Table E18 in Appendix E for a detailed summary of results):

- Models A show: golimumab, infliximab and etanercept being evaluated as most effective (higher effectiveness group, here with [redacted]), followed by certolizumab, secukinumab 150, adalimumab and secukinumab 300 (intermediate effectiveness group, here with [redacted]), followed by apremilast, ustekinumab and tofacitinib 5mg BD (lower effectiveness group, here with [redacted]). The results are similar between random and fixed effects models.

- Models B show infliximab, etanercept and golimumab ([redacted]) as most effective, followed by secukinumab 150, certolizumab, secukinumab 300 and adalimumab (intermediate effectiveness group, here with [redacted]), followed by ustekinumab, apremilast and tofacitinib 5mg BD (lower effectiveness group, here with [redacted]). Placebo-response adjustment does not significantly alter the composition of the effectiveness groups, but there are some changes in the rankings within the effectiveness groups.

- Results for models C and D do not differ significantly from models B.

Figure 4: Network diagrams for evidence on the different outcome measures



The company used goodness of fit to select from the above model specifications (see TableE18 in Appendix E). Results show that class-effects models (C and D) do not fit as well as models assuming independent effects of the different treatments, and that the placebo adjustment leads to better fitting models (B1 and B2). Within placebo-adjusted models, the random effect model, B2, has the lowest DIC. The company used model B2 as the base case for the economic model.

The results from this model are shown in
Table18, where treatments are ordered according to their relative effectiveness estimates (most effective treatment is ranked 1 and the least effective is ranked 11). Effect estimates are presented using logOR against placebo (the scale in which treatment effect estimates were pooled across studies), ORs for tofacitinib 5mg BD vs other comparators, and absolute predicted PsARC response (this depends on assumptions about placebo response which were not justified in the CS).

The results highlight that all comparators were significantly better than placebo except for tofacitinib 5 mg BD (OR=[redacted]). However, when comparing across interventions, tofacitinib 5 mg BD was not significantly different to treatments in the low or intermediate effectiveness group (apremilast, ustekinumab, adalimumab, secukinumab, and certolizumab pegol), but was statistically inferior to those in the high effectiveness group (etanercept, infliximab, and golimumab). The probability of PsARC response with tofacitinib 5 mg BD was [redacted].

Table18: Main results used in the base case of company's submission (PsARC response, model B2)

	r	treat	LOR comparator vs PBO*	OR of TOF5 vs comparator	PsARC
Hig h	1	IFX	[redacted]	[redacted]	[redacted]
	2	ETN			
	3	GOL			
Interm ediate	4	SEC 150	[redacted]	[redacted]	[redacted]
	5	CZP			
	6	SEC 300			
	7	ADA			
Low	8	USK	[redacted]	[redacted]	[redacted]
	9	APR			
	10	TOF 5			
	11	PBO	[redacted]	[redacted]	[redacted]

* CI not presented in Table E18

The company also notes that OPAL Broaden is the study with the highest placebo PsARC response ([redacted]) among the included trials. For a summary of company discussion of the placebo response in OPAL Broaden and ERG critique see section 4.5.

To further explore this issue, the company submitted an additional analysis, using the specification in model A, where the placebo arm from OPAL Broaden was excluded (model A*). The manufacturer

justifies this analysis on the basis of an elevated placebo response, poor model fit in terms of residual deviance and having the support of the clinical expert that advised on the submission (see Section D.2.3 in Appendix D). This analyses returns very similar results to model A1, with the exceptions of adalimumab and tofacitinib 5mg BD, which now present better effectiveness. Specifically, in model A1 tofacitinib 5mg BD was the lowest ranking treatment (LOR of [redacted]) and in model A1* it presented better effectiveness than apremilast and ustekinumab (LOR of [redacted]).

Summary of main analyses on PASI

The evidence network used by the company is shown in Figure 4. The IMPACT trial was excluded from the NMA due to the extreme values reported in the trial (PASI 50 response was 0% for placebo and 100% for IFX). Ixekizumab was not NICE approved in the UK for PsA at the time of company's review; however the phase III study SPIRIT P1 had been published and was included in the network.

The NMA estimated the probability of PASI response at different thresholds (50/75/90) within a multinomial probit model. The single model included all categories of PASI and evaluated a single effect estimate for each treatment (expressed as a probit) that is then used to obtain probabilities of achieving PASI 50, PASI 75 and PASI 90. The company considered two alternative model specifications:

- Model E: Independent treatment effect and no placebo-response adjustment, and
- Model F: Independent treatment effect and placebo-response adjustment.

The results show that:

- Model E2 (Table E31, Appendix E and Table 2 below) identifies infliximab and ixekizumab as most effective (highest effectiveness group), followed by secukinumab and golimumab, (intermediate/high effectiveness group), followed by adalimumab and ustekinumab (intermediate/low effectiveness group), and lastly tofacitinib 5mg BD, certolizumab pegol, etanercept, apremilast (lowest effectiveness group). Results for model E1 (Table E29, Appendix E) only differ for ustekinumab, which had an effect estimate closer to adalimumab. Note that in Table 2 we omit results on ixekizumab as this is not a comparator in the submission.
- Model F does not differ from E1 indicating no effect of placebo-response adjustment.

Model selection used DIC as a goodness of fit criterion. The company found that the placebo-response adjusted FE model fitted the data as well as unadjusted FE models. The random effect model (E2), implemented only without placebo-adjustment, was used as the base case as DIC was significantly lower for this model.

The results of the base case model (E2) showed that tofacitinib 5 mg BD was not significantly different from placebo, nor from its comparators (see Table 19 and Table E31 in Appendix E). Tofacitinib 5 mg BD was estimated to have a [redacted] probability for a PASI 50 response , [redacted] for a PASI 75 response, and [redacted] for PASI 90 response

Table 19: Main results used in the base case of company's submission (PASI) (adapted from Table E31 in CS)

PASI Base case model (E2)						
			probit	PASI50	PASI75	PASI90
High	1	IFX	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate to High	2	SEC 300	[redacted]	[redacted]	[redacted]	[redacted]
	3	GOL	[redacted]	[redacted]	[redacted]	[redacted]
	4	SEC 150	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate to High	5	USK	[redacted]	[redacted]	[redacted]	[redacted]
	6	ADA	[redacted]	[redacted]	[redacted]	[redacted]
	7	TOF 5	[redacted]	[redacted]	[redacted]	[redacted]
Low	8	CZP	[redacted]	[redacted]	[redacted]	[redacted]
	9	ETN	[redacted]	[redacted]	[redacted]	[redacted]
	10	APR	[redacted]	[redacted]	[redacted]	[redacted]
PBO	11	PBO	[redacted]	[redacted]	[redacted]	[redacted]

Summary of main analyses on HAQ change conditional on PsARC response

The network of evidence for HAQ change conditional on PsARC response used by the company is shown in Figure 4. The analyses did not include Future 2 and RAPID-PsA, as the bDMARD-naïve data were redacted in TA445 and were not available in the primary publications. Hence, no results for certolizumab pegol and secukinumab for HAQ-DI could be presented in the submission.

Two alternative Normal models were used for HAQ-DI conditional on PsARC response status.

- Both G and H model the difference between placebo responders, treated responders and treated non-responders all in relation to placebo non-responders (approach used in TA445). Model G considers independent treatment effects while H evaluates class effects (classes: tofacitinib 5mg BD, apremilast, TNFi, anti-IL)
- Model K is an alternative model to the above, where data from the PsARC responder subgroup are analysed separately from the data for the PsARC non-responders. The common baseline is change in HAQ-DI for placebo responders in the PsARC responder analyses, and change in HAQ-DI for placebo non-responders in the PsARC non-responders analyses. The model adjusts the trial variance to account for multi-arm studies and the manufacturer hypothesises that a RE model would take a better account of heterogeneity.
- Placebo-adjusted models were not undertaken (in line with TA445).

In response to ERG request for clarifications, the company submitted more detailed results, corrected NMA estimates for HAQ-DI change for responders in the bDMARD-naïve population. The updated values are shown below in Table 20.

Infliximab and ETA are associated with the highest HAQ reductions in PsARC responders across all models. Of the remainder, ustekinumab, adalimumab, tofacitinib 5mg BD, and golimumab show similar results for PsARC responders, but tofacitinib 5mg BD shows much higher effects than others on HAQ for non-responders (comparable to infliximab and ETN)

Table 20: Main results used in the base case of company's submission (HAQ conditional on PsARC response, model K2) -- Corrected

	r		Predicted HAQ change	
			Responders *	Non-responders
High	1	IFX	[redacted]	[redacted]
	2	ETN		
Intermediate	3	USK		
	4	ADA		
	5	TOF 5		
Low	6	GOL		
	7	APR		
PBO	8	PBO		

*results corrected in clarification

4.6.2 BDMARD-experienced

4.6.2.1 Summary of main analyses in company's submission

Summary of main analyses on PsARC

Data from 2 studies were included in the network (see Figure 5). Only model A1 was implemented (independent treatment effects, no placebo-response adjustment, see section 4.6.1). The results from the model are shown in Table 21, where tofacitinib 5mg BD is estimated to have a PsARC response very similar to ustekinumab.

Summary of main analyses on PASI

The company analyses on PASI included new evidence from the TOF comparison from OPAL Beyond, IXE from SPIRIT-P2, and ABA from ASTRAEA in addition to that used in TA445. Data from FUTURE 2 on secukinumab 300mg at 12 weeks were redacted in TA445. Therefore, the company's analyses included data at 16 weeks for PASI 75/90 and at 24 weeks for ACR 20/50/70.

Only model E1 was implemented, with and without 24-week data (the latter excludes the comparison with IXE). The results of the NMA model (with 24-week data) is shown in Table 21. Ustekinumab and secukinumab show best PASI responses, followed by IXE. Tofacitinib 5mg BD had a PASI response slightly higher but not significantly different from placebo. ABA shows response levels similar to placebo. The exclusion of 24-week data does not alter results significantly. The secukinumab 300mg estimates were substantially lower for PASI 75 using the new data (TA445: 59.8% (23% to 89%); Model E1 company analyses [redacted]) but similar for PASI 90 (TA445: 36.5% (8% to 75%); Model E1 company analyses [redacted]).

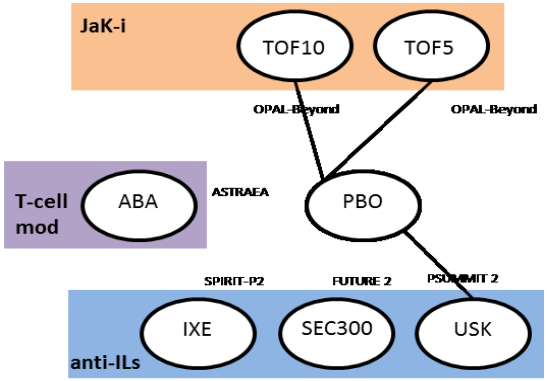
Summary of main analyses on HAQ change conditional on PsARC response

The manufacturer implemented models G and K, which were both fixed effects. Contrary to the bDMARD naïve population, in experienced patients the manufacturer chose model G for the base case and K for sensitivity analyses.

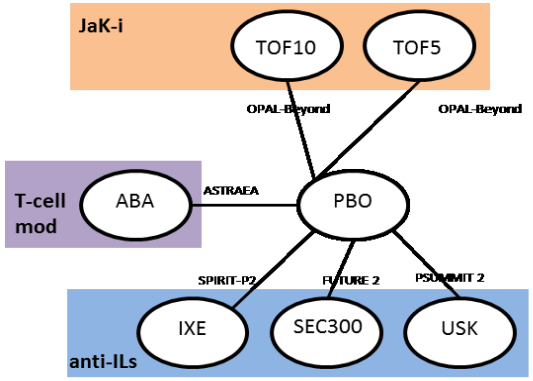
The results from model G are shown in Table 21. Results show that model G (chosen for the base case) evaluates tofacitinib 5mg BD to have higher HAQ changes than ustekinumab in both responders and non-responders, while model K presents ustekinumab as having the highest HAQ improvement in responders.

Figure 5: Network diagrams for DMARD experienced population

PsARC



PASI



HAQ conditional on PsARC

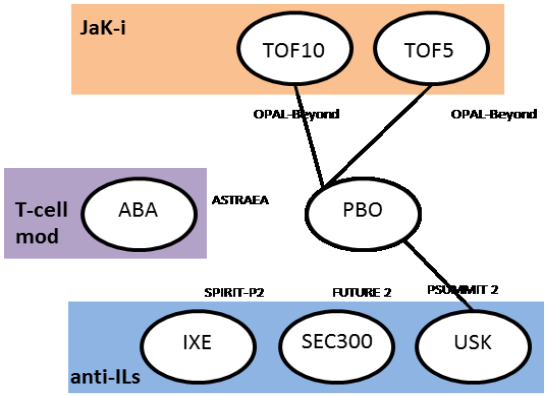


Table 21 Results from NMA in DMARD experienced population

PsARC Base case model (A1)

Rank	treat	PsARC
1	USK	[redacted]
2	TOF5	[redacted]
3	TOF10	[redacted]
4	PBO	[redacted]

PASI Base case model (E1)

		PASI50	PASI75	PASI90
1	USK	[redacted]	[redacted]	[redacted]
2	SEC 300	[redacted]	[redacted]	[redacted]
3	IXE 80 Q2W	[redacted]	[redacted]	[redacted]
4	IXE 80 Q4W	[redacted]	[redacted]	[redacted]
5	TOF 10	[redacted]	[redacted]	[redacted]
6	TOF 5	[redacted]	[redacted]	[redacted]
7	PBO	[redacted]	[redacted]	[redacted]
8	ABA	[redacted]	[redacted]	[redacted]

HAQ conditional on PsARC (Model G1)

		Predicted HAQ change	
		Responders	*Non-responders*
1	TOF10	[redacted]	[redacted]
2	TOF5	[redacted]	[redacted]
3	USK	[redacted]	[redacted]
4	PBO	[redacted]	[redacted]

4.6.3 Critique of NMA and outstanding issues

4.6.3.1 Critique of analyses implemented for bDMARD naïve population

Across all analyses of PsARC response, presented by the company, tofacitinib 5mg BD is consistently in the lower effectiveness group, which also includes apremilast. Results vary slightly across specifications in how similar its effectiveness is in relation to apremilast: e.g. in model A the LOR for apremilast is [redacted] and for tofacitinib 5mg BD is [redacted] and in model B2 (base case) apremilast's LOR is [redacted] and tofacitinib 5mg BD is [redacted]

The evidence network and data included in the company NMAs substantially overlap with TA445 (see Figure 4 for new evidence since TA445 illustrated with dashed lines).

PsARC response

The range of model specifications tested in the company analyses of PsARC outcomes was similar to TA445. However, the company's NMA results differed from those obtained in TA445:

- Results of the independent models (not adjusted for placebo response) are very similar except for adalimumab which was found to be more effective in TA445 (LOR= 1.352) than in the company submission (LOR= [redacted]).
- The results of the placebo-adjusted models (B1 and B2) differ substantially. In TA445, placebo-response adjustment had a pronounced impact on the rankings: secukinumab became most effective with a LOR of 2.1. Etanercept, infliximab and certolizumab pegol were of similar effectiveness (but LOR values reduced to below 2). Golimumab moved down in the ranking to LOR values around 1.6. LORs for ustekinumab and adalimumab were close to, but above, 1. Apremilast was still the least effective (LOR of 0.765).
- The AG in TA445 also explored placebo-response adjusted models with class effects. However, although the company include similar models data were not used to inform the cost-effectiveness analyses
- The AG in TA445 concluded that without any clear rationale for the placebo effect, the results of the placebo-response adjusted model should be interpreted with caution. The model with independent treatment effects was hence used in the base case in TA445, and the best fitting model including placebo-response adjustment and class effect was used in sensitivity analysis.
- OPAL Broaden showed a much higher PsARC placebo response (of 44.8%) than that modelled.

PASI response

TA445 applied models equivalent to E1 and F1, but random effects models were not evaluated. The results were relatively similar to the company's except for secukinumab and adalimumab. In TA445 secukinumab and adalimumab were estimated to have higher PASI responses.

As with PsARC, OPAL Broaden showed a higher placebo response on PASI (of [redacted] respectively for PASI50, PASI75 and PASI90) than that modelled. The model found adalimumab response was similar to tofacitinib 5mg BD; the trial shows, however, that while this holds for PASI 50 ([redacted] for tofacitinib 5mg BD and [redacted] for adalimumab), PASI75 and PASI90 show better results for tofacitinib 5mg BD ([redacted] for PASI75 and [redacted] for PASI90).

HAQ conditional on PsARC response

Model specifications and findings of the company analyses (model G) were similar to TA445 for HAQ changes conditional on PsARC. Predictions from model G were also consistent with the results from OPAL Broaden, including for placebo. However, there are significant differences in predictions from model K particularly in what concerns responders to PsARC.

4.6.3.2 Critique of analyses implemented for bDMARD experienced population

The PsARC response rates from the company analyses for ustekinumab were similar to those in TA445, but TA445 was able to include data for secukinumab, which showed higher effectiveness than ustekinumab. OPAL Beyond showed a similar placebo response (of [redacted]) and tofacitinib 5mg BD response (of [redacted]) to that modelled.

TA445 found lower placebo response rates for PASI (8.8% to PASI 50), and higher responses to secukinumab 300 than ustekinumab (PASI 50 of, respectively, 87.5% and 62.8%).

OPAL Beyond had a higher placebo PASI responses rate (of 26.7%, 15% and 10%, respectively for PASI50, PASI75 and PASI90) than those modelled. Responses observed in the trial for TOF are 45%, 21% and 13.75% respectively for PASI50, PASI75 and PASI90.

[redacted]. The predictions for model G are slightly closer to trial results. HAQ changes in non-responders were low and very similar in the trial.

4.6.3.3 Outstanding issues

The ERG identified no significant issues with analyses relating to the bDMARD-experienced population. There are two outstanding issues on the evidence synthesis for the bDMARD-naïve population. The first issue is of key importance, concerning the validity of the placebo-response adjusted models for the estimation of treatment effects over PsARC response on the bDMARD-naïve population. This is be explored in the next section. The second outstanding issue is the level of placebo-response for PsARC and PASI response outcomes. The manufacturer has not identified the assumptions underlying the placebo-response assumed in the models. Typically, placebo response rates are informed by synthesising data from the literature but it is not clear whether this is the case in the company analyses. However, given the values used are similar to those in TA445, this issue will not be explored further.

4.7 Additional work on clinical effectiveness undertaken by the ERG

This section will focus on two aspects of the submission on the bDMARD-naïve population:

- A correction on the PsARC models with adjustment for placebo-response (models B)
- Revisiting model selection following the model correction (models C and D).

4.7.1 Correction of placebo-response adjusted models for PsARC

Given the disparities found in the placebo-adjusted models between the company's submission and TA445, the company was asked, in response to ERG requests for clarification, to justify the differences and explore why the placebo arm of the OPAL Broaden trial did not fit well in the NMA model with placebo adjustment for PsARC. In response to clarifications two additional analyses were submitted by the company:

1. Placebo comparator arms were split into two separate comparators:
   This new analysis splits the placebo arms into two: PBO 1 (older trials and apremilast trials) and PBO 2 (newer trials, PSUMMIT, RAPID-PsA, FUTURE 2 and OPAL Broaden). The company argued the higher placebo response in newer trials might reflect a difference in previous and/or concomitant treatments between newer and older trials (except for apremilast, which has a similar placebo response to the older trials). For further discussion of differences between newer and older trials, please see section 4.5 above. The results of this new analysis (detailed in Table 2 in response to clarification document) indicate that PBO 1 had lower odds of PsARC response compared to PBO 2. All treatments hence had lower OR vs. PBO 2 than with PBO1. The model specification means that the rankings are retained between comparisons to PBO 1 and PBO 2 (no placebo adjustment). The ORs for tofacitinib, certolizumab, secukinumab, and ustekinumab when compared to PBO 2 are a better match to the trial data placebo comparisons (OPAL Broaden, RAPID-PSA, FUTURE 2, PSUMMIT1 and 2). The ORs for the TNFis etanercept, infliximab, and golimumab when compared to PBO 1 were a better match to the placebo comparisons reported in the trials (Mease 2000, 2004, IMPACT1 and 2, GO-REVEAL). In this analysis tofacitinib 5mg BD was more effective than apremilast.
2. Placebo adjustment was allowed to differ by treatment: a placebo-adjusted model specification was used, but instead of assuming a common placebo effect across treatments, the coefficient beta was allowed to vary by treatment, with all betas drawn from a common random-effects distribution. (Results in Sheet A18 in the Excel workbook that accompanies the response to clarification). This model returned different rankings to all previous models, and some nonsensical results, with apremilast evaluated as second most effective treatment.

In the clarification questions, the company was also asked to provide all files required to run the NMA models in WinBUGS (including data, model, and initial values for every chain). The ERG checked the models and found that placebo-response adjusted models were incorrectly implemented (see appendix A). This means that results presented in the main submission for models B, C and D, and for the two analyses described above, are thus incorrect.

The company's base case, model B2, was corrected by the ERG (based on 100,000 iterations with a thin of 15 from 3 independent chains after a burn-in of 50,000), and results are shown in Table **22**. The treatment effects are interpreted as the effects for patients with a baseline probability of PsARC of [redacted] (logit probability of [redacted]). The model estimates a credible region for the interaction term B far from zero, suggesting a strong interaction effect between the baseline risk and the treatment effects.

Table 22: Main results used in the base case of company's submission (PsARC response, model B2) -- Corrected

	r	treat	LOR, comparator vs PBO*	OR of TOF5 vs comparator	PsARC response
High	1	ETN	[redacted]	[redacted]	[redacted]
	2	IFX	[redacted]	[redacted]	[redacted]
Intermediate high	3	SEC 150	[redacted]	[redacted]	[redacted]
	4	GOL	[redacted]	[redacted]	[redacted]
	5	CZP	[redacted]	[redacted]	[redacted]
	6	SEC 300	[redacted]	[redacted]	[redacted]
Intermediate low	7	ADA	[redacted]	[redacted]	[redacted]
	8	USK	[redacted]	[redacted]	[redacted]
low	9	TOF 5	[redacted]	[redacted]	[redacted]
	10	APR	[redacted]	[redacted]	[redacted]
	11	PBO	[redacted]	[redacted]	[redacted]
		B	[redacted]		
		sd	[redacted]		
		sumdev	[redacted]		
		DIC	[redacted]		
		dev[13,1]	[redacted]		

* CI not presented in Table E18

Whilst only multiple studies on the same treatment and with placebo comparison contribute to estimating the placebo-response adjustment coefficient, B, the assumption of a common regression term allows this to be assumed valid in comparisons which only have one trial. This means the change in the rankings is expected (in relation to a model without placebo-response adjustment) and this also affects treatments that have only been trialled once.

Also note that the Table reports the model fit to the OPAL Broaden placebo arm -- dev[13,1] which shows residual deviance for this data point is substantially lower ([redacted] compared with [redacted] in company analyses) and implies a good fit between the data and the model.

The corrected base case model shows:

- etanercept and infliximab are the most effective drugs (higher effectiveness group, here with [redacted]), followed by secukinumab, golimumab and certolizumab (intermediate/high

effectiveness group, here with [redacted]), followed by adalimumab and ustekinumab (intermediate/low effectiveness group, here with [redacted]), and lastly tofacitinib 5mg BD and apremilast (lower effectiveness group, here with [redacted]).

The results highlight that all comparators were significantly better than placebo including tofacitinib 5 mg BD. When comparing across interventions tofacitinib 5 mg BD was not significantly different to any other treatment. The probability of PsARC response with tofacitinib 5 mg BD was [redacted].

Comparison with TA445

There is a noticeable difference in the magnitude of the coefficient on placebo-response when compared to TA445 (-1.4 in TA445 vs. -[redacted] in the CS), which explains the less pronounced effect of placebo-response adjustment on treatment rankings. This is due to the inclusion of OPAL Broaden, a study that includes a pairwise comparison between adalimumab and placebo and therefore informs the PBO effect (together with Genovese and ADEPT). [redacted] plots the crude data from the trials (log odds of placebo response on the x-axis and the log odds ratio for the intervention arm on the y-axis). Each dot in the plot represents pairwise comparisons from each study. The red dots show evidence on adalimumab vs placebo, with the far right dot representing the data for OPAL Broaden.

Commercial in confidence - redacted

The trend lines in the figure show the information that contributes to the placebo effect and in red the subset of adalimumab trials. The slope of the red trend line hence represents the information conveyed in the ADA studies on the coefficient for the meta-regression. OPAL Broaden conveys information that complements, and does not contradict, the remaining adalimumab trials (Genovese and ADEPT) regarding the placebo effect coefficient. This information should therefore not be dismissed.

4.7.2 Revisiting model selection for placebo-response adjusted models for PsARC

In this subsection, we implement all model specifications submitted by the manufacturer in order to revisit model selection after the correction to placebo-response adjusted models. The corrected inferences are presented below (Table 23), alongside goodness of fit statistics.

Table 23 : Results of a range of NMA models (PsARC response) – Corrected

model	A1	A2	B1c	B2c	C1c	D1c	ERG
ADA							
APR							
ETN							
IFX							
USK							
GOL							
TOF 5							
TOF 10							
SEC 150							
SEC 300							
CZP							
B							
SD							
Class: APR							
Class: TOF5, TOF10							
Class: TNFi							
Class: TNFi and anti-IL							
Class: Anti-IL							
Class: TOF5							
Class: TOF10							
precclass							
sumdev							
DIC							

*TNFi: ADA, ETN, IFX, GOL, CZP; Anti-IL: SEC, USK

Results show that:

- placebo-adjustment improves model fit. There is also strong evidence for the impact of placebo-response on effectiveness as its coefficient is statistically significant.
- placebo-adjustment may account for some of the heterogeneity across trials, and hence the fixed effect model (B1) now presents a marginally lower DIC than the random effects model (B2).
- Both class effect models proposed by the company (C and D) fit the data well, and provide better fit to the data than the independent treatment effect models. Model D fits the data as well as C but is most parsimonious. Note, however, that both C and D include TOF5 and TOF10 in the same class. Therefore, the effectiveness of TOF 5 is increased as information is shared across the two doses.
- The ERG extended model D to separate TOF5 and TOF10, whilst keeping all other aspects of the model the same as the company analyses. This model fitted the data as well as the other class effect models tested, but results in the lowest residual deviance and the precision for the class effect is increased.

Whilst the placebo-response adjusted models fit best to the data, the rationale for the differences in placebo-response across trials is not clear and therefore, as highlighted in TA445, the results of the placebo-response adjusted model should be interpreted with caution. We will therefore explore the use of both the independent treatment effects (A2), and of the class effect model proposed by the ERG (placebo-response adjusted class effect model) in Section 6. More detailed summaries of these two models are presented in Table 24.

Table 24: Additional summaries on preferred models for analyses (models A2 and ERG model)

		A2		ERG model	
r	treat	OR of TOF5 vs treat	PsARC treat	OR of TOF5 vs treat	PsARC treat
1	GOL	[redacted]	[redacted]	[redacted]	[redacted]
2	IFX				
3	ETN				
4	CZP				
5	SEC 150				
6	SEC 300				
7	ADA				
8	APR				
9	USK				
10	TOF 5				
11	PBO				

4.8 Conclusions of the clinical effectiveness section

Clinical effectiveness of tofacitinib

The clinical effectiveness of tofacitinib was informed by two good quality RCTs; one for TNFi naïve (OPAL Broaden) and one for TNFi experienced patients (OPAL Beyond). There was also long-term open label follow-up (OPAL Balance).

The trials demonstrated that compared with placebo tofacitib has some degree of efficacy across a range of outcomes in both TNFi naïve and TNFi experienced patients. There were no statistically significant differences between tofacitinib 5mg and adalimumab on radiographic outcomes but OPAL Broaden was not powered to test for non-inferiority.

Non-inferiority of tofacitinib compared with adalimumab on radiographic outcomes

Population adjusted analyses were also conducted to compare tofacitinib and adalimumab, using data from the ADEPT trial as baseline. Findings were inconclusive as the upper confidence interval crossed both the upper and lower NI margins in unadjusted and multivariable models. In addition, there is only data comparing tofacitinib and adalimumab up to 52 weeks and therefore longer term data on the effectiveness of tofacitinib is lacking. Therefore, concurring with the FDA conclusions, there is currently insufficient evidence to support the assumption that tofacitinib halts radiographic progression.

Generalisability

The ERG identified some issues regarding the generalisability of the trials to clinical practice:

- A significant proportion of patients in each RCT (18% and 24%) were treated in combination with sulfasalazine and leflunomide, whereas the marketing authorisation is for tofacitinib in combination with methotrexate (MXT) only.
- The adalimumab comparator in OPAL Broaden was in combination with a csDMARD. This is not reflective of adalimumab in clinical practice or in other trials: usually only a proportion of patients would use adalimumab concomitantly with a csdMARD.
- [redacted]In OPAL Beyond the number and nature of previous TNFis might not reflect how tofacitnib will be used in current practice.
- Treatment with tofacitinib is long-term but the placebo controlled phase was limited to only 3 months.

Network meta-analyses

The data and network meta-analyses (NMA) models used in the company analyses were similar to TA445, a recent multiple technology appraisal. There were two corrections made to the CS: one on HAQ changes conditional on PsARC response (detected by the manufacturer at clarification stage) and another on the placebo adjusted NMAs for PsARC (detected by the ERG).

The final NMA analyses showed that tofacitinib 5mg was consistently ranked among the least effective of the treatments for PsARC, at a similar level of effectiveness to apremilast. Whereas for PASI response and HAQ-DI conditional on PsARC response, tofacitinib 5 mg was associated with level of effectiveness more similar to adalimumab (although uncertainty over the magnitude of effect for tofacitinib is higher than for adalimumab).

The NMA on PsARC response explored an adjustment for the differing placebo response rates seen across trials (as in TA445). The best fitting model used such an adjustment, together with class effects (ERG model). However, the rationale for the differences in placebo response observed across trials is not clear, and hence the independent treatment effects (A2) was also used in the economic model.

Adverse events

The adverse events profile of tofacitnib in PsA patients appears similar to, and no worse than that of adalimumab. The tolerability of tofacitinib is reflected in the low rate of withdrawals due to AEs. An increased risk of herpes zoster appears to be a specific AE of tofacitinib.

5 Cost Effectiveness

This section focuses on the economic evidence submitted by the company and the additional information provided in response to the ERG points for clarification. The submission was subject to a critical review on the basis of the company's report and by direct examination of the electronic version of the model. Section 6 presents additional work undertaken by the ERG to address any errors, further explore key assumptions and possible limitations.

The company's economic submission included:

• A description of the systematic literature review conducted to identify published evidence on the cost-effectiveness of tofacitinib for PsA (CS, Section B.3.1.1) with a complete description of the search strategy in a separate appendix (CS, Appendix G).

• A report on the de novo economic evaluation by the company. The report described the patient population, model structure and treatment pathway (CS, Section B.3.2), the clinical parameters and variables (CS, Section B.3.3), measurement and valuation of health effects (CS, Section B.3.4), cost and healthcare resource use identification, measurement and valuation (CS, Section B.3.5), a summary of the base-case analysis inputs and assumptions (CS, Section B.3.6), the cost-effectiveness results for the base-case and sensitivity analyses (CS, Section B.3.7 and B.3.8) .

• An electronic copy of the company's economic model developed in Microsoft Excel.

In response to a number of points for clarification raised by the ERG, the company submitted:

- A descriptive reply to the ERG's points for clarification, as well as appendices with additional data requested by the ERG.
- An updated version of the company's electronic model incorporating;
    - Corrections to a data entry error in the HAQ-DI NMA results
    - Modifications to the response rate reported in the NMA that were inconsistent between the CS and the economic model
    - Flexibility to specify a separate withdrawal rate for tofacitinib

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 Searches

Cost-effectiveness searches

The search strategies used by the company to identify 1) relevant economic evaluations of tofacitinib and other treatments for PsA and 2) relevant studies of resource use and costs associated with the management of PsA in the UK were presented in full detail in Appendix G.

The following electronic databases were searched on 20th October 2017: Cochrane Library (including the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Cochrane Central Register of Controlled Trials (CENTRAL), NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment Database (HTA)) and EconLit. In addition, MEDLINE, MEDLINE In-Process and EMBASE were searched on 13th November 2017 with a limit applied to restrict retrieval to English language studies. EMBASE was searched from 1996 onwards and MEDLINE was searched back to 1946.

Manual searches of the abstracts of sixteen conference proceedings were conducted for the years of 2015-2017 and publicly available information from the following HTA bodies were searched for any previous, relevant HTA submissions: National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), Common Drug Review (CADTH CDR) and Pharmaceutical Benefits Advisory Committee (PBAC).

In addition, the company searched the reference lists of any identified systematic reviews and included references identified from the clinical effectiveness searches which met the economic inclusion criteria.

Appropriate sources of literature were searched to identify both published and unpublished studies for the cost-effectiveness systematic review and to identify studies of cost and resource use in the management of PsA. The search strategy for EconLit was missing from the company submission, however was provided by the company in their responses to the questions for clarification.

The reporting of the number of hits in the economic PRISMA flow diagram (page 23, Appendix G) was unclear in the company submission. The number of hits from MEDLINE and EMBASE was queried by the ERG, as the numbers did not match those presented in the final results of the search tables (Table G1 EMBASE and Table G2 MEDLINE, pages 5-14, Appendix G). The company replied in their responses to the points for clarification that this was due to additional economic studies found for the review from the clinical effectiveness searches. This seems reasonable but could have been presented more clearly in the PRISMA flow diagram.

The structure of the database search strategies was appropriate, however, the ERG noted that the biosimilar Resima (also known as CT-P13) was missing from the search strategies. The search strategy for the Cochrane Library in Table G3 was found to have missed searches for one of the comparator drugs abatacept. In addition, searches for abatacept and adalimumab were missing from the EconLit strategy. Therefore it is a possibility that relevant economic studies of abatacept or adalimumab for the treatment of PsA would not have been identified by the search strategies presented in the submission.

As with the clinical effectiveness searches, the EMBASE search strategy contained a line to remove conference abstracts from the search results. Although manual searches of relevant conference proceedings were carried out by the company, these were limited to those from 2015-2017. EMBASE could have provided results of relevant conference abstracts prior to this date. It was also noted that the EMBASE strategy did not include searches of the drug trade name field (tn). Searching in this additional field could have improved the comprehensiveness of the EMBASE search.

Health-related quality-of-life searches

The search strategies used by the company to identify health-related quality of life studies were described in full detail in Apppendix H.

The electronic databases MEDLINE (including MEDLINE, Epub Ahead of Print, In-Process & Other Non-Indexed Citations and MEDLINE Daily), EMBASE and the Cochrane Library (including the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Cochrane Central Register of Controlled Trials (CENTRAL), NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment Database (HTA)) and EconLit were searched on 24th January 2018. The searches were restricted to publications from 2016 onwards.

The database searches were supplemented by a manual search of the Health Economics Research Centre Database of Mapping Studies from 2016 onwards. In addition, the company searched the reference lists of any identified systematic reviews.

The searches were designed to update previous quality of life searches for PsA carried out for TA445 in February 2016. The date limit restriction applied to the searches reported in the submission is appropriate to identify any new studies regarding HRQL in PsA published during the period 2016 to 2018. The searches were fit for purpose, conducted correctly and are clearly reported.

5.1.2 Inclusion/exclusion criteria used for study selection

Population

Inclusion criteria: Adult patients with active PsA who have had an inadequate response or who have been intolerant to a prior disease-modifying anti-rheumatic drug (DMARD) therapy

Exclusion criteria: Patients suffering from other rheumatic conditions.

Interventions/Comparators

Inclusion criteria: Tofacitinib, Biologic DMARDs (abatacept SC injection/IV infusion, adalimumab SC injection, etanercept SC injection, golimumab SC injection, infliximab IV infusion, certolizumab pegol SC injection, ustekinumab SC injection, secukinumab SC injection, ixekizumab SC injection)

and PDE-4 inhibitor (apremilast administered orally).

Exclusion criteria: Diagnostics. No restrictions placed on dosing regimen, including whether the treatments are used as monotherapy or in combination with another treatment or whether the UK-licensed dose is used.

Outcomes

Inclusion criteria: cost in combination with any of the following; LYGs, QALYs, DALYs.

No exclusion criteria specified for this domain.

Study design

Inclusion criteria: Comparative economic evaluations including cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses, cost-minimisation analyses, cost-minimisation analyses, cost-consequence studies and economic evaluations of a single cohort.

Exclusion criteria: case reports and case studies. Editorials and any other non-systematic reviews.

Publication type

Systematic reviews of economic evaluations were included at the title/abstract screening stage and used for identification of any additional primary studies not identified through the database searches but were excluded during the full-text review stage.

Language restrictions

Inclusion criteria: English

Exclusion criteria: Non-English

The inclusion and exclusion criteria for the systematic review were supported by the rationale for each criteria as provided in Table G5 in Appendix G. However, excluding non-English language papers

means relevant foreign language papers may have been missed.

5.1.3 Studies included and excluded in the cost effectiveness review

No previously published cost-effectiveness studies of tofacitinib for PsA were identified.

The systematic review identified 17 evaluations that met the inclusion criteria. Fourteen of these were UK publications and the remaining 3 were non-UK evaluations which were deemed not relevant for decision-making in England. Of the 14 UK publications, 3 were NICE HTA monographs, 2 were NICE ERG reports, 3 were UK HTA review articles and 6 were some other form of UK evaluation.

Table 25 describes the UK publications that met the inclusion criteria and identifies the type of publication.

Table 25 Studies included in the cost-effectiveness review

Year	Author	Title	Type of publication
2006	Bansback et al	Estimating the cost and health status consequences of treatment with TNF antagonists in patients with psoriatic arthritis.	Other form of UK evaluation
2006	Woolacott et al	Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.	HTA monograph for TA104
2007	Bravo Vergel et al	The cost-effectiveness of etanercept and infliximab for the treatment of patients with psoriatic arthritis.	Other form of UK evaluation
2011	Cummins et al	Cost-effectiveness of infliximab for the treatment of active and progressive psoriatic arthritis.	Other form of UK evaluation
2011	Rodgers et al	Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.	HTA monograph for TA199

2011	Bojke et al	Modelling the cost-effectiveness of biologic treatments for psoriatic arthritis.	Other form of UK evaluation
2012	Yang et al	Golimumab for the Treatment of Psoriatic Arthritis: A NICE Single Technology Appraisal.	Review article
2012	Cummins et al	Cost effectiveness of golimumab for the treatment of active psoriatic arthritis.	Other form of UK evaluation
2014	Cawson et al	Systematic review, network meta-analysis and economic evaluation of biological therapy for the management of active psoriatic arthritis.	Other form of UK evaluation
2016	O'Connor et al	The Clinical and Cost Effectiveness of Ustekinumab for the Treatment of Psoriatic Arthritis: A Critique of the Evidence.	Review article
2016	Sideris et al	The Clinical and Cost Effectiveness of Apremilast for the Treatment of Psoriatic Arthritis: A Critique of the Evidence.	Review article
2017	Corbett et al	Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease-modifying antirheumatic drugs: a systematic review and economic evaluation.	HTA monograph for TA445

As described in Section 5.1.1, the company performed a search of the HTA websites. This search revealed the following appraisals: NICE (n=5 complete; n=1withdrawn; n=3 in progress), SMC (n=8), PBAC (n=6) and CADTH (n=6) ranging from 2005 to 2017. Tables G28-G33 in Appendix G summarise each of the identified TAs but it is unclear from the CS or Appendix how the company incorporated the result of this HTA search into their review.

5.1.4 Conclusions of the cost effectiveness review

Aside from the exclusion of non-English language papers, the search strategies were well specified and the searches appear to have been conducted appropriately.

The review identified a number of previous economic models but as mentioned in Section 5.1.3, no previous models were found which included tofacitinib as a comparator. Most of the evaluations identified were developed for, or based on those developed for, NICE technology appraisals. [1, 14-16]The company performed a quality assessment of the included studies and provided this in Appendix G (Tables G19-G27). The majority of the models adopted the same structure, and the company chose a similar structure to model the cost-effectiveness of tofacitinib.

It is clear from the systematic review that TA445 is the most comparable economic evaluation to the company's submission. However, the company does not explicitly identify this in the CS.

5.2 ERG's summary and critique of company's submitted economic evaluation

An overall summary of the company's approach and references to the relevant sections in the CS are reported in Table 26 below.

Table 26 Summary of the Company's economic evaluation (and signposts to company's submission)

Element	Approach	Source/Justification	CS reference
Model	A Markov model with 40 year time horizon and a 3-month cycle length. The model evaluates the cost-effectiveness of tofacitinib versus NICE-recommended comparators. The model reflects initial response to treatments, continued use or withdrawal from the treatment. Both the skin and joint symptoms of PsA are taken into account.	The model structure, methods and assumptions are reflective of current NICE guidance.	Section B3; p115
States and events	Response to treatment was evaluated according to PsARC response three months from baseline for all comparators. Non-responders transitioned to the subsequent treatment in the pathway; responders were assumed to continue treatment until they withdrew due to either a loss of efficacy, adverse events or death. Transitions from the treatment state to alternative pathways were determined by initial response rates and discontinuation rates. Adverse events were not modelled.	Transition response criteria according to BSR guidance and company's NMA. Withdrawals based on recent NICE guidance and [1].	Section B3; p115
Population and subgroups	Adults with active PsA whose disease has not responded adequately to previous DMARD therapy or for whom DMARDs are not tolerated or contraindicated.		Section B.1.1, Table 1, p;12 Section B.3.2.1. p113-114.

	The baseline characteristics were sourced from the tofacitinib trial population which includes both patients who had previously received biologic therapies and biologic-naïve patients. Four sub-populations were defined: 1) People whose disease has not responded adequately to 1 non-biological DMARD (Results not submitted for sub-population 1) 2) People whose disease has not responded adequately to at least 2 non-biological DMARDs 3) People whose disease has not responded adequately to non-biological DMARDs and 1 or more TNFis 4) People in whom TNFi are contraindicated or not tolerated.	The drug company seek to align the sup-populations assessed in the TA of tofacitinib for treating active PsA with cDMARDS to the populations that have received positive recommendations from NICE in previous TAs (i.e. sup-populations 2, 3 and 4)	
Comparators	Sequences of treatments are modelled. These include the comparator technologies: TNFis (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), secukinumab (an IL 17A inhibitor), ustekinumab (an IL12/IL23 inhibitor), apremilast (a PDE4 inhibitor), and best supportive care (BSC).	The NICE scope lists certolizumab pegol as a comparator for sub-population 3, which includes people whose disease has not responded adequately to non-biological DMARDs and 1 or more TNFi. Certolizumab pegol has been excluded from sub-population 3 because the data available from the RAPID PsA trial informs only a subset of patients in this sub-population (i.e., primary responders to a prior TNFi who were secondary failures [primary non-responders were explicitly excluded from this trial]) [1].	Section B.3.2.3; p118-119
Natural history	For patients receiving BSC or csDMARDS, a HAQ progression rate of 0.077 per year was applied. Patients can reach a maximum score of 3.	Obtained from NICE PsA guidance[14, 15] as estimated from Norfolk Arthritis Register [17].	Section B.3.3.1.5; P125
Treatment effectiveness	Criterion for continuing treatment was the probability of PsARC response, assessed at 12 weeks. Following initial response (or non-response) to treatment at 12 weeks, the arthritis and psoriasis-specific components of PsA are modelled separately.	Obtained from the company's NMA.	Section B.3.2.2; p114-117

	The arthritis component was modelled via a change in HAQ-DI score conditional on PsARC at 12 weeks. The psoriasis component was modelled via changes in PASI score at 12 weeks.		
Effectiveness of subsequent lines of therapy	For comparisons involving more than one line of treatment, subsequent treatments are assumed to be as efficacious as first line, i.e. no effect degradation is assumed.		
Discontinuation	12-week probability of withdrawal of 3.96% was included in the model. Patients who discontinued a treatment transitioned to the next treatment option or BSC when they had failed all treatments. Rebound to the baseline HAQ value was assumed for patients entering BSC (termed as rebound to initial gain).	NICE PsA Guidance as obtained from the York model [14].	Section B.3.3.1.; p 125
Adverse events	Adverse events were not explicitly modelled. AEs were only considered implicitly in terms of their effect on initial response and withdrawal for each treatment.	NICE PsA guidance as obtained from Corbett et al in 2017 [1].	
Mortality	Mortality rates were derived from life table for England and Wales (2014-2016).	A standardised mortality rate (1.36) reported by Ali et al [18] and as applied in TA445 was used [15].	Section B.3.3.1.7 p; 129
Health-related quality of life	Patients HRQoL is defined in the model in terms of HAQ and PASI scores, and these are mapped to EQ-5D. Patients HAQ-DI and PASI scores change according to treatment response. HAQ-DI scores remain constant while patients are on treatment with bDMARDS or tofacitinib but progress linearly while patients are on apremilast or BSC (reflecting worsening of physical functions following failure to respond to treatment. PASI scores do not progress on BSC as they are not progressive. Whilst on treatment, improvements in PASI scores are possible.	In the base case analysis utilities were based on a linear regression. A utility model based on tofacitinib trial data was used in scenario analysis and applied to either tofacitinib alone, or to tofacitinib and its comparators.	Section 3.4.2. p; 130-131
Resource utilization and costs	Costs included were: drug acquisition costs; drug administration costs and monitoring costs. Arthritis and psoriasis-related costs were also applied in the model and based on the HAQ-DI and PASI scores.	Resource use associated with drug administration and monitoring costs were obtained from the BNF [19] and TA199 and TA445, respectively [14, 15]. Acquisition costs were taken from the BNF and electronic market information tool (eMIT)	Section B.3.5. p;133-142

	Costs for the following treatments differ between the first cycle and subsequent cycles to account for loading doses or PAS arrangements; Apremilast, Certolizumab Pegol, Infliximab, Secukinumab and Ustekinumab.	database [19, 20]. No drug costs are assumed for BSC. Patient Access Scheme prices are listed where information is in the public domain. Administration and monitoring costs (except for liver function text, chest x-ray and TB heaf test costs)* were obtained from the NHS reference costs and PSSRU [21, 22]. Arthritis-related costs were estimated as a function of HAQ-DI score, based on Rodgers et al. Psoriasis-related costs based on PASI scores were obtained from TA445 [15]. Adverse events were not considered in the model	
Discount rates	3.5% for utilities and costs	NICE reference case	Section B.3.2.2. p; 117
Sensitivity analysis	Probabilistic sensitivity analysis and scenario analysis were performed. Deterministic sensitivity analysis were not performed.	Deterministic sensitivity analysis was not performed.	Section B.3.8.1. p;147 Section B.3.8.2 p;154

*Obtained from TA445

5.2.1 Model structure

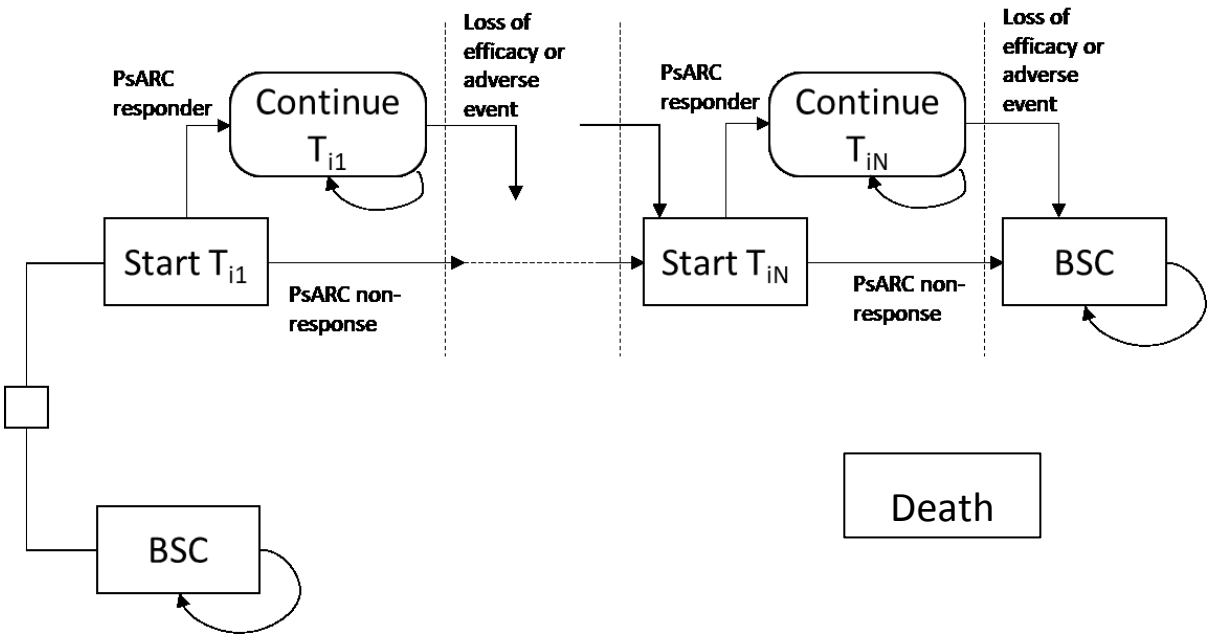
The company describes a de novo economic evaluation based on a Markov cohort model similar to the model structure used by the York Assessment Group (AG) in TA445 [15]. The model was developed in Microsoft Excel to evaluate the cost-effectiveness of tofacitinib. The model structure allows a comparison of multiple treatment sequences (see Section 5.2.4). The model allows patients to cycle through sequences of therapy, with patients remaining on a treatment after the first 3 months if they have met the required criteria.

After an initial response to treatment, patients remain on therapy until either a loss of efficacy, the occurrence of particular adverse events or death. Transition to death (all cause and excess due to PsA) is included at each cycle of the model.

A schematic representation of the company's model is shown in

Figure 7. Rather than specifying health states, between which patients transition, the company defines states relating to which treatment is being received and if this is during the primary response or maintenance phase.

Figure 7 Model Summary (Figure 15, p115 in CS)



Patients may transition to the death state from any other state. Abbreviations: BSC, best supportive care; PsARC, Psoriatic Arthritis Response Criteria; T_{I1}, first therapy in the i^{th} sequence; T_{iN}, n^{th} therapy in the i^{th} sequence.

In the base case model, Psoriatic Arthritis Response Criteria [PsARC] response at 3 months is used to determine the proportion of patients remaining on treatment. This reflects the clinical management of PsA as recommended by NICE [14, 15, 23, 24] and the BSR [25]. A PsARC response is binary, representing the proportion of people who respond or do not respond to treatment. The psoriasis component of PsA is modelled via changes in Psoriasis Area and Severity Index (PASI) scores, these are defined as the proportion of patients with a 50, 75 and 90% change in their baseline PASI score. In the base case model, it is assumed that PASI change does not determine treatment continuation, thus only PsARC scores are used as the response criteria. PASI response is assumed to be correlated with PsARC responses (Section B3.3.2.1 in CS). Conditional on PsARC response, patients were categorised as PASI-75 (See Section 5.2.3) responders and non-responders, respectively.

Following the initial response (or non-response) to treatment at 3 months, the psoriasis- and arthritis-specific components of PsA are modelled separately. The arthritis component of PsA is modelled via a change in the Health Assessment Questionnaire-Disability Index (HAQ-DI) score conditional on PsARC response at 3 months. Mean changes in HAQ-DI scores for PsARC responders and non-responders were treatment specific and taken from the NMA (Section B.3.2.2 in CS). For PsARC

responders, HAQ-DI change from baseline is maintained beyond 3 months in line with previous modelling approaches, such as that adopted by the AG in TA445 [15] (Section B.3.2.2 in CS), with the exception of apremilast (as per TA433 [26]) and best supportive care (BSC), whereby HAQ scores increase in a linear fashion (see Figure 8 and Section B.3.2.2 in CS).

Figure 8 HAQ score changes over time (Figure 16, p116 in CS)

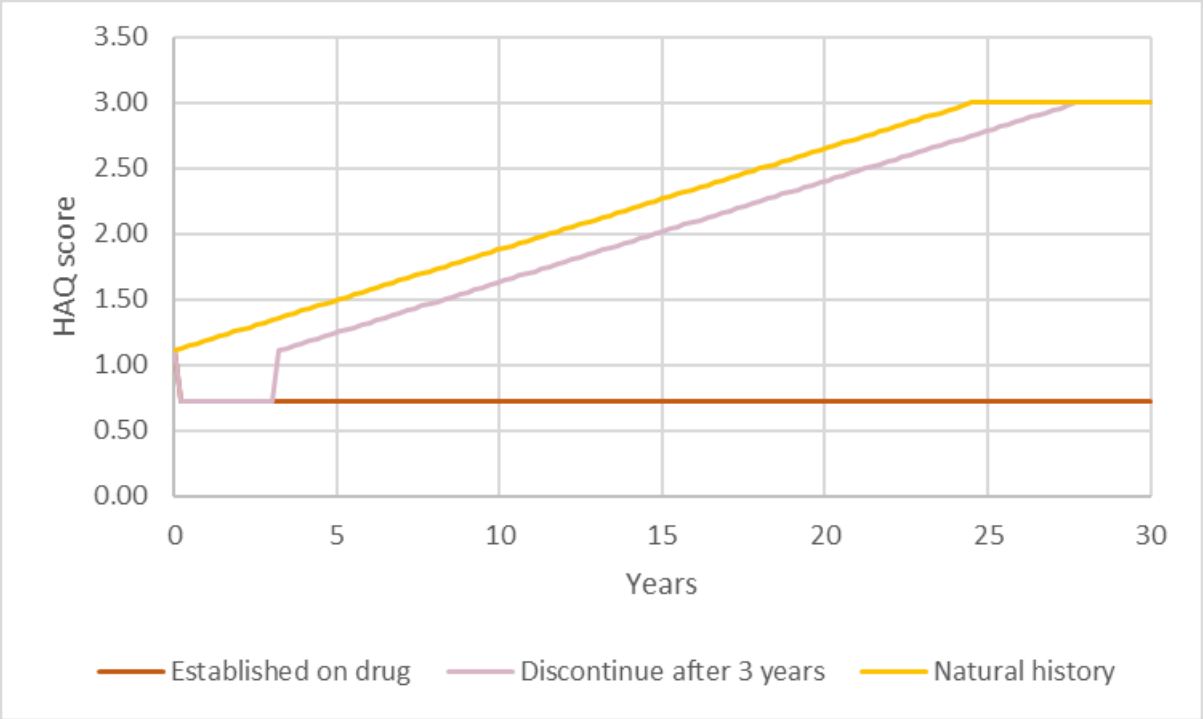


Figure 8 illustrates the progression HAQ-DI over time for three types of patients: a patient successfully established on a bDMARD; a patient discontinuing after 3 years (and transitioning to BSC); and a patient receiving BSC. When patients discontinue treatment, it is assumed that they experience a rebound in HAQ-DI and PASI scores equal to their initial gain. These assumptions are in line with the York AG model [1] from TA445 [15].

For those remaining on treatment (responders) an assumption of no HAQ-DI progression was made for the 'continued use' health state (see Section 5.2.6.3). Patients who discontinued a treatment and transitioned to the next treatment option were assigned the HAQ-DI score for PsARC non-responders receiving the previous treatment for the duration of the trial period of the current treatment, after which they rebound to their starting HAQ-DI score. The psoriasis component of PsA is assumed to be non-progressive and therefore PASI scores do not increase while patients remain on therapy or BSC.

For those patients that progress to BSC the HAQ-DI rebounds back to the pre-treatment level (see Figure 5.1), which is consistent with the rebound equal to gain applied in previous economic models. In addition HAQ-DI subsequently increases at a rate consistent with the natural history of PsA in patients who receive no treatment up to a maximum value of 3. This assumption has been applied in previous economic models in PsA [14]. It is not made explicit in the CS what happens to HAQ-DI post 3 months for non-responders, however in the electronic model this appears to equate to a rebound back to starting HAQ-DI.

Similar to previous models (TA445), a scenario is specified where disease activity is modelled using the American College of Rheumatology response criteria (ACR20/50/90). For example, an ACR20 response is defined as a 20% reduction in ACR, with corresponding terminology used for alternative percentage reductions (e.g., ACR 50 and ACR 70 for 50% and 70% reductions in ACR, respectively) (Section B.3.3.1.4.). The company model allowed additional alternative response scenarios: PASI alone and PASI and PsARC response. The results of these scenarios are not presented in the CS.

5.2.2 The company's economic evaluation compared with the NICE reference case checklist

Table 27 summarises the economic submission and the ERG's assessment of whether the *de novo* evaluation meets NICE's reference case.

Table 27 NICE reference case list

Attribute	Reference Case	Included in CS	Comment on whether de novo evaluation meets requirement of NICE reference case
Comparator(s)	As listed in the scope developed by NICE	Partly	Omitted sub-population 1 (People whose disease has not responded adequately to 1 non-biological DMARD
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes	QALY benefits to patients treated were considered
Perspective on costs	NHS and PSS	Yes	NHS and PSS costs were taken into account
Type of economic evaluation	Cost-effectiveness analysis with fully incremental analysis	Yes	A Markov cohort model was employed for the cost-effectiveness analysis. The model compared the costs and QALY outcomes of treatment sequences.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	Yes	A 40 year time horizon was adopted, consistent with recent published cost-effectiveness analyses. PsA is a chronic, lifetime condition with no known cure. Disease management aims to improve symptoms

			and HRQoL over a patients' lifetime. A 40 year time horizon accounts for the long-term consequences of the disease. However, long-term time-horizons rely on assumptions, due to the lack of long-term data.
Synthesis of evidence on health effects	Based on systematic review	Yes	In the absence of head-to-head trials between the identified comparators, a network meta-analysis was conducted to inform the clinical efficacy parameters in the economic model
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes	A regression equation was used which maps HAQ-DI and PASI scores to EQ-5D. The algorithm generated as part of TA445 [15] was used. Regression coefficients calculated using the EQ-5D results from the tofacitinib trial were only tested in sensitivity analysis and applied to all treatments. (CHECK THIS)
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes	
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes	Utility values were based on ED-5D estimates.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
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	
Discounting	The same annual rate for both costs and health effects.	Yes	Costs and benefits were discounted at 3.5%.

5.2.3 Population

The CS defined the target population for the base case analysis as patients with active PsA whose disease has not responded adequately to previous DMARD therapy or for whom DMARDs are not tolerated or contraindicated. Four sub-populations were outlined in the NICE scope:

1). People whose disease has not responded adequately to 1 non-biological DMARD.

2). People whose disease has not responded adequately to at least 2 non-biological DMARDs.

3). People whose disease has not responded adequately to non-biological DMARDs and 1 or more TNFis

4). People in whom TNFi are contraindicated or not tolerated.

The company sought to align the sup-populations assessed in this technology appraisal (TA) to the populations that have received positive recommendations from NICE in previous TAs (i.e. sup-populations 2, 3 and 4). As a result, the company did not submit results for sub-population 1.

The base case of the company's economic model included patient data from two key Phase III clinical trials, OPAL Broaden and OPAL Beyond (See Section 4). Sub-populations 2 and 4 were informed by the bDMARD-naïve evidence synthesis with data for tofacitinib from OPAL Broaden (csDMARD-IR and TNFi-naïve); and subpopulation 3 was informed by the bDMARD-experienced evidence synthesis with data for tofacitinib from OPAL Beyond (TNFi-IR). Patient characteristics in the tofacitinib trials are discussed in more detail in Section 5.2.6.1.

For all sub- populations (2, 3 and 4), baseline psoriasis is derived from data reported by the British Association of Dermatologists [27]. As per TA445, the population is split into 50% with no psoriasis, 25% with mild to moderate psoriasis, and 25% with moderate to severe psoriasis. In TA445, PASI response was assessed separately for each sub-group defined by its baseline level of psoriasis; no psoriasis (baseline PASI = 0.00), mild to moderate psoriasis (baseline PASI = 7.3) and moderate to severe psoriasis (baseline PASI = 12.5). In the company's model however, a weighted average PASI score of these three subgroups was calculated for the entire population, for each model cycle, therefore sub-populations were not defined according to psoriasis level. It is important to explore this assumption given the impact that differences in baseline characteristics such as HAQ-DI, and particularly PASI scores can have on cost-effectiveness results. More importantly, the severity of psoriasis determines the appropriate dosing of the comparator secukinumab; where secukinumab 300mg is approved for patients with severe psoriasis as opposed to the standard does of secukinumab 150mg. This assumption is explored in section 6**Error! Reference source not found.**.

5.2.4 Interventions and comparators

All technologies included in the cost-effectiveness analysis i.e. TNFis (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), IL inhibitors (secukinumab and ustekinumab) and PDE4 inhibitor (apremilast) were modelled in line with their marketing authorisation. BSC is also

included as a comparator for each sub-population and is representative of the placebo arm of the clinical trials included in the NMA, therefore assuming the same efficacy of placebo. No separate costs are associated with BSC as these costs are assumed to be captured in the estimates of resource use associated with HAQ-DI. It was unclear in the CS how BSC was defined, the ERG asked for clarification on this. In their response to clarification, the company defined BSC as a mixture of csDMARDs and/or usual care (e.g.NSAIDs, corticosteroids). They state that BSC reflects the clinical effectiveness estimates of the placebo groups in the trials of tofacitinib and the relevant comparators of the NMA. They justify their definition as being consistent with TA445 [15].

For tofacitinib, a dosage of 5mg twice daily was assumed, taken orally. The included comparators and their respective dosage regimens are listed below:

- adalimumab 40mg given every other week, administered as a subcutaneous injection
- certolizumab pegol 200mg every other week, administered as a subcutaneous injection
- etanercept 25mg twice weekly, administered as a subcutaneous injection
- golimumab 50mg once a month, administered as a subcutaneous injection
- inflixumab 5mg/kg of body weight every 8 weeks, administered as an intravenous infusion
- secukinumab 150mg once a month, administered as a subcutaneous injection
- secukinumab 300mg once a month, administered as a subcutaneous injection
- secukinumab weighted dose once a month, administered as a subcutaneous injection
- ustekinumab 45mg every 12 weeks, administered as a subcutaneous injection
- apremilast 30mg twice daily, taken orally

The selection of the first treatment in a sequence for each sub-population is based on previous NICE recommendations [14, 15, 23, 24, 26] and the NICE scope. The selection of the second and third treatment options reflects TA445 [15]. As some sub-populations are eligible for more lines of treatment (prior to moving to BSC) than others, the length of treatment sequence varies across the sub-populations.

In terms of the comparators, the final scope issued by NICE included different comparators for different patient populations (see Table 28).

Table 28 Treatment sequences for each patient sub-population (Table 42, p119 in CS)

Patient sub-population	Treatment option as per NICE scope†		
	First in sequence	Second in sequence	Third in sequence
Sub-population 2: Disease has not responded to at least 2 nbDMARDs*	TOF		
	ADA		
	APR		

	CZP	UST	BSC
	ETN		
	GOL		
	INF		
	SEC (188mg, weighted dose)		
	BSC	-	-
Sub-population 3: Disease has not responded to nbDMARDs and at least 1 TNFi	TOF	BSC	-
	SEC (300mg)		
	UST		
	BSC	-	-
Sub-population 4: TNFi contraindicated or not tolerated	TOF	BSC	-
	SEC (188mg, weighted dose)		
	UST		
	BSC	-	-

†First treatment in sequence options are chosen in accordance with NICE guidance [14, 15, 23, 24, 26]. Second- and third treatment in sequence options are aligned with those used in TA445[15].*nbDMARDs ~ csDMARDs

Abbreviations: ADA, adalimumab; APR, apremilast; BSC, best supportive care; bDMARD, biological disease-modifying anti-rheumatic drug; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; nbDMARD, non-biological disease-modifying anti-rheumatic drug; SEC, secukinumab; TNFi, TNF inhibitor; TOF, tofacitinib; UST, ustekinumab.

The NICE scope lists CZP as a comparator for sub-population 3, which includes people whose disease has not responded adequately to non-biological DMARDs and 1 or more TNFi. Similar to TA445, the company excluded CZP from sub-population 3 because the data available from the RAPID PsA trial informs only a subset of patients in this sub-population (i.e., primary responders to a prior TNFi who were secondary failures [primary non-responders were explicitly excluded from this trial]) [1].

For all sub-populations, following a lack of response to PsARC or subsequent withdrawal for PsARC responders, patients moving onto the next line of treatment, are assumed to have the same response probabilities as first line treatment, i.e. no effect degradation is applied for subsequent lines of therapy. The ERG has concerns that the CS does not address the issue of effect degradation for subsequent lines of treatment in the model and question the validity of this assumption [15] . This assumption is discussed further in Section 5.2.6.2.

5.2.5 Perspective, time horizon and discounting

The perspective of the company's de novo economic analysis was the NHS and Personal Social Services and an annual discount rate of 3.5% for both costs and health effects was applied, in line with the NICE reference case.

The time horizon of the model was 40 years, which was stated to be consistent with the most recent published cost-effectiveness analyses in PsA and accounts for the long-term consequences of a chronic, lifetime disease like PsA.

A 3 month cycle length was used. Given the short cycle length, a half-cycle correction was not applied.

5.2.6 Treatment effectiveness and extrapolation

The details of the effectiveness data used in the economic model are discussed in Sections 5.2.6.1. to 5.2.6.6.

5.2.6.1 Baseline Patients Characteristics

The baseline patient characteristics applied in the model were sourced from the tofacitinib clinical trials. Given that the company implemented a network meta-analysis (NMA) to inform treatment efficacy parameters for all treatment in the economic model, the ERG considers that the set of studies included in the NMA could be a more appropriate evidence base to inform the baseline characteristic of the patient population.

Baseline patient characteristics from the NMA are not included in the CS or Appendices for comparison. Instead, Table 29 provides a comparison of baseline characteristics between the bDMARD-naïve and bDMARD-experienced population from the OPAL Broaden and Beyond tofacitinib trial with the baseline characteristics used previously in TA445.

Table 29 Comparison of baseline characteristics

Description	CS (bDMARD-naïve)	CS (bDMARD-experienced)	TA445
Baseline age	47.9	50	47
Gender (% female)	53%	55%	Not identified
Baseline HAQ	1.11	1.30	1.22
Baseline PASI for no psoriasis	0.0	0.0	0.0
Baseline PASI for mild to moderate psoriasis	7.3	7.3	7.3
Baseline PASI for moderate to severe psoriasis	12.5	12.5	12.5

The ERG requested justification for the use of baseline characteristics from the tofacitinib trials (as opposed to the baseline patient characteristics from the trials included in the NMA). The ERG also requested a scenario using the baseline patient characteristics from the NMA.

The company justified the use of baseline characteristics from the trials as the most representative of the populations under consideration due to changes in standard of care since some of the previous trials were conducted, particularly in terms of prior treatments. For example, the company identify that the trials conducted by Mease et al (2000) and the ADEPT trial in 2005 do not include inadequate response to previous DMARD in their inclusion criteria. This does form part of the inclusion criteria in the OPAL trials therefore reflecting the changes in standard of care over time. The company provided the results of the scenario analyses using the baseline patient characteristics from the NMA. Tables 14 to 16 in the company's response to clarification provide these results, which results in only a small change in the ICERs for subpopulations 2-4.

5.2.6.2 Response Rates

In the absence of head-to-head trial data, response rates for all treatments included in the model were obtained primarily from the company NMA. Three outcomes were included in the NMA to inform the economic model; (1) PsARC response, (2) change in HAQ-DI score conditional on PsARC response and (3) PASI 50, PASI 75 and PASI 90 responses. The probability of PsARC response for the bDMARD-naïve and bDMARD-experienced population as implemented in the model and changes in HAQ-DI score conditional on PsARC response are presented in Table 30. Probabilities of PASI 50, PASI 75 and PASI 90 responses for the bDMARD-naïve and bDMARD-experienced population as implemented in the model are reported in Table 31.

In the base case, the model uses PsARC response rates at 3 months to determine the proportion of patients remaining on treatment. This reflects the clinical management of PsA as recommended by NICE [14, 15, 23, 24, 26, 28]. The 3 month cycle length is also reflective of the continuation rule which means that patients must achieve a PsARC response within 3 months to remain on therapy. This continuation rule is in line with guidance from the BSR [29] and previous NICE appraisals [14, 15, 23, 24, 26]. However, this does not reflect the continuation rule for all comparators in the model e.g. APR and SEC, according to their SPCs, should be assessed at week 16 and UST at 24 weeks.

For the bDMARD-experienced population (sub-population 3), in the NMA, it was only possible to estimate PsARC response for tofacitinib 5 mg BD, ustekinumab and placebo due to a lack of response data available in primary and secondary publications. To include PsARC response for secukinumab in the economic model, the odds ratio for secukinumab 300 mg versus placebo was taken from the base-case analysis for the bDMARD-experienced population from TA445 [15]. HAQ-DI change conditional on PsARC response was not available in either the naïve or experienced populations for secukinumab and certolizumab, therefore the values from the TA445 meta-regression NMA of HAQ scores have been incorporated into the model for these comparators in the bDMARD naïve populations. In the

bDMARD experienced population the values have been taken from the TA445 [15] and bDMARD experienced NMA.

Consistent with previous economic models (TA199 [14] and TA445 [15]), it was assumed that PASI-75 response rates may vary by treatment response (based on PsARC). In order to capture this, a positive correlation between PsARC and PASI-75 response was included in the model. The company adopted the correlation coefficient between PsARC and PASI-75 (0.436), as used in the York model in TA199 [14] and TA445 [15].

Table 30 Summary of PsARC response probabilities and HAQ-DI absolute score changes

Variable	bDMARD-naïve population	bDMARD-experienced population
Probability of PsARC Response		
Placebo	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]
Tofacitinib 5mg	[redacted]	[redacted]
Secukinumab 150mg	[redacted]	[redacted]
Secukinumab 300mg	[redacted]	[redacted]
Certolizumab	[redacted]	[redacted]
Ixekizumab 80 Q2W	[redacted]	[redacted]
Ixekizumab 80 Q4W	[redacted]	[redacted]
HAQ-DI score change for PsARC responder		
Placebo	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]
Tofacitinib 5mg	[redacted]	[redacted]
Secukinumab 150mg	[redacted]	[redacted]
Secukinumab 300mg	[redacted]	[redacted]
Certolizumab	[redacted]	[redacted]
Ixekizumab 80 Q2W	[redacted]	[redacted]
Ixekizumab 80 Q4W	[redacted]	[redacted]
HAQ-DI score change for PsARC non-responder-		
Placebo	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]

Golimumab	[redacted]	[redacted]
Tofacitinib 5mg	[redacted]	[redacted]
Secukinumab 150mg	[redacted]	[redacted]
Secukinumab 300mg	[redacted]	[redacted]
Certolizumab	[redacted]	[redacted]
Ixekizumab 80 Q2W	[redacted]	[redacted]
Ixekizumab 80 Q4W	[redacted]	[redacted]

Table 31 Summary of PASI-50, PASI-75 and PASI-90 response probabilities

Variable	bDMARD-naïve population	bDMARD-experienced population
Probability of PASI-50 response		
Placebo	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]
Tofacitinib 5mg	[redacted]	[redacted]
Secukinumab 150mg	[redacted]	[redacted]
Secukinumab 300mg	[redacted]	[redacted]
Certolizumab	[redacted]	[redacted]
Ixekizumab 80 Q2W	[redacted]	[redacted]
Ixekizumab 80 Q4W	[redacted]	[redacted]
Probability of PASI-75 response		
Placebo	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]
Tofacitinib 5mg	[redacted]	[redacted]
Secukinumab 150mg	[redacted]	[redacted]
Secukinumab 300mg	[redacted]	[redacted]
Certolizumab	[redacted]	[redacted]
Ixekizumab 80 Q2W	[redacted]	[redacted]
Ixekizumab 80 Q4W	[redacted]	[redacted]
Probability of PASI-90 response		
Placebo	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]
Apremilast	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]
Tofacitinib 5mg	[redacted]	[redacted]
Secukinumab 150mg	[redacted]	[redacted]
Secukinumab 300mg	[redacted]	[redacted]
Certolizumab	[redacted]	[redacted]
Ixekizumab 80 Q2W	[redacted]	[redacted]

Ixekizumab 80 Q4W	[redacted]	[redacted]

The ERG identified discrepancies in several of the efficacy results reported in the results of the NMA compared to the response rates used in the economic model. The results reported in the CS on the probability of PsARC, PASI and HAQ-DI conditional on PsARC response in the bDMARD-naïve population with ustekinumab do not match the NMA results that are used in the economic model. The majority of the results for PsARC, PASI and HAQ-DI conditional on PsARC response with all comparators reported in the CS for the bDMARD-experienced population do not correspond to those reported in the model. In terms of the ACR response rates, the company submission states that model E1 FE with 24-week data was selected as the 'pessimistic' case for the ACR endpoint and model E1 FE without 24-week data was selected as both the 'optimistic' and base case for the ACR response. However, in the model for all sub-populations, model E1 FE without 24-week data was selected for the base case and 'pessimistic' case while model E1 FE with 24-week data was used for the 'optimistic' case data. Additional details and justification were requested from the company.

The company reported that the differences in the NMA data between the economic model and company submission were caused primarily by differences in the outcomes reported. In the CS, the median values were presented (as per TA445), while the economic model uses the mean values. The company indicated that these are more appropriate for economic modelling (as per TA445). For the bDMARD naïve results, the company reported that the median values were mistakenly copied into the model in some instances (instead of the mean values from the NMA). The company identified that the values presented in the economic model for ustekinumab for the bDMARD naïve analysis were the mean values from the bDMARD experienced NMA (which was deemed the appropriate NMA as ustekinumab was second option in the treatment sequence, usually post bDMARD). The company stated that it was these factors that resulted in inconsistencies between data in the model and those in the main CS.

In their clarification response, the company reported that the economic model used the incorrect version of the ACR NMAs for the pessimistic and optimistic scenarios in the bDMARD-experienced population and that those reported in the submission are correct. As stated in Section 5.2.1, the ACR response (ACR20) was only used in scenario analyses and therefore do not affect the base case results.

In addition, when comparing the base case NMA models informing the effectiveness data included in the company's model, there were differences in the NMA models used in the current TA and the previous TA on which the current evaluation is based [15]. One reason for these variations is due to data that was previously publicly available for TA445 and no longer publicly available for the current TA.

More specifically, in terms of HAQ response, the company implemented a different base case model compared to that used in TA445. This differs from the TA445 [30] base case in that it uses random effects, adjusts for trials with more than two arms, and uses separate models for responders and non-responders. The analyses using separate models for responders and non-responders predict larger changes in HAQ-DI for responders than do the combined models, including for placebo responders. The ERG requested justification for this model specification. The ERG explores the validity of the NMA in Section 4.6 and explores the sensitivity of the economic model results to alternative NMA models in Section 6.2.

The response rates applied in the economic model assume that the treatment effect is maintained for subsequent lines of therapy, i.e. no reduction in effectiveness is applied for patients failing to respond to first line therapy or for those that initially respond but later withdraw due to loss of efficacy of adverse events. As discussed in TA445, this assumption is unlikely to be valid; however there is a paucity of data from which to estimate this effect degradation. For treatments with a lower PsARC response rate, i.e. higher number of patients moving onto 2nd line treatment, an assumption of no effect degradation may overestimate cost-effectiveness. Due to the lack of flexibility in the company model, the ERG is unable to explore the sensitivity of the cost-effectiveness results to this assumption in Section 6.

5.2.6.3 Natural history disease progression

As the psoriasis element of PsA is not progressive, the company assumes that PASI scores do not increase over time for patients receiving BSC. The arthritis element of PsA is assumed to be progressive, therefore, for patients not receiving biologic therapies (BSC), the company assumes the HAQ-DI score worsens overtime.

In the base case model the rate of progression for BSC was obtained from the York AG model [14]. This HAQ-DI progression was estimated based on an extract of data for PsA patients receiving palliative care included in the Norfolk Arthritis Register [17] until 2009. A worsening (increase) in HAQ-DI score of 0.077 per year was applied as the rate of natural disease progression in the company's economic model. Patients could reach a maximum HAQ-DI score of 3.

For biologic drugs, excluding apremilast, the company assumed no progression of disease whilst on treatment. The appraisal committee for TA433 concluded that there was insufficient evidence to demonstrate that apremilast halts radiographic disease progression (49), and concluded that the rate of disease progression experienced while receiving apremilast was assumed to be half of the progression rate for BSC/csDMARDs (i.e. 0.0385 per year). The same assumption was applied for apremilast in this analysis.

There is uncertainty about the trajectory of HAQ-DI over time, for both patients maintained on active therapies (responders) and those receiving BSC (either because of primary non-response or due to withdrawal).

Firstly, for patients receiving BSC they are assumed to follow a natural history trajectory through HAQ, with HAQ scores worsening at every cycle of the model. There are two main issues with this simplifying assumption. Firstly there appears to have been no attempts to update work from 2009 with a more recent extract from NOAR (or similar register such as ERAS). Practice regarding cDMARDs may change over time and this should be reflected in the HAQ change applied to the BSC comparator. In addition it is unlikely that the relationship between HAQ and time is linear over the entire extrapolation period (40 years). Recent work by Norton et al [31] looks at the progression of HAQ scores over 15 years in a largely RA population (but including some PsA patients in one dataset). This showed that HAQ progression becomes less linear over time, particularly post 5 years where scores stabilise.

For patients maintained on active therapies (responders), the CS assumes that patients responding to treatment do not progress further in terms of HAQ (full disease modification). The ERG has concerns regarding the validity of this assumption. As discussed in Section B.3.3.1 to assess the radiographic progression of tofacitinib 5mg BD, the company performed a population-adjusted analysis using pre-specified effect modifiers and prognostic factors centred using the baseline characteristics from the ADEPT trial, to adjust the OPAL Broaden data to a target population more at risk of progression. On the basis of this analysis, the company conclude that there are no differences between tofacitinib 5mg BD and adalimumab with respect to radiographic progression but that the analysis is limited given that the OPAL Broaden trial was underpowered to detect differences between tofacitinib 5mg BD and adalimumab. In addition, the company acknowledges that the prognostic factors for radiographic progression in the OPAL Broaden clinical trial were different (lower) (e.g., baseline CRP levels, baseline mTSS, baseline erosion and joint space narrowing scores) than a number of previous bDMARD studies in PsA [32]. As the evidence presented on radiographic progression is based on short-term follow-up and 11.3% of patients experience a progression (increase in mTSS) [33] the ERG considers that the rate of progression for tofacitinib is uncertain and therefore the ERG explores this assumption in Section 6.3.

5.2.6.4 Discontinuation

For PsARC responders, there is a risk of withdrawal following the first 3 months of treatment. Based on previous appraisals [14, 15], this probability is estimated from a meta-analysis of registry data from several countries to be -1.823. Withdrawal rates were assumed to be independent of HAQ-DI and PASI scores in the model. The same withdrawal rate is applied to tofacitinib and all comparators and

is assumed to be constant over time. The assumption of equal withdrawal rate is subject to uncertainty. This uncertainty is based on the mode of administration of tofacitinib and its impact on patient adherence. Following a discussion with its clinical advisor, the ERG are concerned regarding patient compliance with tofacitinib. As tofacitinib is an oral treatment taken twice daily, there is a possibility that patients may not take the drug appropriately and consistently over time.

In the CS, the company did not provide additional evidence or justification to support this assumption given the different mechanism and mode of delivery of tofacitinib. The ERG requested this information to be provided. More specifically, the ERG requested the withdrawal data for patients whose disease initially responds to treatment and subsequently discontinued treatment due to loss of efficacy of adverse events. The ERG requested a revised version of the model that allows a separate withdrawal rate to be specified for tofacitinib. Finally, the ERG request additional scenarios which use the withdrawal based on the data from the OPAL trials for tofacitinib.

In response, the company provided tables detailing the discontinuation rates and reasons for discontinuation among those whose disease initially responded to treatment in the OPAL Broaden and OPAL Beyond trials. They also provided a revised version of the model which allows a separate withdrawal rate to be specified for tofacitinib. The company provided an additional scenario using the rate of withdrawal from the OPAL trials for tofacitinib. However, the rate of withdrawal they used in the scenario analyses includes data for PsARC responders, PsARC non-responders and patients in which PsARC response data was missing at 3 months. The ERG recalculated the rate of withdrawal for PsARC responders using the data provided in response to clarifications (Table 00099.2.2.2 in company response). This suggests that the rate of withdrawal is around 5.5% per year, and therefore the ERG is satisfied that the base case assumption of equivalent withdrawal to the other biologics is valid.

5.2.6.5 Mortality

Mortality was not measured as an outcome in the tofacitinib clinical trials, so the treatment-specific impact on mortality was not assessed. The base case analysis of the economic model included all-cause, age-dependent probabilities of death based on the general England and Wales population from the national life tables published by the Office for National Statistics (ONS) [34]. The excess mortality risk associated with PsA is modelled using a HR of 1.36. This ratio was obtained from a prospective study of patients with PsA [18] and was applied in TA445 [15]. The ERG considers this to be a valid assumption.

5.2.6.6 Adverse Events

The incidence of adverse events leading to discontinuation from treatment was captured in the clinical trials for tofacitinib. Adverse events (AEs) are not explicitly included in the model, neither as a utility decrement nor as additional cost for their treatment. In the model, AEs were considered in terms of their effect on initial response and on the long-term rates of withdrawal from the continued use for each treatment. The ERG considers this to be a valid assumption.

5.2.7 Health related quality of life

Patients' HRQoL is defined in the model in terms of HAQ and PASI scores and these are mapped to EQ-5D. The health states in the model are defined by the treatment received and response to treatment. Patients' HAQ-DI and PASI scores remain constant while patients are on treatment with bDMARDs or tofacitinib, but they progress linearly while patients are on apremilast or BSC (reflecting worsening of physical function following failure to response to treatment (See Section 5.2.6.6).

EQ-5D data were available from the OPAL Broaden and OPAL Beyond clinical trials for tofacitinib. The company states that to be consistent with previous appraisals (TA119 [14] and TA445 [15]), the mapping algorithm used in the York model for the base case is implemented here. For the base case, the following formula from the York model was used:

Equation 5.1 Mapping algorithm

$$EQ-5D = 0.897 - 0.289 * HAQ - 0.004 * PASI$$

Scenario analysis was performed in which the *de novo* mapping algorithms derived using individual patient data (IPD) from the OPAL Broaden and Beyond clinical data were applied to tofacitinib alone or tofacitinib and its comparators.

Statistical models were developed using data from the OPAL Broaden (sub-populations 2 and 4) and OPAL Beyond (sub-population 3) studies separately. Two models were estimated using each study:

- A 'main effect' model predicting EQ-5D in which HAQ and PASI scores were included as independent covariates.
- An 'interaction effect' model which augmented the 'main effect' model by including the interaction between HAQ and PASI scores as a covariate.

Both models pool all non-missing data at all time points from across all arms of the respective clinical trials. Models were implemented as mixed effects models to account for repeated measures within subjects. The CS refers to Appendix Q for the results of these models but Appendix Q was not provided. The ERG requested this and also requested that the specific covariates and regression function be provided.

In addition, the CS does not provide the EQ-5D data as collected in the OPAL trials. The ERG requested results of any EQ-5D assessments in OPAL Broaden, OPAL Beyond and OPAL Balance including sample sizes, missing data, follow up points, EQ-5D scores at baseline and follow up for each treatment and details and results of any statistical tests performed.

In response, the company provided Appendix Q. Appendix Q details the specific covariates included in the company's scenario analyses which used the *do novo* mapping algorithm applied initially to all treatments and then to the tofacitinib arm only. The ERG compared the covariates used in these scenario analyses with those used in the previous models and conclude that the covariates are very similar to those used in previous appraisals (TA119 [14] and TA445 [15]). The company clarified that a mixed effects regression function was used to account for repeated measures in the data. The company provided tables reporting the EQ-5D assessments in the OPAL Broaden, OPAL Beyond and OPAL Balance tofacitinib trials. These tables described the average EQ-5D utilities up to 12 months for tofacitinib, tofacitinib 10mg BD, adalimumab, placebo, placebo → tofacitinib and placebo → tofacitinib 10mg BD, the change from baseline in EQ-5D utilities, EQ-5D utilities by PsARC response and the change in EQ-5D utilities from baseline by PsARC response assessed in each of the OPAL trials. [redacted]

5.2.8 Resources and costs

The CS provided a detailed description of resource use and costs incurred in PsA patients. These included: drug acquisition costs (Section B.3.5.2.2 in CS); drug administration costs (Section B.3.5.2.3 in CS) and drug monitoring costs (Section B.3.5.2.4). AEs costs were not considered in the model. A systematic review was conducted to identify alternative evidence regarding resource use and the costs associated with the management of PsA in the UK. The company reports that they did find one publication, Poole et al [35], that specifically reported estimates of costs according to HAQ-DI and/or PASI which was eligible for inclusion [35], however, it was not used to inform the model. The CS does not justify why this was not included. In TA445, HAQ-DI and PASI costs were based on the

same function as used in the York model (TA199) rather than the costs reported by Poole et al [35] TA445 concluded that this was due to limitations in the Poole et al study and to ensure consistency across NICE TAs.

Costs for acquisition, administration and monitoring differ between the first cycle (initiation phase) and subsequent cycles to reflect clinical management practices associated with switching a patient onto a new treatment. In addition, in the first cycle, monitoring is more intensive while the decision to continue with treatment is made. For comparators with a recommended initiation phase greater than 12 weeks (ustekinumab and sekukinumab), costs for the SPC recommended length of initiation phase were applied, for example up to 24 weeks. For other comparators the first cycle incorporates 12 weeks of drug treatment.

Table 46 in the CS (p138) provides a table detailing a summary of the treatment costs.

5.2.8.1 Drug acquisition costs

Costs for the bDMARDs and apremilast were sourced from the British National Formulary [19] and the cost of methotrexate was obtained from the electronic market information tool (eMIT) database [20]. PAS prices were used in the model where information is in the public domain. A list price analysis for tofacitinib was not provided. Instead the PAS price which employs a simple discount was used. Since the submission of the manuscript, the company have provided an updated PAS price for tofacitinib (See confidential PAS appendix). List prices were used for secukinumab and apremilast but these are subject a confidential PAS. The ERG conducted additional analysis using PAS prices for secukinumab and apremilast and these are presented in a confidential appendix. Biosimilar prices were used when available (etanercept and infliximab). No drug costs were assumed for BSC as it was assumed that these drug costs are captured in the estimates of resource use associated with HAQ-DI.

Following the update on the PAS price for tofacitinib, the company submitted a PAS submission template including tables detailing the new ICER using the confidential PAS price. They also provided an updated version of the model for each sub-population including the new PAS price. In sub-population 3, the incremental ICERs reported in the submission do not correspond to the incremental ICERs in the base case results in the economic model.

5.2.8.2 Drug administration costs

Administration costs were taken from the NHS reference costs [21, 22].

An intravenous infusion cost of £241 [21] is applied in each cycle for infliximab. This value is a weighted average cost for simple parenteral chemotherapy at first attendance, taking into account day case, outpatient and other costs, taken from NHS reference costs [21] as per TA445 [15]. For treatments

that require administration by subcutaneous injection, the cost of one hour of hospital-based nurse specialist time is applied (£45) to reflect clinical practice for bDMARDs prescribed by rheumatologists [22]. This cost is implemented in the first cycle only as it is assumed that the patient will self-administer subsequent treatment following training by the nurse.

The company did not assign a resource use associated with the administration of tofacitinib, apremilast or csDMARDs as these are taken orally.

5.2.8.3 Drug monitoring costs

Monitoring activities included in the model and their frequency of use (Table 45) are based on the assumptions from TA199 [14] and TA445 [15].

In the first cycle, patients undergo tests – full blood count, erythrocyte sedimentation rate, liver function test and urea and electrolytes – at the start of treatment and at month 3. In subsequent cycles, these tests are conducted every 6 months. The chest x-ray, tuberculosis Heaf test, antinuclear antibody, double-stranded DNA test and specialist visit are assumed to occur in the first cycle only.

Costs were taken from NHS reference costs [21], except for the liver function test, chest x-ray and tuberculosis Heaf test costs, which were inflated from the costs presented by the AG in TA445 [15].

The company assumes that the monitoring of tofacitinib is not considered as additional to current practice, and is in line with NHS policy for bDMARDs. However, in Table 3 of the CS (page 18), the company reports that tofacitinib monitoring requirements and identifies lipid testing at 8 weeks after commencing treatment. This monitoring requirement for tofacitinib was also identified by the ERG's clinical advisor. This is not included as a monitoring cost in the economic model.

In addition, as an oral therapy taken twice daily, patient adherence to tofacitinib may be an issue that would also justify additional monitoring. As additional monitoring or testing is likely to be of minimal cost (based on blood test costs in Table 45, page 136 in the CS), the ERG do not deem it necessary to explore this further in Section 6.

5.2.8.4 Disease related costs

In addition to drug acquisition, administration and monitoring costs, disease-related costs were also incorporated into the economic model.

Arthritis-related costs were estimated as a function of HAQ-DI score (Equation 5.1). For the model presented in this submission the annual direct cost was calculated using the formula from Rodgers et al [36], with costs inflated to 2017 prices:

Equation 5.2 Arthritis annual direct cost

$$Annual\ direct\ cost = £466.47\ x\ HAQ + £1{,}547.04$$

With the exception of BSC, these costs incorporate a 15% reduction to account for drug costs, in accordance with the York PsA model [14]. This is not applied to BSC as drug costs are assumed to be captured within health state costs and are not applied separately. This accords with the approach used in TA445[15].

The psoriasis component of resource use has previously been estimated based on PASI scores. Costs associated with the psoriasis component based on PASI scores were taken from the AG report in TA445 [15] and inflated to 2017 prices.

This analysis follows the approach taken in the York PsA model in TA199 [14] and TA445 [15]. The AG estimated costs for patients receiving bDMARDs based on baseline severity of psoriasis and whether or not they had a PASI75 response. For patients with mild–moderate or moderate–severe psoriasis at baseline achieving a PASI 75 response, the monthly estimated cost of a patient in remission [37] was applied. The source of this cost is a study which considered the cost-effectiveness of an intervention for patients with moderate to severe psoriasis in a Dutch setting. Costs from this analysis were similar to NHS reference costs and the company argues that the Dutch costs were generalizable to the UK after currency conversion.

Patients with moderate to severe psoriasis not achieving a PASI75 response were assumed to undergo one course of ultraviolet B treatment (UVB) per year. This incorporated the cost of the initial course of treatment and the cost of follow-up for the year. Patients were put into three categories for response – no response, response maintained for 12 months, and response maintained for 6 months followed by relapse. The total cost for the year was weighted by the frequency of these outcomes in the Hartman analysis (2002) [37].

Patients with mild to moderate psoriasis and no PASI 75 response were also assumed to receive a course of UVB but with the cost taken from NHS reference costs. The proportion of responders was taken from an analysis by Poyner et al (1999) (197). Patients with no baseline psoriasis incurred no costs.

5.2.8.5 Adverse reaction unit costs and resource use

As discussed in Section 5.2.6.6, AEs were not included explicitly in the model, neither as a treatment-related utility decrement nor as additional cost for treatment of adverse events. The company stated in their submission that this is consistent with previous TAs [15].

Adverse event costs were not explicitly included in the cost-effectiveness analysis; however, they influence response probabilities and withdrawal rates. This is in line with the approach used in previous models [15].

5.2.9 Base case cost effectiveness results

The following base case cost effectiveness results are the updated results provided by the company following clarification (including the updated PAS price for tofacitinib and corrected NMA results).

The expected costs and QALYs of the alternative treatments are reported for each sub-population and the relative cost-effectiveness of each strategy is compared using standard decision rules, estimating ICERs as appropriate. The base case analysis considers PAS prices for tofacitinib (updated PAS price) and its comparators, where these PAS prices are publicly available; certolizumab, golimumab and ustekinumab. Biosimilar prices are used for etanercept and infliximab. List prices were used for two products for which PAS schemes are approved but not publicly available; secukinumab and apremilast. The ERG conducted further analysis using the confidential PAS schemes for apremilast and secukinumab and these are presented in a separate confidential appendix.

5.2.9.1 People whose disease has not responded adequately to at least 2 non-biological DMARDs

The ICER for tofacitinib vs BSC (Table 32) is £13,419 per QALY. This result indicates that the inclusion of tofacitinib as an additional line of treatment for this sub-population falls within acceptable WTP thresholds as defined by NICE (between £20,000 and £30,000 per QALY gained). Based on the full incremental analysis, a strategy commencing with etanercept offers higher QALYs and falls within acceptable thresholds.

Table 32 Base case analysis (sub-population 2) (Table 8, p16 of PAS Template)

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
BSC	[redacted]	[redacted]	-	-	-	-
TOF→UST→BSC	[redacted]	[redacted]	£32,881	2.45	£13,419	£13,419
APR→UST→BSC	[redacted]	[redacted]	£40,499	2.07	£19,569	Dominated
ADA→UST→BSC	[redacted]	[redacted]	£47,901	2.71	£17,687	Extendedly dominated
CTZ→UST→BSC	[redacted]	[redacted]	£48,839	2.85	£17,126	Extendedly dominated
ETN→UST→BSC	[redacted]	[redacted]	£51,700	3.27	£15,798	£22,886
SEK→UST→BSC	[redacted]	[redacted]	£52,978	2.86	£18,543	Dominated
GOL→UST→BSC	[redacted]	[redacted]	£53,557	2.99	£17,904	Dominated
INF→UST→BSC	[redacted]	[redacted]	£71,190	3.35	£21,225	£239,101

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life-year.

5.2.9.2 People whose disease has not responded adequately to non-biological DMARDs and one or more TNFis

The ICER for tofacitinib 5 mg BD vs BSC (Table 33) is £9,001 per QALY. This result indicates that the inclusion of tofacitinib as an additional line of treatment for this sub-population falls within acceptable WTP thresholds as defined by NICE (between £20,000 and £30,000 per QALY gained). Based on the incremental analysis, a strategy commencing with tofacitinib is the only strategy that falls within an acceptable threshold.

Table 33 Base case analysis (sub-population 3) (Table 10, p17 of PAS Template)

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
BSC	[redacted]	[redacted]	-	-	-	-
TOF→BSC	[redacted]	[redacted]	£11,732	1.30	£9,001	£9,001
UST→BSC	[redacted]	[redacted]	£26,709	1.42	£18,761	£124,510
SEC→BSC	[redacted]	[redacted]	£54,206	1.60	£33,914	£157,429

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life-year.

5.2.9.3 People in whom TNFis are contraindicated or not tolerated

The ICER for tofacitinib 5 mg BD vs BSC (Table 34) is £7,825 per QALY. Similar to the previous results, this indicates that the inclusion of tofacitinib as an additional line of treatment for this sub-population falls within acceptable WTP thresholds as defined by NICE (between £20,000 and £30,000 per QALY gained). Based on the incremental analysis and similar to sub-population 3, a strategy commencing with tofacitinib is the only strategy that falls within an acceptable threshold.

Table 34 Base case analysis (sub-population 4) (Table 12, p 18 of PAS Template)

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
BSC	[redacted]	[redacted]	-	-	-	-
TOF→BSC	[redacted]	[redacted]	£8,930	1.14	£7,825	£7,825
UST→BSC	[redacted]	[redacted]	£24,979	1.33	£18,837	Extendedly dominated
SEK→BSC	[redacted]	[redacted]	£30,153	1.62	£18,557	£43,872

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life-year.

5.2.9.4 Conclusion on cost-effectiveness results

In each of the three sub-populations assessed, the deterministic ICER for tofacitinib 5 mg BD vs BSC was below £20,000 per QALY. In terms of the incremental analysis, a strategy commencing with tofacitinib is the only strategy that falls within an acceptable threshold in sub-populations 3 and 4,

whilst in sub-population 2, in addition to tofacitinib, etanercept provides higher QALYs whilst also falling within the acceptable threshold.

The cost-effectiveness results may, however, be sensitive to a number of assumptions made in the model, namely the choice of the NMA model and the PAS drug cost included for tofacitinib compared to the list prices incorporated for the other comparators for which PAS schemes are available but CiC, e.g. apremilast and secukinumab. The impact of these assumptions on cost-effectiveness is addressed by the ERG in Section 6.3 and in a separate confidential appendix.

As the economic model is similar to TA445 and included similar treatment comparators, the ERG have compared the costs and QALYs of the cost-effectiveness results with those in TA445. Given the difference in the psoriasis groups, this comparison is problematic so the ERG compared the average costs and QALYs across the psoriasis sub-groups in TA445 to compare with the current TA. The ERG conclude that the costs and QALYS between both TAs are relatively similar for each treatment. (See Appendix B in section 10)

5.2.10 Sensitivity analysis

The company presented a series of probabilistic sensitivity analysis (PSA) to assess the implications of parameter uncertainty, in terms of the estimates of cost-effectiveness. All parameters were assigned distributions and varied jointly. Ten thousand Monte Carlo simulations were recorded. Scatter plots and cost-effectiveness acceptability curves for the three sub-populations were presented in the CS (Figures 23-28 in CS).

The average results of PSA in all three sub-populations were consistent with the deterministic analyses and demonstrate that the ICER for tofacitinib 5 mg BD sequence remains below a threshold of £20,000 per QALY versus BSC in all sub-populations, where parameter uncertainty is explored.

In sub-population 2, the ICER versus BSC for the tofacitinib 5 mg BD sequence was only second to etanercept biosimilar, and in sub-populations 3 and 4, the tofacitinib 5 mg BD sequence was associated with the highest probability of being cost-effective at conventional willingness to pay thresholds of £20,000 and £30,000 per QALY.

Given that the probabilistic results in each of the sub-populations are similar to the results described in the deterministic analysis, Section 5.2.9, the ERG concludes that there are no particular concerns regarding non-linearity in the model.

5.2.12 Scenario Analysis

The CS included a series of scenario analysis that were performed to check the robustness of the model to structural assumptions made in the model The scenarios that were investigated along with a brief description of the assumptions for each are provided below.

List price analysis

- An alternative scenario using the list price of tofacitinib was considered.

Pessimistic NMA

- Alternate NMAs with worst outcomes for tofacitinib only were implemented to present a lower bound on the NMA analysis

Optimistic NMA

- Alternate NMAs with best outcome for tofacitinib only were used to present an upper bound on the NMA analysis.

ACR20 stopping rules

- To test the assumption of the PsARC stopping rules, response was defined by ACR20 response.

Pfizer mapping algorithm for all treatments

- To allow population-specific prediction of utility, the Pfizer mapping algorithm was applied instead of the algorithm from TA199 [14].

Pfizer mapping algorithm for tofacitinib only

- To allow population-specific prediction of utility, the Pfizer mapping algorithm is applied to the tofacitinib arm only.

The scenario analysis showed that tofacitinib 5 mg BD falls below (or between) the conventional NICE threshold of £20,000 to £30,000 per QALY across a range of plausible settings for all sub-populations (Tables 57 to 61 in CS). The results of the scenario analysis are consistent with the results presented in the base case analysis.

5.2.11 Model validation and face validity check

The CS reports that the cost-effectiveness model was validated by the model developers and by health economists not involved in the construction of the model. Validation was completed using standard procedures such as; cell-by-cell checks of logic and consistency, logical check of model outputs, and comparing outputs to those from previous economic analyses. The company did not provide specific details of the validation conducted and if the model failed on any aspects of the validation.

The ERG identified discrepancies in several of the efficacy results between those reported in the clinical section of the submission and the values that were subsequently used in the economic model.

The code for the PSA is complex and difficult to validate. In order to validate the model, the ERG requested the following;

- A step-by-step description of how the VBA code implements the PSA, including how the Monte Carlo is implemented.
- Confirmation of whether the simulations are done simultaneously for all comparators or separately for each individual comparator.
- Detailed annotations within the VBA code for each step.

In their response to clarification, the company confirmed that the simulations are performed simultaneously for all comparators and the company provided a detailed response on how the VBA code implements the PSA. They also provided additional annotation of the VBA code in the updated versions of the electronic models. Following the company response the ERG were able to validate the PSA and confirm that the PSA was conducted appropriately.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG checked the model for consistency with the CS. In consistencies are detailed in the sections above. The ERG also checked the company model for any errors and validated assumptions noted in the CS.

Sensitivity analyses conducted by the ERG are detailed in Section 6.

5.4 Conclusions of the cost effectiveness section

The ERG has a number of concerns regarding some of the approaches, assumptions and data used in the CS and economic model. The main concerns expressed by the ERG are:

The PsARC response data used by the company in the optimistic and pessimistic scenarios may not reflect the best fitting NMA model. There is also no clear rationale for the placebo effect, and hence that the results of the placebo-response adjusted model should be interpreted with caution. We will therefore explore the use of use the independent treatment effects model and the class effect model proposed by the in sensitivity analysis in Section 6. The corrected errors in the company preferred model (B2) are also propagated through the company model in Section 6.

Disease progression

As stated in Section 5.2.1, the company assumes that HAQ-DI progression stops when a patient responds to tofacitinib. The ERG is concerned about this assumption given that there is no long-term evidence on radiographic progression on tofacitinib to support this assumption. In section 6, the ERG addresses this assumption by conducting scenario analyses using different rates of HAQ-DI progression. The first scenario considers the impact of tofacitinib progression equal to that of apremilast. The second scenario considers radiographic progression reported in the adalimumab study [33] where 11% of patients progressed on treatment. Finally, the ERG considers the impact on cost-effectiveness if 11% of the population progress at the same rate as assumed for apremilast (0.010). The rates used in the scenario analysis are reflective of the radiographic progression study referred to in the CS [33].

Psoriasis sub-groups

As stated in Section 5.2.3, the sub-populations in the model are not defined according to psoriasis level and the ERG have concerns about this assumption given the impact that differences in baseline characteristics such as HAQ-DI, and particularly PASI scores can have on cost-effectiveness results. This is an issue in terms of the severity of psoriasis and the consequent dosing of comparators such as secukinumab; where secukinumab 300mg is approved for patients with severe psoriasis as opposed to the standard does of secukinumab 150mg. The ERG considers the impact of defining the sub-populations by psoriasis level to reflect the approach taken previously in TA445.

Drug acquisition costs

The company used PAS prices that were publicly available, namely for ustekinumab and certolizumab. Biosimilar costs were assumed for infliximab and etanercept. For other comparators the list price of the drug was implemented in the model. The ERG has concerns regarding the impact of other PAS schemes, apremilast and secukinumab and the impact that this may have on the cost-effectiveness of tofacitinib. The ERG considers the impact of including the PAS prices for APR and SEC in the confidential appendix.

Effect degradation for subsequent lines of therapy

The CS does not apply a reduction in effectiveness for subsequent lines of therapy. As discussed in Section 5.2.6.2, this may overestimate the cost-effectiveness of treatments with a lower PsARC response rate. In TA445 the effect degradation was estimated from observational data for RA patients from the BSR register. For a patient that failed first line therapy due to lack of efficacy, the risk of failing the second-line therapy due to lack of efficacy increases by 2.7 (95% CI 2.1-3.4). The ERG is

unable to explore the sensitivity of the cost-effectiveness results to this assumption, due to the inflexibility of the company model provided.

Given the importance of the issues discussed, additional analyses undertaken by the ERG are presented in Section 6, which consider the potential impact of these uncertainties on the cost-effectiveness results.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

This section details the ERG's further exploration of the assumptions and uncertainties raised in the review and critique of the manufacturer's cost effectiveness analysis, presented in Section 5. The ERG present alternative estimates of cost effectiveness, correcting the company model and also explore assumptions and data incorporated in the manufacturer's analysis.

The ERG's exploratory analyses focused on the following key issue and uncertainty:

- NMA sensitivity analyses with PsARC corrected base case model in sub-population 2. (Section 4.7.1).

Additional scenarios around specific model parameters were:

- Severity of psoriasis by subgroup.
- Tofacitinib progression rates for PsARC responders.
- Drug costs for comparator drugs. The drug cost analyses are based on PAS schemes that are approved for Secukinumab and Apremilast but are not in the public domain. The results of the additional analyses by each sub-population are included in a separate confidential appendix.

These scenarios are meant to be exploratory in nature and are intended to show the impact of different parameter assumptions on the cost-effectiveness results. The ICERs for all scenarios are presented both compared to the cheapest strategy (BSC) and as a fully incremental analysis. For the ERG conducted sensitivity analyses, both deterministic and probabilistic results are presented. For the additional scenarios, deterministic results are presented using the most valid NMA model concluded in Section 6.2.1.

6.2 ERG corrections and adjustments to the company's base case model

6.2.1 NMA Sensitivity analysis

In Section 4.7.1 the ERG present a corrected NMA for B2, the placebo adjusted random effects model, generating alternative estimates of PsARC response for subpopulation 2 (see Table 23). In addition the ERG explored the use of a class effects model (D2) and an independent treatment effects model (A2), concluding that D2 represents the model with the best fit (lowest DIC). The ERG also conclude that the placebo adjusted model should be interpreted with caution, due to a lack of rationale for the placebo effect.

In this section the ERG explore the sensitivity of the company cost-effectiveness results to alternative NMA models to estimate PsARC response rates, specifically the corrected B2, D2 and A2 for subpopulation 2. The results for these sensitivity analyses are presented below in Table 35 to Table 42, for both the deterministic and the probabilistic analysis. The equivalent confidential PAS results are presented in a separate confidential appendix.

Table 35 Company base case results B2 (deterministic)

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£32,881	2.45	£13,419	£13,419
APR	[redacted]	[redacted]	£40,499	2.07	£19,569	Dominated
ADA	[redacted]	[redacted]	£47,901	2.71	£17,687	Extendedly dominated
CTZ	[redacted]	[redacted]	£48,839	2.85	£17,126	Extendedly dominated
ETN	[redacted]	[redacted]	£51,700	3.27	£15,798	£22,886
SEK	[redacted]	[redacted]	£52,978	2.86	£18,543	Dominated
GOL	[redacted]	[redacted]	£53,557	2.99	£17,904	Dominated
INF	[redacted]	[redacted]	£71,190	3.35	£21,225	£239,101

Table 36 Company base case results B2 (probabilistic)

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£33,231	2.39	£13,918	£13,918
APR	[redacted]	[redacted]	£40,841	2.00	£20,422	Dominated
ADA	[redacted]	[redacted]	£48,350	2.64	£18,318	Extendedly dominated
CTZ	[redacted]	[redacted]	£49,313	2.77	£17,815	Extendedly dominated
ETN	[redacted]	[redacted]	£52,182	3.19	£16,371	£23,696
SEK	[redacted]	[redacted]	£53,510	2.78	£19,253	Dominated
GOL	[redacted]	[redacted]	£54,009	2.90	£18,641	Dominated
INF	[redacted]	[redacted]	£71,630	3.27	£21,900	£233,602

Table 37 ERG B2 – base case results (deterministic)

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£32,822	2.52	£13,029	£13,029
APR	[redacted]	[redacted]	£39,434	2.02	£19,555	Dominated
ADA	[redacted]	[redacted]	£47,275	2.67	£17,701	Extendedly dominated
CTZ	[redacted]	[redacted]	£49,490	2.89	£17,145	Extendedly dominated
ETN	[redacted]	[redacted]	£50,598	3.20	£15,799	£26,006
GOL	[redacted]	[redacted]	£51,143	2.85	£17,931	Dominated
SEK	[redacted]	[redacted]	£53,774	2.91	£18,507	Dominated
INF	[redacted]	[redacted]	£69,389	3.26	£21,270	£315,590

Table 38 ERG B2 – base case results (probabilistic)

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£33,231	2.39	£13,918	£13,0244
APR	[redacted]	[redacted]	£40,841	2.00	£20,422	Dominated
ADA	[redacted]	[redacted]	£48,350	2.64	£18,318	Extendedly dominated
CTZ	[redacted]	[redacted]	£49,313	2.77	£17,815	Extendedly dominated
ETN	[redacted]	[redacted]	£52,182	3.19	£16,371	£25,762
GOL	[redacted]	[redacted]	£54,009	2.90	£18,641	Dominated
SEK	[redacted]	[redacted]	£53,510	2.78	£19,253	Dominated
INF	[redacted]	[redacted]	£71,630	3.27	£21,900	£216,088

The corrected B2 NMA produces very similar results to the company base case results, with only small differences in costs and QALYs and ICERs compared to BSC and the full incremental. The deterministic and probabilistic versions also provide similar results in terms of ordering, although there are some discrepancies in terms of absolute costs and QALYs. For all comparators the ICERs versus BSC fall within acceptable thresholds for cost-effectiveness. For the company B2 model and the corrected B2 model, both tofacitinib and etanercept fall within acceptable thresholds for the full incremental analysis.

Table 39 ERG D –base case results (deterministic)

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER

BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£34,099	2.62	£13,011	£13,011
APR	[redacted]	[redacted]	£40,487	2.07	£19,533	Dominated
ADA	[redacted]	[redacted]	£48,963	2.77	£17,665	Extendedly dominated
CTZ	[redacted]	[redacted]	£50,481	2.95	£17,138	Extendedly dominated
ETN	[redacted]	[redacted]	£50,635	3.19	£15,855	£28,866
GOL	[redacted]	[redacted]	£51,798	2.89	£17,911	Dominated
SEK	[redacted]	[redacted]	£54,680	2.96	£18,476	Dominated
INF	[redacted]	[redacted]	£68,835	3.25	£21,176	£320,148

Table 40 ERG D –base case results (probabilistic)

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£34,514	2.55	£13,530	£13,529
APR	[redacted]	[redacted]	£40,870	2.01	£20,310	Dominated
ADA	[redacted]	[redacted]	£49,520	2.71	£18,276	Extendedly dominated
CTZ	[redacted]	[redacted]	£51,200	2.88	£17,789	Extendedly dominated
ETN	[redacted]	[redacted]	£51,317	3.13	£16,414	£29,199
GOL	[redacted]	[redacted]	£52,258	2.81	£18,601	Dominated
SEK	[redacted]	[redacted]	£55,277	2.89	£19,156	Dominated
INF	[redacted]	[redacted]	£69,735	3.20	£21,801	£255,288

Again the D2 NMA produces very similar results to the company base case results and the correct B2 results. There are only small differences in costs and QALYs and ICERs compared to BSC and the full incremental. The deterministic and probabilistic versions also provide similar results, suggesting that the ICERs for all comparators versus BSC fall within acceptable thresholds for cost-effectiveness. In the full incremental the ICERs for both tofacitinib and etanercept both fall within acceptable thresholds.

Table 41 ERG A2 - base case results (deterministic)

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER

BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£29,255	2.19	£13,355	£13,355
APR	[redacted]	[redacted]	£37,505	1.91	£19,664	Dominated
ADA	[redacted]	[redacted]	£44,565	2.51	£17,771	Extendedly dominated
CTZ	[redacted]	[redacted]	£44,690	2.61	£17,151	Extendedly dominated
SEK	[redacted]	[redacted]	£48,122	2.56	£18,765	Dominated
ETN	[redacted]	[redacted]	£49,290	3.14	£15,716	£21,186
GOL	[redacted]	[redacted]	£52,253	2.91	£17,959	Dominated
INF	[redacted]	[redacted]	£70,233	3.27	£21,480	£156,878

Table 42 ERG A2 base case results (probabilistic)

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
BSC	[redacted]	[redacted]				
TOF	[redacted]	[redacted]	£29,780	2.11	£14,109	£14,109
APR	[redacted]	[redacted]	£38,027	1.82	£20,871	Dominated
CTZ	[redacted]	[redacted]	£45,149	2.50	£18,031	Extendedly dominated
ADA	[redacted]	[redacted]	£45,177	2.42	£18,654	Dominated
SEK	[redacted]	[redacted]	£48,633	2.47	£19,713	Dominated
ETN	[redacted]	[redacted]	£49,936	3.04	£16,448	£21,782
GOL	[redacted]	[redacted]	£52,840	2.80	£18,874	Dominated
INF	[redacted]	[redacted]	£70,781	3.17	£22,336	£156,769

The A2 NMA produces very similar results to the company base case results and the correct B2 results in terms of costs and QALYs. The QALYs are however consistently lower for all comparators compared to the B2 and D2 models. This is expected due to the lower PsARC response rates predicted using the independent treatment effects model (A2) compared with the placebo adjusted models (B2 and D2) (see Table 23).

There are only small differences in the ICERs compared to BSC, suggesting that the ICERs for all comparators versus BSC fall within acceptable thresholds for cost-effectiveness. The full incremental ICERs also show that etanercept and tofacitinib are likely to fall within acceptable ranges for the threshold and these are lower than the ICERs for the B2 and D2 NMA models. The deterministic and probabilistic versions provide similar results.

6.3 Additional ERG analyses

6.3.1 Severity of psoriasis

As discussed in Section 5.2.3, the sub-populations were not defined according to psoriasis level as specified in TA445. Instead, a weighted average PASI score of the psoriasis subgroups was calculated

for the entire population. The ERG had concerns about this assumption given the impact that differences in baseline characteristics such as HAQ-DI, and particularly PASI scores can have on cost-effectiveness results and the appropriateness of some comparators for particular levels of psoriasis. In particular, different secukinumab dosages are appropriate for the separate sub-populations: 150mg of SEC for naïve patients without psoriasis or with mild to moderate psoriasis and 300mg of SEC for experienced patients and for naïve patients with moderate to severe psoriasis[15]. The company model assumes a SEC weighted dose for sub-populations 2 and 4. For sub-population 3 the appropriate 300mg dose for secukinumab was applied in the company model. The ERG considered the impact of defining sub-populations 2 and 4 by psoriasis level and applying the appropriate dosage of secukinumab as described previously. This sensitivity analysis uses the ERG preferred NMA model (D2).

Table 43 Sub-population 2 defined by psoriasis level

NO PSORIASIS – SEK 150MG						
Strategy	**Total discounted costs**	**Total discounted QALYs**	**Incremental cost vs. cheapest strategy**	**Incremental QALYs vs. cheapest strategy**	**ICER vs. cheapest strategy**	**Incremental ICER**
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£37,000	2.57	£14,400	£14,396
APR	[redacted]	[redacted]	£43,110	2.03	£21,272	Dominated
SEK	[redacted]	[redacted]	£51,072	2.89	£17,675	Extendedly dominated
ADA	[redacted]	[redacted]	£52,057	2.72	£19,165	Dominated
CTZ	[redacted]	[redacted]	£53,358	2.89	£18,433	Extendedly dominated
ETN	[redacted]	[redacted]	£53,417	3.14	£16,986	£28,530
GOL	[redacted]	[redacted]	£55,525	2.82	£19,658	Dominated
INF	[redacted]	[redacted]	£73,195	3.17	£23,076	£732,175
MILD TO MODERATE PSORIASIS – SEK150MG						
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£34,115	2.65	£12,897	£12,896
APR	[redacted]	[redacted]	£40,501	2.09	£19,336	Dominated
SEK	[redacted]	[redacted]	£47,388	2.99	£15,859	Extendedly dominated
ADA	[redacted]	[redacted]	£48,979	2.80	£17,505	Dominated
CTZ	[redacted]	[redacted]	£50,497	2.97	£17,003	Dominated
ETN	[redacted]	[redacted]	£50,650	3.22	£15,745	£28,925
GOL	[redacted]	[redacted]	£51,818	2.92	£17,722	Dominated
INF	[redacted]	[redacted]	£68,859	3.29	£20,943	£256,411
MODERATE TO SEVERE – SEK300MG DOSE						
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£28,282	2.70	£10,477	£10,477

APR	[redacted]	[redacted]	£35,227	2.14	£16,438	Dominated
SEK	[redacted]	[redacted]	£69,046	3.11	£22,187	Dominated
ADA	[redacted]	[redacted]	£42,757	2.86	£14,970	Extendedly dominated
CTZ	[redacted]	[redacted]	£44,711	3.02	£14,789	Extendedly dominated
ETN	[redacted]	[redacted]	£45,056	3.27	£13,786	£29,483
GOL	[redacted]	[redacted]	£44,323	2.99	£14,801	Extendedly dominated
INF	[redacted]	[redacted]	£60,091	3.37	£17,828	£146,891

In sub-population 2, the ICERs for tofacitinib in each psoriasis sub-group fall below the conventional NICE threshold range of £20,000 to £30,000 per QALY (Table 43). Based on the fully incremental analysis (also Table 43), a strategy commencing with etanercept is more effective (i.e. offers higher QALYs) than tofacitinib and falls within acceptable NICE thresholds.

Similarly, in sub-population 4, the tofacitinib ICERs in each psoriasis sub-group fall below the acceptable NICE thresholds (Table 44). In the *no psoriasis* and *moderate to severe* sub-group, tofacitinib is the only treatment with an ICER that does not exceed that of the NICE threshold. However, in the *mild to moderate* psoriasis sub-group, secukinumab offers higher QALYs than tofacitinib and lies just below the NICE acceptable threshold of £30,000.

Table 44 Sub-population 4 defined by psoriasis level

NO PSORIASIS – SEK 150MG						
Strategy	**Total discounted costs**	**Total discounted QALYs**	**Incremental cost vs. cheapest strategy**	**Incremental QALYs vs. cheapest strategy**	**ICER vs. cheapest strategy**	**Incremental ICER**
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£10,068	1.12	£8,972	£8,972
SEK	[redacted]	[redacted]	£25,274	1.59	£15,936	£32,789
UST	[redacted]	[redacted]	£26,467	1.30	£20,353	Dominated
MILD TO MODERATE PSORIASIS – SEK150MG						
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£8,936	1.15	£7,769	£7,769
SEK	[redacted]	[redacted]	£23,246	1.64	£14,181	£29,262
UST	[redacted]	[redacted]	£24,987	1.34	£18,671	Dominated
MODERATE TO SEVERE PSORIASIS – SEK300MG						
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£6,647	1.17	£5,680	£5,680
UST	[redacted]	[redacted]	£21,997	1.37	£16,112	Extendedly dominated
SEK	[redacted]	[redacted]	£45,795	1.69	£27,137	£75,660

6.3.2 Tofacitinib progression rates

As described in Section 5.2.6.3, the ERG had concerns regarding the rate of tofacitinib progression given the lack of long-term evidence on radiographic progression. To assess this assumption, the ERG conducted scenario analyses using different HAQ-DI progression rates for tofacitinib. The first scenario assesses the impact on cost-effectiveness when tofacitinib progression is equal to that of Apremilast. In addition, based on the progression rates reported for Adalimumab [33], the ERG also considers a scenario where 11% of the population progress at the BSC rate and another scenario where 11% of the population progress at the apremilast progression rate. This sensitivity analysis uses the ERG preferred NMA model (D2) and the weighted level of psoriasis as in the company base-case.

Table 45 Sub-population 2: Tofacitinib progression rate scenarios

TOFACITINIB PROGRESSION = APREMILAST PROGRESSION						
Strategy	**Total discounted costs**	**Total discounted QALYs**	**Incremental cost vs. cheapest strategy**	**Incremental QALYs vs. cheapest strategy**	**ICER vs. cheapest strategy**	**Incremental ICER**
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£34,785	2.21	£15,706	£15,706
APR	[redacted]	[redacted]	£40,487	2.07	£19,533	Dominated
ADA	[redacted]	[redacted]	£48,963	2.77	£17,665	Extendedly dominated
CTZ	[redacted]	[redacted]	£50,481	2.95	£17,138	Extendedly dominated
ETN	[redacted]	[redacted]	£50,635	3.19	£15,855	£16,191
GOL	[redacted]	[redacted]	£51,798	2.89	£17,911	Dominated
SEK	[redacted]	[redacted]	£54,680	2.96	£18,476	Dominated
INF	[redacted]	[redacted]	£68,835	3.25	£21,176	£320,148
TOFACITINIB PROGRESSION: 11% PROGRESS AT BSC (TOF PROGRESSION UPDATED TO 0.002)						
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£34,251	2.53	£13,531	£13,531
APR	[redacted]	[redacted]	£40,487	2.07	£19,533	Dominated
ADA	[redacted]	[redacted]	£48,963	2.77	£17,665	Extendedly dominated
CTZ	[redacted]	[redacted]	£50,481	2.95	£17,138	Extendedly dominated
ETN	[redacted]	[redacted]	£50,635	3.19	£15,855	£24,735
GOL	[redacted]	[redacted]	£51,798	2.89	£17,911	Dominated
SEK	[redacted]	[redacted]	£54,680	2.96	£18,476	Dominated
INF	[redacted]	[redacted]	£68,835	3.25	£21,176	£320,148
TOFACITINIB: 11% PROGRESS AT SAME RATE AS APREMILAST (TOF PROGRESSION UPDATED TO 0.001)						
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£34,175	2.58	£13,266	£13,266
APR	[redacted]	[redacted]	£40,487	2.07	£19,533	Dominated
ADA	[redacted]	[redacted]	£48,963	2.77	£17,665	Extendedly dominated

CTZ	[redacted]	[redacted]	£50,481	2.95	£17,138	Extendedly dominated
ETN	[redacted]	[redacted]	£50,635	3.19	£15,855	£26,650
GOL	[redacted]	[redacted]	£51,798	2.89	£17,911	Dominated
SEK	[redacted]	[redacted]	£54,680	2.96	£18,476	Dominated
INF	[redacted]	[redacted]	£68,835	3.25	£21,176	£320,148

Table 45 shows that for all progression scenarios, all comparators fall within the acceptable thresholds for cost-effectiveness, compared to BSC. For the fully incremental analysis for sub-population 2, a strategy commencing with etanercept offers higher QALYs in each scenario, however tofacitinib also has an ICER that falls below (or within) the acceptable NICE thresholds.

Table 46 Sub-population 3: Tofacitinib progression rate scenarios

TOFACITINIB PROGRESSION = APREMILAST PROGRESSION						
Strategy	**Total discounted costs**	**Total discounted QALYs**	**Incremental cost vs. cheapest strategy**	**Incremental QALYs vs. cheapest strategy**	**ICER vs. cheapest strategy**	**Incremental ICER**
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£12,583	0.82	£15,400	£15,400
UST	[redacted]	[redacted]	£26,709	1.42	£18,761	£23,287
SEK	[redacted]	[redacted]	£54,206	1.60	£33,914	£157,429
TOFACITINIB: (11% PROGRESS AT BSC (TOF PROGRESSION UPDATED TO 0.002)						
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£11,923	1.19	£9,984	£9,984
UST	[redacted]	[redacted]	£26,709	1.42	£18,761	£64,441
SEK	[redacted]	[redacted]	£54,206	1.60	£33,914	£157,429
TOFACITINIB: 11% PROGRESS AT SAME RATE AS APREMILAST (TOF PROGRESSION UPDATED TO 0.001)						
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£11,828	1.25	£9,472	£9,472
UST	[redacted]	[redacted]	£26,709	1.42	£18,761	£85,041
SEK	[redacted]	[redacted]	£54,206	1.60	£33,914	£157,429

In sub-population 3 (Table 46), when the tofacitinib progression rate is equal to that of apremilast, ustekinumab offers higher QALYs and is associated with an ICER of £23,287. When 11% of patients progress at the same rate as BSC or apremilast, a strategy commencing with tofacitinib is the only strategy that falls within (below) the NICE acceptable threshold.

Table 47 Sub-population 4: tofacitinib progression rate scenarios

TOFACITINIB PROGRESSION = APREMILAST PROGRESSION						
Strategy	**Total discounted costs**	**Total discounted QALYs**	**Incremental cost vs. cheapest strategy**	**Incremental QALYs vs. cheapest strategy**	**ICER vs. cheapest strategy**	**Incremental ICER**
BSC	[redacted]	[redacted]	-	-	-	-

TOF	[redacted]	[redacted]	£9,655	0.73	£13,266	£13,266
UST	[redacted]	[redacted]	£24,979	1.33	£18,837	Extendedly dominated
SEK	[redacted]	[redacted]	£30,153	1.62	£18,557	£22,849
TOFACITINIB: (11% PROGRESS AT BSC (TOF PROGRESSION UPDATED TO 0.002)						
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£9,092	1.05	£8,670	£8,670
UST	[redacted]	[redacted]	£24,979	1.33	£18,837	Extendedly dominated
SEK	[redacted]	[redacted]	£30,153	1.62	£18,557	£36,554
TOFACITINIB: 11% PROGRESS AT SAME RATE AS APREMILAST (TOF PROGRESSION UPDATED TO 0.001)						
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£9,011	1.09	£8,230	£8,230
UST	[redacted]	[redacted]	£24,979	1.33	£18,837	Extendedly dominated
SEK	[redacted]	[redacted]	£30,153	1.62	£18,557	£39,888

Similar results for sub-population 4 are shown in Table 47 except for the first progression scenario (tofacitinib is equal to apremilast) where secukinumab offers higher QALYs and has an ICER within the NICE acceptable threshold.

6.4 Conclusions from ERG analyses

The ERG conducted a range of exploratory analyses to assess the uncertainties raised in the review and critique of the manufacturer's clinical and cost-effectiveness evidence. The ERG's exploratory analyses focussed on, severity of psoriasis, tofacitinib progression rates and drug costs for comparator drugs that are approved but not available publicly.

The additional analyses undertaken by the ERG suggested that whilst the ICERs for all subpopulations changed in each of the scenarios, they remained within the acceptable willingness to pay threshold, compared to BSC. In all scenarios, the fully incremental ICERs for tofacitinib are also within conventional willingness to pay thresholds, although etanercept may offer higher QALYs within an acceptable threshold. The confidential PAS appendix considers the impact of the PAS prices for apremilast and secukinumab on the cost-effectiveness results.

7 End of life

Not applicable.

8 Overall conclusions

The evidence for the clinical effectiveness of tofacitinib is based on good quality randomised trials and the results are likely to be reliable.

The ERG identified limitations in the generalisability of the RCT evidence to clinical practice:

- A significant proportion of patients in each RCT (18% and 24%) was treated in combination with sulfasalazine and leflunomide, when the marketing authorisation is for tofacitinib in combination with methotrexate (MTX) only.
- In both OPAL Broaden and OPAL Beyond the placebo-controlled phase was limited to 3 months: treatment with tofacitinib in clinical practice is long-term.
- The use of adalimumab in OPAL Broaden in combination with a csDMARD, is not reflective of adalimumab in clinical practice or in other trials;
- the number of previous TNFis (and the specific previous TNFis) in OPAL Beyond may not reflect the patient population in which tofacitnib will be used in current practice;
- and finally, in OPAL Balance (the long-term follow-up study) [redacted], whereas the licenced dose for tofacitinib in 5mg BD.

The ERG identified errors in the implementation of the company's placebo-adjusted NMAs. Models corrected by the ERG found a more meaningful interaction between baseline risk and treatment effect than the company analyses. The corrected ERG analyses also showed statistical support for models considering class-effects. Additionally, residual deviance for the placebo arm of OPAL BROADEN no longer indicated a poor fit. Therefore the ERG corrected models did not provide support for the company's 'optimistic analyses' (sensitivity analyses to improve goodness of fit) that excluded the placebo arm of OPAL Broaden.

The ERG had concerns regarding assumptions in the CS and economic model. In particular, the assumption that tofacitinib halts HAQ-DI progression while patients remain on treatment. The ERG is cautious of this assumption given that no long-term clinical evidence is available to support this, such as data assessing radiographic disease progression. The ERG assessed this assumption by conducting scenario analyses using different HAQ-DI progression rates. The ERG conclude that whilst the ICERs change for each sub-population, they remain within the acceptable willingness to pay threshold, compared to BSC. However, in the fully incremental analyses, tofacitinib is bettered by etanercept in sub-population 2 in each progression scenario. In sub-population 3, when tofacitinib progression is equal to apremilast progression, ustekinumab is more effective (i.e. offers more QALYs) than

tofacitinib. Similarly, in sub-population 4, when tofacitinib is equal to apremilast progression, secukinumab offers higher QALYs within an acceptable cost-effectiveness threshold.

The ERG also had concerns about assumptions made regarding effect degradation for subsequent lines of therapy. The CS does not apply a reduction in effectiveness for subsequent lines of therapy. This may over-estimate the cost-effectiveness of treatments with a lower PsARC response rate. Due to the lack of flexibility in the company model, the ERG is unable to explore the sensitivity of the cost-effectiveness results to this assumption.

8.1 Implications for research

Longer term data are required to confirm the efficacy of tofacitinib, particularly for the outcome of progression of joint disease and the implications this may have on cost-effectiveness.

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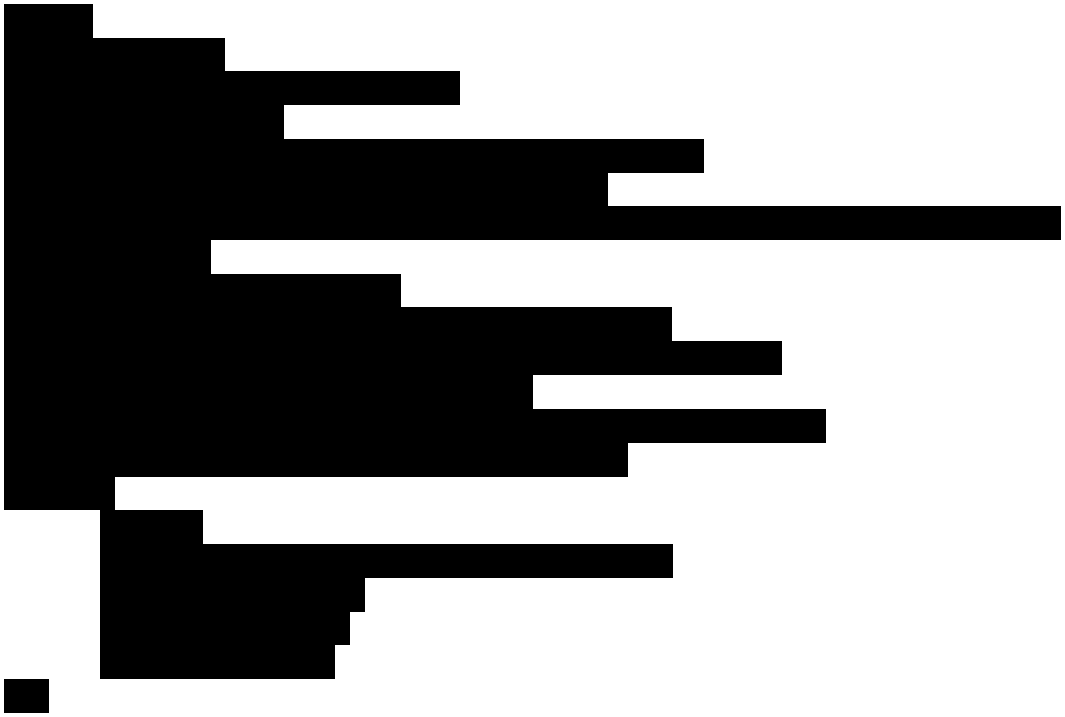
10 Appendices

Appendix A: Manufacturer's model with error in the implementation of the placebo-response adjustment



Corrected placebo-response adjustment model:

```
model{
for(i in 1:NS){
            mu[i] ~ dnorm(0,.0001)
            w[i,1] <-0
            delta[i,1]<-0      for (k in 1:na[i])  {
                  r[i,k] ~ dbin(p[i,k],n[i,k])
                  logit(p[i,k])<-mu[i] + delta[i,k]  + (beta[t[i,k]]-beta[t[i,1]]) *(mu[i]-meanmA)
                  }
          for (k in 2:na[i]) {
            delta[i,k] ~ dnorm(md[i,k],taud[i,k])
            md[i,k] <-  d[t[i,k]] - d[t[i,1]]  + sw[i,k]
            taud[i,k] <- tau *2*(k-1)/k
            w[i,k] <- (delta[i,k]  - d[t[i,k]] + d[t[i,1]])
            sw[i,k] <-sum(w[i,1:k-1])/(k-1) }
          }
          d[1]<-0
          beta[1] <- 0
          for (k in 2:NT){
                  d[k] ~ dnorm(0,.0001)
                  beta[k] <- B
```

```
            }
        B ~ dnorm(0,.0001)
        sd~dunif(0.001,2)
        tau<-1/pow(sd,2)
}}
```

Appendix B: Comparison of costs and QALYs between TA445 and TA1220

Treatment	Average QALYs in TA445	QALYs in TA1220	Average costs in TA445	Costs in TA1220
Sub-population 2				
BSC	5.7	[redacted]	£71467	[redacted]
ADA	7.7	[redacted]	£117680	[redacted]
CTZ	7.5	[redacted]	£115719	[redacted]
ETN	8.1	[redacted]	£123167	[redacted]
SEK	7.6	[redacted]	£120409	[redacted]
GOL	8.0	[redacted]	£123123	[redacted]
INF	8.2	[redacted]	£148786	[redacted]
Sub-population 3				
BSC	5.7	[redacted]	£71467	[redacted]
UST	6.7	[redacted]	£95362	[redacted]
SEC	7.0	[redacted]	£122357	[redacted]
Sub-population 4				
BSC	5.7	[redacted]	£71467	[redacted]
UST	6.7	[redacted]	£92404	[redacted]
SEC	6.8	[redacted]	£99764	[redacted]

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Tofacitinib for treating active psoriatic arthritis after DMARDs [ID1220]

You are asked to check the ERG report from Centre for Reviews and Dissemination and Centre for Health Economics – York to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 27 June 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Tofacitinib has been misspelled in a number of places throughout the ERG report	Pfizer propose that the spelling is corrected throughout the document.	This will improve readability of the ERG report.	Correction made - NB because this is a minor typographical error and the meaning is not affected, erratum pages have not been created for this correction only.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Contra-indicated has been written as “contradicted” in a number of places throughout the ERG report.	Pfizer propose that the spelling is corrected throughout the document.	This will improve readability of the ERG report.	Correction made as proposed.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ACR20 has been written as “ARC20” in a number of places throughout the ERG report.	Pfizer propose that the spelling is corrected throughout the document.	This will improve readability of the ERG report and minimise the risk of misinterpretation by the reader	Correction made - NB because this is a minor typographical error and the meaning is not affected, erratum pages have not

			been created for this correction only.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 11 of the ERG report states: "For the subpopulation, those who had not adequately responded to csDMARDS, certolizumab pegol was not addressed"	Pfizer propose that the statement is amended to: "For the subpopulation **of patients** who had not adequately responded to csDMARDs **and one or more TNFi,** certolizumab pegol was not addressed"	This statement should be amended for clarity (to ensure the reader is clear that certolizumab was not addressed in sub-population 3, but was addressed in sub-population 2).	Correction made as proposed.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 12 of the ERG report includes the statement: "key efficacy outcomes; ARC [sic] 20/50/70, PASI70 response rate"	Pfizer propose that the statement is amended to: "key efficacy outcomes; **ACR** 20/50/70, **PASI75** response rate"	This will improve readability and accuracy of the ERG report and minimise the risk of misinterpretation by the reader.	We apologise for this copy editing failure. Correction made as proposed.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 12 of the ERG report	Pfizer propose that this statement is	This statement should be	Correction made as

states: “Modified PsARC response and PASI-75 response”	amended to: “**PsARC response** and PASI-75 response”	amended for accuracy. There is no reference to a ‘modified PsARC’ response within the CS.	proposed

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 13, 72 and 120 of the ERG report states: “These were owing to a significant proportion of patients in each RCT (18% and 24%) treated in combination with sulfasalazine and leflunomide, […]”.	Pfizer propose that the statement is amended to: “These were owing to a proportion of patients in each RCT (18% and 24%) treated in combination with sulfasalazine **or** leflunomide, […]”. It may also be worth noting that small proportions of participants received hydroxychloroquine or other csDMARDs concomitantly.	1. The statements on pages 13, 72 and 120 imply statistical significance, but no statistical analyses were undertaken in this context. 2. As per OPAL Broaden and Beyond trial protocols, patients were required to receive a single background csDMARD	Correction made as proposed

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 13 of the ERG report lists the following as an issue related to generalisability of the tofacitinib clinical trial data: (1) “The use of adalimumab in OPAL Broaden in	Pfizer request that this is more explicitly written as a matter of opinion, rather than stated as a matter of fact.	The ERG report does not provide factual justification for the statement that this is incongruent with clinical practice. Indeed, a recent paper by Fagerli et al 2018 (as	Not a factual inaccuracy – in clinical practice adalimumab does not have to be given in combination with a csDMARD.

combination with a csDMARD not being reflective of adalimumab in clinical practice or in other trials. The similar point is made later in the report, on page 29.		referenced in the ERG report) reporting data from the BSRBR (2002-2006) states that among patients with PsA receiving adalimumab, 53.5% received concomitant methotrexate and 14.1% received other concomitant medications. Fagerli KM, Kearsley-Fleet l, Watson KD, et al. long-term persistence of tnF-inhibitor treatment in patients with psoriatic arthritis. Data from the British Society for rheumatology Biologics register. RMD Open 2018;**4**:e000596. doi:10.1136/ rmdopen-2017-000596	

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 13 of the ERG report states: (3.) Almost [redacted] of patients in OPAL Balance (the long-term follow-up study) received an average tofacitinib dose of 10 mg BD, whereas the licenced dose for	Pfizer request that the following statement is marked as CIC: "and finally, in OPAL Balance (the long-term follow-up study) [redacted] whereas the licenced dose for tofacitinib in 5mg BD."	The percentages of patients receiving each dose is marked as CiC in the response to ERG clarification question A23 (Table 00099.5) and should be marked as such in the ERG report.	Marking updated as proposed.

tofacitinib in 5mg BD.			

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 17 of the ERG report states: "as an alternative to other currently recommended biologic disease-modifying anti-rheumatic drugs (bDMARD/tsDMARDs)"	Pfizer propose that this statement is amended to: "as an alternative to other currently recommended biologic **or targeted synthetic** disease-modifying anti-rheumatic drugs (bDMARD/tsDMARDs)"	This statement should be amended for clarity.	Correction made as proposed.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 19 of the ERG report states: Furthermore, adherence and compliance with twice-daily tablets may well be poorer than to less frequent injections, and the clinical monitoring of adherence to tablets likely to more difficult than that of adherence to biologic therapies."	Pfizer request that this is more explicitly written as a matter of opinion, rather than stated as a matter of fact.	The statement within the ERG report is drafted as a matter of fact. However, the report does not provide factual justification for the statement. This is important to ensure clarity for the reader.	Not a factual inaccuracy

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 19 of the ERG report states: "In addition, the ERG notes that due to the requirement [sic] for tofacitinib to be given concomitantly with MTX (which many patients self-administer as a subcutaneous injection), treatment will not necessarily avoid an injection-based administration."	Pfizer propose that the statement regarding many patients self-administering MTX is written with less definitive language. A proposal is below: "In addition, the ERG notes that due to the requirement [sic] for tofacitinib to be given concomitantly with MTX (which patients **may** self-administer as a subcutaneous injection), treatment will not necessarily avoid an injection-based administration."	The ERG report does not provide a reference to substantiate "many patients self-administer…"	Not a factual inaccuracy

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 20 of the ERG report states: "The clinical advisor to the ERG suggested that given there is limited knowledge of the use of ofacitinib [sic] in clinical practice […]".	Pfizer propose that the statement is amended to: "The clinical advisor to the ERG suggested that given there is limited knowledge of the use of **t**ofacitinib in **UK PsA** clinical practice […]".	As written, the statement implies that there is limited knowledge of tofacitinib in clinical practice. As the CS makes clear on page 101, there are more than 19,400 patient-years of experience with tofacitinib. Similarly, tofacitinib has been approved for use in the UK for the treatment of rheumatoid arthritis since 2017. Therefore, the current statement	Clarification made as suggested.

		is factually incorrect	

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 21 of the ERG report states that: "The intervention stated in the CS was: 'Tofacitinib (in combination with a csDMARD)' This differs from the NICE scope that states 'tofacitinib (alone or in combination with an csDMARD)'[redacted] The clinical effectiveness of tofacitinib was informed by trials some including patients who were treated in combination with sulfasalazine and leflunomide. The licenced dose of tofacitinib is 5mg BD twice daily."	Pfizer propose that this description is amended to read: The intervention stated in the CS was: 'Tofacitinib (in combination with a csDMARD)' This differs from the NICE scope that states 'tofacitinib (alone or in combination with an csDMARD)'. [redacted] The clinical effectiveness of tofacitinib was informed by trials ~~some including~~ **in which a proportion of** patients were treated in combination with **a csDMARD other than MTX, such as** sulfasalazine or leflunomide. The licenced dose of	It may prove useful to provide clarity around the difference between the intervention stated in the CS and the current wording of the anticipated marketing authorisation. We have marked the anticipated marketing authorisation as AiC, pending EC ratification of the license	Not a factual inaccuracy

	tofacitinib is 5mg BD twice daily.”		

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 25 of the ERG report states that: “The inclusion criteria for the systematic review specified randomised control trials (with parallel design) of tofactinib [sic], bDMARDs and the PDE-4 inhibitor apremilast, for the treatment of active PsA in adults with a previous inadequate response to csDMARD therapy, which reported relevant clinical and health-related quality of life, including adverse event outcomes.”	Pfizer propose that this statement is amended to read: “The inclusion criteria for the systematic review specified randomised control trials (with parallel design) of tofacitinib, bDMARDs and the PDE-4 inhibitor apremilast, for the treatment of active PsA in adults with **a previous intolerance of**, or inadequate response to csDMARD therapy, which reported relevant clinical **effectiveness** and health-related quality of life, including adverse event outcomes.	The sentence needs to be amended to reflect the inclusion of patients with PsA that had a previous intolerance to csDMARD therapy and to reflect the collection of clinical effectiveness outcomes.	Correction made as proposed.

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 25 of the ERG report	Pfizer propose that this statement is	This statement should be	Correction made as

states: ”and the comparator treatments: adalimumab, apremilast, etanercept, infliximab, ustekinumab, golimumab, secukinumab, certolizumab pegol and ixekizumab”	amended to: ”and the comparator treatments: adalimumab, apremilast, etanercept, infliximab, ustekinumab, golimumab, secukinumab, certolizumab pegol, **abatacept**, and ixekizumab”	amended for accuracy.	proposed.

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 25 of the ERG report states that: “Relevant data extracted from included studies are detailed in Appendix D, section D.1.6.”	Pfizer propose that this description is amended to read: Relevant data extracted from included studies are detailed in Appendix D, section D.1.6 **and Appendix E, section E1.**	The sentence needs to be amended to reflect the presentation of data in Appendix E, section E1, in addition to those data presented in Appendix D.	Correction made as proposed.

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 27 of the ERG report states: “The inclusion criteria for both trials were: adults aged ≥18 years;”	Pfizer propose that this statement is amended to: “The inclusion criteria for both trials were: adults aged ≥18 years [redacted];”	This statement should be amended for accuracy.	Correction made as proposed.

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 1 on page 27 of the ERG report lists "ACR20 response rate: Week 2, Month 6, 12" This excludes information regarding OPAL Broaden.	Pfizer propose that this description is amended to read: "ACR20 response rate: Week 2, Month 6 **(and Month 12, OPAL Broaden only)**"	This bullet point should be amended for accuracy, as per Table 5 of the CS.	Correction made as proposed.

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 28 of the ERG report states that: "The methods are appropriate with both trials having over 90% power to detect a 20% treatment difference and OPAL Beyond having 84% to detect a 15% treatment difference, though the treatment difference for many outcomes is much smaller than this." This wording does not make	Pfizer propose that this statement is amended to read: "The methods are appropriate. **Both trials were designed to yield over 90% power to detect a 20% treatment difference between tofacitinib and placebo on a co-primary outcome ACR20; OPAL Beyond was designed to yield 84% to detect a 15% treatment difference between tofacitinib and placebo on a co-primary outcome ACR20.** However, the observed treatment difference for ACR20 in both	The statement should be amended for clarity, as the current wording may lead to confusion regarding study power.	Not a factual inaccuracy

the power in each of the studies immediately clear.	trials was much smaller than this."		

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 28 of the ERG report states that: "Type I error was adjusted for multiple comparisons for ARC 20, change in HAQ-DI at three months"	Pfizer propose that this statement is amended to read: "Type I error was adjusted for multiple comparisons for ACR 20 **and** change in HAQ-DI at three months"	This statement should be amended for clarity, as per wording in Table 8 in CS.	Although there is a typo the meaning is not unclear – no correction made

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 28 of the ERG report states that: "The response stated that a gate-keeping or step-down strategy was used to protect the global type one error; specifically which step-down method was used was not clear."	Pfizer propose that this statement is amended to read: The response stated that a gate-keeping or step-down strategy was used to protect the global type one error. **A figure illustrating the step-down method was provided in the clarification response.**	It does not provide an accurate representation of the clarification response to say that the step-down method was not specified.	Not factual inaccuracy, the ERG report was pointing out the response was a little ambiguous. However, as noted in the next paragraph 'The ERG considers the methods to be broadly appropriate'.

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 29 of the ERG report states that: "Adverse events were roughly equal across all treatment arms"	Pfizer propose that this statement is amended to read: "**Discontinuations due to** adverse events were roughly equal across all treatment arms"	This statement should be amended for accuracy, as per CONSORT diagram Figure D15 in Appendix D of the CS.	Correction made as proposed.

Issue 24

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 29 of the ERG report states that: "In their clarification response the company clarified that in the group randomised to tofacitinib 5 mg, [redacted] patients withdrew by 3 months, [redacted] by month 12. [redacted]." [confidentiality marking not	Pfizer request that this statement is amended as follows: ""In their clarification response, the company clarified that in the group randomised to tofacitinib 5 mg, [redacted] patients withdrew by 3 months, [redacted] by month 12. [redacted]."	This statement should be amended for accuracy, as per the data provided in OPAL Broaden CSR table 14.1.1.2.1 in response to ERG clarification question A19. As indicated in the Pfizer clarification response, the contents of that table are confidential and should therefore be marked as such.	Correction made as proposed.

included in ERG report]			

Issue 25

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In the summary of OPAL Broaden on page 30 of the ERG report, it states: "Importantly only 262 (82.39%) patients were receiving concomitant MTX. The ERG notes that almost 18% of patients were therefore not receiving tofacitinib in accordance with the product licence" A similar statement is made with respect to OPAL Beyond on page 35: "The ERG notes that almost 24% of patients in OPAL Beyond were not receiving tofacitinib in accordance with the product licence"	Pfizer request that these statements are amended to read: [redacted]	[redacted]	Not a factual inaccuracy that warrants an amendment – the licence will reflect the CHMP positive opinion

Issue 26

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 30 of the ERG report states: "Table 3 Efficacy results for OPAL Broaden (FAS) ACR 20, 50 and 90, PSARC, PASI 75 and HAQ-DI."	Pfizer propose that this statement is amended to read: "Table 3 Efficacy results for OPAL Broaden (FAS) ACR 20, 50 and **70**, PSARC, PASI 75 and HAQ-DI."	This statement should be amended for accuracy.	Correction made as proposed.

Issue 27

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 31 of the ERG report states that: "Modified TSS values at Month 12 were available for [redacted]"	Pfizer propose that this statement is amended to read: "Modified TSS values at Month 12 were available for [redacted]	This statement should be amended for accuracy, as per the data presented in Table 12 on page 48 of the CS	Correction made as proposed

Issue 28

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In Table 3 on page 31 of the ERG report, the number of subjects in the FAS are missing for the following outcomes:	Pfizer propose that the content of Table 3 is amended to read: ACR20 at month 6 for TOF5 should be [redacted] and ADA should be [redacted], and ACR20 at month 12 for TOF5 should be 73**/107** (68)	These numbers should be added for completeness, in line with the information presented for the other outcomes in the table.	Correction made as proposed

• ACR20 at month 6 for TOF5 and ADA • ACR20 at month 12 for TOF5 and ADA	and ADA are should be 64**/106** (60)		

Issue 29

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 32 of the ERG report states that: "At the 3 months for all outcomes in these tables, adalimumab was statistically significantly more effective than placebo."	Pfizer propose that this statement is amended to read: "At 3 months, for all outcomes listed in Table 3 above, adalimumab was **numerically** superior to placebo"	This statement should be amended for accuracy, as the OPAL Broaden trial was not designed to establish superiority or non-inferiority of adalimumab to placebo.	Not a factual inaccuracy

Issue 30

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 32 of the ERG report states that: "Comparison of tofacitinib with adalimumab at 3, 6 and 12 months shows that numerically for most outcomes adalimumab was very slightly better than tofacitinib, but for no outcome was the difference statistically significant; the trial was not powered to test such a	Pfizer propose that this statement is amended to read: "Comparison of tofacitinib with adalimumab at 3, 6 and 12 months shows that numerically for most outcomes adalimumab was very slightly better than tofacitinib, but for no outcome was the difference statistically significant, as the trial was not designed or powered **to detect non-inferiority or superiority between**	This statement should be amended for accuracy, as per page 44 of the CS, this trial was not designed or sufficiently powered to establish non-inferiority or superiority of tofacitinib to adalimumab	Not a factual inaccuracy

small difference.”	**tofacitinib and adalimumab**”.		

Issue 31

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 32 of the ERG report states that: “The results for adalimumab were similar to those for tofacitinib except for the LEI score, for which adalimumab was statistically significantly greater than placebo and the difference for adalimumab from placebo (-0.7 (95% CI -1.2, -0.1) was numerically superior to tofacitinib from placebo (-0.4 (95% CI -0.9, 0.2.”	Pfizer propose that this statement is amended to read: “The results for adalimumab were similar to those for tofacitinib except for the LEI score, for which adalimumab was **numerically** greater than placebo and the difference for adalimumab from placebo (-0.7 (95% CI -1.2, -0.1) was numerically superior to tofacitinib from placebo (-0.4 (95% CI -0.9, 0.2.”	This statement should be amended for accuracy, as the OPAL Broaden trial was not designed to establish superiority or non-inferiority of adalimumab to placebo.	Not a factual inaccuracy

Issue 32

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 33 of the ERG report states that: “Although most differences were nominally statistically significant, statistical significance could not be	Pfizer propose that this statement is amended to read: “Although **some** of the differences were nominally statistically significant, statistical significance could not be claimed due to the hierarchical testing scheme (tofacitinib	This statement should be amended for accuracy, as half of the differences were not significant and half were significant, as per Table M7 on page 14 in the CS	Correction made as proposed.

claimed due to the hierarchical testing scheme (tofacitinib was not statistically significantly superior for LEI score)."	was not statistically significantly superior for LEI score)."		

Issue 33

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 33 of the ERG report states that: "Results were similar for adalimumab, though the difference from placebo for adalimumab was numerically lower for FACIT-F and ISI score ([redacted])." [confidentiality marking not present in ERG report]	Pfizer request that confidentiality marking of this statement is amended as follows: "Results were similar for adalimumab, though the difference from placebo for adalimumab was numerically lower for FACIT-F and ISI score ([redacted])."	ISI data are CiC, as indicated in the CS. Comparisons between ADA and PBO are nominal, as OPAL Broaden was not designed or powered to establish superiority of inferiority of ADA to PBO.	Correction made as proposed.

Issue 34

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 33 of the ERG report states that: "The results suggest [redacted]	Pfizer request that confidentiality marking of this statement is amended as follows: "The results suggest [redacted]	The EQ-5D data tables that were sent to ERG as part of the clarification questions are confidential, as per page 76 of the ERG clarification questions answer sheet.	CIC marking amended

[redacted]; no formal testing was presented." [confidentiality marking not present in ERG report]	[redacted]; no formal testing was presented."		

Issue 35

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 33 of the ERG report states that: "At 12 months, there was evidence of a reduction in progression in the adalimumab but not the tofactinib [sic] arm, though the treatment difference was not statistically significant; again, the trial was not powered to test such a small difference"	Pfizer propose that this statement is amended to read: "At 12 months, there was evidence of a reduction in progression in the adalimumab but not the tofacitinib arm, though the treatment difference was not statistically significant; **it should be noted that the trial was not designed or sufficiently powered to establish non-inferiority or superiority of tofacitinib to adalimumab**."	This statement should be amended for accuracy. As per page 44 of the CS, this trial was not designed or sufficiently powered to establish non-inferiority or superiority of tofacitinib to adalimumab	Not a factual inaccuracy

Issue 36

Description of problem	Description of proposed amendment	Justification for amendment	ERG Report
Page 34 of the ERG report states that the following number of participants in the tofacitinib 5mg arm completed the trial:	Pfizer request that this statement is amended to read: "Tof 5 mg **122/131 (93.1)**"	This statement should be amended for accuracy. As per Figure D15 of Appendix D of the CS, 131 patients were randomised into the Tof 5mg	Correction made as proposed

"Tof 5 mg 122/132 (92.4)"		group.	

Issue 37

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 36 of the ERG report states that: "The ERG notes that whilst all patients had been exposed to one or more TNFi, [redacted]	Pfizer propose that this statement is amended to read: "The ERG notes that whilst all patients had been exposed to one or more TNFi, [redacted]	This statement should be amended for clarity.	Not a factual inaccuracy – the report states clearly that only the results of the 5 mg group, not the 10 mg group, are presented.

Issue 38

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 36 of the ERG report states that: "In clinical practice, it might be expected that this figure would be lower, with tofacitinib reserved for later in the treatment pathway	Pfizer request that this is more explicitly written as a matter of opinion, rather than stated as a matter of fact.	The ERG report does not provide factual justification for the statement that a lower proportion of patients would have received only one TNFi prior to treatment with tofacitinib.	Not a factual inaccuracy

Issue 39

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 38 of the ERG report states: "The MDA response rate at month 3 in the tofacitinib 5 mg BD group was 23% vs 15% in the placebo group, though the difference was not statistically significant ([redacted])" [confidentiality marking not included in ERG report]	Pfizer propose that this statement is amended to read: "The MDA response rate at month 3 in the tofacitinib 5 mg BD group was 23% vs 15% in the placebo group, though the difference was not statistically significant [redacted]"	The p-value for the statistical comparison between tofacitinib and adalimumab should be marked as CIC, as indicated in Table M15 in Appendix M of the CS.	CIC marking added

Issue 40

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 39 of the ERG report states: "Compared with OPAL Broaden the placebo response was lower in Beyond for ACR 20, but it was higher for ACR 50 and 70, and also PSARC."	Pfizer propose that this statement is amended to read: ""Compared with OPAL Broaden, the placebo response was lower in Beyond for ACR 20 **and PsARC**, but it was higher for ACR 50 and 70~~, and also PsARC~~."	This statement should be amended for accuracy, as per Tables 13 and 18 of the CS.	Correction made as proposed

Issue 41

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p.39 of the ERG report states: "For PASI75 the placebo response rates in the two trials were very similar; the lack of a statistically significant effect of tofacitininb in Beyond was due to a much lower tofacitinib 5 mg arm response rate compared with that seen in Broaden 21% vs 43%)."	Pfizer propose that a statement is added: "For PASI75 the placebo response rates in the two trials were very similar; the lack of a statistically significant effect of tofacitininb in Beyond was due to a much lower tofacitinib 5 mg arm response rate compared with that seen in Broaden 21% vs 43%). **The elevated placebo response in a more treatment refractory group of patients may have contributed to the lack of statistically significant difference**."	The statement should be amended for clarification.	Not a factual inaccuracy

Issue 42

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 39 of the ERG report states : "OPAL Balance is ongoing, with an anticipated completion date of January 2020"	Pfizer propose that this statement is amended to read: "OPAL Balance is ongoing, with **the anticipated completion date at the time of submission** reported as January 2020"	The study completion date has been recently updated to August 2019, to reflect the study completion date on the clinicaltrials.gov website. This occurred following submission of the dossier	Not a factual inaccuracy

Issue 43

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 8 on page 40 of the ERG report contains data from OPAL Balance. The number of patients calculated as enrolling in the study from a tofacitinib 10mg BD dose is incorrectly reported as [redacted] The table also states that % are provided; however it only contains the patient numbers. Additionally, as the data in this table is taken from the CSR, the entire table should be marked as commercial in confidence	Pfizer request that this table be corrected and appropriately marked as CiC	To facilitate factual reporting of the data and ensure the data is appropriately marked as CiC	CIC marking added

Issue 44

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 40 of the ERG report states: "Further information provided in the company's clarification	Pfizer request that this statement be appropriately marked as CiC, as follows: "Further information provided in the company's clarification response	To ensure post hoc data analyses developed for this submission remain CiC	CIC marking added

response [redacted]	[redacted]		

Issue 45

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 9 on page 41 of the ERG report states: [redacted]	Pfizer propose that this table column is amended to read: [redacted]	This table column should be amended based on Pfizer's re-calculations of the Pfizer data from OPAL Balance CSR Tables 14.1.1.2 reported in the answer to question A5 of the ERG clarification questions document.	Correction made as proposed

Issue 46

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 41 of the ERG report states: "Withdrawals at 2 years (2.5 to 3 years since start of tofacitinib) were roughly [redacted] remained on their first TNFi."	Pfizer propose that this statement is amended to: "Withdrawals at 2 years (2.5 to 3 years since start of tofacitinib) were roughly [redacted] remained on **tofacitinib**"	This statement should be amended for clarity as patients received tofacitinib in OPAL Balance (not TNFis)	Correction made a proposed

Issue 47

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 10 on page 42 of the ERG report contains PsARC data that are confidential but is not marked as such.	Pfizer propose that the PsARC data in this table are marked as confidential.	The data are taken from the interim CSR and are confidential.	CIC marking added

Issue 48

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 49 of the ERG report states: "From the trial CONSORT diagrams (CS Appendix D) and the clarification response the ERG calculated that in [redacted] and [redacted] of patients withdrew due to an adverse event in OPAL Broaden and Beyond respectively, though none of the events were considered to be treatment related"	Pfizer propose that this statement is amended to read: ""From the trial CONSORT diagrams (CS Appendix D) and the clarification response the ERG calculated that in [redacted] and [redacted] of patients withdrew due to an adverse event in OPAL Broaden and Beyond respectively, though none of the events were considered to be treatment related"	This statement should be amended for accuracy.	Correction made as proposed

Issue 49

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51 of the ERG report states: "These new data did not make a substantial impact on the findings, although in some models this may have led to an underestimate of the effectiveness of secukinumab and certolizumab pegol (placebo adjusted and class-effect models)."	Pfizer propose that this statement is amended to remove the statement about underestimate of effect: "These new data did not make a substantial impact on the findings. ~~, although in some models this may have led to an underestimate of the effectiveness of secukinumab and certolizumab pegol (placebo adjusted and class-effect models).~~"	This statement should be amended to contextualize interpretation, as the models cannot be strictly said to underestimate secukinumab and certolizumab pegol in the bDMARD naive population. If the ORs for the PsARC outcome from the Pfizer NMA are compared with the ORs from TA 445, then some of the CS results are higher	Not a factual inaccuracy as the ERG reports 'some' rather than 'all'. In most models the ORs were lower in the CS and the ERG corrected company analyses compared with TA445.

Issue 50

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51 of the ERG report states: "New data on ixekizumab versus placebo from the SPIRIT-P2 trial and tofacitinib versus placebo from the OPAL Beyond trial were included in the company NMA analyses and these inclusions were judged to be appropriate."	Pfizer propose that this statement is amended to read: ""New data on ixekizumab versus placebo from the SPIRIT-P2 trial and tofacitinib versus placebo from the OPAL Beyond trial were included in the company NMA analyses and these inclusions were judged to be appropriate. **Where available, data for abatacept versus placebo were also included from ASTRAEA as sensitivity**	The statement should be amended for accuracy.	Not a factual inaccuracy as inclusion of data on abatacept vs placebo in the NMA analyses is already mentioned in section 4.5

	analysis."		

Issue 51

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 17 on Page 50 of the ERG reports the AEs of special interest reported across all OPAL studies up to 36 months. The report notes that the numbers in the table were calculated from the text in CS Appendix M. The number of cardiovascular events listed in Table 17 differs from those numbers reported in the text of Appendix M. In Table 17, this is reported as [redacted] [CiC marking not included in ERG report]. Section M.3.1.1.1 report 3 three subjects with adjudicated cardiovascular events in OPAL Broaden. Section M.3.2.1.4 reports [redacted] with adjudicated cardiovascular events in OPAL	Pfizer propose that the number of cardiovascular events in Table 17 is amended to [redacted], and that this number is marked as CiC.	The content reported in Table 17 differs that reported in the text of Appendix M. Additionally, the total number must be marked as confidential so the confidential number from OPAL Beyond cannot be calculated.	Corrected as proposed

Beyond. Please note that this figure is marked as confidential in Appendix M. Section M.3.3.2 reports 2 subjects major cardiovascular events.			

Issue 52

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 54 of the ERG report states: "This subsection summarises methods and results of the synthesis of relative treatment effects, but the company has not reported how evidence on placebo-response was considered."	Pfizer propose that this statement is amended to read: "This subsection summarises methods and results of the synthesis of relative treatment effects. The company ~~has not~~ **also** reported how evidence on placebo-response was considered."	In Appendix D of the CS in section titled "Analysis of absolute change from baseline or probability of event", it was explained that: "We adopted the same approach as the assessment group analysis for the NICE appraisal TA445 (16) in order to calculate absolute effects. In all analysis this is calculated using the relative effects and the absolute change for the reference arm (12). The reference treatment across all of the analysis is placebo. The section then explains calculation for change in HAQ	We correct the statement in Page 54 of the ERG report to: "…, but the company has provided little detail on how evidence on placebo-response was considered (section "Analysis of absolute change from baseline or probability of event" in Appendix D of the CS)."

		and for categorical outcomes. Pfizer therefore requests that the statement is amended so that the explanation provided in the CS is appropriately characterised.	

Issue 53

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 57 of the ERG report states: "and absolute predicted PsARC response (this depends on assumptions about placebo response which were not justified in the CS)."	Pfizer propose that this statement is amended to read: ""and absolute predicted PsARC response (this depends on assumptions about placebo response which were ~~not~~ justified in the CS)."	In Appendix D of the CS in section titled "Analysis of absolute change from baseline or probability of event", it was explained that: "We adopted the same approach as the assessment group analysis for the NICE appraisal TA445 (16) in order to calculate absolute effects. In all analysis this is calculated using the relative effects and the absolute change for the reference arm(12). The reference treatment across all of the analysis is placebo. The section then explains calculation for change in HAQ and for categorical outcomes.	We have revised the statement in Page 57 of the ERG report to: "…and absolute predicted PsARC response (this depends on assumptions about placebo response which were not clearly justified in the CS)."

		Pfizer therefore requests that the statement is amended so that the explanation provided in the CS is appropriately characterised.	

Issue 54

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 58 of the ERG report states: "better effectiveness than apremilast and ustekinumab (LOR of [redacted])."	Pfizer request that this statement is amended to read: "better effectiveness than apremilast and ustekinumab (LOR of [redacted])."	The statement should be amended for accuracy, as per Table E21 of Appendix E of the CS.	Thanks, amended.

Issue 55

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 58 of the ERG report states: "(Table E31, Appendix E and Table 2 below)"	Pfizer suggest that this statement is amended to read: "(Table E31, Appendix E and **Table 19** below)"	The table is later labelled as Table 19 within the ERG report.	Thanks, amended.

Issue 56

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 58 of the ERG report states: "followed by adalimumab and ustekinumab (intermediate/low effectiveness group), and lastly tofacitinib 5mg BD, certolizumab pegol, etanercept, apremilast (lowest effectiveness group)."	Pfizer request that this statement is amended to read: ""followed by adalimumab, ~~and~~ Ustekinumab, **and tofacitinib** (intermediate/low effectiveness group), and lastly ~~tofacitinib 5mg BD,~~ certolizumab pegol, etanercept, **and** apremilast (lowest effectiveness group)."	This statement should be amended for accuracy, as per Table 19 of the ERG report as the text does not reflect the data in the table.	Thanks, amended

Issue 57

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61 of the ERG report states: "The results of the NMA model (with 24-week data) is shown in Table 21"	Pfizer propose that this statement is amended to read: "The results of the NMA model (with 24-week data; **which does not reflect the base case selected by the company in their submission; the 24-week data were only used in the sensitivity analysis**) ~~is~~ **are** shown in Table 21"	This statement should be amended for clarity.	Not a factual inaccuracy that warrants amendment. As pointed out in the text inclusion, or not, of 24 week data does not impact on results.

Issue 58

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61 of the ERG report states: "Model E1 company analyses [redacted])) but similar for PASI 90 (TA445: 36.5% (8% to 75%); Model E1 company analyses [redacted]))."	Pfizer propose that this statement is amended to read: "Model E1 (**without 24-week data**) company analyses [redacted])) but similar for PASI 90 (TA445: 36.5% (8% to 75%); Model E1 (**without 24-week data**) company analyses [redacted]))."	This statement should be amended for clarity as two sets of analyses were run.	Not a factual inaccuracy. The sentence that immediately precedes that quoted text provides sufficient explanation that this is without 24 week data: 'The exclusion of 24-week data does not alter results significantly.'

Issue 59

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61 of the ERG report states: "in experienced patients the manufacturer chose model G for the base case and K for sensitivity analyses."	Pfizer request that this statement is amended to read: "in experienced patients the manufacturer chose model ~~G~~ **K1** for the base case, **to allow for adjustment for multi-arm studies**, **and model G** ~~and K~~ for sensitivity analyses."	This statement needs to be amended for accuracy, as per Table 30 in Section B.2.10.4.2 of the CS	There is inconsistency between Appendix E (which reports model G as base case and model K as sensitivity analyses) and table 30 in section B.2.10.4.2 of the CS which reports the opposite. It's unclear which is correct.

Issue 60

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61 of the ERG report states: "model G (chosen for the base case) evaluates tofacitinib 5mg BD to have higher HAQ changes than ustekinumab in both responders and non-responders, while model K presents ustekinumab as having the highest HAQ improvement in responders"	Pfizer propose that this statement is amended to read: "model ~~G~~ **K1** (chosen for the base case) evaluates **ustekinumab to have better absolute change from baseline (lower HAQ-DI scores are better) compared to tofacitinib 5 mg BD in responders.** ~~tofacitinib 5mg BD to have higher HAQ changes than ustekinumab in both responders and non-responders, while model K presents ustekinumab as having the highest HAQ improvement in responders~~". **Data for model G (used for sensitivity analysis) are presented as weighted mean difference relative to placebo non-responders, or absolute change from baseline for responders or non-responders.**	This statement needs to be amended for accuracy, as per Section B.2.10.4.2 of the CS	See above Appendix E and section B.2.10.4.2 of the CS contradict one another. It's unclear which is correct.

Issue 61

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 21 on page 63 of the ERG report has omitted the confidence intervals	Pfizer propose that this statement is amended to read: [redacted]	The table should be amended for completeness, as per Table 27 of the CS and Table E62 in Appendix E of the CS	Thanks, amended.

Issue 62

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 21 on page 63 of the ERG report reports PASI data for model E1 with 24-week data as the base case model.	Pfizer request that data from model E1 without the 24-week data is reported as the base case.	Model E1 without 24-week data was the base case model submitted within the CS. Results in the PASI table need to be adjusted accordingly, as per Table E67 of Appendix E of the CS or Table 27 of the CS.	Thanks, we have clarified that the data is for model E1 with 24 week data and not the base case model.

Issue 63

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 21 on page 63 of the ERG report reports data for model G1 as the base case model for the HAQ-DI by PsARC outcome in the bDMARD-experienced population.	Pfizer request that data from model K1 are reported as the base case model.	Model K1 was the base case model for HAQ-DI by PsARC in the bDMARD-experienced population submitted in the CS. Results in the HAQ-DI by PsARC table need to be adjusted accordingly, as per Table 28 in the CS.	As clarified above, Appendix E lists model G1 as the base case whereas Table 28 in the CS lists K1 as base case. It makes it unclear which is correct.

Issue 64

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 65 of the ERG report states:	Pfizer propose that this statement is removed.	It is not a statement of fact that the results are significantly different in model K compared	Not a factual inaccuracy but we accept the company may

"However, there are significant differences in predictions from model K particularly in what concerns responders to PsARC"		with model G.	interpret the data differently.

Issue 65

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 65 of the ERG report states: "OPAL Beyond had a higher placebo PASI responses rate (of [redacted] 15% and [redacted] respectively for PASI50, PASI75 and PASI90) than those modelled. Responses observed in the trial for TOF are [redacted] 21% and [redacted]% respectively for PASI50, PASI75 and PASI90." [confidentiality marking not included in ERG report]	Pfizer propose that this statement is amended to read: "OPAL Beyond had a higher placebo PASI responses rate (of [redacted] ~~15%~~ **14%,** and [redacted] respectively for PASI50, PASI75 and PASI90) than those modelled. Responses observed in the trial for TOF are [redacted] 21% and [redacted] respectively for PASI50, PASI75 and PASI90."	Statement should be amended for factual accuracy, as per Table 19 of the CS. Data from the post-hoc analyses should be marked as confidential.	Thanks, have amended.

Issue 66

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 68 of the ERG report states:	Pfizer propose that this statement is amended to read:	Statement should be amended for factual accuracy, as per	Not a factual inaccuracy

"When comparing across interventions tofacitinib 5 mg BD was not significantly different to any other treatment."	"When comparing across interventions tofacitinib 5 mg BD was not significantly ~~different to~~ **better than** any other treatment."	Table 22 of the ERG report.	

Issue 67

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Figure 6 on page 69 of the ERG report, the labelling of datapoints for ADA and TOF 5 from OPAL Broaden are reversed.	Pfizer request that this figure is relabelled (i.e., the labelling of the ADA and TOF 5 OPAL Broaden data points are switched) and the red trend line is redrawn for ADA.	In OPAL Broaden, trial specific log-odds are: ADA is 0.671 and TOF 5 is 0.266.	Thanks, have amended.

Issue 68

Description of problem	Description of proposed amendment	Justification for amendment
Page 72 of the ERG report states the percentage of patients in OPAL Balance that received an average tofacitinib dose of 10 mg. The percentages of patients receiving each dose is marked as CiC in the response to ERG clarification question A23 (Table	Pfizer request that the following statement is marked as CIC: "In the long-term follow-up study [redacted]	The percentages of patients receiving each dose is marked as CiC in the response to ERG clarification question A23 (Table 00099.5) and should be marked as such in the ERG report.

00099.5) and should be marked as such in the ERG report.		

Issue 69

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 80 of the ERG report states: "It is clear from the systematic review that TA445 is the most comparable economic evaluation to the company's submission. However, the company does not explicitly identify this in the CS."	Pfizer propose that the second sentence is removed: It is clear from the systematic review that TA445 is the most comparable economic evaluation to the company's submission. ~~However, the company does not explicitly identify this in the CS~~.	Section B.3.2.2 of the CS states: "the model structure is based on the modelling approach used by the York Assessment Group (AG) in TA445." And "The treatment sequences used for each sub-population are reflective of current NICE guidance and reflect the sequences used in TA445" It is therefore not correct to state the company does not explicitly acknowledge the comparability of the economic evaluations.	Correction made as proposed.

Issue 70

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 26 on page 81 of the ERG report states: "The drug company seek to align the sup-populations assessed in the TA of tofacitinib for treating active PsA with cDMARDS to the populations that have received positive recommendations from NICE in previous TAs (i.e. sup-populations 2, 3 and 4)	Pfizer propose that the statement is amended to read: "The drug company seek to align the sub-populations assessed in the TA of tofacitinib for treating active PsA **following** cDMARDS to the populations that have received positive recommendations from NICE in previous TAs (i.e. sup-populations 2, 3 and 4)	This statement should be amended for clarity and factual accuracy	Correction made as proposed.

Issue 71

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 26 on page 82 of the ERG report states: "For comparisons involving more than one line of treatment, subsequent treatments are assumed to be as efficacious as first line, i.e. no effect degradation is	Pfizer propose that this statement is amended to indicate that the response rates applied in the economic model for subsequent lines of therapy were taken from the bDMARD experienced NMAs, to reflect differences in efficacy between lines of therapy. No further degradation in effectiveness was applied to the bDMARD experienced population, as it was assumed	As stated in section B3.3.1 of the CS, efficacy data for subsequent lines of therapy have been taken from the bDMARD experienced NMAs. Therefore it is not factually correct to state that subsequent treatments are assumed to be as efficacious as first line	The ERG have updated Table 26 to acknowledge the proposed amendment. The ERG also made an amendment in Section 1.5 of the final report (page 14) to address this.

assumed”	this would be captured in the NMA effect estimates.		

Issue 72

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 26 on page 83 of the ERG report states: “…(except for liver function text….”	Pfizer propose the spelling is corrected to report “…..(except for liver function test…”	This will improve readability of the ERG report.	Correction made as proposed.

Issue 73

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 27 of the ERG report (Page 87) contains the phrase “(CHECK THIS)” in the fourth column of the ‘Measuring and valuing health effects’ column. It is assumed that this was supposed to be removed prior to completion.	Pfizer suggest that the phrase “(CHECK THIS)” is removed.	Removing this will improve readability.	Correction made as proposed.

Issue 74

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 90 of the ERG report states: "…patients moving onto the next line of treatment, are assumed to have the same response probabilities as first line treatment, i.e. no effect degradation is applied for subsequent lines of therapy.	Pfizer propose that this statement is amended to indicate that the response rates applied in the economic model for subsequent lines of therapy were taken from the bDMARD experienced NMAs, to reflect differences in efficacy between lines of therapy. No further degradation in effectiveness was applied to the bDMARD experienced population, as it was assumed this would be captured in the NMA effect estimates.	As stated in section B3.3.1 of the CS, efficacy data for subsequent lines of therapy have been taken from the bDMARD experienced NMAs. Therefore it is not factually correct to state that the treatment effects are maintained for subsequent lines of therapy.	The ERG have changed this sentence to reflect the proposed amendment and the change made in Section 1.5.

Issue 75

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 96 of the ERG report states: "The response rates applied in the economic model assume that the treatment effect is maintained for subsequent lines of therapy, i.e. no reduction in effectiveness is	Pfizer propose that this sentence is amended to say: "The response rates applied in the economic model for subsequent lines of therapy were taken from the bDMARD experienced NMAs, to reflect differences in efficacy between lines of therapy. No further degradation in effectiveness was	As stated in section B3.3.1 of the CS, efficacy data for subsequent lines of therapy have been taken from the bDMARD experienced NMAs. Therefore it is not factually correct to state that the treatment effects are maintained	Correction made as proposed with addition based on change in Section 1.5.

applied for patients failing to respond to first line therapy or for those that initially respond but later withdraw due to loss of efficacy of adverse events."	applied to the bDMARD experienced population, as it was assumed this would be captured in the NMA effect estimates"	for subsequent lines of therapy.	

Issue 76

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 96 of the ERG report states: "This HAQ-DI progression was estimated based on an extract of data for PsA patients receiving palliative care included in the Norfolk Arthritis Register [17] until 2009".	Pfizer propose that this statement is amended to read: "This HAQ-DI progression was estimated based on an extract of data for **rheumatoid factor negative patients with inflammatory polyarthritis eligible for bDMARDs as per BSR guidelines** receiving palliative care included in the Norfolk Arthritis Register [17] until 2009".	This amended statement reflects the data extract as per Appendix 14 of the TA199 AG report (Rodgers et al 2011)	Correction made as proposed.

Issue 77

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 97 of the ERG report states: "Following a discussion with its clinical advisor, the ERG are	Pfizer request that this is more explicitly written as a matter of opinion rather than stated as a matter of fact, or it is removed from the report.	This is a speculative comment which is not supported by empirical evidence in the report	The ERG have amended this sentence to indicate that this is a matter of opinion.

concerned regarding patient compliance with tofacitinib. As tofacitinib is an oral treatment taken twice daily, there is a possibility that patients may not take the drug appropriately and consistently over time"			

Issue 78

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 99 of the ERG report states that: "Patients' HAQ-DI and PASI scores remain constant while patients are on treatment with bDMARDs or tofacitinib, but they progress linearly while patients are on apremilast or BSC"	Pfizer propose that this sentence is rephrased as: "Patients' PASI scores remain constant after the first three months on treatment. Patients' HAQ-DI scores remain constant while patients remain on treatment with bDMARDs or tofacitinib, but they progress linearly while patients are on apremilast or BSC"	Page 116 of the CS states: "The psoriasis component of PsA is assumed to not be progressive and therefore PASI scores do not increase while patients remain on therapy (3) or BSC" The original sentence implies that PASI scores also progress while patients are receiving apremilast or BSC, which is not the case.	Correction made as proposed.

Issue 79

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 100 of the ERG report states: "Poole et al (35), that specifically reported estimates of costs according to HAQ-DI and/or PASI which was eligible for inclusion (35), however, it was not used to inform the model. The CS does not justify why this was not included."	Pfizer request that the second sentence is amended to say: "Poole et al (35), that specifically reported estimates of costs according to HAQ-DI and/or PASI which was eligible for inclusion (35), however, it was not used to inform the model. The CS justifies this by stating that due to methodological limitations, and the desire to remain consistent with previous TAs, they opted to use the same source as used in TA445."	Justification for not using the Poole analysis is provided on pages 139 and 140 of CS.	Correction made as proposed.

Issue 80

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 101 of the ERG report states: "For comparators with a recommended initiation phase greater than 12 weeks (ustekinumab and secukinumab), costs for the SPC recommended length of initiation phase were applied, for example up to 24 weeks."	Pfizer request that this sentence is removed.	The cost of ustekinumab and secukinumab in the first cycle are adjusted to account for more frequent dosing in the initiation phase, for example secukinumab patients receive 5 weekly doses and then switch to monthly dosing. However costs are not applied for the full SPC initiation phase.	The ERG have not removed this sentence. Instead the ERG updated the sentence based on this justification

Issue 81

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 109 of the ERG report states: "The company used PAS prices that were publicly available, namely for ustekinumab and certolizumab"	Pfizer request that the sentence is amended to say: "The company used PAS prices that were publicly available, namely for ustekinumab, certolizumab **and golimumab**"	This amendment makes clear to the reader that publicly available PAS schemes were fully considered by the company	Correction made as proposed.

Issue 82

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 38 on page 112 reports an incremental ICER (£13,0244) for tofacitinib that appears to be incorrect as it is inconsistent with the ICER versus the cheapest strategy/BSC (£13,918)	Pfizer request that the incremental ICER for tofacitinib be corrected	This amendment is necessary for an accurate reflection of the cost effectiveness of tofacitinib and comparators	Incremental ICER for tofacitinib is corrected.

Issue 83

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 40 on page 113 reports an incremental ICER (£13,529) for tofacitinib that appears to be incorrect as it is inconsistent with the ICER versus the cheapest strategy/BSC (£13,530)	Pfizer request that the incremental ICER for tofacitinib be corrected	This amendment is necessary for an accurate reflection of the cost effectiveness of tofacitinib and comparators.	Incremental ICER for tofacitinib is corrected.

Issue 84

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 114 of the ERG report states: "The full incremental ICERs also show that etanercept and tofacitinib are likely to fall within acceptable ranges for the threshold and these are lower than the ICERs for the B2 and D2 NMA models".	Pfizer propose that this statement should be qualified to state that ICERs come down for etanercept in the model comparisons	This amendment is necessary for an accurate reflection of the results.	No amendment made as the current description states that the ICER for etanercept is lower compared to the other models

Issue 85

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 120 of the ERG report states the percentage of patients in OPAL Balance that received an average tofacitinib dose of 10 mg. The percentages of patients receiving each dose is marked as CiC in the response to ERG clarification question A23 (Table 00099.5) and should be marked as such in the ERG report.	Pfizer request that the following statement is marked as CIC: "and finally, in OPAL Balance (the long-term follow-up study) [redacted] whereas the licenced dose for tofacitinib in 5mg BD."	The percentages of patients receiving each dose is marked as CiC in the response to ERG clarification question A23 (Table 00099.5) and should be marked as such in the ERG report.	Marking updated as proposed.

Evidence Review Group Report

Tofacitinib for treating active psoriatic arthritis

Erratum

Issue 2: Pg. 11 contradicted.
Should read: Contra-indicated

Issue 4: Pg. 11 "For the subpopulation, those who had not adequately responded to csDMARDS, certolizumab pegol was not addressed".

Should read: "For the subpopulation of patients who had not adequately responded to csDMARDs and one or more TNFi, certolizumab pegol was not addressed."

Issue 5: Pg 12 "key efficacy outcomes; ARC [sic] 20/50/70, PASI70 response rate"

Should read: "key efficacy outcomes; ACR 20/50/70, PASI75 response rate."

Issue 6: Pg 12 "Modified PsARC response and PASI-75 response"

Should read: "PsARC response and PASI-75 response"

Issue 7: Pg 13 "These were owing to a significant proportion of patients in each RCT (18% and 24%) treated in combination with sulfasalazine and leflunomide, […]".

Should read: "These were owing to a proportion of patients in each RCT (18% and 24%) treated in combination with sulfasalazine or leflunomide, […]".

Issue 9: Pg 13 The following now marked as CIC: "and finally, in OPAL Balance (the long-term follow-up study) [redacted] where as the licenced dose for tofacitinib in 5mg BD."

Issue 10: Pg 17. "as an alternative to other currently recommended biologic disease-modifying anti-rheumatic drugs (bDMARD/tsDMARDs)"

Should read: "as an alternative to other currently recommended biologic or targeted synthetic disease-modifying anti-rheumatic drugs (bDMARD/tsDMARDs)"

Issue 13: Pg 20. "The clinical advisor to the ERG suggested that given there is limited knowledge of the use of ofacitinib [sic] in clinical practice […]".

Should read: "The clinical advisor to the ERG suggested that given there is limited knowledge of the use of tofacitinib in UK PsA clinical practice […]".

Issue 15: Pg 25. "The inclusion criteria for the systematic review specified randomised control trials (with parallel design) of tofactinib [sic], bDMARDs and the PDE-4 inhibitor apremilast, for the treatment of active PsA in adults with a previous inadequate response to csDMARD therapy, which reported relevant clinical and health-related quality of life, including adverse event outcomes."

> Should read: "The inclusion criteria for the systematic review specified randomised control trials (with parallel design) of tofacitinib, bDMARDs and the PDE-4 inhibitor apremilast, for the treatment of active PsA in adults with a previous intolerance of, or inadequate response to csDMARD therapy, which reported relevant clinical effectiveness and health-related quality of life, including adverse event outcomes.

Issue 16: Pg 25: "and the comparator treatments: adalimumab, apremilast, etanercept, infliximab, ustekinumab, golimumab, secukinumab, certolizumab pegol and ixekizumab"

> Should read: "and the comparator treatments: adalimumab, apremilast, etanercept, infliximab, ustekinumab, golimumab, secukinumab, certolizumab pegol, abatacept, and ixekizumab"

Issue 17. Pg 25: "Relevant data extracted from included studies are detailed in Appendix D, section D.1.6."

> Should read: Relevant data extracted from included studies are detailed in Appendix D, section D.1.6 and Appendix E, section E1.

Issue 18: Pg 27. "The inclusion criteria for both trials were: adults aged ≥18 years;"

> Should read: "The inclusion criteria for both trials were: adults aged ≥18 years [redacted];"

Issue 19: Pg 27. "ACR20 response rate: Week 2, Month 6, 12"

> Should read: "ACR20 response rate: Week 2, Month 6 (and Month 12, OPAL Broaden only)"

Issue 23: Pg 29: "Adverse events were roughly equal across all treatment arms"

> Should read: "Discontinuations due to adverse events were roughly equal across all treatment arms"

Issue 23: Pg 29: The following now marked as CIC: ""In their clarification response, the company clarified that in the group randomised to tofacitinib 5 mg, [redacted] patients withdrew by 3 months, [redacted] by month 12. [redacted]"

Issue 26: Pg 30. “Table 3 Efficacy results for OPAL Broaden (FAS) ACR 20, 50 and 90, PSARC, PASI 75 and HAQ-DI.”

Should read: “Table 3 Efficacy results for OPAL Broaden (FAS) ACR 20, 50 and 70, PSARC, PASI 75 and HAQ-DI.”

Issue 27: Pg 31. “Modified TSS values at Month 12 were available for [redacted]”

Should read: “Modified TSS values at Month 12 were available for [redacted]

Issue 28: Pg. 31. ACR20 at month 6 for TOF5 and ADA, ACR20 at month 12 for TOF5 and ADA.

Should read: ACR20 at month 6 for TOF5 should be [redacted] and ADA should be [redacted] and ACR20 at month 12 for TOF5 should be 73/107 (68) and ADA are should be 64/106 (60)

Issue 32: pg. 33 “Although most differences were nominally statistically significant, statistical significance could not be claimed due to the hierarchical testing scheme (tofacitinib was not statistically significantly superior for LEI score).”

Should read: “Although some of the differences were nominally statistically significant, statistical significance could not be claimed due to the hierarchical testing scheme (tofacitinib was not statistically significantly superior for LEI score).”

Issue 33: pg. 33. The following is now marked as CIC: “Results were similar for adalimumab, though the difference from placebo for adalimumab was numerically lower for FACIT-F and ISI score ([redacted]).”

Issue 34: pg. 33. The following is now marked as CIC: “The results suggest [redacted] no formal testing was presented.”

Issue 36: pg 34. tofacitinib 5mg

Should read: “Tof 5 mg 122/131 (93.1)”

Issue 39: Pg. 38. The following is now marked as CIC: “The MDA response rate at month 3 in the tofacitinib 5 mg BD group was 23% vs 15% in the placebo group, though the difference was not statistically significant ([redacted])”

Issue 40. Pg 39. “Compared with OPAL Broaden the placebo response was lower in Beyond for ACR 20, but it was higher for ACR 50 and 70, and also PSARC.”

Should read: “Compared with OPAL Broaden, the placebo response was lower in Beyond for ACR 20 and PsARC, but it was higher for ACR 50 and 70.

Issue 43: Pg 40. Table now marked as CIC

Issue 44: Pg 40. The following is now marked as CIC: “Further information provided in the company’s clarification response [redacted]

Issue 45: Pg. 41. Table amended.

Issue 45: Pg. 41. “Withdrawals at 2 years (2.5 to 3 years since start of tofacitinib) were roughly [redacted] remained on their first TNFi.”

> Should read: “Withdrawals at 2 years (2.5 to 3 years since start of tofacitinib) were roughly [redacted] remained on tofacitinib”

Issue 47: Pg 42. Table now marked as CIC

Issue 48: Pg. 49. “From the trial CONSORT diagrams (CS Appendix D) and the clarification response the ERG calculated that in [redacted] of patients withdrew due to an adverse event in OPAL Broaden and Beyond respectively, though none of the events were considered to be treatment related”

> Should read: ““From the trial CONSORT diagrams (CS Appendix D) and the clarification response the ERG calculated that in [redacted] and [redacted] of patients withdrew due to an adverse event in OPAL Broaden and Beyond respectively, though none of the events were considered to be treatment related”

Issue 51: pg.50. Cardiovascular events in Table 17 now reads to [redacted], and marked as CiC.

Issue 52: Pg 54. “This subsection summarises methods and results of the synthesis of relative treatment effects, but the company has not reported how evidence on placebo-response was considered.”

> Should read: “but the company has provided little detail on how evidence on placebo-response was considered (section “Analysis of absolute change from baseline or probability of event” in Appendix D of the CS).”

Issue 53: Pg. 57. “and absolute predicted PsARC response (this depends on assumptions about placebo response which were not justified in the CS).”

> Should read: “…and absolute predicted PsARC response (this depends on assumptions about placebo response which were not clearly justified in the CS).”

Issue 54: Pg. 58. “better effectiveness than apremilast and ustekinumab (LOR of [redacted]).”

> Should read: “better effectiveness than apremilast and ustekinumab (LOR of [redacted]).”

Issue 55: Pg. 58. “(Table E31, Appendix E and Table 2 below)”

> Should read: “(Table E31, Appendix E and Table 19 below)”

Issue 56: Pg. 58: “followed by adalimumab and ustekinumab (intermediate/low effectiveness group), and lastly tofacitinib 5mg BD, certolizumab pegol, etanercept, apremilast (lowest effectiveness group).”

> Should read: ““followed by adalimumab, Ustekinumab, and tofacitinib (intermediate/low effectiveness group), and lastly certolizumab pegol, etanercept, and apremilast (lowest effectiveness group).”

Issue 61: Pg. 63. Table amended.

Issue 62: Pg. 63 clarification added that the data is for model E1 with 24 week data and not the base case model.

Issue 65: Pg 65: "OPAL Beyond had a higher placebo PASI responses rate (of [redacted] 15% and [redacted] respectively for PASI50, PASI75 and PASI90) than those modelled. Responses observed in the trial for TOF are [redacted] 21% and [redacted]% respectively for PASI50, PASI75 and PASI90."

> Should read: "OPAL Beyond had a higher placebo PASI responses rate (of [redacted] 14%, and [redacted] respectively for PASI50, PASI75 and PASI90) than those modelled. Responses observed in the trial for TOF are [redacted] 21% and [redacted] respectively for PASI50, PASI75 and PASI90."

Issue 67: Pg 69. Figure is relabelled (i.e., the labelling of the ADA and TOF 5 OPAL Broaden data points are switched) and the red trend line is redrawn for ADA.

Issue 69: Pg. 80 "It is clear from the systematic review that TA445 is the most comparable economic evaluation to the company's submission.

> Should read: It is clear from the systematic review that TA445 is the most comparable economic evaluation to the company's submission.

Issue 70: Pg 80. "The drug company seek to align the sup-populations assessed in the TA of tofacitinib for treating active PsA with cDMARDS to the populations that have received positive recommendations from NICE in previous TAs (i.e. sup-populations 2, 3 and 4).

> Should read: "The drug company seek to align the sub-populations assessed in the TA of tofacitinib for treating active PsA following cDMARDS to the populations that have received positive recommendations from NICE in previous TAs (i.e. sup-populations 2, 3 and 4)

Issue 71: Pg. 82. Table 26 to acknowledge the proposed amendment.

Issue 72: Pg 83. "…(except for liver function text…."

> Should read: "…..(except for liver function test…"

Issue 73: Pg. 87 phrase "(CHECK THIS)" is removed.

Issue 74: Pg. 90. Sentence changed to reflect the proposed amendment

Issue 75: Pg. 96. Correction made as proposed with addition based on change in Section 1.5.

Issue 76: Pg. 96. "This HAQ-DI progression was estimated based on an extract of data for PsA patients receiving palliative care included in the Norfolk Arthritis Register [17] until 2009".

> Should read: "This HAQ-DI progression was estimated based on an extract of data for rheumatoid factor negative patients with inflammatory polyarthritis eligible for bDMARDs as per BSR guidelines receiving palliative care included in the Norfolk Arthritis Register [17] until 2009".

Issue 77: Pg. 97. Sentence amended to indicate that this is a matter of opinion

Issue 78: Pg. 99. “Patients’ HAQ-DI and PASI scores remain constant while patients are on treatment with bDMARDs or tofacitinib, but they progress linearly while patients are on apremilast or BSC”

> Should read: “Patients’ PASI scores remain constant after the first three months on treatment. Patients’ HAQ-DI scores remain constant while patients remain on treatment with bDMARDs or tofacitinib, but they progress linearly while patients are on apremilast or BSC”

Issue 79: Pg. 100. “Poole et al (35), that specifically reported estimates of costs according to HAQ-DI and/or PASI which was eligible for inclusion (35), however, it was not used to inform the model. The CS does not justify why this was not included.”

> Should read: “Poole et al (35), that specifically reported estimates of costs according to HAQ-DI and/or PASI which was eligible for inclusion (35), however, it was not used to inform the model. The CS justifies this by stating that due to methodological limitations, and the desire to remain consistent with previous TAs, they opted to use the same source as used in TA445.”

Issue 80: Pg 101: Sentence not removed, updated based on justification

Issue 81: Pg 101. “The company used PAS prices that were publicly available, namely for ustekinumab and certolizumab”

> Should read: “The company used PAS prices that were publicly available, namely for ustekinumab, certolizumab and golimumab”

Issue 82 & 83: Pg 112 & 113. Incremental ICER for tofacitinib corrected.

Issue 85. Pg. 120. The following marked as CIC: “and finally, in OPAL Balance (the long-term follow-up study) [redacted]whereas the licenced dose for tofacitinib in 5mg BD.”

1. Summary

1.1 Critique of the decision problem in the company's submission

Tofacitinib is an oral, small molecule, targeted Janus Kinase (JAK) inhibitor. A positive opinion from the Committee for Medicinal Products for Human Use (CHMP) was adopted in April 2018 for the use of tofacitinib 5mg BD, twice daily,

''in combination with methotrexate (MTX) for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy''.

The NICE scope differed from the licence in that tofacitinib could be used alone or in combination with non-biological DMARD. The CS assessed tofacitinib in combination with any csDMARD and did not restrict to the use of MTX.

The CS addressed three sub-populations, those who had not adequately responded to at least two non-biologic DMARDS, those who had not adequately responded to non-biologic DMARDS and one or more tumour necrosis factor inhibitors (TNFis), and those for whom TNFis are contraindicated or not tolerated. The CS did not include a fourth sub-population that had been included in the NICE scope (those who had failed one non-biological DMARD) as there were insufficient data.

The comparators addressed in the company's decision problem matched those in the NICE scope for (1) those who had not adequately responded to at least two non-biologic DMARDS and (2) those for whom TNFis are contraindicated or not tolerated. For the subpopulation of patients who had not adequately responded to csDMARDs and one or more TNFi**,**, certolizumab pegol was not addressed. The ERG agreed with the exclusion of this comparator as the RAPID PsA trial did not include all TNFi experienced patients, but only those who had initially responded to a TNFi and then lost their response [1].

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidence for the use of tofacitinib in active PsA consisted of two placebo-controlled RCT's; one for TNFi naïve (OPAL Broaden) and one for TNFi experienced patients (OPAL Beyond). Patients from these trials who received tocacitinib 10mg BD doses did not contribute to the clinical effectiveness evidence submitted by the company, as the use of tofacitinib is licenced for dose 5mg BD. Supporting evidence from a non-RCT open-label follow-up study of tofacitinib, OPAL Balance, was also presented.

OPAL Broaden and OPAL Beyond were well conducted Phase III randomised, multicentre trials. OPAL Broaden also included a comparison with adalimumab and after 3-months, patients receiving placebo were followed up on tofacitinib or adalimumab to 12 months. OPAL Beyond did not include a comparison with adalimumab and after the 3 months, patients receiving placebo were followed up on tofacitinib to 6 months.

Baseline characteristics were similar across both trials. The primary efficacy outcomes were ACR20 response rate at 3 months and ΔHAQ-DI at 3 months. PsARC response and PASI-75 response were also included as outcomes. Radiographic assessment of joint damage was also assessed at 12 months within OPAL Broaden.

TNFi naive population

For TNFi naïve patients, OPAL Broaden demonstrated that tofacitinib 5mg BD (N= 107) was statistically significantly more effective than placebo (N=105) for the key efficacy outcomes; ACR 20/50/70, PASI75 response rate and mean ΔHAQ-DI at 3 months, but not PSARC response rate. Comparisons of tofacitinib with adalimumab show that numerically for most key efficacy outcomes adalimumab was very slightly better than tofacitinib, however the trial was not powered to test for a statistically significant difference or non-inferiority. For radiographic assessment of joint damage the proportion of progressors (change in mTSS of >0.5) was low in both treatment arms but the upper confidence interval in the population adjusted analyses (to be comparable with the ADEPT trial for adalimumab) crossed the non-inferiority margin indicating it was inconclusive whether tofacitinib 5mg was non-inferior to adalimumab. The ERG agreed with the FDA conclusion that there is insufficient evidence to support the assumption that tofacitinib is associated with halting radiographic progression.

Network meta-analyses across outcomes (e.g. PsARC, ACR, PASI, and HAQ changes conditional on PsARC response) found that golimumab, infliximab, and etanercept were generally the most effective treatments; followed by certolizumab, secukinumab 150, adalimumab, and secukinumab 300. Apremilast, ustekinumab and tofacitinib 5mg were consistently ranked among the lowest in effectiveness. The company found that the placebo arm of OPAL Broaden fitted poorly in their NMA models, and attributed this to the high placebo response observed in their trial. They therefore presented alternative analyses including one where the placebo arm of OPAL Broaden was excluded which also resulted in increased effectiveness estimates for tofacitinib 5mg.

TNFi experienced population

For TNFi experienced patients, OPAL Beyond demonstrated that tofacitinib 5mg BD (N= 131) was statistically significantly more effective than placebo (N=131) for the key efficacy outcomes

outcomes; ACR 20/50, PsARC response rate and mean ΔHAQ-DI at 3 months but not ACR 70 or PASI 75.

Network meta-analyses for PsARC and HAQ changes conditional on PsARC response only included ustekinumab and tofacitinib and were found to be of similar effectiveness. Tofacitinib was associated with only slightly higher HAQ changes than placebo. More treatments were included for PASI response, the results of which found that tofacitinib 5mg was among the least effective in the network meta-analysis: ustekinumab, secukinumab, ixekizumab were ranked higher and only abatacept was ranked less effective.

Adverse effects

The adverse events profile of tofacitinib in PsA patients appears similar to, and no worse than that of adalimumab. The tolerability of tofacitinib is reflected in the low rate of withdrawals due to AEs. An increased risk of herpes zoster appears to be a specific AE of tofacitinib.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The evidence for the clinical effectiveness of tofacitinib is based on good quality randomised trials and the results are likely to be reliable.

The ERG identified limitations in the generalisability of the RCT evidence to clinical practice. These were owing to a significant proportion of patients in each RCT (18% and 24%) treated in combination with sulfasalazine or leflunomide, when the marketing authorisation is for tofacitinib in combination with methotrexate (MTX) only. Furthermore, in both OPAL Broaden and OPAL Beyond the placebo-controlled phase was limited to 3 months: treatment with tofacitinib in clinical practice is long-term. Additional issues relating to generalisability included:

(1) The use of adalimumab in OPAL Broaden in combination with a csDMARD not being reflective of adalimumab in clinical practice or in other trials.
(2) The number of previous TNFis (and the specific previous TNFis) in OPAL Beyond not being reflective of the patient population in which tofacitnib will be used in current practice.
(3) Almost [redacted] whereas the licenced dose for tofacitinib in 5mg BD.

The ERG identified errors in the implementation of the company's placebo-adjusted NMAs. Models corrected by the ERG found a more meaningful interaction between baseline risk and treatment effect than the company analyses.

2 Background

2.1 Critique of company's description of underlying health problem

The description of the underlying health problem in the company's submission was appropriate and relevant to the decision problem under consideration. Psoriatic arthritis (PsA) is an inflammatory condition with onset usually occurring between 30 and 50 years of age. Clinical manifestations are heterogeneous and may include both articular (joint) and non-articular disease features. The CS states patients have an onset of psoriasis occurring 7 to15 years prior their PsA diagnosis [2]. PsA is a chronic, progressive condition leading to irreversible joint damage and is additionally associated with a range of comorbidities including hypertension, hyperlipidaemia, depression, fibromyalgia and type II diabetes [3]. The five health domains of pain (in the joints and spine), skin problems (including itching), fatigue (both physical and mental), ability to pursue work and leisure activities, and functional capacity are identified as the most important from the patients' perspective [4].

2.2 Critique of company's overview of current service provision

The manufacturers' overview of current service provision is broadly appropriate and relevant to the decision problem under consideration. NICE clinical guidance (NG65) is outlined in the CS and in full in CS Appendix L; in addition guidance from the European League Against Rheumatism (EULAR), the British Society for Rheumatology (BSR) and the Group for Research and Assessment for Psoriasis and Psoriatic Arthritis (GRAPPA) is also detailed in the CS. Clinical guidelines for PsA emphasise the control of symptoms, prevention of structural damage, and normalisation of functional and social participation and propose disease remission or low/ minimal disease activity as the therapeutic treatment goal.

The CS states the proposed positioning of tofacitinib (**Error! Reference source not found.**) is after conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) as an alternative to other currently recommended biologic or targeted synthetic disease-modifying anti-rheumatic drugs (bDMARD/tsDMARDs), after treatment failure or for those intolerance or contraindication to tumour necrosis factor alpha inhibitors (TNFi).

The rationale in the CS for the position of tofacitinib as an alternative to other currently recommended treatment options, for patients with active PsA who have had an inadequate response to previous treatments (csDMARDS and TNFis), was made on the basis of providing a treatment with the following characteristics:

- Oral route of administration
- A novel mechanism of action

57% [8]. The CS also states that the British Society of Rheumatology Biologics Register (BSRBR) indicates that only 59% of patients remain on their first TNFi for PsA after three years of treatment.[9]The ERG identified a recently published analysis of the UK based BSRBR data (625 PsA patients), which reported long-term persistence of etanercept, infliximab and adalimumab at 3, 5 and 8 years. Etanercept and adalimumab rather than infliximab were associated with better five-year persistence. At five years 46.7% were still on their initial TNFi treatment. Furthermore, at eight years, 33% remained on the first TNFi, 16% on the second and 12% on the third, and only 5% of patients were on a non-TNFi biologic and 10% not on a biologic treatment [10]. This suggests that within the UK, whilst patients may switch treatments, discontinuation from all biologic therapy is low at 8 years. In TNFi-IR patients, the extent to which issues with drug survival translate into the requirement for additional treatments options may be less than the CS suggests.

The CS also states that tofacitinib, as a small molecule JAK inhibitor would not be expected to induce any immunogenicity, as is associated with infliximab and adalimumab. Additional justification for this was provided in the company's response to points for clarification. This stated that the lack of association with immunogenicity was due to the lower molecular weight of tofacitinib compared to bDMARD's. The clinical advisor to the ERG advised that in clinical practice immunogenicity is not a significant issue.

Overall, the ERG acknowledges the novel mode of action of tofacitinib, but suggests that the company may have overstated the need for an oral treatment option for PsA. The efficacy relative to existing therapies is probably the key factor when deciding whether or not to use tofacitinib.

The clinical advisor to the ERG suggested that given there is limited knowledge of the use of tofacitinib for PsA in UK clinical practice, it would likely be reserved for an end of line treatment or possibly for specific individuals with certain clinical characteristics, for whom TNFis are contraindicated or not tolerated.

3 Critique of company's definition of decision problem

3.1 Population

The population stated in the CS was:

'Adults with active PsA whose disease has not responded adequately to previous DMARD therapy or for whom DMARDs are not tolerated or contraindicated.

This matches the NICE scope and accurately reflects the marketing authorisation.

in adults with a previous inadequate response to or intolerance to csDMARD therapy, which reported relevant clinical and health-related quality of life, including adverse event outcomes. The inclusion criteria were further refined to include studies of the licensed formulation of tofacitinib (5mg, BD). Studies that recruited patients who suffered from other rheumatic or dermatological conditions and DMARD naïve patients were excluded. Case reports, commentaries and editorials, observational studies, and cross-sectional studies were also excluded. Only studies reported in English were eligible for inclusion. Comparators included bDMARDs, the PDE-4 inhibitor apremilast and controls including placebo, best supportive care, and any csDMARD. Studies were screened by title and abstract according to pre-defined PICOS criteria. Those that met the criteria were screened at full text. Appropriate methods were used to reduce reviewer error and bias with two blinded reviewers conducted screening of literature and any discrepancies resolved with assistance from a third reviewer.

Appropriate methods were used to extract data from the included studies. Two reviewers, blinded to each other's decisions, conducted data extraction independently, with a third reviewer involved in resolving discrepancies. Relevant data extracted from included studies are detailed in Appendix D, Section D.1.6 and Appendix E, Section E1.

4.1.3 Quality assessment

Randomised control trials were assessed using the NICE Quality Appraisal checklist for quantitative interventions that assesses RCT's based on seven domains. The results of this quality assessment are presented in CS Appendix D, section D.1.7. A risk of bias assessment was also conducted assessing sequence generation, allocation concealment, baseline imbalances, blinding of participants and researchers, incomplete outcome data and selective reporting. These results are also presented in CS Appendix D; section D.1.7, along with support for judgement. The results of these assessments are given in Section 4.2.2 and Section 4.2.3 of this report.

4.1.4 Evidence synthesis

The CS focuses on two studies with distinct populations, OPAL Broaden for TNFi-naïve and OPAL Beyond for TNFi-experienced patients. The company presents the effectiveness of tofacitinib compared with the comparator treatments in forest plots in CS Appendix E. Pooled direct estimates of treatment vs placebo were presented for tofacitinib (in combination with a csDMARD) (for which results remained the same given there was only one trial per population), and the comparator treatments: adalimumab, apremilast, etanercept, infliximab, ustekinumab, golimumab, secukinumab, certolizumab pegol, abatacept and ixekizumab. These analyses were conducted for the outcomes, ACR 20, 50 and 70, PASI 50, 75 and 90, PsARC and HAQ for PsARC responders and non-responders. Direct estimates pooled by drug class are also presented for the outcome PsARC.

Outcomes assessed in the trials and relevant to the decision problem	Primary outcomes • **ACR20 response rate at Month 3** • **ΔHAQ-DI at Month 3** Supportive analysis of primary outcomes • HAQ-DI responder analysis (≥0.35 as the cutpoint for response) at Month 3 Secondary outcomes • ACR20 response rate: Week 2, Month 6 , (and 12 OPAL Broaden only) • Δ van der Heijde-mTSS, progressor rates, and non-progressor rates: Month 12 (OPAL Broaden only) • ΔACR components: Month 3 • ACR50/70 response ratea: Month 3, 6, (and 12 OPAL Broaden only) • **PASI75 response rate: Month 3,** 6, (and 12 OPAL Broaden only) • **PsARC response rate: Month 3**, 6, (and 12 OPAL Broaden only) • ΔLEI, ΔSPARCC, ΔDSS: Month 3, 6, (and 12 OPAL Broaden only) • ΔSF-36 (PF component), FACIT-F (total score): Month 3, 6, (and 12 OPAL Broaden only) (EQ-5D) Other outcomes • MDA response rate: Month 3, 6, (and 12 OPAL Broaden only) • ΔDLQI, ΔISI: Month 3, 6, (and 12 OPAL Broaden only) • ΔHAQ-DI: Month 6, (and 12 OPAL Broaden only) • ΔACR components: Month 6, (and 12 OPAL Broaden only) Post-hoc analyses used in the economic model • PASI50/90 response rate: Months 3, 6, (and 12 OPAL Broaden only) • ΔHAQ-DI conditional on PSARC response status: Month 3, 6, (and 12 OPAL Broaden only)

The inclusion criteria for both trials were: adults aged ≥18 years ([redacted]); diagnosis of PsA for ≥6 months; meeting the CASPAR[11] criteria at screening; active arthritis (≥3 tender/painful and ≥3 swollen joints); and active plaque psoriasis at screening and baseline. For OPAL Broaden, patients had to have demonstrated an inadequate response (lack of efficacy and/or tolerability) to ≥1 csDMARD and to have received no previous TNFi treatment; prior use of non-TNFi bDMARDs for treatment of psoriasis must have been discontinued for ≥6 months prior to the first dose of study drug. For OPAL Beyond, patients had to have demonstrated an inadequate response to ≥1 TNFi. Details of exclusion criteria, which were the same for both trials, are given in CS Table 6.

Analysis sets and statistical methods

In both trials the analysis of efficacy was based on the full analysis set (FAS) which comprised all randomized patients who received at least one dose of the randomised study drug. In OPAL Broaden this comprised all randomized patients (tofacitinib 5 mg n=107, adalimumab n=106, and placebo n=105); in OPAL Beyond it comprised all but one patient randomized to tofacitinib 5 mg (tofacitinib 5 mg n=131 and placebo n=131). It should be noted that [redacted]

It is important to note that in all arms of the trials patients receive a csDMARD in addition to the trial therapy. Therefore the tofacitinib arm is not fully reflective of clinical practice as the licence for tofacitinib in PsA specifies concomitant therapy with MTX. This is discussed further in Section 0. Also of particular interest in OPAL Broaden is the comparison with adalimumab: this randomised, double-blind comparison had a 12-month follow-up, providing clear evidence for the comparison with an established TNFi. It should be noted again however, that the concomitant use of a csDMARD means the results in the adalimumab arm are not fully reflective of clinical practice, nor comparable with those from other adalimumab trials: in both contexts only a proportion of patients would take concomitant csDMARD. In addition, it should be noted that the trial was not powered to test the comparison between tofacitinib and adalimumab; this needs to be taken into consideration when interpreting any noteworthy treatment differences that do not reach statistical significance.

4.2.2 Results of OPAL Broaden

4.2.2.1 Participant flow in OPAL Broaden

Participant flow in OPAL Broaden is presented in Appendix Figure D13. In summary, 422 patients were randomised and 373 (88.4%) completed the trial (Placebo 87/105 (82.9%), tofacitinib 5 mg 96/107 (89.7); tofacitinib 10 mg 96/104 (92.3%); and adalimumab 94/106 (88.7%). Percentage discontinuations were higher in the placebo arms, though somewhat surprisingly none of the discontinuations from the 10mg placebo group were for insufficient response. Discontinuations due to adverse events were roughly equal across all treatment arms. In their clarification response the company clarified that in the group randomised to tofacitinib 5 mg, [redacted] patients withdrew by 3 months,

[redacted] by month 12.

[redacted].

4.2.2.2 Patient characteristics of OPAL Broaden

As the tofacitinib 10 mg dose is not licensed and is therefore not relevant to the present appraisal, results for this treatment arm were not included in the CS nor in this report. The main baseline patient characteristics are presented in CS Table 7. These were similar across the tofacitinib 5 mg, adalimumab, and placebo groups, with the exception of significant differences between groups in the mean swollen-joint count (unadjusted p=0.03 for the comparison among all four trial groups), mean Leeds Enthesitis Index (LEI) score (unadjusted p=0.02 for the comparison among all four groups),

and the rate (%) of MTX use at baseline (unadjusted p=0.02 for the comparison among all four groups), which were all lower in the adalimumab group, and significant differences among trial

groups in the rate of glucocorticoid use at day 1 (unadjusted p=0.02 for the comparison of the 10 mg tofacitinib BD group with other groups), which was 27% for tofacitinib 5 mg BD, 22% for adalimumab, 17% for placebo, and 11% for tofacitinib 10 mg BD. These differences would favour adalimumab slightly.

The majority of the subjects were white (97 to 99%); the mean age ranged from 47.4 to 49.4 years and the mean duration of PsA ranged from 5.3 to 7.3 years. Out of the 318 patients, 216 (67.92%) had enthesitis and 177 (55.66%) had dactylitis. Importantly only 262 (82.39%) patients were receiving concomitant MTX. The ERG notes that almost 18% of patients were therefore not receiving tofacitinib in accordance with the product licence. An analysis of the data relating to the concomitant MTX subgroup was not presented in the CS (or the CSR).

4.2.2.3 Summary of the quality of OPAL Broaden

Table 1 Quality assessment and Risk of bias assessment (Adapted from CS Tables D16 and D17

OPAL Broaden	ERG comment	Quality Assessment (NICE checklist)	Risk of Bias
	Support		Judgement
Appropriate randomization / Sequence generation	"Randomly assigned in a 2:2:2:1:1 ratio, by means of an automated Web-based randomization system"	Yes	Low
Treatment allocation concealment	"Randomly assigned in a 2:2:2:1:1 ratio, by means of an automated Web-based randomization system"	Yes	Low
Prognostic factors balanced at study outset	"The demographic and disease characteristics of the patients at baseline were similar across groups"	No	Low
Blinded to treatment		Yes	
Blinding of participants and researchers	"Placebo was provided as oral tablets and prefilled syringes matching those of tofacitinib and adalimumab, respectively. All patients received both tablets and injections to maintain the blind."		Low
Blinding of Outcome assessment	All rheumatological and dermatological assessments were performed by qualified, trained assessors who were blinded to the patient's safety data, previous efficacy data, and treatment randomization		Low
Unexpected imbalances in dropouts		no	
Incomplete outcome data	10-30% drop-outs in all groups except one, Reasons reported. No ITT. "Efficacy analyses included all the patients who underwent randomization and received at least one dose of tofacitinib, adalimumab, or placebo"		High
Measured more outcomes than reported/selective reporting	Results reported for all key outcomes	No	Low
Appropriate analysis performed		Yes	
Overall judgement			High

The ERG agrees with the quality/risk of bias assessment results reported except for the high risk of bias assigned due to incomplete outcome data. This should not apply to those outcomes where non-response imputations were applied (response-type/binary endpoints: ACR20, ACR50, ACR70, ΔHAQ-DI (decrease) ≥0.35, PsARC, PASI75, and MDA) No imputation was applied to missing HAQ-DI data, and therefore a high risk of bias might apply, but at 3-months data were almost complete (95 to 97%) and at 6 and 12 months (tofacitinib vs adalimumab) they were 93% and 89% to 90% respectively. Modified TSS values at Month 12 were available for [redacted] were imputed via linear extrapolation, but the impact on the results was small and the risk of bias appears to be low for this outcome.

4.2.2.4 Summary of efficacy results for OPAL Broaden

The results for the key efficacy outcomes are summarised in Table .

Table 2 Efficacy results for OPAL Broaden (FAS) ACR 20, 50 and 70, PSARC, PASI 75 and HAQ-DI.

	Month	PBO	TOF 5 mg	ADA	TOF 5 mg vs placebo (% Difference and 95% CI) p value	ADA vs placebo (% Difference and 95% CI Nominal p value	TOF 5 mg vs ADA Nominal p value
ACR 20 Response rate, n (%)	3	35/105 (33)	54/107 (50)	55/106 (52)	17.1 (4.1, 30.2), 0.01§	18.6% (5.5, 31.7), [redacted]†	[redacted]
	6		[redacted]	[redacted]	_	_	[redacted]
	12		73/107 (68)	64/106 (60)	_	_	[redacted]
ACR 50 Response rate, n (%)	3	10/105 (10)	30/107 (28)	35/106 (33)	18.5% (8.3, 28.7) 0.001	23.5% (12.9, 34.1) [redacted]†	[redacted]
	6		[redacted]	[redacted]			[redacted]
	12		48/107 (45)	43/106 (41)			[redacted]
ACR 70 Response rate, n (%)	3	5/105 (5)	18/107 (17)	20/106 (19)	12.1% (3.9, 20.2) 0.004	14.1% (5.6, 22.6) [redacted]†	[redacted]
	6		[redacted]	[redacted]			[redacted]
	12		25/107 (23)	31/106 (29)			[redacted]
PSARC response rate, n (%)	3	47/105 (44.8)	55/107 (51.4)	65/106 (61.3)	6.6 -6.8, 20.1 [redacted]	16.6 3.3, 29.8 [redacted]†	[redacted]
	6		[redacted]	[redacted]			[redacted]

Results were similar for other secondary measures of disease activity at Month 3, Month 6, and Month 12 and were reported and presented in CS Appendix M.

- The MDA response rate (CS Table M6) at Month 3 in the tofacitinib 5 mg BD, adalimumab and placebo groups was 26%, 25% and 7% respectively, with [redacted] for both comparisons with placebo. For tofacitinib 5 mg vs adalimumab, [redacted] The rates were sustained up to Month 12.
- Across measures of enthesitis (LEI, SPARCC) and dactylitis (DSS) (CS Table M5) at month 3 tofacitinib 5 mg BD was numerically but not statistically superior to placebo, with responses sustained up to month 6 and month 12. The results for adalimumab were similar to those for tofacitinib except for the LEI score, for which adalimumab was statistically significantly greater than placebo and the difference for adalimumab from placebo (-0.7 (95% CI -1.2, -0.1) was numerically superior to tofacitinib from placebo (-0.4 (95% CI -0.9, 0.2).
- The results for quality of life measures were presented in CS Table M7. Although some differences were nominally statistically significant, statistical significance could not be claimed due to the hierarchical testing scheme (tofacitinib was not statistically significantly superior for LEI score). Tofacitinib 5 mg BD was numerically (SF-36 PF, FACIT-F total score) and significantly (DLQI, ISI) superior to placebo at Month 3, with responses sustained up to Month 6 and Month 12. Results were similar for adalimumab, though the difference from placebo for adalimumab was numerically lower for FACIT-F and ISI score ([redacted]). It should be noted that although EQ-5D data were collected in the trial these data were not included in the CS. The ERG requested these data and they were provided in the company's clarification response. The results suggest [redacted] no formal testing was presented.

Radiographic assessment of disease progression at 12 months is summarised in Table 3. There is no placebo comparison as the placebo controlled phase of the study stopped at 3 months. At 12 months, there was evidence of a reduction in progression in the adalimumab but not the tofacitinib arm, though the treatment difference was not statistically significant; again, the trial was not powered to test such a small difference. The proportion of progressors (defined as patients with an increase in mTSS of >0.5) was low in both treatment arms.

Table 3 Radiographic progression results for OPAL Broaden (FAS)

	Month	TOF 5 mg	ADA	TOF 5 mg vs ADA Nominal p value
Change in van der Heide-mTSS (LS mean) (SE)	12	0.01 (0.07) [98]	-0.07 (0.07) [95]	[redacted]
mTSS progressor rate, n/N (%)	12	[redacted]	[redacted]	[redacted]

;[§]p-value is subject to the step-down approach; [†]nominal p-value for comparison between adalimumab and placebo; [a]One placebo subject was excluded from the analysis (no post-baseline assessments)

The ERG enquired about the data, if any collected on those patients who were randomised to placebo and then switched to active treatment at the 3-month time point. In their clarification response the company provided the results at 6 and 12 months for these patients. Overall, the results reflect those for patients randomised to tofacitinib 5 mg group and are supportive of the main analysis data, though the results for PASI75 were lower than those at 3 and 6 months in the main analysis tofacitinib group.

4.2.3 Results of OPAL Beyond

Participant flow in OPAL Beyond

Participant flow in OPAL Beyond is presented in Appendix figure D15 of the CS. In summary, 395 randomised and 345(87.3%) completed the trial (Placebo 112/131 (85.5%), Tof 5 mg 122/131 (93.1%); tofacitinib 10 mg 111/132 (84.1%). Percentage discontinuations and withdrawals due to adverse events were roughly equal across all relevant treatment arms (were higher in the tofacitinib 10 mg arms). In their clarification response, the company clarified that in the group randomised to tofacitinib 5 mg, five patients withdrew by 3 months, two due to AEs, one due to inadequate response and two due to other reasons. Nine discontinued by 6 months (a further four patients (three due to AEs and one for other reasons). None of the adverse events were considered to be treatment related.

4.2.3.1 Patient characteristics of OPAL Beyond

As for OPAL Broaden, the tofacitinib 10 mg dose is not included in the CS or in this report. The main baseline patient characteristics are presented in CS Table 7 were similar across the tofacitinib 5 mg and placebo groups except that there were more female subjects in the placebo group (61%) than the tofacitinib 5 mg BD group (49%). The majority of the subjects were white (90 to 92%); the mean age ranged from 49.0 to 49.5 years; and the mean duration of PsA ranged from 9.4 to 9.6 years. Out of the 262 subjects, 176 (67.18%) had enthesitis and 129 (49.24%) had dactylitis; 199 (75.95%) of subjects were receiving concomitant MTX. This is similar to the OPAL Broaden population except that the mean duration of PsA is longer. The ERG notes that almost 24% of patients in OPAL Beyond were

4.2.3.4 Summary of efficacy results for OPAL Beyond

Table 4 Efficacy results for OPAL Beyond (FAS) ACR 20, 50 and 90, PSARC, PASI 75 and HAQ-DI (adapted from CS Tables 15 to19).

	Month	TOF 5 mg	PBO	TOF 5 mg vs placebo (% Difference and 95% CI) p value
ACR 20 Response rate, n (%)	3	65/131(50)	31/131 (24)	26.0 (14.7, 37.2) <0.001§
	6	78/131 (60)		
ACR 50 Response rate, n (%)	3	39/131 (30)	19/131 (15)	15.3(5.4, 25.2), 0.003
	6	50/131 (38)		
ACR 70 Response rate, n (%)	3	22/131 (17)	13/131 (10)	6.9 (-1.3, 15.1), [redacted]
	6	28/131 (21)		
PSARC response rate, n (%)	3	[redacted]	[redacted]	29.8 (18.3, 41.2), [redacted]
	6	[redacted]		
PASI75 response rate, n (%)	3	17/80 (21)	12/86 (14)	7.3 (-4.3, 18.9), [redacted]
	6	27/80 (34)		
HAQ-DI score LS mean change from baseline	3	-0.39 (N=124)	-0.14 (N=117)	-0.3 (-0.4, -0.1), <0.001§
	6	-0.44 (SE 0.05) (N=122)		

§p-value is subject to the step-down approach;

PASI50 and PASI90 response at month 3 were additional outcomes examined in a post-hoc analysis conducted to inform the economic model for the UK NICE submission and are presented in CS Appendix M.

The results in Table 4 above show that there was a statistically significant benefit of tofacitinib 5 mg over placebo for the primary outcomes (ACR 20 and HAQ-DI), and also for ACR 50 and PSARC, but not for ACR 70 or PASI 75.

Results for other secondary measures of disease activity are presented in Appendix M of the CS (Tables M14 and M16). The MDA response rate at month 3 in the tofacitinib 5 mg BD group was 23% vs 15% in the placebo group, though the difference was not statistically significant [redacted]. The response rate in the tofacitinib group was sustained up to Month 6. For all other of these outcomes the p values for the improvements seen with tofacitinib 5 mg BD compared with placebo were all $\leq$0.01, although for LEI score, DSS, SF-36 physical functioning score, and FACIT-F total score statistical significance could not be claimed because they were subject to a hierarchical testing

scheme (because the PASI75 response rate was not significant). Responses were sustained up to Month 6. It should be noted that, as for OPAL Broaden, although EQ-5D data were collected in the trial these data were not included in the CS but were provided in the company's clarification response. The results suggest [redacted] no formal testing presented.

The ERG also enquired about the data, if any, collected on those patients who were randomised to placebo and then switched to active treatment at the 3-month time point. In their clarification response the company provided the results at 6 months for these patients. Overall, the results reflect those of those patients randomised to tofacitinib 5 mg group and are supportive of the main analysis data.

Comparison of results from OPAL Broaden and OPAL Beyond

A comparison of the results from these two trials does not reveal a consistent pattern, i.e. there is no clear indication from the results that the Beyond population is the more refractory to treatment. Compared with OPAL Broaden the placebo response was lower in Beyond for ACR 20 and PsARC, but it was higher for ACR 50 and 70. For PASI75 the placebo response rates in the two trials were very similar; the lack of a statistically significant effect of tofacitininb in Beyond was due to a much lower tofacitinib 5 mg arm response rate compared with that seen in Broaden 21% vs 43%). The HAQ-DI results were similar across the two trials.

Regarding withdrawals from trial therapy, the ERG requested information on the number of withdrawals and whether from OPAL Beyond or OPAL Broaden, and whether the next treatment was a csDMARD or bDMARD. This information could have indicated the position of tofacitinib in the treatment pathway. However, in their clarification response the Company confirmed that neither OPAL Beyond nor OPAL Broaden were designed to assess subsequent treatments after discontinuation of tofacitinib; the requested information was not available.

The Company stated that the drug survival rates for the relevant dose of 5 mg BD tofacitinib were very high: 90% in OPAL Broaden at 12 months, and 93% in OPAL Beyond at 6 months, and only 20 patients would have required an alternative line of treatment following tofacitinib within the study duration.

4.2.4. Relevant non-randomised evidence – OPAL Balance

One relevant non-randomised study of tofacitinib in PsA was included in the CS: OPAL Balance. OPAL Balance is an open-label extension study of the long-term safety and efficacy of patients who had previously participated in OPAL Broaden and OPAL Beyond. OPAL Balance is ongoing, with an

anticipated completion date of January 2020. Details are presented in CS Appendix M 2.1. In summary, all patients in OPAL Balance received tofacitinib upon entry into the study: patients were to receive TOF 5 mg BD for one month, after which, the dose could be increased to 10 mg BD for efficacy reasons at the investigator's discretion. Doses could be reduced back to 5 mg BD for safety reasons at the investigator's discretion. The primary outcome of OPAL Balance was incidence and severity of adverse events; and change from baseline in laboratory values. Key secondary outcomes were ACR20/50/70, HAQ-DI, PsARC, PASI75, LEI, DSS.

Clarification from the company provided indirect information on the dose of tofacitinib patients entering OPAL Balance had been treated with: the trial arms are summarised in ***[redacted] . This information revealed that of the [redacted] patients enrolled and treated in OPAL Balance from OPAL Broaden [redacted] had been treated with TOF 5 mg, [redacted] TOF 10mg and [redacted] adalimumab. Of the [redacted] patients enrolled and treated in OPAL Balance from OPAL Beyond, [redacted] had been treated with TOF 5 mg, and [redacted] TOF 10mg.

[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]

This information is not particularly useful as all patients, irrespective of the treatment in the source trial, on entering Balance initially received 5 mg dose, but increasing the dose to 10 mg was permitted. Whilst the information in ***[redacted] tells us that only [redacted] did not have a treatment / dose alteration at the start of this study, it does not tell us how many patients were on the 10 mg dose and therefore how representative of the licensed dose (5 mg) these data are. Further information provided in the company's clarification response

[redacted]. As the 10 mg dose of tofacitnib is not licensed, there is a question over the generalisability to clinical practice of the OPAL Balance data.

Table 5 OPAL Balance Patient discontinuations by month (data from second interim analysis (25 January 2017) Information taken from Company clarification response (CCR))

OPAL Balance n=686				
	Discontinuations from CCR question A5	Table 00099.4	Table 00099.4	Table 00099.4
Assessment month	Total	Total	Due to Lack of efficacy	Due to AE
3	[redacted]			
6	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]			
12	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]			

For the January 25, 2017 data cut, safety and efficacy data from all patients in OPAL Balance were pooled, regardless of dose, due to flexible dosing between 5 mg BD and 10 mg BD. [redacted]

Baseline values for efficacy endpoints were the same baseline values used for patients in their previous clinical trial of tofacitinib.

Results

Withdrawals from OPAL Balance are presented in **Table 5**. Withdrawals at 2 years (2.5 to 3 years since start of tofacitinib) were roughly [redacted] remained on tofacitinib. This compares with 61% remaining on first anti TNFi reported for the BSBR Register.[10]The results for the change from baseline up to Month 24 (interim data analysis up to 25 January 2017) in the pooled tofacitinib group (5 mg and 10 mg BD doses) are shown in**Table 6**. These results demonstrated that improvements in signs and symptoms of the disease and physical functioning achieved by tofacitinib treatment are generally sustained long term for those patients who remain on tofacitinib therapy. The ERG notes that the number of patients in the study reduce dramatically over the 18-month period, from 634 at month 6 to 82 at month 24, presumably due to limited follow-up in a significant number of patients. This doesn't necessarily reflect drop-outs from the study, but rather the fact that the study is ongoing. Similar improvements were demonstrated for other measures of signs and symptoms of the disease (ACR50, ACR70, and PASI75), as well as measures of enthesitis (LEI), dactylitis (DSS), and pain. The ERG noted that, even though a high proportion of patients remain on tofacitinib therapy, not all

achieved an ACR 20 response. In their clarification, the company confirmed that in OPAL Balance a lack of efficacy determined by an ACR 20 response was not a criterion for withdrawal from the study.

Table 6 Summary of efficacy through to Month 24 in OPAL Balance interim data analysis up to 25 January 2017 – includes TOF 5 mg and TOF 10 mg)- Includes PsARC results provided in the Company's Clarification response.

Outcome	TOF (all patients, N=686)			
Timepoint	Month 6	Month 12	Month 18	Month 24
ACR20, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
ACR50, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
ACR70, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
ΔHAQ-DI, mean (SD) [N]	[redacted]	[redacted]	[redacted]	[redacted]
PSARC n/N	[redacted]	[redacted]	[redacted]	[redacted]
PASI75 response rate, n/N1 (%)	[redacted]	[redacted]	[redacted]	[redacted]
ΔLEI, mean (SD) [N1]	[redacted]	[redacted]	[redacted]	[redacted]
ΔDSS, mean (SD) [N1]	[redacted]	[redacted]	[redacted]	[redacted]
ΔPain, mean (SD) [N1]	[redacted]	[redacted]	[redacted]	[redacted]

1= number of evaluable patients at visit. No imputation.

[redacted]

In OPAL Broaden, where comparison with adalimumab was possible, AEs were slightly more common in the adalimumab group (see **Table 7**)

Table 7 Summary of AEs Reported up to Month 3 and Month 12 (Safety Analysis Set, All Causalities) for OPAL Broaden (adapted from CS Tables 31 and 33)

Number (%) of Subjects:	TOF 5mg n (%)	ADA n (%)	PBO n (%)
To 3 months			
Subjects evaluable for AEs	107	106	105
[redacted]	[redacted]	[redacted]	[redacted]
Subjects with AEs	42 (39)	49 (46)	37 (35)
Subjects with SAEs	3 (3)	1 (1)	1 (1)
[redacted]	[redacted]	[redacted]	[redacted]
To 12 months			
Subjects evaluable for AEs	107	106	52
[redacted]	[redacted]	[redacted]	[redacted]
Subjects with AEs	71 (66)	76 (72)	36 (69)
Subjects with SAEs	8 (7)	9 (8)	3 (6)
[redacted]	[redacted]	[redacted]	[redacted]

Withdrawals due to AEs were not reported in the adverse effects section of the CS. From the trial CONSORT diagrams (CS Appendix D) and the clarification response the ERG calculated that [redacted] and [redacted] of patients withdrew due to an adverse event in OPAL Broaden and Beyond respectively, though none of the events were considered to be treatment related. In the longer-term OPAL Balance the rate was 5.8% at 24 months.

Adverse events of special interest are summarised in the CS. These are gastrointestinal perforation and inflammatory bowel disease: tuberculosis, serious infection/herpes zoster; opportunistic infection; interstitial lung disease; cardiovascular events; and cancer. These were summarised by trial (OPAL Broaden, Beyond and Balance) but not overall; the overall totals as calculated by the ERG from the information provided are given in Table 8.

Table 8 Adverse events of special interest reported across all OPAL studies up to 36 months (ERG calculated from text in CS Appendix M)

Adverse events of special interest	N
gastrointestinal perforation and inflammatory bowel disease:	1
tuberculosis,	4 latent
serious infection	15
herpes zoster;	22
opportunistic infection;	2+ (No information from OPAL Balance)
interstitial lung disease;	0+ (No information from OPAL Balance)
cardiovascular events;	[redacted]
cancer	13

To provide long-term safety information, interim data from the long-term extension study OPAL Balance were analysed. As of January 25, 2017, no new risks or safety signals were identified in the long-term extension data from the tofacitinib PsA 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. Recommendations on how to appropriately manage the risks associated with tofacitinib (including vaccinations and risks of serious infection) are outlined within the SmPC.

The CS also referred to a health claims database study conducted in an American cohort of PsA patients, in which the incidence of most AEs reported in tofacitinib PsA phase III studies was generally comparable with that observed in a general PsA population, with the exception of the rates of herpes zoster, which were somewhat higher in the tofacitinib cohort than in the real-world comparison cohort (Truven Marketscan Comparison Cohort).[13]

In summary, the adverse events profile of tofacitinib in PsA patients appears similar to, and no worse than that of adalimumab. The tolerability of tofacitinib is reflected in the low rate of withdrawals due to AEs. An increased risk of herpes zoster appears to be a specific AE of tofacitinib.

4.5 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The CS included a systematic review across the intervention of interest (tofacitinib 5 mg) and identified data on all relevant comparators (i.e. adalimumab, secukinumab, golimumab, infliximab, etanercept, apremilast, ustekinumab, certolizumab pegol). In addition, RCTs in the same populations but of interventions not included in the scope for this appraisal (abatacept and ixekizumab) were also included in the network meta-analyses this was judged to be appropriate by the ERG and discussed in

(of which the OPAL Beyond trial is assumed representative). OPAL Broaden evaluates two doses of tofacitinib (10mg BD and 5mg BD) and both were included in the NMA for bDMARD-naïve. The company, however, only presented cost-effectiveness results for tofacitinib 5mg BD and hence we here omit NMA results on tofacitinib 10mg BD. This critique section will focus on the most relevant outcomes for the economic analyses (PsARC response, PASI response, HAQ conditional on PsARC response). The company presents more detailed information relevant to the NMA analyses in the appendices of the main submission:

- The results of the pivotal trials are presented in the main submission and in Appendix M.
- A description of the evidence included in the NMA, of its methods, and of the opinion of the clinical expert on the assumptions of the NMA is in Appendix D,
- The results of the NMA are presented in Appendix E.

Section 4.6 is structured as follows: We will first focus on bDMARD-naïve (section 4.6.1) and only after on bDMARD-experienced (section 4.6.2). Within each subsection, a summary of the main analyses in company's submission (including methods and results) is initially presented separately for each outcome. Note that methods of analyses differ by outcome but are similar across the two subpopulations. Hence, the general approach to modelling each outcome will be described only for the bDMARD-naïve. After summarising the company's submission, we briefly critique it. The critique will be based on comparisons with the recent TA445 that focussed on the same decision problem, and on comparison with the OPAL trials results. Finally, further detail presented in the company's submission, relevant to issues deemed important in the critique are discussed in Section 4.6.3.

bDMARD-naïve

This subsection summarises methods and results of the synthesis of relative treatment effects, but the company has provided only little detail on how evidence on placebo-response was considered (section "Analysis of absolute change from baseline or probability of event" in Appendix D of the CS)..

4.6.1.1 Summary of main analyses in company's submission

Summary of main analyses on PsARC

The company identified 14 studies that report PsARC and organised these in a network (**Error! Reference source not found.**, PsARC). The company only had access to the published results of Future 2 and RAPID-PsA study results (secukinumab and certolizumab pegol), which included a combination of bDMARD-naïve and bDMARD-experienced patients. In TA445 subgroup specific outcome data was used. The data on PsARC response was modelled using a standard logit model with Binomial likelihood (in line with

The company used goodness of fit to select from the above model specifications (see TableE18 in Appendix E). Results show that class-effects models (C and D) do not fit as well as models assuming independent effects of the different treatments, and that the placebo adjustment leads to better fitting models (B1 and B2). Within placebo-adjusted models, the random effect model, B2, has the lowest DIC. The company used model B2 as the base case for the economic model.

The results from this model are shown in **Error! Reference source not found.**, where treatments are ordered according to their relative effectiveness estimates (most effective treatment is ranked 1 and the least effective is ranked 11). Effect estimates are presented using logOR against placebo (the scale in which treatment effect estimates were pooled across studies), ORs for tofacitinib 5mg BD vs other comparators, and absolute predicted PsARC response (this depends on assumptions about placebo response which were not clearly justified in the CS).

The results highlight that all comparators were significantly better than placebo except for tofacitinib 5 mg BD (OR=[redacted]). However, when comparing across interventions, tofacitinib 5 mg BD was not significantly different to treatments in the low or intermediate effectiveness group (apremilast, ustekinumab, adalimumab, secukinumab, and certolizumab pegol), but was statistically inferior to those in the high effectiveness group (etanercept, infliximab, and golimumab). The probability of PsARC response with tofacitinib 5 mg BD was [redacted].

Table9: Main results used in the base case of company's submission (PsARC response, model B2)

	r	treat	LOR comparator vs PBO*	OR of TOF5 vs comparator	PsARC
Hig h	1	IFX	[redacted]	[redacted]	[redacted]
	2	ETN			
	3	GOL			
Interm ediate	4	SEC 150	[redacted]	[redacted]	[redacted]
	5	CZP			
	6	SEC 300			
	7	ADA			
Low	8	USK	[redacted]	[redacted]	[redacted]
	9	APR			
	10	TOF 5			
	11	PBO	[redacted]	[redacted]	[redacted]

* CI not presented in Table E18

The company also notes that OPAL Broaden is the study with the highest placebo PsARC response

([redacted]) among the included trials. For a summary of company discussion of the placebo response in OPAL Broaden and ERG critique see section 4.5.

To further explore this issue, the company submitted an additional analysis, using the specification in model A, where the placebo arm from OPAL Broaden was excluded (model A*). The manufacturer justifies this analysis on the basis of an elevated placebo response, poor model fit in terms of residual deviance and having the support of the clinical expert that advised on the submission (see Section D.2.3 in Appendix D). This analyses returns very similar results to model A1, with the exceptions of adalimumab and tofacitinib 5mg BD, which now present better effectiveness. Specifically, in model A1 tofacitinib 5mg BD was the lowest ranking treatment (LOR of [redacted]) and in model A1* it presented better effectiveness than apremilast and ustekinumab (LOR of [redacted] vs. placebo).

1.1.1.1.1 Summary of main analyses on PASI

The evidence network used by the company is shown in **Error! Reference source not found.**. The IMPACT trial was excluded from the NMA due to the extreme values reported in the trial (PASI 50 response was 0% for placebo and 100% for IFX). Ixekizumab was not NICE approved in the UK for PsA at the time of company's review; however the phase III study SPIRIT P1 had been published and was included in the network.

The NMA estimated the probability of PASI response at different thresholds (50/75/90) within a multinomial probit model. The single model included all categories of PASI and evaluated a single effect estimate for each treatment (expressed as a probit) that is then used to obtain probabilities of achieving PASI 50, PASI 75 and PASI 90. The company considered two alternative model specifications:

- Model E: Independent treatment effect and no placebo-response adjustment, and
- Model F: Independent treatment effect and placebo-response adjustment.

The results show that:

- Model E2 (Table E31, Appendix E and **Error! Reference source not found.** below) identifies infliximab and ixekizumab as most effective (highest effectiveness group), followed by secukinumab and golimumab, (intermediate/high effectiveness group), followed by adalimumab, ustekinumab and tofacitinib (intermediate/low effectiveness group), and lastly certolizumab pegol, etanercept, and apremilast (lowest effectiveness group). Results for model E1 (Table E29, Appendix E) only differ for ustekinumab, which had an effect estimate closer to adalimumab. Note that in Table 2 we omit results on ixekizumab as this is not a comparator in the submission.
- Model F does not differ from E1 indicating no effect of placebo-response adjustment.

Table 10 Results from NMA in DMARD experienced population

PsARC Base case model (A1)

Rank	treat	PsARC
1	USK	[redacted]
2	TOF5	[redacted]
3	TOF10	[redacted]
4	PBO	[redacted]

PASI with 24 week data (E1)

		PASI50	PASI75	PASI90
1	USK	[redacted]	[redacted]	[redacted]
2	SEC 300	[redacted]	[redacted]	[redacted]
3	IXE 80 Q2W	[redacted]	[redacted]	[redacted]
4	IXE 80 Q4W	[redacted]	[redacted]	[redacted]
5	TOF 10	[redacted]	[redacted]	[redacted]
6	TOF 5	[redacted]	[redacted]	[redacted]
7	PBO	[redacted]	[redacted]	[redacted]
8	ABA	[redacted]	[redacted]	[redacted]

HAQ conditional on PsARC (Model G1)

		Predicted HAQ change	
		Responders	*Non-responders*
1	TOF10	[redacted]	[redacted]
2	TOF5	[redacted]	[redacted]
3	USK	[redacted]	[redacted]
4	PBO	[redacted]	[redacted]

As with PsARC, OPAL Broaden showed a higher placebo response on PASI (of [redacted] respectively for PASI50, PASI75 and PASI90) than that modelled. The model found adalimumab response was similar to tofacitinib 5mg BD; the trial shows, however, that while this holds for PASI 50 ([redacted] for tofacitinib 5mg BD and [redacted] for adalimumab), PASI75 and PASI90 show better results for tofacitinib 5mg BD ([redacted] for PASI75 and [redacted] for PASI90).

HAQ conditional on PsARC response

Model specifications and findings of the company analyses (model G) were similar to TA445 for HAQ changes conditional on PsARC. Predictions from model G were also consistent with the results from OPAL Broaden, including for placebo. However, there are significant differences in predictions from model K particularly in what concerns responders to PsARC.

4.6.3.2 Critique of analyses implemented for bDMARD experienced population

The PsARC response rates from the company analyses for ustekinumab were similar to those in TA445, but TA445 was able to include data for secukinumab, which showed higher effectiveness than ustekinumab. OPAL Beyond showed a similar placebo response (of [redacted]) and tofacitinib 5mg BD response (of [redacted]) to that modelled.

TA445 found lower placebo response rates for PASI (8.8% to PASI 50), and higher responses to secukinumab 300 than ustekinumab (PASI 50 of, respectively, 87.5% and 62.8%).

OPAL Beyond had a higher placebo PASI responses rate (of [redacted] and [redacted], respectively for PASI50, PASI75 and PASI90) than those modelled. Responses observed in the trial for TOF are [redacted], [redacted] and [redacted] respectively for PASI50, PASI75 and PASI90.

[redacted]. The predictions for model G are slightly closer to trial results. HAQ changes in non-responders were low and very similar in the trial.

4.6.3.3 Outstanding issues

The ERG identified no significant issues with analyses relating to the bDMARD-experienced population. There are two outstanding issues on the evidence synthesis for the bDMARD-naïve population. The first issue is of key importance, concerning the validity of the placebo-response adjusted models for the estimation of treatment effects over PsARC response on the bDMARD-naïve population. This is be explored in the next section. The second outstanding issue is the level of placebo-response for PsARC and PASI response outcomes. The manufacturer has not identified the

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[1]

The trend lines in the figure show the information that contributes to the placebo effect and in red the subset of adalimumab trials. The slope of the red trend line hence represents the information conveyed in the ADA studies on the coefficient for the meta-regression. OPAL Broaden conveys information that complements, and does not contradict, the remaining adalimumab trials (Genovese and ADEPT) regarding the placebo effect coefficient. This information should therefore not be dismissed.

Revisiting model selection for placebo-response adjusted models for PsARC

In this subsection, we implement all model specifications submitted by the manufacturer in order to revisit model selection after the correction to placebo-response adjusted models. The corrected inferences are presented below (**Error! Reference source not found.**), alongside goodness of fit statistics.

The review identified a number of previous economic models but as mentioned in Section **Error! Reference source not found.**, no previous models were found which included tofacitinib as a comparator. Most of the evaluations identified were developed for, or based on those developed for, NICE technology appraisals. [1, 14-16]The company performed a quality assessment of the included studies and provided this in Appendix G (Tables G19-G27). The majority of the models adopted the same structure, and the company chose a similar structure to model the cost-effectiveness of tofacitinib.

It is clear from the systematic review that TA445 is the most comparable economic evaluation to the company's submission. ERG's summary and critique of company's submitted economic evaluation

An overall summary of the company's approach and references to the relevant sections in the CS are reported in

Table 11 below.

Table 11 Summary of the Company's economic evaluation (and signposts to company's submission)

Element	Approach	Source/Justification	CS reference
Model	A Markov model with 40 year time horizon and a 3-month cycle length. The model evaluates the cost-effectiveness of tofacitinib versus NICE-recommended comparators. The model reflects initial response to treatments, continued use or withdrawal from the treatment. Both the skin and joint symptoms of PsA are taken into account.	The model structure, methods and assumptions are reflective of current NICE guidance.	Section B3; p115
States and events	Response to treatment was evaluated according to PsARC response three months from baseline for all comparators. Non-responders transitioned to the subsequent treatment in the pathway; responders were assumed to continue treatment until they withdrew due to either a loss of efficacy, adverse events or death. Transitions from the treatment state to alternative pathways were determined by initial response rates and discontinuation rates. Adverse events were not modelled.	Transition response criteria according to BSR guidance and company's NMA. Withdrawals based on recent NICE guidance and [1].	Section B3; p115
Population and subgroups	Adults with active PsA whose disease has not responded adequately to previous DMARD therapy or for whom DMARDs are not tolerated or contraindicated.		Section B.1.1, Table 1, p;12 Section B.3.2.1. p113-114.

	score conditional on PsARC at 12 weeks. The psoriasis component was modelled via changes in PASI score at 12 weeks.		
Effectiveness of subsequent lines of therapy	Response rates applied in the economic model for subsequent lines of therapy were taken from the bDMARD experienced NMAs, to reflect differences in efficacy between lines of therapy. No further degradation in effectiveness was applied to the bDMARD experienced population, as it was assumed this would be captured in the NMA effect estimates.		
Discontinuation	12-week probability of withdrawal of 3.96% was included in the model. Patients who discontinued a treatment transitioned to the next treatment option or BSC when they had failed all treatments. Rebound to the baseline HAQ value was assumed for patients entering BSC (termed as rebound to initial gain).	NICE PsA Guidance as obtained from the York model [14].	Section B.3.3.1.; p 125
Adverse events	Adverse events were not explicitly modelled. AEs were only considered implicitly in terms of their effect on initial response and withdrawal for each treatment.	NICE PsA guidance as obtained from Corbett et al in 2017 [1].	
Mortality	Mortality rates were derived from life table for England and Wales (2014-2016).	A standardised mortality rate (1.36) reported by Ali et al [18] and as applied in TA445 was used [15].	Section B.3.3.1.7 p; 129
Health-related quality of life	Patients HRQoL is defined in the model in terms of HAQ and PASI scores, and these are mapped to EQ-5D. Patients HAQ-DI and PASI scores change according to treatment response. HAQ-DI scores remain constant while patients are on treatment with bDMARDS or tofacitinib but progress linearly while patients are on apremilast or BSC (reflecting worsening of physical functions following failure to respond to treatment. PASI scores do not progress on BSC as they are not progressive. Whilst on treatment, improvements in PASI scores are possible.	In the base case analysis utilities were based on a linear regression. A utility model based on tofacitinib trial data was used in scenario analysis and applied to either tofacitinib alone, or to tofacitinib and its comparators.	Section 3.4.2. p; 130-131
Resource utilization and costs	Costs included were: drug acquisition costs; drug administration costs and monitoring costs. Arthritis and psoriasis-related costs were also applied in the model and based on the HAQ-DI and PASI scores.	Resource use associated with drug administration and monitoring costs were obtained from the BNF [19] and TA199 and TA445, respectively [14, 15]. Acquisition costs were taken from the BNF and electronic market	Section B.3.5. p;133-142

	Costs for the following treatments differ between the first cycle and subsequent cycles to account for loading doses or PAS arrangements; Apremilast, Certolizumab Pegol, Infliximab, Secukinumab and Ustekinumab.	information tool (eMIT) database [19, 20]. No drug costs are assumed for BSC. Patient Access Scheme prices are listed where information is in the public domain. Administration and monitoring costs (except for liver function test, chest x-ray and TB heaf test costs)* were obtained from the NHS reference costs and PSSRU [21, 22]. Arthritis-related costs were estimated as a function of HAQ-DI score, based on Rodgers et al. Psoriasis-related costs based on PASI scores were obtained from TA445 [15]. Adverse events were not considered in the model	
Discount rates	3.5% for utilities and costs	NICE reference case	Section B.3.2.2. p; 117
Sensitivity analysis	Probabilistic sensitivity analysis and scenario analysis were performed. Deterministic sensitivity analysis were not performed.	Deterministic sensitivity analysis was not performed.	Section B.3.8.1. p;147 Section B.3.8.2 p;154

Model structure

The company describes a de novo economic evaluation based on a Markov cohort model similar to the model structure used by the York Assessment Group (AG) in TA445 [15]. The model was developed in Microsoft Excel to evaluate the cost-effectiveness of tofacitinib. The model structure allows a comparison of multiple treatment sequences (see Section **Error! Reference source not found.**). The model allows patients to cycle through sequences of therapy, with patients remaining on a treatment after the first 3 months if they have met the required criteria.

After an initial response to treatment, patients remain on therapy until either a loss of efficacy, the occurrence of particular adverse events or death. Transition to death (all cause and excess due to PsA) is included at each cycle of the model.

	costs or outcomes between the technologies being compared.		recent published cost-effectiveness analyses. PsA is a chronic, lifetime condition with no known cure. Disease management aims to improve symptoms and HRQoL over a patients' lifetime. A 40 year time horizon accounts for the long-term consequences of the disease. However, long-term time-horizons rely on assumptions, due to the lack of long-term data.
Synthesis of evidence on health effects	Based on systematic review	Yes	In the absence of head-to-head trials between the identified comparators, a network meta-analysis was conducted to inform the clinical efficacy parameters in the economic model
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes	A regression equation was used which maps HAQ-DI and PASI scores to EQ-5D. The algorithm generated as part of TA445 [15] was used. Regression coefficients calculated using the EQ-5D results from the tofacitinib trial were only tested in sensitivity analysis and applied to all treatments.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes	
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes	Utility values were based on ED-5D estimates.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
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	
Discounting	The same annual rate for both costs and health effects.	Yes	Costs and benefits were discounted at 3.5%.

	First in sequence	Second in sequence	Third in sequence
Sub-population 2: Disease has not responded to at least 2 nbDMARDs*	TOF	UST	BSC
	ADA		
	APR		
	CZP		
	ETN		
	GOL		
	INF		
	SEC (188mg, weighted dose)		
	BSC	-	-
Sub-population 3: Disease has not responded to nbDMARDs and at least 1 TNFi	TOF	BSC	-
	SEC (300mg)		
	UST		
	BSC	-	-
Sub-population 4: TNFi contraindicated or not tolerated	TOF	BSC	-
	SEC (188mg, weighted dose)		
	UST		
	BSC	-	-

†First treatment in sequence options are chosen in accordance with NICE guidance [14, 15, 23, 24, 26]. Second- and third treatment in sequence options are aligned with those used in TA445[15].*nbDMARDs ~ csDMARDs

Abbreviations: ADA, adalimumab; APR, apremilast; BSC, best supportive care; bDMARD, biological disease-modifying anti-rheumatic drug; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; nbDMARD, non-biological disease-modifying anti-rheumatic drug; SEC, secukinumab; TNFi, TNF inhibitor; TOF, tofacitinib; UST, ustekinumab.

The NICE scope lists CZP as a comparator for sub-population 3, which includes people whose disease has not responded adequately to non-biological DMARDs and 1 or more TNFi. Similar to TA445, the company excluded CZP from sub-population 3 because the data available from the RAPID PsA trial informs only a subset of patients in this sub-population (i.e., primary responders to a prior TNFi who were secondary failures [primary non-responders were explicitly excluded from this trial]) [1].

For all sub-populations, following a lack of response to PsARC or subsequent withdrawal for PsARC responders, patients move onto the next line of treatment. The ERG had concerns about assumptions made regarding effect degradation for some subsequent lines of therapy. For treatments other than ustekinumab and secukinumab, subsequent treatments are assumed to be as efficacious as first line, i.e. no effect degradation is assumed. Only second line therepay with ustekinumab and secukinumab was presented in the company submission"

In addition, when comparing the base case NMA models informing the effectiveness data included in the company's model, there were differences in the NMA models used in the current TA and the previous TA on which the current evaluation is based [15]. One reason for these variations is due to data that was previously publicly available for TA445 and no longer publicly available for the current TA. More specifically, in terms of HAQ response, the company implemented a different base case model compared to that used in TA445. This differs from the TA445 [30] base case in that it uses random effects, adjusts for trials with more than two arms, and uses separate models for responders and non-responders. The analyses using separate models for responders and non-responders predict larger changes in HAQ-DI for responders than do the combined models, including for placebo responders. The ERG requested justification for this model specification. The ERG explores the validity of the NMA in Section 4.6 and explores the sensitivity of the economic model results to alternative NMA models in Section **Error! Reference source not found.**.

The response rates applied in the economic model for subsequent lines of therapy were taken from the bDMARD experienced NMAs, to reflect differences in efficacy between lines of therapy. No further degradation in effectiveness was applied to the bDMARD experienced population, as it was assumed this would be captured in the NMA effect estimates. The ERG had concerns about these assumptions made regarding effect degradation for some subsequent lines of therapy. For treatments other than ustekinumab and secukinumab, subsequent treatments are assumed to be as efficacious as first line, i.e. no effect degradation is assumed. Only second line therapy with ustekinumab and secukinumab was presented in the company submission.

5.1.10.3 Natural history disease progression

As the psoriasis element of PsA is not progressive, the company assumes that PASI scores do not increase over time for patients receiving BSC. The arthritis element of PsA is assumed to be progressive, therefore, for patients not receiving biologic therapies (BSC), the company assumes the HAQ-DI score worsens overtime.

In the base case model the rate of progression for BSC was obtained from the York AG model [14]. This HAQ-DI progression was estimated based on an extract of data for rheumatoid factor negative patients with inflammatory polyarthritis eligible for bDMARDs as per BSR guidelines receiving palliative care included in the Norfolk Arthritis Register [17] until 2009. A worsening (increase) in HAQ-DI score of 0.077 per year was applied as the rate of natural disease progression in the company's economic model. Patients could reach a maximum HAQ-DI score of 3.

For biologic drugs, excluding apremilast, the company assumed no progression of disease whilst on treatment. The appraisal committee for TA433 concluded that there was insufficient evidence to

demonstrate that apremilast halts radiographic disease progression (49), and concluded that the rate of disease progression experienced while receiving apremilast was assumed to be half of the progression rate for BSC/csDMARDs (i.e. 0.0385 per year). The same assumption was applied for apremilast in this analysis.

There is uncertainty about the trajectory of HAQ-DI over time, for both patients maintained on active therapies (responders) and those receiving BSC (either because of primary non-response or due to withdrawal).

Firstly, for patients receiving BSC they are assumed to follow a natural history trajectory through HAQ, with HAQ scores worsening at every cycle of the model. There are two main issues with this simplifying assumption. Firstly there appears to have been no attempts to update work from 2009 with a more recent extract from NOAR (or similar register such as ERAS). Practice regarding cDMARDs may change over time and this should be reflected in the HAQ change applied to the BSC comparator. In addition it is unlikely that the relationship between HAQ and time is linear over the entire extrapolation period (40 years). Recent work by Norton et al [31] looks at the progression of HAQ scores over 15 years in a largely RA population (but including some PsA patients in one dataset). This showed that HAQ progression becomes less linear over time, particularly post 5 years where scores stabilise

For patients maintained on active therapies (responders), the CS assumes that patients responding to treatment do not progress further in terms of HAQ (full disease modification). The ERG has concerns regarding the validity of this assumption. As discussed in Section .3.3.1 [redacted] n addition, the company acknowledges that the prognostic factors for radiographic progression in the OPAL Broaden clinical trial were different (lower) (e.g., baseline CRP levels, baseline mTSS, baseline erosion and joint space narrowing scores) than a number of previous bDMARD studies in PsA [32]. As the evidence presented on radiographic progression is based on short-term follow-up and 11.3% of patients experience a progression (increase in mTSS) [33] the ERG considers that the rate of progression for tofacitinib is uncertain and therefore the ERG explores this assumption in Section **Error! Reference source not found.**

risk associated with PsA is modelled using a HR of 1.36. This ratio was obtained from a prospective study of patients with PsA [18] and was applied in TA445 [15]. The ERG considers this to be a valid assumption.

5.1.10.6 Adverse Events

The incidence of adverse events leading to discontinuation from treatment was captured in the clinical trials for tofacitinib. Adverse events (AEs) are not explicitly included in the model, neither as a utility decrement nor as additional cost for their treatment. In the model, AEs were considered in terms of their effect on initial response and on the long-term rates of withdrawal from the continued use for each treatment. The ERG considers this to be a valid assumption.

5.1.11 Health related quality of life

Patients' HRQoL is defined in the model in terms of HAQ and PASI scores and these are mapped to EQ-5D. The health states in the model are defined by the treatment received and response to treatment. Patients' PASI scores remain constant after the first three months on treatment. Patients' HAQ-DI scores remain constant while patients remain on treatment with bDMARDs or tofacitinib, but they progress linearly while patients are on apremilast or BSC (reflecting worsening of physical function following failure to response to treatment (See Section 0).

EQ-5D data were available from the OPAL Broaden and OPAL Beyond clinical trials for tofacitinib. The company states that to be consistent with previous appraisals (TA119 [14] and TA445 [15]), the mapping algorithm used in the York model for the base case is implemented here. For the base case, the following formula from the York model was used:

Equation Error! No text of specified style in document.**.1 Mapping algorithm**

$$\boldsymbol{EQ-5D = 0.897 - 0.289 * HAQ - 0.004 * PASI}$$

Scenario analysis was performed in which the *de novo* mapping algorithms derived using individual patient data (IPD) from the OPAL Broaden and Beyond clinical data were applied to tofacitinib alone or tofacitinib and its comparators.

Statistical models were developed using data from the OPAL Broaden (sub-populations 2 and 4) and OPAL Beyond (sub-population 3) studies separately. Two models were estimated using each study:

- A 'main effect' model predicting EQ-5D in which HAQ and PASI scores were included as independent covariates.
- An 'interaction effect' model which augmented the 'main effect' model by including the interaction between HAQ and PASI scores as a covariate.

Both models pool all non-missing data at all time points from across all arms of the respective clinical trials. Models were implemented as mixed effects models to account for repeated measures within subjects. The CS refers to Appendix Q for the results of these models but Appendix Q was not provided. The ERG requested this and also requested that the specific covariates and regression function be provided.

In addition, the CS does not provide the EQ-5D data as collected in the OPAL trials. The ERG requested results of any EQ-5D assessments in OPAL Broaden, OPAL Beyond and OPAL Balance including sample sizes, missing data, follow up points, EQ-5D scores at baseline and follow up for each treatment and details and results of any statistical tests performed.

In response, the company provided Appendix Q. Appendix Q details the specific covariates included in the company's scenario analyses which used the *do novo* mapping algorithm applied initially to all treatments and then to the tofacitinib arm only. The ERG compared the covariates used in these scenario analyses with those used in the previous models and conclude that the covariates are very similar to those used in previous appraisals (TA119 [14] and TA445 [15]). The company clarified that a mixed effects regression function was used to account for repeated measures in the data. The company provided tables reporting the EQ-5D assessments in the OPAL Broaden, OPAL Beyond and OPAL Balance tofacitinib trials. These tables described the average EQ-5D utilities up to 12 months for tofacitinib, tofacitinib 10mg BD, adalimumab, placebo, placebo → tofacitinib and placebo → tofacitinib 10mg BD, the change from baseline in EQ-5D utilities, EQ-5D utilities by PsARC response and the change in EQ-5D utilities from baseline by PsARC response assessed in each of the OPAL trials. [redacted]

Resources and costs

The CS provided a detailed description of resource use and costs incurred in PsA patients. These included: drug acquisition costs (Section B.3.5.2.2 in CS); drug administration costs (Section B.3.5.2.3 in CS) and drug monitoring costs (Section B.3.5.2.4). AEs costs were not considered in the

model. A systematic review was conducted to identify alternative evidence regarding resource use and the costs associated with the management of PsA in the UK. The company reports that they did find one publication, Poole et al [35], that specifically reported estimates of costs according to HAQ-DI and/or PASI which was eligible for inclusion [35], however, it was not used to inform the model. The CS justifies this by stating that due to methodological limitations, and the desire to remain consistent with previous TAs, they opted to use the same source as used in TA445.

Costs for acquisition, administration and monitoring differ between the first cycle (initiation phase) and subsequent cycles to reflect clinical management practices associated with switching a patient onto a new treatment. In addition, in the first cycle, monitoring is more intensive while the decision to continue with treatment is made. For comparators with a recommended initiation phase greater than 12 weeks (ustekinumab and sekukinumab), costs for the SPC recommended length of initiation phase were not applied, for example up to 24 weeks. Instead, the cost of ustekinumab and secukinumab in the first cycle are adjusted to account for more frequent dosing in the initiation phase, for example secukinumab patients receive 5 weekly doses and then switch to monthly dosing. For other comparators the first cycle incorporates 12 weeks of drug treatment.

Table 46 in the CS (p138) provides a table detailing a summary of the treatment costs.

5.1.12.1 Drug acquisition costs

Costs for the bDMARDs and apremilast were sourced from the British National Formulary [19] and the cost of methotrexate was obtained from the electronic market information tool (eMIT) database [20]. PAS prices were used in the model where information is in the public domain. A list price analysis for tofacitinib was not provided. Instead the PAS price which employs a simple discount was used. Since the submission of the manuscript, the company have provided an updated PAS price for tofacitinib (See confidential PAS appendix). List prices were used for secukinumab and apremilast but these are subject a confidential PAS. The ERG conducted additional analysis using PAS prices for secukinumab and apremilast and these are presented in a confidential appendix. Biosimilar prices were used when available (etanercept and infliximab). No drug costs were assumed for BSC as it was assumed that these drug costs are captured in the estimates of resource use associated with HAQ-DI.

Following the update on the PAS price for tofacitinib, the company submitted a PAS submission template including tables detailing the new ICER using the confidential PAS price. They also provided an updated version of the model for each sub-population including the new PAS price. In sub-population 3, the incremental ICERs reported in the submission do not correspond to the incremental ICERs in the base case results in the economic model.

In this section the ERG explore the sensitivity of the company cost-effectiveness results to alternative NMA models to estimate PsARC response rates, specifically the corrected B2, D2 and A2 for subpopulation 2. The results for these sensitivity analyses are presented below in **Table 12** to **Error! Reference source not found.**, for both the deterministic and the probabilistic analysis. The equivalent confidential PAS results are presented in a separate confidential appendix.

Table 12 Company base case results B2 (deterministic)

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£32,881	2.45	£13,419	£13,419
APR	[redacted]	[redacted]	£40,499	2.07	£19,569	Dominated
ADA	[redacted]	[redacted]	£47,901	2.71	£17,687	Extendedly dominated
CTZ	[redacted]	[redacted]	£48,839	2.85	£17,126	Extendedly dominated
ETN	[redacted]	[redacted]	£51,700	3.27	£15,798	£22,886
SEK	[redacted]	[redacted]	£52,978	2.86	£18,543	Dominated
GOL	[redacted]	[redacted]	£53,557	2.99	£17,904	Dominated
INF	[redacted]	[redacted]	£71,190	3.35	£21,225	£239,101

Table 13 Company base case results B2 (probabilistic)

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£33,231	2.39	£13,918	£13,918
APR	[redacted]	[redacted]	£40,841	2.00	£20,422	Dominated
ADA	[redacted]	[redacted]	£48,350	2.64	£18,318	Extendedly dominated
CTZ	[redacted]	[redacted]	£49,313	2.77	£17,815	Extendedly dominated
ETN	[redacted]	[redacted]	£52,182	3.19	£16,371	£23,696
SEK	[redacted]	[redacted]	£53,510	2.78	£19,253	Dominated
GOL	[redacted]	[redacted]	£54,009	2.90	£18,641	Dominated
INF	[redacted]	[redacted]	£71,630	3.27	£21,900	£233,602

Table 14 ERG B2 – base case results (deterministic)

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£32,822	2.52	£13,029	£13,029
APR	[redacted]	[redacted]	£39,434	2.02	£19,555	Dominated
ADA	[redacted]	[redacted]	£47,275	2.67	£17,701	Extendedly dominated
CTZ	[redacted]	[redacted]	£49,490	2.89	£17,145	Extendedly dominated
ETN	[redacted]	[redacted]	£50,598	3.20	£15,799	£26,006
GOL	[redacted]	[redacted]	£51,143	2.85	£17,931	Dominated
SEK	[redacted]	[redacted]	£53,774	2.91	£18,507	Dominated
INF	[redacted]	[redacted]	£69,389	3.26	£21,270	£315,590

Table 15 ERG B2 – base case results (probabilistic)

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£33,231	2.39	£13,918	£13,918
APR	[redacted]	[redacted]	£40,841	2.00	£20,422	Dominated
ADA	[redacted]	[redacted]	£48,350	2.64	£18,318	Extendedly dominated
CTZ	[redacted]	[redacted]	£49,313	2.77	£17,815	Extendedly dominated
ETN	[redacted]	[redacted]	£52,182	3.19	£16,371	£25,762
GOL	[redacted]	[redacted]	£54,009	2.90	£18,641	Dominated
SEK	[redacted]	[redacted]	£53,510	2.78	£19,253	Dominated
INF	[redacted]	[redacted]	£71,630	3.27	£21,900	£216,088

The corrected B2 NMA produces very similar results to the company base case results, with only small differences in costs and QALYs and ICERs compared to BSC and the full incremental. The deterministic and probabilistic versions also provide similar results in terms of ordering, although there are some discrepancies in terms of absolute costs and QALYs. For all comparators the ICERs versus BSC fall within acceptable thresholds for cost-effectiveness. For the company B2 model and the corrected B2 model, both tofacitinib and etanercept fall within acceptable thresholds for the full incremental analysis.

Table 16 ERG D –base case results (deterministic)

Strategy	Total discounted costs	Total discounted QALYs	Incremental cost vs. cheapest strategy	Incremental QALYs vs. cheapest strategy	ICER vs. cheapest strategy	Incremental ICER

TOF	[redacted]	[redacted]	£9,655	0.73	£13,266	£13,266
UST	[redacted]	[redacted]	£24,979	1.33	£18,837	Extendedly dominated
SEK	[redacted]	[redacted]	£30,153	1.62	£18,557	£22,849
TOFACITINIB: (11% PROGRESS AT BSC (TOF PROGRESSION UPDATED TO 0.002)						
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£9,092	1.05	£8,670	£8,670
UST	[redacted]	[redacted]	£24,979	1.33	£18,837	Extendedly dominated
SEK	[redacted]	[redacted]	£30,153	1.62	£18,557	£36,554
TOFACITINIB: 11% PROGRESS AT SAME RATE AS APREMILAST (TOF PROGRESSION UPDATED TO 0.001)						
BSC	[redacted]	[redacted]	-	-	-	-
TOF	[redacted]	[redacted]	£9,011	1.09	£8,230	£8,230
UST	[redacted]	[redacted]	£24,979	1.33	£18,837	Extendedly dominated
SEK	[redacted]	[redacted]	£30,153	1.62	£18,557	£39,888

Similar results for sub-population 4 are shown in **Error! Reference source not found.** except for the first progression scenario (tofacitinib is equal to apremilast) where secukinumab offers higher QALYs and has an ICER within the NICE acceptable threshold.

Conclusions from ERG analyses

The ERG conducted a range of exploratory analyses to assess the uncertainties raised in the review and critique of the manufacturer's clinical and cost-effectiveness evidence. The ERG's exploratory analyses focussed on, severity of psoriasis, tofacitinib progression rates and drug costs for comparator drugs that are approved but not available publicly.

The additional analyses undertaken by the ERG suggested that whilst the ICERs for all subpopulations changed in each of the scenarios, they remained within the acceptable willingness to pay threshold, compared to BSC. In all scenarios, the fully incremental ICERs for tofacitinib are also within conventional willingness to pay thresholds, although etanercept may offer higher QALYs within an acceptable threshold. The confidential PAS appendix considers the impact of the PAS prices for apremilast and secukinumab on the cost-effectiveness results.

End of life

Not applicable.

Addendum: Summary and key drivers of cost-effectiveness (list price analysis)

The ERG conducted a series of scenarios to test the sensitivity of the company cost-effectiveness results. In particular the ERG focussed on the choice of NMA model to determine PsARC response in sub-population 2, sub-groups according to level of psoriasis and assumptions regarding the rate of progression whilst on treatment.

In sub-population 2, the ICER for tofacitinib was £13,918 in the company submission. The ERG corrected the B2 NMA model; however this had little effect on the ICER (£13, 0244 from the means of the probabilistic analysis). In the company basecase and the ERG corrected results, etanercept remained the most cost-effective option in the full incremental analysis (ICERs around £20,000 compared to tofacitinib). The ERG also specified two alternative models for the NMA and again the ICERs for tofacitinib were broadly similar to the company base case (£13,529 and £14, 109 for models D2 and A2 respectively).

The ERG concluded that the NMAs conducted for sub-populations 3 and 4 were correct, and therefore scenario analyses using alternative model specifications were not conducted.

For the remaining scenarios, the ERG concludes that whilst the ICERs change for each sub-population, they remain within the acceptable willingness to pay threshold, compared to BSC. Specifically the results show:

- In sub-population 2, the ICER for tofacitinib versus BSC ranges from £10,477 in the severe psoriasis group to £14,396 in no psoriasis group.
- In sub-population 4, the ICER for tofacitinib versus BSC ranges from £5,680 in the severe psoriasis group to £8,972 in no psoriasis group.
- In sub-population 2, the ICER for tofacitinib versus BSC is relatively robust to alternative assumptions regarding the progression of PsARC responders, with the ICER ranging from £13,266 assuming that 11% patients progress in line with apremilast (50% of BSC) to £15,706 assuming that all patients progress in line with apremilast.
- In sub-population 3, the ICER for tofacitinib versus BSC is relatively robust to alternative assumptions regarding the progression of PsARC responders, with the ICER ranging from £9,472 assuming that 11% patients progress in line with apremilast (50% of BSC) to £15,400 assuming that all patients progress in line with apremilast.

- In sub-population 4, the ICER for tofacitinib versus BSC is relatively robust to alternative assumptions regarding the progression of PsARC responders, with the ICER ranging from £8,230 assuming that 11% patients progress in line with apremilast (50% of BSC) to £13,266 assuming that all patients progress in line with apremilast.
- Across all scenarios, in sub-population 2, in the full incremental analysis, etanercept was the only option that was within an acceptable range for the threshold (ICERs below £30,000).
- In sub-population 3, in the full incremental analysis, ustekinumab is the only option that was within an acceptable range for the threshold (ICERs below £30,000) for the scenario assuming the same progression as apremilast for tofacitinib. In scenarios assigning 11% of patients to either progression equal to BSC or apremilast, tofacitinib becomes the only option that was within an acceptable range for the threshold.
- In sub-population 4, in the full incremental analysis, tofacitinib is the only option that was within an acceptable range for the threshold (ICERs below £30,000) for all scenarios apart from the mild to moderate psoriasis patients, where the ICER for secukinumab is £29,262 compared to tofacitinib.

Whilst there are some changes in the ICERs for the full incremental analysis it should be noted that the differences in costs and QALYs are often minimal and as such the ICERS compared to BSC are fairly robust to assumptions regarding the choice of NMA model, level of psoriasis and rate of progression for PsARC responders.

The ERG were not able to explore the impact of effect degradation using the company model, however they do recognise that this is only really a concern for scenarios where UST and SEC are not 2nd line treatment, i.e. where biologic experienced data is not available. Other drivers of cost-effectiveness are likely to be assumptions regarding rate of progression for BSC, rebound following treatment withdrawal and the algorithms used for costs and utilities. The assumptions used in the company model are consistent with the assumptions used in previous appraisals.