NICE National Institute for Health and Care Excellence

Fast Track Appraisal (FTA)

Tofacitinib for treating juvenile idiopathic arthritis [ID2718]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

FAST TRACK APPRAISAL (FTA)

Tofacitinib for treating juvenile idiopathic arthritis [ID2718]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Pfizer
2. **Company response to NICE's request for clarification**
3. **Evidence Review Group report** prepared by Centre for Reviews and Dissemination and Centre for Health Economics, University of York
4. **Evidence Review Group – factual accuracy check**
5. **Company addendum for the juvenile psoriatic arthritis indication**
6. **Technical Briefing** from NICE

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Fast track appraisal: cost-comparison case

Tofacitinib for treating juvenile idiopathic arthritis [ID2718]

Document B

Company evidence submission

February 2021

File name	Version	Contains confidential information	Date
ID2718 Tofacitinib for JIA – Document B	1.0	Yes	16.02.2021

Contents

Tables and figures

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Abbreviations

Term	Definition
ACR	American College of Rheumatology
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
bDMARD	Biologic disease-modifying anti-rheumatic drug
BID	Twice-daily
BL	Baseline
CHAQ	Child Health Assessment Questionnaire
CHMP	Committee for Medicinal Products for Human Use
CHQ	Child Health Questionnaire
CI	Confidence interval
CRP	C-reactive protein
csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug
DB	Double-blind
DBFAS	Double-blind full analysis set
DBJAS	Double-blind pcJIA analysis set
DBSAS	Double-blind safety analysis set
DMARD	Disease-modifying anti-rheumatic drug
EMA	European Medicines Agency
ERA	Enthesitis-related arthritis
ESR	Erythrocyte sedimentation rate
GI	Gastrointestinal
HRQoL	Health-related quality of life
HUI3	Health utilities index-3
IL	Interleukin
ILAR	International League of Associations for Rheumatology
ITC	Indirect treatment comparison

Term	Definition
IV	Intravenous
JADAS	Juvenile Arthritis Disease Activity Score
JAK	Janus kinase
JIA	Juvenile idiopathic arthritis
JRA	Juvenile rheumatoid arthritis
LOCF	Last observation carried forward
LS mean	Least squares mean
MAA	Marketing authorisation application
MDA	Minimum disease activity
MIMS	Monthly Index of Medical Specialties
MMRM	Mixed model for repeated measures
MNAR	Missing not at random
NMA	Network meta-analysis
NRI	Non-responder imputation
NSAID	Non-steroidal anti-inflammatory drug
OLFAS	Open-label full analysis set
pcJIA	Polyarticular course juvenile idiopathic arthritis
PGA	Physician's global assessment
PhS	Physical score
PRCSG	Pediatric Rheumatology Collaborative Study Group
PRINTO	Pediatric Rheumatology INternational Trials Organisation
PsA	Psoriatic arthritis
PsS	Psychosocial score
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RF	Rheumatoid factor
RR	Risk ratio
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation

Term	Definition
SEM	Standard error of the mean
sJIA	Systemic juvenile idiopathic arthritis
SLR	Systematic literature review
STAT	Signal transducer and activator of transcription
TEAE	Treatment-emergent adverse event
TNF	Tumour necrosis factor
ULN	Upper limit of normal
URTI	Upper respiratory tract infection

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

B.1.1 Decision problem

B.1.1.1 Population

The submission covers the technology, tofacitinib's full anticipated marketing authorisation for this indication, which is [redacted] Therefore, the pcJIA cohort of the pivotal trial for tofacitinib, Study A3921104, which included patients with extended oligoarticular JIA, polyarthritis rheumatoid factor positive (RF+), polyarthritis rheumatoid factor negative (RF-), or systemic JIA with active arthritis but without active symptoms (Figure 5) is the focus of the current submission. The study also included patients with enthesitis-related arthritis (ERA) and psoriatic arthritis (PsA); however, it is important to highlight, that these categories are not included in the proposed marketing authorisation and were not included in analysis of the primary endpoint. Efficacy data from patients with ERA and PsA are not presented in this submission; however, these categories are included in the safety analyses.

The decision problem addressed by the submission is shown in Table 1.

B.1.1.2 Comparators

Pfizer believes that the two most relevant comparators from the list specified in the scope are adalimumab and tocilizumab, for the following reasons:

- Adalimumab, a tumour necrosis factor inhibitor (TNFi) is the technology that is most frequently initiated in pcJIA, due to its established efficacy, effectiveness in treating JIA-associated uveitis (1), a comorbidity associated with JIA and the availability of biosimilars, which have lower net price than Humira, the originator adalimumab.

- Tocilizumab, an interleukin-6 (IL-6) inhibitor is also considered as a relevant comparator because this is the most frequently used technology with an alternative mode of action to TNFi and is also approved for polyarticular JIA in children from 2 years of age.

Pfizer believes that these two comparators adequately represent the NICE recommended treatment options. According to UK registry data between 2004 and 2019, most patients (91%) initiated treatment with a TNFi (2). Currently the most commonly initiated TNFi is adalimumab, because of the above-mentioned reasons. Etanercept is less frequently initiated as the first TNFi. The most commonly used non-TNFi is tocilizumab and abatacept is less frequently used (3).

Tofacitinib offers a different formulation (oral) and mode of action to both these comparators (see Section B.1.3B.1.3).

See Table 1 for details of other comparators included in the final scope but not included in the decision problem addressed in this submission.

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	People aged 2 years and older with JIA	[redacted] It should be noted that this excludes sJIA with active systemic disease.	In line with expected marketing authorisation indication
Intervention	Tofacitinib	Tofacitinib	-
Comparators	Methotrexate for people with PsA or ERA whose disease has responded inadequately to NSAIDs and who have not been offered a DMARD Currently available biologic DMARDs (abatacept, adalimumab, etanercept, tocilizumab): for people whose disease has responded inadequately to, or who are intolerant of, one or more DMARDs Infliximab (uveitis-associated JIA) Rituximab (RF-positive arthritis)	The position of tofacitinib in the treatment pathway is for people whose disease has responded inadequately to or who are intolerant of, one or more DMARDs. The most relevant comparators from the list of currently available biologic DMARDs for tofacitinib are adalimumab and tocilizumab, as explained in B.1.1.2.	Abatacept, adalimumab, etanercept and tocilizumab are all relevant comparators as per the expected indication for tofacitinib. However, for the current FTA comparison, Pfizer selected two of these comparators to demonstrate similarity in clinical effectiveness and costs. Adalimumab is the most frequently used biologic DMARD in pcJIA, and tocilizumab represents an alternative mode of action to TNF inhibitors. Infliximab does not have a marketing authorisation for JIA; however, it has been used off-label for a specific subgroup of patients with uveitis

	Anakinra (sJIA, subject to ongoing NICE appraisal)		associated with JIA or for whom self-injection may be challenging. JIA associated uveitis is outside the proposed marketing authorisation for tofacitinib. Rituximab does not have marketing authorisation for JIA; however, it has been used off label for patients with RF+ arthritis. Most patients with pcJIA have RF- disease, therefore it is also unlikely to be relevant comparator for this appraisal. Anakinra has a marketing authorisation for systemic JIA only, which is outside the proposed marketing authorisation for tofacitinib
Outcomes	Disease activity (including disease flares and remission) Physical function Joint damage Body weight and height Pain Corticosteroid sparing JIA-specific outcomes where relevant (e.g. enthesitis and dactylitis counts) Mortality Adverse effects of treatment HRQoL	Disease activity (including disease flares and remission) Physical function Pain (collected as part of JIA ACR and CHAQ questionnaire) Mortality Adverse effects of treatment HRQoL	Joint damage was not collected as an outcome in Study A3921104. The trial required stable concomitant medication therefore no corticosteroid sparing data are available. Enthesitis and dactylitis counts are relevant to enthesitis-related and juvenile psoriatic arthritis only; these subtypes are not included in the polyarticular cohort and are not

			included in the proposed marketing authorisation of tofacitinib. Body weight and height has been collected at each visit according to schedule of activities in the protocol, however the trial has not been powered to detect difference on this endpoint and no effectiveness analysis has been presented. This is in line with other trials conducted in this patient population and included in previous NICE appraisals.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	Tofacitinib provides similar health benefits at similar cost to biologic DMARDs, as demonstrated by an indirect treatment comparison. Therefore, a cost comparison analysis versus adalimumab and tocilizumab has been carried out. Costs are considered from an NHS and Personal Social Services perspective. A patient access scheme for tofacitinib has been included as part of the analysis.	Tofacitinib provides similar health benefits at similar costs than technologies recommended in published NICE technology appraisal guidance, TA373. As such, a cost-comparison analysis was conducted. The cost comparison compares the drug acquisition and administration costs for tofacitinib versus adalimumab and tocilizumab. Adalimumab and tocilizumab were selected as the most appropriate

	Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	The model considered the costs of adalimumab biosimilars.	comparators given their wide usage in clinical practice.
Subgroups to be considered	If evidence allows, subgroups by JIA category will be considered	JIA category Open-label baseline CRP levels Geographical region Baseline body weight Age	In line with subgroup analyses in Study A3921104
Special considerations including issues related to equity or equality	The availability and cost of biosimilar products should be taken into account.	The model considered the costs of adalimumab biosimilars. Additional benefits of tofacitinib versus the comparators: Patients with fear of needles or needle phobia have significant distress relating to administration of treatment by injection.	Tofacitinib is the first advanced treatment option that is available in oral formulation as tablet or oral solution. Current DMARD treatments for JIA are mainly administered via IV or SC injection or infusion. However, these routes of administration can be painful and may lead to a fear of needles or needle phobia. These are more common among children and adolescents than adults. High levels of injection fear can correlate with worse disease outcomes.

ACR, American College of Rheumatology; CHAQ, Child Health Assessment Questionnaire; CRP, C-reactive protein; DMARD, disease modifying anti-rheumatic drug; ERA, enthesitis related arthritis; HRQoL, health-related quality of life; IV, intravenous; JIA, juvenile idiopathic arthritis; NSAID, non-steroidal anti-inflammatory drug; pcJIA polyarticular course JIA; PsA, psoriatic arthritis; RF, rheumatoid factor; SC, subcutaneous; sJIA, systemic juvenile idiopathic arthritis.

B.1.2 Description of the technology being appraised

Table 2 gives an overview of tofacitinib. The draft SmPC is included in Appendix C; however, at the time of submission, an EPAR was not available.

Table 2 Technology being appraised

UK approved name and brand name	Tofacitinib (Xeljanz®)
Mechanism of action	Tofacitinib is a Janus kinase (JAK) inhibitor. It preferentially inhibits signalling by cytokine receptors that associate with JAK3 and/or JAK1. Inhibition of JAK disrupts signalling pathways that are critical to immune and inflammatory responses.
Marketing authorisation/CE mark status	Tofacitinib does not currently have marketing authorisation for the indication in this submission. A marketing authorisation application was submitted to the European Medicines Agency (EMA) in [redacted]; Committee for Medicinal Products for Human Use (CHMP) positive opinion is anticipated in [redacted]. Tofacitinib is already approved for the treatment of rheumatoid arthritis, psoriatic arthritis and ulcerative colitis in adults.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication is for the treatment of [redacted].
Method of administration and dosage	Tofacitinib is administered twice daily (BID), either as 5 mg tablets or weight-based equivalent oral solution, as shown in Table 3 below. Tofacitinib may be used as monotherapy or in combination with methotrexate.
Additional tests or investigations	Not applicable.
List price and average cost of a course of treatment	5 mg tablets: 1 pack of 56 tablets costs £690.03. At this dose, the annual cost is approximately £8,995. 1 mg/mL solution: a 240 mL bottle costs [redacted]. It would provide 30 days' medication at a dose of 4 mg BID (8 mL/day) and approximately 37 days' medication at a dose of 3.2 mg BID (6.4 mL/day). At this dose, the annual cost is approximately [redacted], respectively.
Patient access scheme (if applicable)	The current patient access scheme for tofacitinib will also apply to the pcJIA indication. The scheme provides a simple discount of [redacted] to the list price.

Table 3 Tofacitinib dosing schedule according to body weight

Body weight (kg)	Dosing regimen
10 to <20	3.2 mg BID (as 3.2 mL oral solution)
20 to <40	4 mg BID (as 4 mL oral solution)
≥40	5 mg BID (as one 5 mg tablet or 5 mL oral solution)

BID, twice-daily
Source: Tofacitinib draft SmPC (5)

Population pharmacokinetic analyses were conducted using data from Phase 1, Phase 3, and long-term extension studies. Based on this analysis, the dosing recommendations used in the trial described in this submission were simplified while still maintaining the same goal of achieving consistent average tofacitinib plasma concentration for all JIA patients (see Section

Key points:

- In Study A3921104, the pcJIA cohort included patients with 5 or more active joints who had extended oligoarthritis, polyarthritis RF-, polyarthritis RF+, or systemic JIA with active arthritis but without active symptoms
- Significantly fewer patients experienced disease flare with tofacitinib than with placebo (29.2% vs 52.9% at Week 44; P = 0.0031)
- Significantly more patients achieved JIA ACR 30, 50 and 70 responses at Week 44 with tofacitinib than with placebo
- Patients treated with tofacitinib had greater reductions in disease activity than those who received placebo, as illustrated by results of CHAQ, JADAS, JIA ACR inactive disease and clinical remission, as well as JIA ACR core set variables outcomes
- In terms of comparative effectiveness, no head-to-head clinical trial was conducted to compare tofacitinib with adalimumab or tocilizumab, therefore an indirect treatment comparison was conducted. The results shown that the risk of disease flare and ACR

Pedi responses with tofacitinib are similar to that of adalimumab and tocilizumab; none of the comparisons were statistically significant

B.3.1 Identification and selection of relevant studies

An SLR was carried out to identify evidence from RCTs on the efficacy and safety of tofacitinib and biological therapies recommended by NICE in TA373 for the treatment of pcJIA. The SLR identified 12 RCTs, 5 of which were relevant to the decision problem of the current appraisal. Only 1 of these was a trial of tofacitinib (57). Of the other RCTs identified, 3 were trials of adalimumab (58-60), and 1 was a trial of tocilizumab (51).

A second SLR was carried out to identify non-RCT evidence on the efficacy and safety of tofacitinib in pcJIA that could be used to supplement evidence from the RCT. No non-RCT evidence was identified.

See Appendix D for full details of the process and methods used in the SLRs.

B.3.2 List of relevant clinical effectiveness evidence

There are no RCTs that compare tofacitinib with other treatments for pcJIA. Evidence for the clinical effectiveness of tofacitinib is available from one placebo-controlled trial, Study A3921104 (Table 7).

Table 7 Clinical effectiveness evidence

Study	Study A3921104 (NCT02592434)	
Study design	Phase 3, randomised, double-blind, placebo-controlled withdrawal study	
Population	Patients aged 2 to <18 years with pcJIA[a], PsA or ERA	
Interventions	Tofacitinib	
Comparators	Placebo	
Indicate if trial supports application for marketing authorisation	Yes	✓
	No	
Rationale for use/non-use in the model	Study A3921104 is the pivotal trial of tofacitinib in pcJIA. It provided data for the application for MA and represents the primary evidence base in this submission.	
Reported outcomes specified in the decision problem	• Disease activity (including occurrence of disease flare, JIA ACR 30/50/70 response rates, JADAS, JIA ACR inactive disease/clinical remission) • Physical function • HRQoL (CHQ and CHAQ) • Adverse events • Mortality • Pain (JIA ACR and CHAQ)	
All other reported outcomes	N/A	

[a]pcJIA included extended oligoarthritis, polyarthritis RF+, polyarthritis RF- and systemic JIA with active arthritis but without active symptoms. ACR, American College of Rheumatology; CHAQ, Child Health Assessment Questionnaire; CHQ, Child Health Questionnaire; ERA, enthesitis-related arthritis; HRQoL, health-related quality of life; JADAS, Juvenile Arthritis Disease Activity Scale; JIA, juvenile idiopathic arthritis; MAA, marketing authorization application; pcJIA, polyarticular course JIA; PsA, psoriatic arthritis; RF, rheumatoid factor
Source: Study A3921104 clinical study report (61)

Efficacy and safety data from Study A3921104 have been presented at the 2019 American College of Rheumatology/Association of Rheumatology Professionals Annual Meeting (57) and at the 2020 European League Against Rheumatism (EULAR) Congress (62). Data included in this submission are taken from these two abstracts, the clinical study report (61) and the EMA assessment report on Study A3921104 (63).

B.3.3).

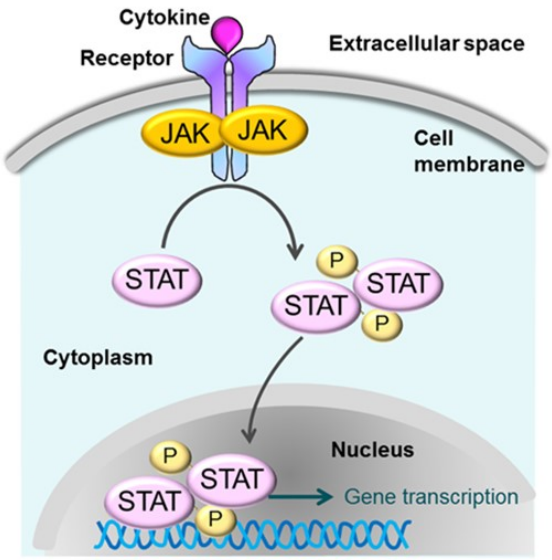
Note that patients weighing ≥40 kg treated with tofacitinib oral solution may be switched to tofacitinib tablets. Patients weighing <40 kg cannot be switched from the oral solution to the tablets.

For simplicity, the tofacitinib dose will be referred to as 5 mg BID throughout this submission.

B.1.2.1 Tofacitinib's mode of action

The pathogenesis of JIA is driven by pro-inflammatory cytokines and chemokines activating immune cells, which infiltrate the joint synovium, causing inflammation and tissue damage. Many of these cytokines utilise the JAK-signal transducer and activator of transcription (STAT) pathway to induce the intracellular signalling cascade that leads to the inflammatory response. JAKs are non-receptor protein tyrosine kinases that associate with cytokine receptors. There are four members of the JAK family: JAK1, JAK2, JAK 3 and TYK2; each JAK has specificity for a different set of cytokine receptors and each cytokine receptor needs at least two associated JAKs in order to signal (6). Consequently, different combinations of JAKs are associated with different cytokine receptors. Binding of the cytokine to its receptor activates JAK, which then phosphorylates the cytokine receptor to allow binding of STATs. The STATs are phosphorylated by JAK and released into the cytoplasm, where they form dimers and translocate to the cell nucleus. Here, STATs activate gene expression, leading to further cytokine production and therefore further immune cell activation (6, 7) (**Error! Reference source not found.**).

Figure 1 The JAK-STAT signalling pathway



Cytokine binding to its cell surface receptor leads to receptor polymerisation and autophosphorylation of associated JAKs

Activated JAKs phosphorylate the receptors that dock STATs

Activated JAKs phosphorylate STATs, which dimerise and move to the nucleus to activate new gene transcription

JAK, Janus kinase; P, phosphate group; STAT, signal transducer and activation of transcription

Tofacitinib preferentially inhibits signalling by cytokine receptors that associate with JAK3 and/or JAK1 (6). The pairing of JAK3 with JAK1 is associated with cytokines that signal through the gamma common chain-containing receptor, including IL-2, -4, -7, -9, -15, and -21. These cytokines are integral to lymphocyte activation, proliferation, and function. Other pairs containing JAK1 are associated with additional pro-inflammatory cytokines, including IL-6 and interferon-ɣ.

By targeting the JAK/STAT pathway, tofacitinib can modulate the response to multiple cytokines, which results in modulation of the immune and inflammatory response.

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

Key points

- JIA is an arthritis of unknown cause that begins before the age of 16 years and persists for 6 or more weeks. It is characterised by inflammation of the affected joint, which causes pain, swelling, joint stiffness and limited movement. If untreated, this inflammation causes progressive erosive arthritis, which can lead to disability and growth disorders.
- Treatment of polyarticular course JIA may consist of corticosteroids, followed by methotrexate. Patients with active disease whose symptoms do not respond to or who are intolerant to methotrexate are treated with parenteral biological DMARD as per NICE guidance TA373 (abatacept, adalimumab, etanercept or tocilizumab)
- Parenteral administration is associated with pain, injection site reactions and may lead to needle phobia
- Up to 50% of patients do not respond to their first biologic and are switched to another biologic DMARD, therefore patients, carers and clinicians would value an alternative treatment option
- It is intended that tofacitinib will be used as an alternative to biologics in both biologic-naïve and biologic-experienced patients
- Tofacitinib is a small molecule that inhibits JAK and downregulates production of pro-inflammatory cytokines, therefore it offers an alternative mode of action compared to the currently available biologic DMARDs
- Tofacitinib is orally administered (as a liquid or tablet) and as the first oral advanced treatment option, tofacitinib has the potential to improve treatment convenience and quality of life of patients and carers, especially those affected by needle fear or phobia

- Tofacitinib, as an oral treatment also allows reducing the number of in-person clinic visits and increase remote/virtual patient management, which has been a trend in the NHS as a result of the current pandemic

B.1.3.1 Disease overview

JIA is an arthritis of unknown cause that begins before the age of 16 years and persists for 6 or more weeks (8). It is characterised by inflammation of the synovial membrane of the affected joint, which causes pain, swelling, joint stiffness and limited movement. If untreated, this inflammation causes progressive erosive arthritis, which can lead to disability and growth disorders (9).

For many children with JIA, the condition resolves before adulthood (10). However, at least one-third of patients will still require treatment as adults (11) and therefore face the possibility of ongoing disease activity, medication-associated morbidity, life-long disability, and emotional and social dysfunction (12).

Complications of JIA include skeletal abnormalities, foot problems, amyloidosis and osteoporosis (12, 13). Uveitis (inflammation of the middle layer of the eye) is a serious complication that can lead to cataracts, glaucoma and blindness (13, 14). JIA therefore places a substantial burden on patients as well as on their carers and family (12, 15-21).

The International League of Associations for Rheumatology (ILAR) classifies JIA into seven subtypes (**Error! Reference source not found.**).

Table 4 ILAR classification of JIA subtypes

Subtype	Definition
Oligoarthritis	Arthritis in 1 to 4 joints during the first 6 months. Two subcategories: • Persistent: no more than 4 joints affected throughout the disease course • Extended: affects more than 4 joints after the first 6 months
Polyarthritis RF-	Arthritis in ≥5 joints during the first 6 months Negative test for RF
Polyarthritis RF+	Arthritis in ≥5 joints during the first 6 months 2 positive tests for RF during the first 6 months (tests should be at least 3 months apart)
Systemic JIA	Arthritis in ≥1 joint with or preceded by Fever for ≥2 weeks that occurs daily for ≥3 days and accompanied by ≥1 of the following: evanescent erythematous rash, generalized lymph node enlargement, hepatomegaly/splenomegaly, serositis
Psoriatic arthritis (PsA)	Arthritis and psoriasis or Arthritis and ≥2 of the following: dactylitis; nail pitting or onycholysis; psoriasis in a first-degree relative
Enthesitis-related arthritis (ERA)	Arthritis and enthesitis or Arthritis or enthesitis with ≥2 of the following: history/presence of sacroiliac joint tenderness and/or inflammatory lumbosacral pain; presence of HLA-B27 antigen; onset of arthritis in a male over 6 years old; acute (symptomatic) anterior uveitis; history of ankylosing spondylitis, ERA, sacroiliitis with IBD, Reiter's syndrome, or acute anterior uveitis in a first-degree relative
Undifferentiated	Arthritis that does not fit into any of the above categories, or has features of more than one subtype

ERA, enthesitis-related arthritis; IBD, inflammatory bowel disease; ILAR, International League of Associations for Rheumatology; JIA, juvenile idiopathic arthritis; psoriatic arthritis, PSA; RF, rheumatoid factor
Source: Petty et al, 2004 (8)

Polyarticular course JIA (pcJIA) can include any subtype of JIA with 5 or more active joints at 6 months or more after diagnosis (22). Patients with pcJIA tend to have a

more refractory course than those with fewer involved joints; this puts them at increased risk of joint damage with poorer functional outcomes and decreased quality of life (23).

The pcJIA subgroup can include patients with extended oligoarthritis, polyarthritis rheumatoid factor (RF) negative, polyarthritis RF positive, and systemic JIA with active arthritis but without active symptoms. This population is the focus of the submission.

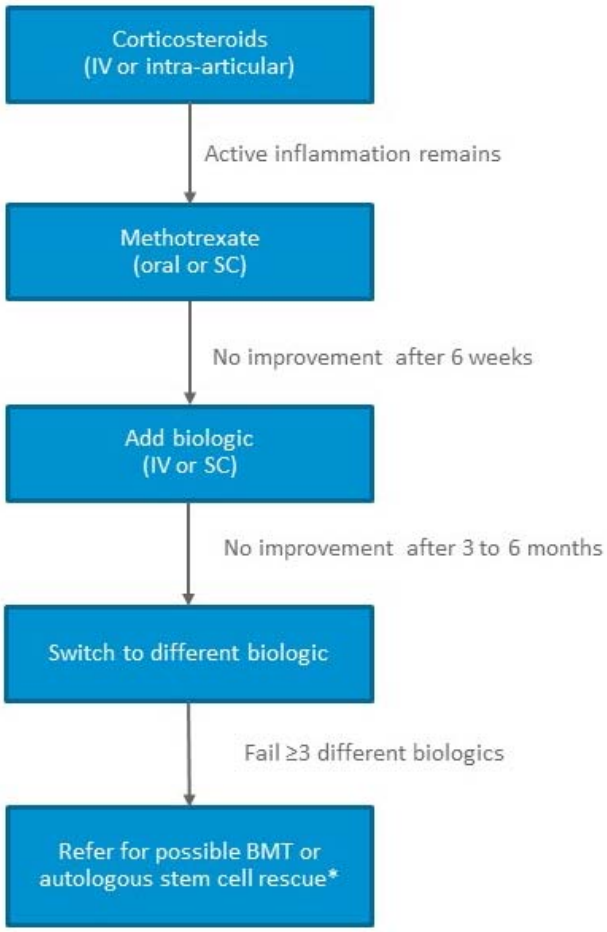
B.1.3.2 Epidemiology

JIA is the most common chronic rheumatic disease in children. Its estimated annual incidence in the UK is 1 in 10,000 (24); this equates to 1,200 cases per year in England and 63 cases/year in Wales (based on mid-2019 population estimates (25)). Its estimated annual prevalence in the UK is 1 in 1,000 (24); this equates to 12,000 children overall in England and 630 in Wales with JIA. Overall, JIA is more common in girls than in boys (23, 26).

B.1.3.3 Current treatment pathway

Error! Reference source not found. shows the current treatment pathway for JIA in the UK.

Figure 2 Current UK treatment pathway for JIA



*Not a relevant treatment option in pcJIA. BMT, bone marrow transplant; IV, intravenous; SC subcutaneous

Following diagnosis, patients are first given steroids. If active inflammation remains, methotrexate is used; this can be oral or SC, although SC is advised before escalation to biologic treatment. If there is no improvement in symptoms with methotrexate treatment, a biologic disease-modifying anti-rheumatic drug (bDMARD; either adalimumab, etanercept, tocilizumab or abatacept) is added. Patients who have not responded to treatment after 3-6 months are then switched to a different biologic. If patients have still not responded after trying at least three different biologics, they may be referred for bone marrow transplant or autologous stem cell rescue, although this is rare in polyarticular course JIA.

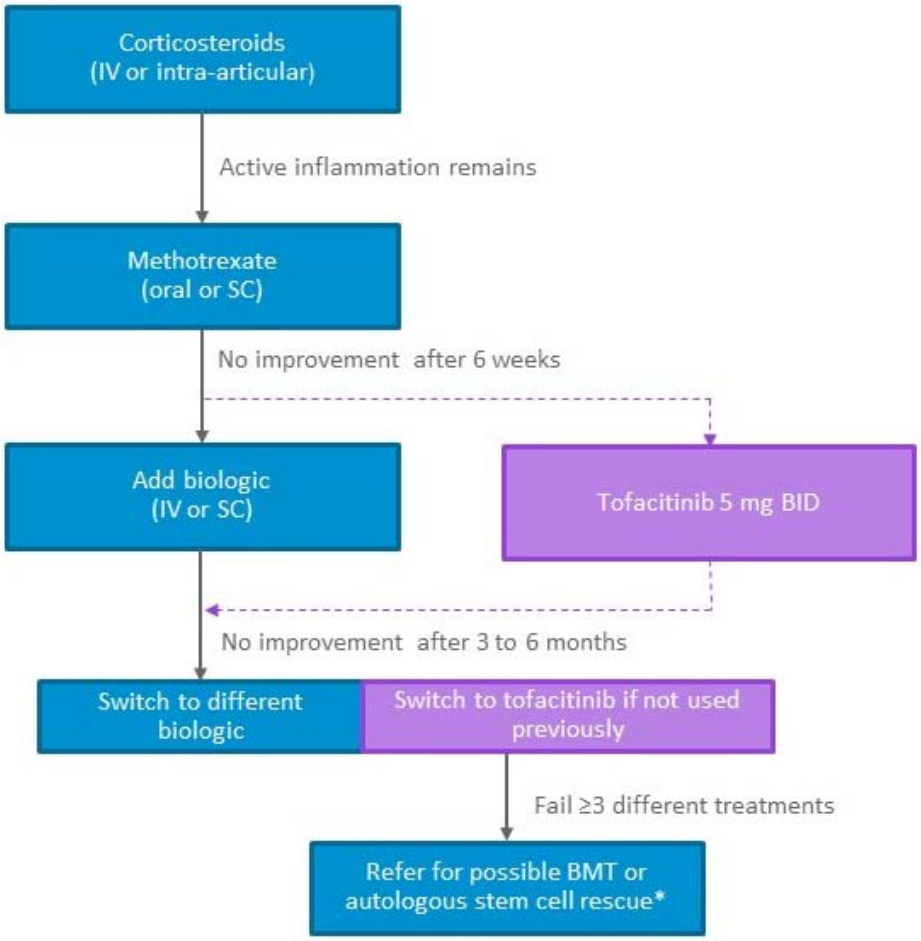
Currently approved biologic DMARDs for JIA belong to different drug classes: etanercept and adalimumab are TNF inhibitors, abatacept is a T-cell co-stimulatory modulator and tocilizumab is an IL-6 inhibitor. The best choice of biologic to use after failure of the first biologic remains unclear (2).

Clinical experts consulted during the development of NICE guidance TA373 stated that they consider the available biologics to be similar in terms of effectiveness and that their choice of biologic takes into account patient preference, patient characteristics and previous treatments (4).

B.1.3.4 Proposed place for tofacitinib in the treatment pathway

Error! Reference source not found. shows the clinical pathway of care for JIA and the proposed position of tofacitinib in the JIA treatment pathway. It is anticipated that tofacitinib will be used at the same place as currently recommended biologic DMARDs. It will be applicable both to biologic-naïve and biologic-experienced patients (i.e. it could be used immediately after failure of methotrexate, or after failure of a biologic DMARD).

Figure 3 Proposed position of tofacitinib in the JIA treatment pathway



*Not a relevant treatment option in pcJIA. BID, twice-daily; BMT, bone marrow transplant; IV, intravenous; SC, subcutaneous

B.1.3.5 Burden of disease

Patient burden

The symptoms and complications of JIA place a substantial physical burden on patients. Patients with JIA have decreased functional ability due to the inflammation in the joints. In a longitudinal analysis, Magni-Manzoni et al. found that younger age at disease onset and a greater number of affected joints are the main determinants of poor functional ability and that children with these features are more likely to develop a long-term physical disability (27).

Children with JIA are less physically active than their healthy counterparts and become tired more quickly during physical exertion (9, 28). In order to participate in

physical activity, patients need to plan time for pain management therapy before and after the activity (21).

Stiffening and deformation of affected joints can lead to growth retardation (9). Between 10% and 40% of patients have severely reduced stature, which is most often caused by decreased growth in the legs, rather than the spine (9). In addition to disease-related factors, long-term use of corticosteroids is also known to affect growth. Puberty may also be delayed in patients with JIA (9).

Sleep is disrupted in JIA, with patients reporting significantly more night awakenings, parasomnia, sleep anxiety, sleep-disordered breathing, early morning awakening and daytime sleepiness than healthy children (29). Sleep disturbances and fatigue are associated with increased pain and decreased health-related quality of life (HRQoL) (30).

In addition to the physical burden, JIA has a significant psychological burden, with patients reporting social isolation, depression/anxiety and low self-esteem (12). Data from the Childhood Arthritis Prospective Study revealed that 15% of adolescent JIA patients (aged 11 to 16 years) in the UK had significant depressive symptoms at their first visit to a rheumatologist (31). Patients with polyarthritis had a greater level of depression than those with oligoarthritis or ERA. Depression at the first visit to a rheumatologist was associated with number of active joints, pain and disability; the association between depressive symptoms and both pain and disability continued for at least one year. In other words, depressive symptoms at baseline can predict future disability and pain (31). In a Bangladeshi study, the incidence of psychiatric disorders was found to be significantly higher among JIA patients aged 10 to 18 years than among matched healthy controls (35% vs 12.5%; $P<0.001$) (32). Those JIA patients with psychiatric disorders had difficulties with learning, peer relationships and leisure activities (32). Interviews with Swedish JIA patients revealed that they feel frustrated because their peers do not always believe them when they say they are in pain and accuse them of lying to get out of an activity. This contributes to both physical and social isolation (18).

A systematic review by Tong et al. found that JIA affects patients' sense of normality – they feel they are different from others because of the unpredictable episodes of

pain, disability and a reliance on others to help with everyday tasks (21). Patients often keep their diagnosis a secret from others to avoid rejection, and many feel that others trivialise their condition. Their emotions can swing between hope and despair, depending on the severity of symptoms at any given time.

Treatment of JIA is complex, involving a combination of physical therapy and ongoing medication. Patients require frequent monitoring of their physical development and regular screening for uveitis. Methotrexate and biologics are associated with long-term safety concerns and have a number of monitoring requirements, including regular full blood counts, lipid levels, liver function tests, blood glucose measurements and blood pressure and heart monitoring (33, 34). Between 7% and 28% of patients need joint replacements (4). Children who have joint replacements are likely to need multiple revisions over the course of their lives (4).

Both children and adolescents with JIA have a significantly lower HRQoL in most domains compared with healthy controls or children with other chronic conditions, such as asthma, congenital defects, skin disease and migraine (19). Functional ability, pain, subjective burden of medication use, disease duration, school absence, social isolation and depression/anxiety are important predictors of HRQoL in JIA patients (15, 19, 20).

Caregiver burden

JIA has a substantial emotional, financial and logistical burden on parents and caregivers. They often have to take time off work to care for the patient and take them to appointments (this includes both scheduled consultations and emergency visits during disease flare or infection) (12). A US-based study identified that parents having a child with JIA missed on average 281.81 hours of work, versus 183.36 hours of work missed by other parents. Parents having a child with JIA were 2.78 times more likely to miss work than those having no children with JIA (35).

A UK study by Angelis et al. found that HRQoL is reduced in caregivers of patients with JIA: mean EQ-5D index scores were 0.66 for caregivers, compared with 0.91 for the age-adjusted general population (16).

Bruns et al. investigated HRQoL and disease burden in primary caregivers of 70 Brazilian JIA patients (17). They reported that 34.3% of caregivers had psycho emotional disorders (anxiety/depression), as measured by the psychiatric screening questionnaire (SRQ-20). Caregivers' HRQoL appeared to be influenced more by the emotional aspects of the disease, rather than by the physical aspects. A study conducted in Mexico, assessing the impact of JIA on caregivers, with the involvement of 32 primary caregivers also revealed that the majority of caregivers reports depression (90%), feel sadness at diagnosis (56%), mentioned that JIA has influenced in their financial situation (63%), feel anxiety about the future (72%), and considered that their family relationships have changed (37%) (36).

Fear of needles

Current DMARD treatments for JIA are mainly administered via intravenous (IV) or subcutaneous (SC) injection or infusion. However, these routes of administration can be painful and may lead to a fear of needles or needle phobia (37, 38). Both needle fear and needle phobia cause anxiety and distress (for both the patient and the carer) (38, 39); this is more extreme in needle phobia and can result in changes in blood pressure that cause the patient to faint (39). Fear of pain and needle fear are barriers to adherence to injectable medication adherence (40). In other chronic diseases, high levels of injection fear correlate with worse disease outcomes (40). Fear of needles and needle phobia are more common among children and adolescents than adults (38). More than one-third of children and young people with JIA (average age 9 years) who received SC methotrexate were reported by their parents to 'often' or 'almost always' feel a fear of injections and/or blood tests (41). Another study revealed that the prevalence of needle fear can be as high as 64% in patients with JIA, which is much higher than in paediatric patients with type-1 diabetes (between 23% to 37%).

Fear of needles and needle phobia means that a proportion of patients requires community nurse assistance with administering SC injection. Based on clinical expert advice between a third and half of JIA patients may require assistance from community nurses or attend hospital for treatment due to fear of needles. In the cost-minimisation analysis 25% was assumed, based on Mulligan et al. 2013.This does

not only mean extra cost-implications to the NHS, but also means distress to patients. This is also illustrated by the trend that the need for clinical psychologists was increasing amongst patients with JIA (3).

Treatment failure/treatment switching

NHS England reports that only 30% to 50% of patients have a complete remission with methotrexate (42), despite its place as the first-line DMARD for pcJIA for more than three decades. This means that a proportion of patients need to escalate onto biologic treatment. Patients who fail on one biologic (because of lack of efficacy or intolerable adverse events [AEs]) are switched to another and this can happen multiple times. An analysis of UK data showed that more than one-fifth of children and young people (aged <16 years) with JIA who started biologic DMARD treatment went onto receive a second biologic, and 5% received at least three biologics (2). Based on discontinuation rates in randomised clinical trials (RCTs), it is estimated that between 4.3% and 10% of patients discontinue biologics every 3 months (11).

Immunogenicity

Studies in adult patients with chronic inflammatory diseases have shown that biologic therapies (which are large proteins) are associated with production of anti-drug antibodies that can cause primary non-response, reduce efficacy over time and cause hypersensitivity (43-45). A systematic review and meta-analysis by Doeleman et al. examined the immunogenicity of nine biologics in JIA, including adalimumab, tocilizumab, abatacept and etanercept (46). Tofacitinib was not part of the analysis. The results showed that overall, approximately 17% of JIA patients treated with biologics developed anti-drug antibodies, although this percentage varied considerably across the biologics. The pooled prevalence of anti-drug antibodies was 21.5% for adalimumab, 10% for abatacept, 8.5% for etanercept and 2% for tocilizumab. Antibodies to adalimumab and tocilizumab were associated with treatment failure and/or hypersensitivity reactions.

As a small molecule, tofacitinib is also unlikely to be associated with immunogenicity.

Unmet need

The limitations described above illustrate that there is a high unmet need for JIA treatments with alternative modes of administration and mode of action.

Tofacitinib is the first JAK inhibitor to become available for patients with pcJIA, but it has already been used in routine NHS practice and approved by NICE to treat adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ulcerative colitis. As a JAK inhibitor it offers an alternative mode of action to patients and it modulates multiple inflammatory cytokines. In contrast, the current biologic treatment options each target a single cytokine or receptor (see below). Inhibition of cytokines results in modulation of the immune and inflammatory response.

Unlike current biologic therapies, tofacitinib is administered orally, thus avoiding painful injections, injection site reactions and issues such as needle fear/phobia. As it is available as both a tablet and an oral grape flavoured solution for younger children, tofacitinib can be administered by the carer, or where appropriate the patient themselves, which is more convenient for both patients and carers. Also, during the current pandemic and with the trend of minimising in-person clinic visits and increased remote/virtual patient management, NICE has advised that patients on IV treatments should switch to the same treatment in SC form if possible (47). If not possible, then rheumatologists should consider switching patients to a different treatment that is available as an SC injection. As tofacitinib is taken orally this would be a convenient treatment option for patients as well as for the NHS under these circumstances.

B.1.4 Equality considerations

Pfizer does not expect that use of tofacitinib to treat pcJIA will raise any equality issues.

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

The relevant NICE guidance for polyarticular course JIA is TA373 Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis (4). A multiple technology appraisal that assessed the clinical and cost effectiveness of 4 biologic DMARDs for treating juvenile idiopathic arthritis. NICE TA373 recommends the use of abatacept, adalimumab, etanercept and tocilizumab, within their marketing authorisations, for all indications listed in the final scope issued by NICE. That is:

- Polyarticular JIA, including polyarticular-onset juvenile idiopathic arthritis (JIA), polyarticular-course JIA and extended oligoarthritis (all 4 technologies);
- enthesitis-related JIA (etanercept and adalimumab);
- psoriatic JIA (etanercept).

The relevant population for the current appraisal is polyarticular JIA, where the Committee concluded that the cost-effectiveness of the technologies was likely to be better in clinical practice than had been modelled because numerous potential benefits of these technologies had not been modelled because of data limitations. These were treating uveitis, preventing long-term joint damage, avoiding surgery, and minimising the adverse effects of corticosteroids; however, it was not possible to estimate the extent of these potential benefits.

The clinical outcomes considered in TA373 are summarised in Table 5. The key outcome used in the economic model for measuring clinical effectiveness of biologic DMARDs was risk of disease flare (4). Discontinuation rates and disease remission was also included in the model (48-51) (52). The Committee considered that including disease flare in the model was appropriate, but it did not capture all the potential benefits of biological treatment, for example, treatment response. The Committee suggested that treatment response, measured by ACR Pedi criteria (also referred to as JIA ACR response), a secondary endpoint collected in the trials should also have been included in the modelling. However, the Committee concluded that there was no evidence to suggest that abatacept, adalimumab, etanercept and

tocilizumab were different from each other in terms of clinical effectiveness in treating polyarticular JIA.

There was uncertainty considering the utility values used in the model because of limited data available. The clinical trials did not collect data that could be used to derive utility values, therefore, the Assessment Group used utility values from a study by Prince et al. 2011(53). Prince et al. evaluated costs and effects of etanercept in patients with JIA in a Dutch cohort. It presented utility information collected by the HUI-3 questionnaire. Although the committee considered there were uncertainties associated with using these values, after discussing it with clinical experts it concluded that they provided plausible results and were appropriate to use.

The committee also discussed the inclusion of caregiver disutility in the model and considered it appropriate to include it in the base case analysis. However, it was unclear what exact value should be used as there we no data available from patients with JIA and their caregivers and the AG tested two values, one from carers of children with impaired mobility and one for carers of adults with multiple sclerosis.

Table 5 Clinical outcomes and measures appraised in TA373

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER	Committee's preferred assumptions	Uncertainties
Disease flare	Worsening of at least 30% in three or more of the six core criteria for JIA, and an improvement of 30% or more in no more than one of the criteria.	Yes	A higher rate of disease flare leads to lower QALY gains; therefore, it increases the ICER.	The Committee considered that including disease flare in the model was appropriate, but that it did not reflect all benefits of biological treatments.	The Committee considered that the effect of the 4 technologies on controlling disease activity and duration (including flare, response and remission) was an important benefit, but that the Assessment Group's model did not fully capture this. The additional possible clinical benefits of the technologies were expected to reduce the ICERs had they been included. Although it was not possible to quantify the exact impact of these factors, it was considered likely that they would bring the ICERs into a range considered a cost-effective use of NHS resources if the innovative nature of the technologies was also taken into account.
Treatment response	ACR Pedi response	No	NA	NA	The Committee considered that including disease flare in the model was appropriate, but it did not capture all the potential benefits of biological treatment, for example, treatment response. The Committee suggested that treatment response (ACR Pedi response) should also have been included in the modelling.
Utility value	Values from Prince et al. Baseline: 0.53 Treatment with 1st line biologic 0-3 months: 0.53 3-15 months: 0.69 15-27 months: 0.74 27+ months: 0.78 Treatment with 2nd line biologic: 0.74 Disutility for disease flare: 0.03	Yes	Negligible	The committee accepted these utility values	The Committee discussed the inclusion of a flare disutility in the model. It considered there was a risk of double counting as some people in Prince et al. may have had disease flares. Therefore, it considered that there was uncertainty around whether flares may have been considered twice by using utility values from Prince et al. and applying a separate disutility for disease flare

Caregiver disutility	The AG tested two values (one for carers of children with impaired mobility, and one for carers of adults with multiple sclerosis)	Only in scenario analysis	NA	Committee would have preferred caregiver disutility to be used in the base case analysis	The Committee considered it was appropriate to include a disutility for caregivers of people with JIA, but was unclear which value to use.

Abbreviations: AG; Assessment Group; ICER; incremental cost-effectiveness ratio, JIA, juvenile idiopathic arthritis; NA; not applicable, QALY; quality-adjusted life year, TA; technology appraisal.

B.2.2 Resource use assumptions

The evidence on resource use in TA373 (4) was informed by a UK study, which examined the resource use and patient costs during the first year after diagnosis for patients with JIA (54) summarised in Table 6. The resources and associated costs included were divided into treatment costs, monitoring costs, and adverse event costs. Resource use was the same across all technologies and the only differentiating factor was the cost of each technology.

Table 6 Resource use and unit costs of routine management in the TA373

Resource parameters	Resource use per year	Source to identify unit cost
GP visit	10	Personal Social Services Research Unit (55)
Hospital appointments		
Rheumatology paediatriConsultant (number of visits)	5.58	NHS Reference Costs(56)
Ophthalmologist	2.69	NHS Reference Vosts(56)
Specialist nurse	7.00	Personal Social Services Research Unit(55)
Physiotherapist	4.00	Personal Social Services Research Unit(55)
Occupational therapist	0.65	Personal Social Services Research Unit(55)
Podiatry	0.61	NHS Reference Costs(56)
Hospital test		
Blood tests (a)	1	Thornton et al. (inflated)(54)
Clinical imaging (b)	1	Thornton et al. (inflated)(54)
Disease flare		
Inpatient treatment per disease flare	As modelled	NHS Reference Costs(56)

Abbreviations: GP, General practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit

(a) For example, full blood count, C-reactive protein, urea and electrolytes, liver function test

(b) MRI scan, Dual-energy X-ray absorptiometry (DEXA) scan, ultrasound, X-ray

The systematic literature review (SLR) conducted as part of the current submission (see section G.1.2 for more detail) found no new studies that reported on resource use estimations for JIA. Thornton et al. 2008(54) was still the most relevant study for resource use assumptions, which assumed the same resource use across all biological therapies.

Therefore, in the cost-comparison analysis of tofacitinib versus adalimumab and tocilizumab, the only cost items considered relevant for the comparison were acquisition cost and administration costs as these would have been the only differentiating costs amongst the biological treatments.

B.3 Clinical effectiveness

Key points:

- In Study A3921104, the pcJIA cohort included patients with 5 or more active joints who had extended oligoarthritis, polyarthritis RF-, polyarthritis RF+, or systemic JIA with active arthritis but without active symptoms
- Significantly fewer patients experienced disease flare with tofacitinib than with placebo (29.2% vs 52.9% at Week 44; P = 0.0031)
- Significantly more patients achieved JIA ACR 30, 50 and 70 responses at Week 44 with tofacitinib than with placebo
- Patients treated with tofacitinib had greater reductions in disease activity than those who received placebo, as illustrated by results of CHAQ, JADAS, JIA ACR inactive disease and clinical remission, as well as JIA ACR core set variables outcomes
- In terms of comparative effectiveness, no head-to-head clinical trial was conducted to compare tofacitinib with adalimumab or tocilizumab, therefore an indirect treatment comparison was conducted. The results shown that the risk of disease flare and ACR Pedi responses with tofacitinib are similar to that of adalimumab and tocilizumab; none of the comparisons were statistically significant

B.3.1 Identification and selection of relevant studies

An SLR was carried out to identify evidence from RCTs on the efficacy and safety of tofacitinib and biological therapies recommended by NICE in TA373 for the treatment of pcJIA. The SLR identified 12 RCTs, 5 of which were relevant to the decision problem of the current appraisal. Only 1 of these was a trial of tofacitinib (57). Of the other RCTs identified, 3 were trials of adalimumab (58-60), and 1 was a trial of tocilizumab (51).

A second SLR was carried out to identify non-RCT evidence on the efficacy and safety of tofacitinib in pcJIA that could be used to supplement evidence from the RCT. No non-RCT evidence was identified.

See Appendix D for full details of the process and methods used in the SLRs.

B.3.2 List of relevant clinical effectiveness evidence

There are no RCTs that compare tofacitinib with other treatments for pcJIA. Evidence for the clinical effectiveness of tofacitinib is available from one placebo-controlled trial, Study A3921104 (Table 7).

Table 7 Clinical effectiveness evidence

Study	Study A3921104 (NCT02592434)	
Study design	Phase 3, randomised, double-blind, placebo-controlled withdrawal study	
Population	Patients aged 2 to <18 years with pcJIA[a], PsA or ERA	
Interventions	Tofacitinib	
Comparators	Placebo	
Indicate if trial supports application for marketing authorisation	Yes	✓
	No	
Rationale for use/non-use in the model	Study A3921104 is the pivotal trial of tofacitinib in pcJIA. It provided data for the application for MA and represents the primary evidence base in this submission.	
Reported outcomes specified in the decision problem	• Disease activity (including occurrence of disease flare, JIA ACR 30/50/70 response rates, JADAS, JIA ACR inactive disease/clinical remission) • Physical function • HRQoL (CHQ and CHAQ) • Adverse events • Mortality • Pain (JIA ACR and CHAQ)	
All other reported outcomes	N/A	

[a]pcJIA included extended oligoarthritis, polyarthritis RF+, polyarthritis RF- and systemic JIA with active arthritis but without active symptoms. ACR, American College of Rheumatology; CHAQ, Child Health Assessment Questionnaire; CHQ, Child Health Questionnaire; ERA, enthesitis-related arthritis; HRQoL, health-related quality of life; JADAS, Juvenile Arthritis Disease Activity Scale; JIA, juvenile idiopathic arthritis; MAA, marketing authorization application; pcJIA, polyarticular course JIA; PsA,

psoriatic arthritis; RF, rheumatoid factor
Source: Study A3921104 clinical study report (61)

Efficacy and safety data from Study A3921104 have been presented at the 2019 American College of Rheumatology/Association of Rheumatology Professionals Annual Meeting (57) and at the 2020 European League Against Rheumatism (EULAR) Congress (62). Data included in this submission are taken from these two abstracts, the clinical study report (61) and the EMA assessment report on Study A3921104 (63).

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

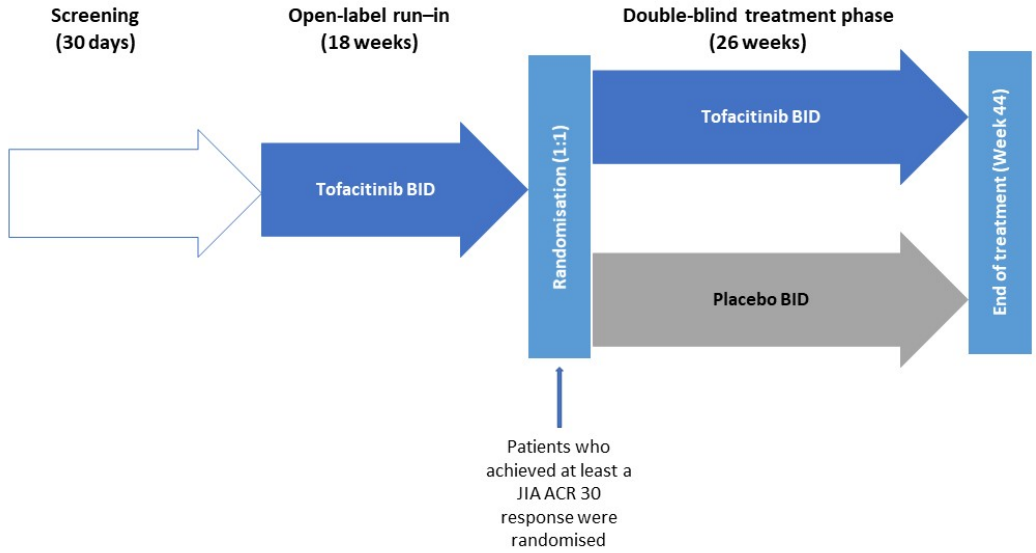
B.3.3.1 Trial design

Study A3921104 was a randomised withdrawal, double-blind, placebo controlled, 44-week study to assess the efficacy, safety and tolerability of tofacitinib in paediatric patients with JIA. Figure 4 shows the study design. After screening, patients entered an 18-week open-label run-in phase, during which they received tofacitinib. At the end of the run-in phase, patients who achieved a JIA American College of Rheumatology (ACR) 30 response were randomised 1:1 to treatment with either tofacitinib or placebo and entered the 26-week double-blind phase. Patients who did not achieve a JIA ACR30 response at the end of run-in were discontinued from the study.

For patients with polyarticular course JIA (pcJIA; defined as extended oligoarticular JIA, polyarthritis RF+, polyarthritis RF-, or systemic JIA with active arthritis but without active symptoms), randomisation was stratified by JIA category and baseline

CRP (normal, above normal). A small cohort of patients with PsA or ERA were also recruited to the study, randomisation was stratified by JIA category.

Figure 4 Study design: A3921104



ACR, American College of Rheumatology; BID, twice-daily; JIA, juvenile idiopathic arthritis
Source: Study A3921104 clinical study report (61)

All patients, including those who discontinued from the study, had the option of continuing treatment with tofacitinib by enrolling in a long-term open-label extension study (Study A3921145). This study is ongoing (64).

B.3.3.2 Eligibility criteria

The key inclusion and exclusion criteria for Study A3921104 are shown in Table 8.

Table 8 Inclusion and exclusion criteria: Study A3921104

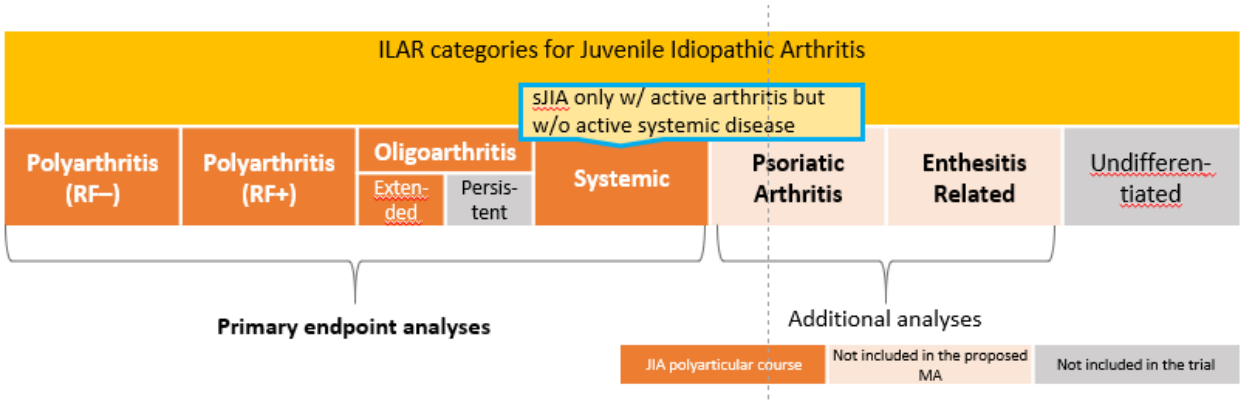
Key inclusion criteria	Key exclusion criteria
• Age 2 to <18 years • Active disease for ≥6 weeks before screening; meets ILAR classification for 1 of the following categories: o Extended oligoarthritis[a] o Polyarthritis RF+ or RF-[a] o Systemic JIA with active arthritis but without active systemic features in the last 6 months[a] o PsA[b]	• Previous tofacitinib treatment • Systemic JIA with any active systemic features other than active joints and elevated acute phase reactants in the last 6 months • Persistent oligoarthritis or undifferentiated JIA • Infections: o Chronic infection o Infection requiring hospitalization, parenteral antimicrobial therapy, or

Key inclusion criteria	Key exclusion criteria
o ERA[b] • Inadequate response or intolerance to: o ≥1 prior DMARD (extended oligoarthritis, polyarthritis, systemic JIA) o NSAIDs (PsA, ERA) • No evidence or history of untreated or inadequately treated active or latent TB infection	judged to be opportunistic in the last 6 months o Treated infections in the last two weeks o HIV, hepatitis B or hepatitis C o History of infected joint prosthesis with prosthesis still in situ • History of recurrent or disseminated herpes zoster or disseminated herpes simplex • Active uveitis in the last 3 months • Blood dyscrasias • History of other rheumatologic disease (except Sjogren's syndrome) • History of or current symptoms of lymphoproliferative disorders • Vaccination in the 6 weeks before the first dose of study medication, or expected vaccination during treatment or in the 6 weeks after discontinuation of study medication • No documented evidence of the varicella vaccine (in countries where this is approved and standard of care) or no evidence of prior exposure to varicella zoster • Failure of >3 prior biologic therapies • First-degree relative with a hereditary immunodeficiency (except IgA deficiency)

[a]Minimum of 5 active joints at screening and baseline; [b]Minimum of 3 active joints at screening and baseline. DMARD, disease-modifying anti-rheumatic drug; ERA, enthesitis-related arthritis; HIV, human immunodeficiency virus; ILAR, International League of Associations for Rheumatology; JIA, juvenile idiopathic arthritis; NSAIDs, non-steroidal anti-inflammatory drugs; PsA, psoriatic arthritis; RF, rheumatoid factor; TB, tuberculosis
Source: Study A3921104 clinical study report (61)

The pcJIA cohort (Figure 5) is the focus of this submission, [redacted]. The study also included patients with ERA and PsA; however, these subgroups [redacted] and were not included in the predefined cohort for the primary endpoint. Efficacy data from patients with ERA and PsA are not presented in this submission; however, these patients are included in the safety analyses.

Figure 5 ILAR categories for JIA in Study A3921104



ILAR, International League of Associations for Rheumatology; MA, marketing authorisation; RF, rheumatoid factor; sJIA, systemic juvenile idiopathic arthritis

B.3.3.3 Study sites

The study was carried out at 103 centres in 14 countries (including the UK).

B.3.3.4 Trial drugs and concomitant medications

In the open-label run-in, patients received tofacitinib twice-daily (BID) for 18 weeks. In the double-blind phase, they received either tofacitinib or placebo twice-daily for up to 26 weeks. Tofacitinib was dosed according to weight (Table 9). For patients weighing <40 kg, the recommended doses matched the predicted steady state concentration of tofacitinib after a 5 mg BID dose in patients weighing ≥40 kg. As highlighted in Section B.1.2, the tofacitinib dose is referred to as 5 mg BID.

Table 9 Tofacitinib dosing schedule according to body weight (Study A3921104)

Body weight (kg)	Dosing regimen
5 to <7	2 mg BID (as oral solution)
7 to <10	2.5 mg BID (as oral solution)
10 to <15	3 mg BID (as oral solution)
15 to <25	3.5 mg BID (as oral solution)
25 to <40	4 mg BID (as oral solution)
≥40	5 mg BID (as tablet or oral solution)

Source: Study A3921104 clinical study report (61)

Patients could continue treatment with stable doses of non-steroidal anti-inflammatory drugs (NSAIDs) during the study. Patients receiving oral glucocorticoids could continue with these provided they had not exceeded a

maximum dose of 0.2 mg prednisone equivalent/kg/day or 10 mg/day (whichever was lower) for ≥2 weeks before baseline. Patients who had received oral or parenteral methotrexate for ≥3 months before the study could continue with this, provided they had not exceeded a maximum dose of 25 mg/week or 20 mg/m^2/week, whichever was lower, for at least 6 weeks before baseline. Patients taking methotrexate were also required to take either folic or folinic acid.

Moderate or potent CYP3A4 inhibitors (e.g. HIV antivirals, clotrimazole and ketoconazole) and inducers (e.g. carbamazepine, phenytoin and rifampin) were not permitted. Patients were also not allowed to receive any other investigational drugs or any biologic DMARDs. With the exception of methotrexate, systemic conventional synthetic DMARDs were not permitted.

Herbal supplements were not allowed; patients were required to discontinue these at least 4 weeks before the first dose of study medication.

B.3.3.5 Outcomes

As the study was designed to evaluate the efficacy of tofacitinib versus placebo, the focus is on the endpoints measured during the double-blind phase. These are listed in Table 10.

Table 10 Outcomes: Study A9321104

	Endpoint
Primary	Occurrence of disease flare (PRCSG/PRINTO criteria) by Week 44/end of study (i.e. the percentage of patients with flare during the double-blind period)
Key secondary	Achievement of JIA ACR 30, 50 or 70 response at Week 44/end of study Change from double-blind baseline in CHAQ disability index at Week 44/end of study
Other secondary	Occurrence of disease flare at each double-blind phase visit Time to disease flare in the double-blind phase Achievement of JIA ACR 30, 50 or 70 response at each double-blind phase visit Change from double-blind baseline in JADAS-27 CRP, JADAS-27 ESR, and achieving JADAS minimum disease activity and inactive disease at each double-blind phase visit Achieving JIA ACR inactive disease at each double-blind phase visit and achieving clinical remission at Week 44 Change from double-blind baseline in each JIA ACR core set variable at each double-blind phase visit; change from open-label baseline in each JIA ACR core set variable at each double-blind phase visit Change from double-blind baseline CHQ responses at each double-blind phase visit Change from double-blind baseline CHAQ responses at each double-blind phase visit

ACR, American College of Rheumatology; BSA, body surface area; CHAQ, Child Health Assessment Questionnaire; CHQ, Child Health Questionnaire; JADAS, Juvenile Arthritis Disease Activity Score; JIA, juvenile idiopathic arthritis; PGA, Physician Global Assessment; PRCSG, Pediatric Rheumatology Collaborative Study Group; PRINTO, Pediatric Rheumatology International Trials Organisation.
Source: Study A3921104 clinical study report (61)

Other secondary endpoints included all of the above measures during open-label run-in, plus taste acceptability of tofacitinib oral solution on Day 14 of run-in.

Disease flare

Assessment of disease flare was based on the PRCSG/PRINTO criteria, i.e. worsening of ≥30% in ≥3 of the six JIA core set variables (65):

- Number of joints with active arthritis
- Number of joints with a limited range of motion

- Physician global assessment of disease activity
- Parent/patient evaluation of overall wellbeing (CHAQ)
- Functional ability (CHAQ disability index)
- ESR

No more than one variable can improve by 30% or more. In addition, if the number of joints with either active disease or limited range of motion is included in the determination of flare, then there must be worsening of at least two joints. If the physician global assessment of disease activity or parent/patient evaluation of wellbeing are included, there must be a worsening of at least two units on the relevant scales. If ESR is used, the second reading must be above the upper limit of normal.

Patients who experienced flare were required to discontinue from the study.

JIA ACR responses

JIA ACR response criteria, equivalent to ACR Pediatric response criteria, is based on the ACR core outcome variables for juvenile arthritis, namely physician global assessment of disease activity (10-cm VAS), parent/patient assessment of overall well-being (10-cm VAS), functional ability, number of joints with active arthritis (defined as joint effusion or limitation of motion accompanied by heat, pain, or tenderness), number of joints with limited range of motion, and ESR. Patients achieved JIA ACR 30, 50 and 70 responses if 3 of the 6 JIA core set variables improved by 30%, 50% or 70%, respectively. No more than 1 of the remaining variables could worsen by ≥30%.

JADAS-27 CRP and JADAS-27 ESR scores

The Juvenile Disease Activity Score (JADAS) is a validated composite disease activity measure (66). Scores are based on:

- Physician global assessment of disease activity
- Parent/patient assessment of wellbeing (CHAQ)
- Number of joints with active disease (27-joint count)
- CRP or ESR levels

Higher JADAS scores indicate higher disease activity. In patients with polyarthritis, inactive disease is indicated by scores ≤1.0, minimal disease activity is indicated by scores between 1.1-3.8, moderate disease activity is indicated by scores between 3.9-10.5 and high disease activity is indicated by scores >10.5 (67).

Childhood Health Assessment Questionnaire (CHAQ)

The CHAQ is a validated health-rated quality of life (HRQoL) questionnaire that measures patients' disability, discomfort and overall wellbeing (68). In Study A3921104, patients aged 14 or older could complete the questionnaire themselves if they were able to do so correctly and consistently. Otherwise, it was completed by their parent or guardian.

For the assessment of disability, parents/patients rated dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities-distributed on a 4-point scale of difficulty in performance, where 0 = 'no difficulty' and 3 = 'unable to do'. For the assessment of discomfort, they rated severity of pain in the last week on a 21-point scale where 0 = 'no pain' and 10 = 'very severe pain'. Overall wellbeing was rated on a 21-point scale, where 0 = 'very well' and 10 = 'very poorly'. These 21-point scales were divided in increments of 0.5.

B.3.3.6 Baseline characteristics

Table 11 shows baseline demographics and disease characteristics. Data are presented for the open-label full analysis set (OLFAS; all patients who were enrolled in the study and received at least one dose of tofacitinib in the open-label run-in) and the double-blind full analysis set (DBFAS; all patients who were randomised to treatment and received at least one dose of study medication in the double-blind phase; reported under 'randomized treatment'). A full description of all analysis sets is given in Section **Error! Not a valid bookmark self-reference.**.

Table 11 Patient demographics and baseline characteristics: Study A3921104

	Patients in open-label phase (OLFAS)	**Patients in double-blind phase (DBFAS)**	
	Tofacitinib 5 mg BID (n = 225)	**Tofacitinib 5 mg BID (n = 88)**	**Placebo (n = 85)**
Female, n (%)	169 (75.1)	66 (75.0)	64 (75.3)

	Patients in open-label phase (OLFAS) Tofacitinib 5 mg BID (n = 225)	Patients in double-blind phase (DBFAS) Tofacitinib 5 mg BID (n = 88)	Placebo (n = 85)
Age (years), median (Q1, Q3)	13.0 (9.0, 15.0)	13.0 (9.0, 15.0)	13.0 (9.0, 15.0)
Race, n (%)			
White	196 (87.1)	76 (86.4)	74 (87.1)
Geographical region, n (%)			
North America	96 (42.7)	31 (35.2)	41 (48.2)
South and Central America	47 (20.9)	22 (25.0)	15 (17.6)
Europe[a]	6 (2.7)	5 (5.7)	1 (1.2)
All other[a]	76 (33.8)	30 (34.1)	28 (32.9)
Primary JIA diagnosis, n (%)			
Extended oligoarthritis	28 (12.4)	8 (9.1)	10 (11.8)
Polyarthritis RF+	39 (17.3)	14 (15.9)	14 (16.5)
Polyarthritis RF-	104 (46.2)	45 (51.1)	42 (49.4)
sJIA with active arthritis but no active systemic features	13 (5.8)	5 (5.7)	4 (4.7)
PsA	20 (8.9)	7 (8.0)	8 (9.4)
ERA	21 (9.3)	9 (10.2)	7 (8.2)
Duration since onset (years), median (Q1, Q3)	2.5 (1.0, 5.6)	2.5 (1.0, 5.6)	2.0 (1.0. 5.1)
PGA overall disease activity median (Q1, Q3)	6.0 (4.5, 7.5)	6.0 (4.5, 7.5)	6.0 (4.5, 7.5)
Joints with active arthritis, median (Q1, Q3)	10.0 (6.0, 15.0)	10.0 (7.0, 16.0)	9.0 (6.0, 14.0)
Joints with limited motion, median (Q1, Q3)	6.0 (3.0, 10.0)	6.0 (3.0, 12.0)	5.0 (3.0, 8.0)
CRP (mg/dL), median (Q1, Q3)*	0.3 (0.1, 1.0)	0.3 (0.1, 1.3)	0.2 (0.1, 0.9)
CHAQ-DI, median (Q1, Q3)	0.9 (0.3, 1.5)	0.8 (0.4, 1.4)	0.9 (0.3, 1.5)
Pt/parent assessment of overall wellbeing, median (Q1, Q3)	5.0 (3.0, 7.0)	5.0 (2.5, 7.0)	5.0 (3.0, 7.0)
JADAS-27 CRP score, median (Q1, Q3)	20.1 (16.2, 26.6)	19.7 (16.2, 27.4)	20.1 (14.7, 25.4)

[a]Europe includes Belgium, Great Britain, Poland and Spain; all other includes Australia, Israel, Russia, Turkey and Ukraine.
BID, twice-daily; CHAQ-DI, Childhood Health Assessment Questionnaire-Disability Index; CRP, C-reactive protein; DBFAS, double-blind full analysis set; ERA, Enthesitis-related arthritis; JIA, juvenile idiopathic arthritis; OLFAS, open-label full analysis set; PsA, psoriatic arthritis; Pt, patient; Q1, 25th percentile; Q3, 75th percentile; RF, rheumatoid factor; sJIA, systemic juvenile idiopathic arthritis.
Source: Brunner et al, 2019 (57)

Table 12 shows patients' medication history. Approximately 38% of patients had previously received biologic DMARDs. The most commonly used csDMARD was methotrexate 90.7%.

Table 12 Medication history: Study A3921104 (OLFAS)

	Tofacitinib 5 mg BID (n = 225)
DMARDs, n (%)	
bDMARDs	85 (37.8)
csDMARDs	206 (91.6)
Corticosteroids, n (%)	111 (49.3)
Immunosuppressants, n (%)	[redacted]

bDMARDs, biologic DMARDs, csDMARDs, conventional synthetic DMARDs; DMARDs, disease-modifying anti-rheumatic drugs; OLFAS, open-label full analysis set (i.e. patients who received at least one dose of study medication during run-in)
Source: Study A392104 clinical study report (61); EMA assessment report (63)

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The primary hypothesis was that in patients with pcJIA, tofacitinib would be superior to placebo for the proportion of patients with disease flare at Week 44/end of study (i.e. the difference between groups in the proportion of patients with flares by Week 44/end of study would result in a two-sided P-value <0.05).

B.3.4.1 Sample size

For the pcJIA cohort, it was planned to enrol approximately 170 patients in the open-label run-in to give approximately 90% power or above to detect a difference between treatment groups in the rate of disease flare during the double-blind phase. This assumed a JIA ACR 30 response rate to 54% to 65% from run-in, a 2-sided 5% Type I error, and a true difference of ≥31% in rate of disease flare between treatments, with a rate of 57% in the placebo group.

B.3.4.2 Statistical analyses

To preserve Type I error, the primary and key secondary endpoints were analysed sequentially using a gate-keeping or step-down approach, i.e. an endpoint was only tested if the previous endpoint was shown to be statistically significant. The order of testing was as follows:

- Disease flare by Week 44/end of study (primary endpoint)
- ACR 50 at Week 44/end of study
- ACR 30 at Week 44/end of study
- ACR 70 at Week 44/end of study
- Change from double-blind baseline in CHAQ disability index at Week 44/end of study

The primary and binary secondary endpoints were analysed using the normal approximation approach for binomial populations. Continuous secondary endpoints were analysed using a mixed model for repeated measures (MMRM). Kaplan-Meier curves were produced for all time-to-event analyses.

Key analysis sets were:

- Double-blind full analysis set (DBFAS) – all patients who were randomised to treatment and received at least one dose of study medication in the double-blind phase; reported under 'randomized treatment'
- Double-blind pcJIA analysis set (DBJAS), i.e. all patients with pcJIA in the DBFAS
- Double-blind safety analysis set (DBSAS) - all patients who were randomised to treatment and received at least one dose of study medication in the double-blind phase; reported under 'received treatment'
- Open-label full analysis set (OLFAS) – all patients who were enrolled in the study and received at least one dose of tofacitinib in the open-label run-in

This submission focuses on efficacy data for the DBJAS. Secondary and disease-specific efficacy endpoints were also analysed separately for patients with PsA or ERA; these data are not presented. Safety analyses were carried out on the DBSAS, and therefore included patients with pcJIA, PsA and ERA.

Table 13 shows the number of patients in the key analysis populations.

Table 13 Analysis populations: Study A3921104

Analysis set	Number of patients	
	Tofacitinib 5 mg BID	Placebo
DBFAS	88	85
DBJAS	72	70
DBSAS	88	85
OLFAS	225	

BID, twice-daily, DBFAS, double-blind full analysis set; DBJAS, double-blind pcJIA analysis set; DBSAS, double-blind safety analysis set; OLFAS, open-label full analysis set.
Source: Study A3921104 clinical study report (61)

B.3.4.3 Handling of missing data

For the composite endpoints flare and JIA ACR responses, last observation carried forward (LOCF) was used to impute missing data at visits prior to study discontinuation. The LOCF method was also used to impute the binary status of flare, JIA ACR responses, JADAS minimum disease activity, JADAS inactive disease, and JIA ACR inactive disease at intermediate visits with missing values, preceding discontinuation. Flare, JIA ACR responses, and other binary endpoints (JADAS minimum disease activity and inactive disease, JIA ACR inactive disease) were set to flare/non-responder/active disease, respectively, for observed assessments on or after discontinuation. Visits without observed assessments after discontinuation were not imputed.

In the double-blind phase, the above LOCF method was used to impute any missing component of flare and JIA ACR responses. LOCF was also used for the missing binary endpoints of flare, JIA ACR responses, JADAS minimum disease activity, JADAS inactive disease, and JIA ACR inactive disease for the visits prior to discontinuation.

Patients who discontinued from double-blind study treatment for any reason were considered as having a flare/non-response/active disease for all the endpoints listed above, as of their study double-blind treatment discontinuation visit through Week 44, except patients who met JIA ACR defined clinical remission criteria (i.e. inactive disease for at least 24 weeks) at the time of discontinuation. Patients who discontinued study treatment while in clinical remission were to have their LOCF from that visit onward through Week 44.

For continuous secondary endpoints, no imputation was performed during the double-blind phase and missing data were handled via an MMRM modelling approach.

The impact of dropouts on the primary analysis was evaluated through model-based multiple imputation. Two tipping point analyses based on 2 imputation models (Weibull regression and binomial distribution) were performed for the primary endpoint. The ACR response type I error controlled secondary endpoints were analysed using the same binomial approach as the tipping point analysis of flares at Week 44. The tipping point analysis of the change from the double-blind baseline in the CHAQ disability index at Week 44 (type I error controlled) employed a missing not at random (MNAR) multiple imputation approach.

B.3.4.4 Participant flow

Patient disposition is summarised in Table 14. Full details of participant flow through the study, including reasons for discontinuation, are given in Appendix D.

Table 14 Patient disposition: Study A3921104

	Number (%) of patients	
Screened	286	
Entered open-label run-in	225	
Discontinued open-label run-in	40 (17.8)	
Completed open-label run-in	185 (82.2)	
Discontinued between end of run-in and randomisation	12 (6.5)	
Randomised to treatment	173 (93.5)	
	Tofacitinib 5 mg BID (n = 88)	**Placebo (n = 85)**
Discontinued double-blind phase	27 (30.7)	47 (55.3)
Completed double-blind phase	61 (69.3)	38 (44.7)

Data include patients with ERA and PsA
Source: Study A3921104 clinical study report (61)
BID, twice-daily,

B.3.5 Quality assessment of the relevant clinical effectiveness evidence

Table 15 shows the results of the quality assessment for Study A3921104, which was carried out using the Cochrane risk of bias criteria (69). The study was found to be robust with a low risk of bias. Full details of the quality assessment can be found in Appendix D.

Table 15 Quality assessment of Study A3921104

	Study A3921104
Was the randomisation method adequate?	Yes
Was the allocation adequately concealed?	Yes
Were participants and investigators blind to exposure and comparison?	Yes
Were the outcome assessors blind to treatment allocation?	Yes
Were drop-outs between groups adequately explained? Were unexpected imbalances adjusted for?	Yes
Were all outcomes adequately reported?	Yes
Did the study appear free from other sources of bias	Yes

Appendix D also details quality assessments for the relevant comparator RCTs that were identified in the SLR and included in an indirect treatment comparison (ITC) (see Section B.3.9).

B.3.6 Clinical effectiveness results of the relevant trials

Unless otherwise stated, data are shown for the DBJAS population.

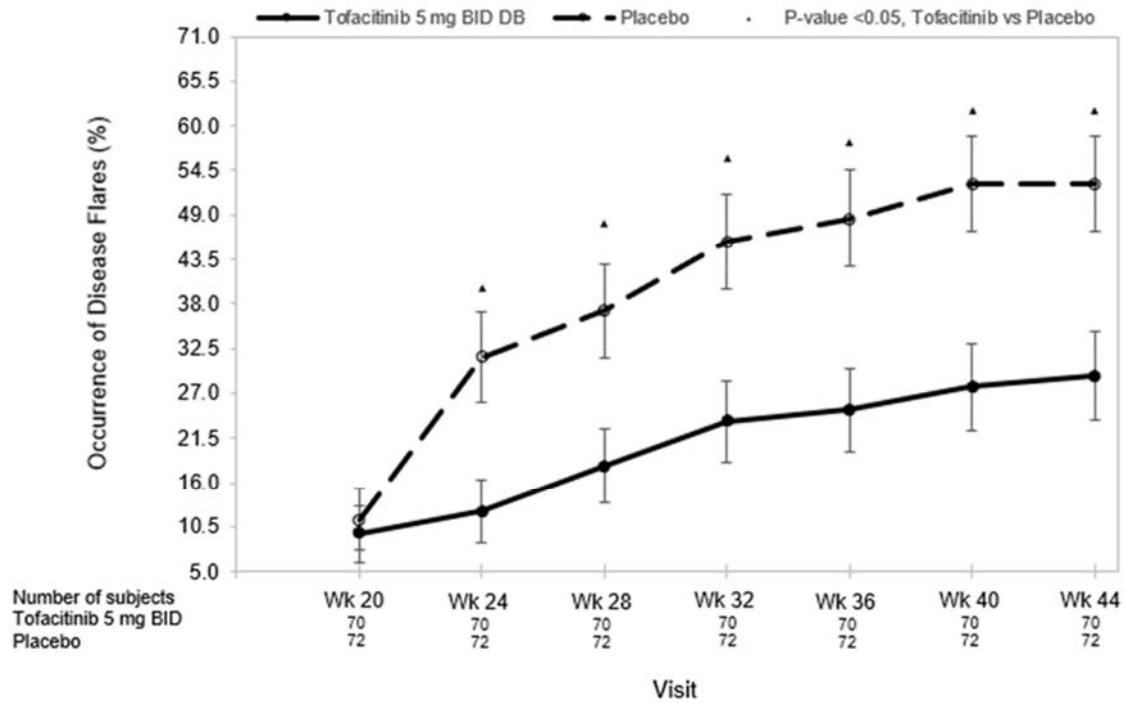
B.3.6.1 Reduction in disease flare

Significantly fewer patients experienced disease flare with tofacitinib than with placebo. At Week 44 (i.e. the end of the double-blind phase), 21 patients (29.2%) in the tofacitinib group had experienced flare, compared with 37 (52.9%) in the placebo group (difference -23.69; 95% CI -39.41 to -7.97; P = 0.0031).

Figure 6 shows the occurrence of disease flare over time during the double-blind phase. From Week 24 (i.e. Week 6 of the double-blind phase), there was a significant reduction in the occurrence of disease flare for patients treated with tofacitinib versus those treated with placebo.

The median time to disease flare could not be estimated in the tofacitinib group as there were too few events. The probability of remaining flare-free in the tofacitinib group was 70.8% (>50%). In the placebo group, the median time to disease flare was 155 days.

Figure 6 Occurrence of disease flare over time: double-blind phase (DBJAS)

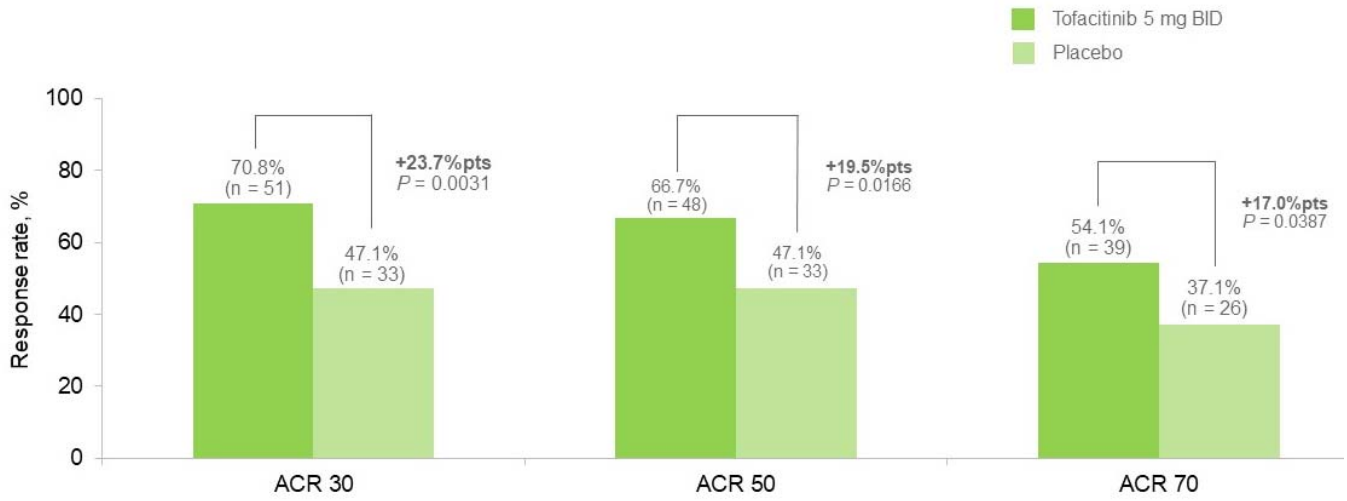


Error bars show standard error. BID, twice-daily; DB, double-blind; DBJAS, double-blind pcJIA analysis set
Source: Study A3921104 clinical study report (61)

B.3.6.2 Improvement in response rates

During the double-blind phase, significantly more patients achieved JIA ACR 30, 50 and 70 responses with tofacitinib than with placebo. Figure 7 shows the JIA ACR response rates at Week 44 (i.e. the end of the double-blind phase).

Figure 7 JIA ACR 30, 50 and 70 responses at Week 44 (DBJAS)



BID, twice-daily; pts, points
Source: Study A3921104 clinical study report (61)

At the end of the open-label run-in phase, 92% of patients had achieved a JIA ACR 30 response, 84% had achieved a JIA ACR 50 response, and 61% had achieved a JIA ACR 70 response.

[redacted]

Throughout the double-blind phase, the proportions of patients with JIA ACR 30, 50 and 70 responses were higher in the tofacitinib group than in the placebo group. A statistically significant difference between tofacitinib and placebo was shown from Week 24 for JIA ACR 30 and 50 responses and from Week 32 for JIA ACR 70.

B.3.6.3 Improvement in disease activity

Child Health Assessment Questionnaire (CHAQ)

Patients receiving tofacitinib reported significantly less disability at the end of the study than those receiving placebo. The LS mean (SEM) change from double-blind baseline in CHAQ disability index scores was -0.09 (0.04) in the tofacitinib group (n = 49) and 0.03 (0.04) in the placebo group (n = 33) (treatment difference -0.12, 95% CI -0.22 to -0.01; P = 0.0292).

[redacted]

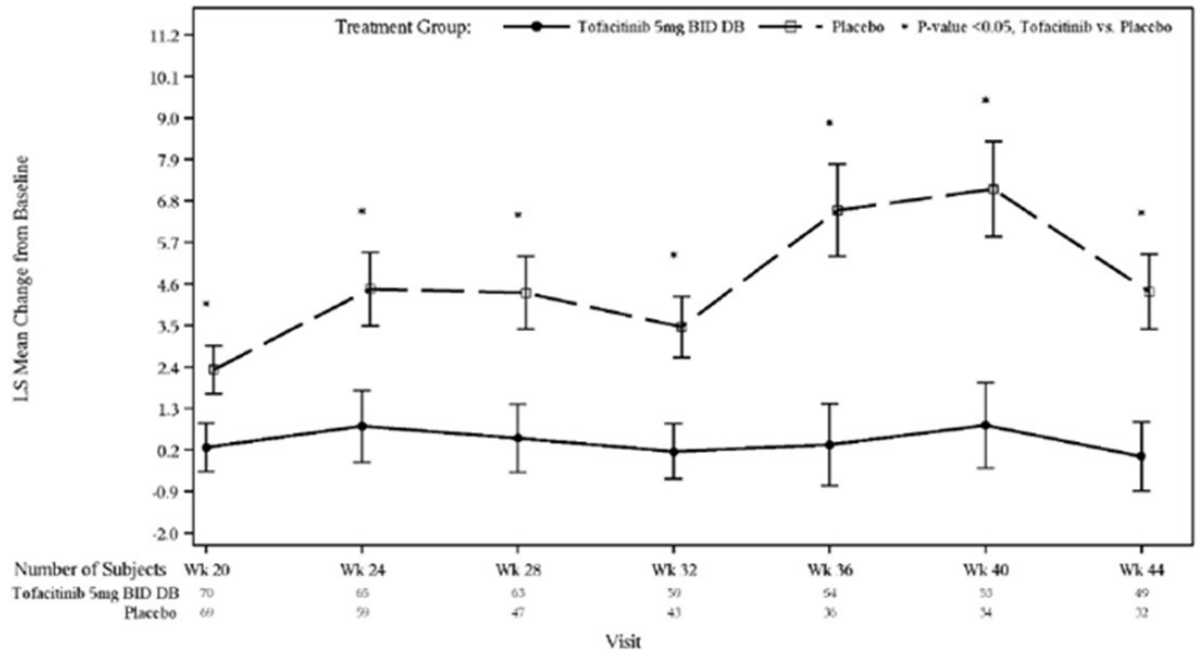
Patients' overall wellbeing remained stable with tofacitinib but worsened with placebo during the double-blind phase. The LS mean change from double-blind baseline in CHAQ parental evaluation of overall wellbeing was significantly lower with tofacitinib than with placebo at all visits except Weeks 36 and 40 (i.e. Weeks 16 and 22 of the double-blind phase).

Juvenile Arthritis Disease Activity Score (JADAS)

The mean change from double-blind baseline in JADAS-27 CRP score was significantly lower in the tofacitinib group than in the placebo group from Week 20 (i.e. Week 2 of the double-blind phase; P = 0.0088) to Week 44 (P = 0.0027) (Figure

8). In other words, disease activity remained stable during the double-blind phase in the tofacitinib group but increased in the placebo group.

Figure 8 Mean change from double-blind baseline in JADAS-27 CRP (DBJAS)



Double-blind baseline was Week 18. Error bars are standard error. BID, twice-daily; CRP, C-reactive protein; DB, double-blind; DBJAS, double-blind pcJIA analysis set; ESR, erythrocyte sedimentation rate; JADAS, Juvenile Arthritis Disease Activity Score; LS mean, least squares mean
Source: Study A3921104 clinical study report (61), Brunner et al, 2019 (57)

The mean change from double-blind baseline in JADAS-27 ESR score was also significantly lower in the tofacitinib group than in the placebo group from Week 20 (P = 0.0172) to Week 44 (P = 0.0018).

More patients in the tofacitinib group achieved JADAS minimum disease activity (MDA), calculated from the JADAS-27 CRP score than in the placebo group throughout the double-blind phase. For JADAS-27 ESR minimum disease activity scores, the difference between treatment groups was statistically significant at Week 44 (P = 0.0228).

The proportion of patients with JADAS inactive disease activity calculated from JADAS-27 CRP scores was also numerically higher for tofacitinib than for placebo throughout the double-blind phase; the difference between treatments was statistically significant at Week 40 (P = 0.0464). A similar numerical trend was seen for JADAS inactive disease activity calculated from the JADAS-27 ESR scores.

JIA ACR inactive disease and clinical remission

In general, the proportion of patients with JIA ACR inactive disease increased during the double-blind phase in the tofacitinib group and decreased in the placebo group. By Week 44, 3 patients (4.17%) in the tofacitinib group and 3 (4.29%) in the placebo group were in clinical remission, i.e. had 24 weeks of inactive disease, which could have started during the open-label run-in phase (treatment difference -0.12, 95% CI -6.74 to 6.50; P = 0.9719).

JIA ACR core set variables

Throughout the double-blind phase, patients in the tofacitinib group had a greater decrease in the number of joints with active arthritis and a greater decrease in the number of joints with limited motion, than patients in the placebo group. Further data for this outcome are presented in Appendix I.

B.3.6.4 Health-related quality of life (Child Health Questionnaire, CHQ)

The change from double-blind baseline in the CHQ family activities subscale standardized score at Week 44 was significantly lower in the tofacitinib group than in the placebo group. There were no significant differences between the treatment groups in any of the other subscales. Changes from double-blind baseline in the CHQ physical and psychosocial summary scores were similar between the treatment groups. Further data for CHQ are presented in Appendix I.

B.3.7 Subgroup analysis

The primary and key secondary endpoints were summarised by the following prespecified subgroups:

- JIA category (extended oligoarthritis, RF+ polyarthritis, RF- polyarthritis, sJIA)
- open-label run-in baseline CRP (normal, above normal)
- geographical region (North America, South and Central America, Europe, all other)
- baseline body weight (<40 kg, ≥40 kg)
- age group (2 to <6 years, 6 to <12 years, 12 to 18 years).

Inferential statistics were performed, and forest plots generated. These analyses were pre-planned and designed to determine whether there were any differences between study arms according to these patient characteristics. The results showed no statistically significant difference, but a consistent benefit in favour of tofacitinib was observed across all subgroups. More detailed results are shown in Appendix E.

B.3.8 Meta-analysis

Due to the nature of the evidence, no pairwise meta-analysis was possible to conduct. Head-to-head evidence was not available comparing tofacitinib with any of the comparators in the assessment scope; therefore, Bucher's ITCs were conducted to estimate the relative efficacy of all relevant therapies (see Section B.3.9).

B.3.9 Indirect and mixed treatment comparisons

No head-to-head clinical trial was conducted that compared tofacitinib with adalimumab or tocilizumab; therefore, it was necessary to evaluate relative effectiveness of treatments using an indirect comparison methodology.

The SLR (see Section B.3.1) identified, 5 clinical trials that were relevant for the decision problem of the current appraisal and provided information on the clinical efficacy and safety of tofacitinib, adalimumab and tocilizumab in polyarticular course JIA. 1 study on tofacitinib versus placebo, Brunner 2019, 3 studies on adalimumab versus placebo ADJUVITE, Burgos-Vargas 2015, DE038 (45-47) and 1 study on tocilizumab versus placebo CHERISH (38).

Studies were excluded from the ITCs if they presented substantial heterogeneity in study design or patient baseline characteristics compared to Brunner 2019 (57) (the tofacitinib trial). RCTs that did not contain a withdrawal phase were also excluded as these studies did not contain a lead-in phase with an ACR Pedi 30 response criteria, and so contained a different patient population that those included in the randomised withdrawal phase of the tofacitinib study. Overall, of the 5 studies identified, 2 studies were ultimately excluded due to heterogeneity concerns, detailed below:

- ADJUVITE (45): Study did not include a withdrawal period, and total study duration (2 months) was substantially shorter than the randomised phase of Brunner 2019 (44) (6.5 months).

- Burgos-Vargas 2015 (46): Study did not include a withdrawal period, and total study duration (3 months) was substantially shorter than the randomised phase of Brunner 2019 (44) (6.5 months).

A feasibility assessment identified that all remaining 3 studies compared a single intervention to placebo, and there was only one study to inform each pairwise comparison. Due to the limited number of studies and treatments informing the ITCs a network meta-analysis was not considered feasible. Therefore, similarly to the methodology used in TA373, a Bucher's indirect comparison (70) was conducted to compare tofacitinib with the comparators of interest, adalimumab and tocilizumab.

For each outcome of interest, a series of indirect comparisons were conducted using placebo as a common comparator to compare tofacitinib with adalimumab and tocilizumab. This is the same approach that was used by the Assessment Group in NICE TA373 (11).

The primary outcome in all three studies was proportion of patients who experienced a disease flare (Brunner 2019, CHERISH, DE038 [non-methotrexate stratum] (51, 57, 59, 71)), it was also a secondary outcome in one of the studies (DE038 [methotrexate stratum] (59, 72)).

ACR Pedi responses, which is equivalent to JIA ACR response as reported in the tofacitinib trial, were widely reported and were considered as a relevant outcome during the previous MTA, TA373. Therefore, the ITC analyses for ACR Pedi 30, 50 and 70 were also explored and are discussed below.

Full details of the methodology for the ITCs are presented in Appendix D, alongside with the SLR that was used to identify studies that may have been relevant for informing an indirect comparison for tofacitinib versus adalimumab and tocilizumab in treating pcJIA.

B.3.9.1 Selection of evidence contributing to the indirect treatment comparisons

Eligibility

For RCTs to be eligible for inclusion in the ITCs, they were required to report at least one of the following outcomes during the randomised trial phase:

- Proportion of patients experiencing a disease flare
- ACR Pedi 30, 50 and/or 70 response
- Proportion of patients who had an infection
- Proportion of patients who had an upper respiratory tract infection (URTI)

Summary of studies included in the ITCs

Of the 12 studies identified by the SLR, 3 were suitable for inclusion in the ITC analyses. The remaining 9 studies were excluded because they presented substantial heterogeneity in study design or patient baseline characteristics compared with Brunner 2019 (57) (the tofacitinib trial), or because they included a comparator not of interest for this assessment (etanercept or abatacept). Furthermore, five of the excluded studies had no open-label phase leading into the randomised study phase, which meant that they contained a different patient population from the tofacitinib trial. Full details of the rationale for excluding these nine studies are provided in Appendix D.

The studies used in the base-case ITCs are summarised in Table 16 and described in detail in Appendix D. All studies had a common direct comparison with placebo. In terms of study design, all studies included an open-label lead-in phase (16-18 weeks) followed by a randomised withdrawal phase (24-32 weeks), and a subsequent open-label extension phase. The adalimumab and tocilizumab studies included in the ITCs were also included in the ITC conducted by the Assessment Group during TA373.

The adalimumab study (59) contained a methotrexate stratum and a non-methotrexate stratum. The methotrexate stratum was selected for the ITC analysis as the majority of patients in the other studies included in the ITC used concomitant

methotrexate (Brunner 2019 (61) [CSR: Table 10]: 65.9-68.2% patients across study arms at start of randomised phase; CHERISH (51): 79% patients at lead-in).

Table 16 Summary of the trials used to carry out Bucher's ITCs

Trial / Comparator	Placebo	Tofacitinib (2-5 mg BID)	Adalimumab (24 mg/m^2 Q2W)	Tocilizumab (8-10 mg/kg Q4W)
Brunner 2019 (57)	Y	Y		
CHERISH (51)	Y			Y
DE038 (59)	Y		Y	

BID, twice-daily; Q2W, every 2 weeks; Q4W, every 4 weeks

Imputation of missing data in included trials

When considering disease flare, non-responder imputation (NRI) was used to impute missing data. This meant that patients who withdrew from the trial or for whom the endpoint could not be calculated were considered to have had a disease flare in the adalimumab (59) and tocilizumab (51) trials.

The tofacitinib trial (57) used a similar NRI approach to the adalimumab and tocilizumab trials for patients who discontinued the randomised trial phase, except for the subset of patients who had maintained JIA ACR inactive disease for at least 24 weeks who were considered to not have had a disease flare. However, as this difference affected a minority of patients, the missing data imputation techniques across trials were considered comparable and were not believed to be a major source of heterogeneity.

ITC analysis approach for other outcomes

Safety data were assessed to determine differences across treatments and were consistently and homogenously reported across the included studies. Serious adverse event (SAE) outcomes were considered for analysis in an indirect comparison; however, these were rare across all study arms (proportion of patients who experienced an SAE across study arms: 1%-3%). Therefore, an indirect comparison of SAEs (or any specific serious adverse event) was not possible to

conduct as the results were unlikely to be meaningful and would have resulted in very large confidence intervals.

Infection outcomes were also of interest. It was not possible to perform ITCs for number of patients who experienced an infection as this was not reported for the adalimumab and tocilizumab trials. Ultimately, the proportion of patients who experienced a URTI were selected for ITC analysis. URTI was selected as a supporting analysis as this AE was more frequently reported across trials included in the ITC analyses.

All-cause discontinuation, discontinuation due to lack of efficacy and discontinuation due to AEs were also considered as outcomes that could be analysed in an ITC. However, it was not possible to synthesise these outcomes using Bucher's methodology due to heterogeneity in study design, as detailed in Table 17.

To summarise, two of the three studies reported that patients discontinued the randomised trial phase if they experienced a disease flare. However, the number of patients who discontinued was lower than the number of patients who experienced a disease flare in the two comparator trials CHERISH and DE038 (51, 57, 59, 71). This suggests that in these two trials, some patients who experienced a disease flare did not discontinue the randomised trial phase. It is unclear why these patients did not discontinue the trial despite experiencing a disease flare and whether such patients are treated consistently across trials.

The reported number of patients who discontinue is generally low across the trials, specifically for discontinuation due to adverse events. An ITC of these outcomes is therefore likely to be imprecise and result in wide confidence intervals. This heterogeneity across discontinuation outcomes is summarised in Table 17.

Table 17 Summary of heterogeneity in discontinuation reporting across included studies

Trial	Protocol if patient experiences a disease flare	Treatment	Disease flare	All-cause discontinuation	Discontinuation due to lack of efficacy (definition)	Discontinuation due to AEs
Brunner 2019 (57)	Patients who experience a single episode of disease flare at any time	Placebo	37/70[a]	47/85	44/85 (insufficient clinical response)	2/85

	during the study (including the open-label run-in and double-blind phase) were discontinued from the study	Tofacitinib	21/72 [a]	27/88	22/88 (insufficient clinical response)	2/88
CHERISH (51)	Patients continued in part 2 (RCT) until week 40 unless they experienced JIA-flare. After JIA-flare, patients entered the open-label study phase	Placebo	39/81	3/81	1/81 (insufficient therapeutic response)	2/81
		Tocilizumab	21/82	3/82	1/82 (insufficient therapeutic response)	1/82
DE038 (59)	NR	Placebo	24/37	1/37	0/37	0/37
		Adalimumab	14/38	3/38	0/38	0/38

[a] Double blind polyarticular course JIA analysis set, patients who did not have pcJIA were excluded from this analysis; JIA, juvenile idiopathic arthritis; NRI non-responder imputation; RCT, randomised controlled trial.

B.3.9.2 Indirect treatment comparisons

Evidence networks

Simple Bucher's ITCs were conducted as all relevant included trials compared active treatment to placebo, and none of the pairwise comparisons were informed by more than one trial. This analysis followed the same approach as was used in TA373. **Error! Reference source not found.**Figure 9 shows the networks for each indirect comparison.

Figure 9 Bucher's ITC networks

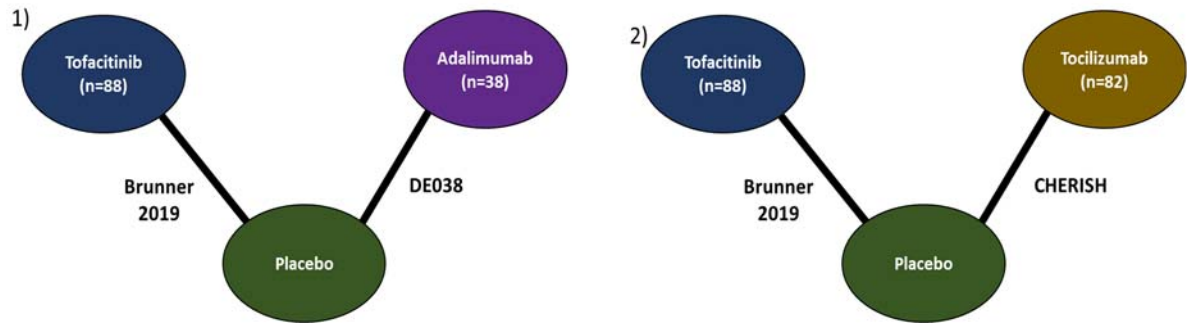


Figure presents the following ITC networks: 1) tofacitinib vs adalimumab (methotrexate stratum); 2) tofacitinib vs tocilizumab

Results

A summary forest plot showing active treatment vs placebo is presented in Figure 10 for proportion of patients experiencing disease flare. These data are taken directly from the corresponding trial publications and are not calculated using ITC analysis. All three treatments resulted in a statistically significant reduction in disease flares compared to placebo, with risk ratio (RR) point estimates ranging from 0.53 to 0.57.

Figure 11 shows the results of the analysis for ACR Pedi results. All treatments resulted in a statistically significant proportion of patients achieving ACR Pedi responses compared to placebo.

Figure 10 Summary forest plot of active treatment versus placebo for disease flares

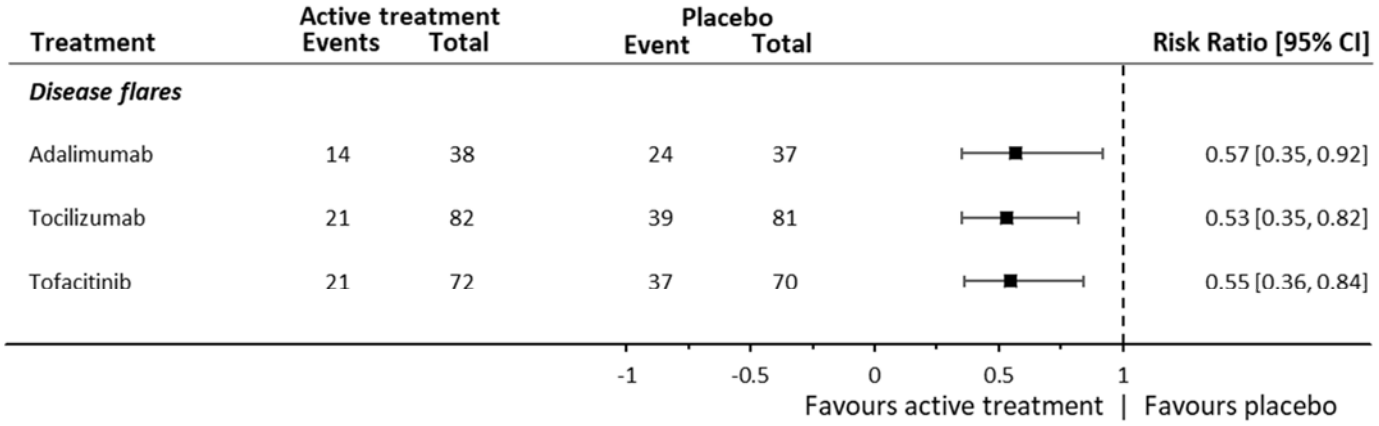
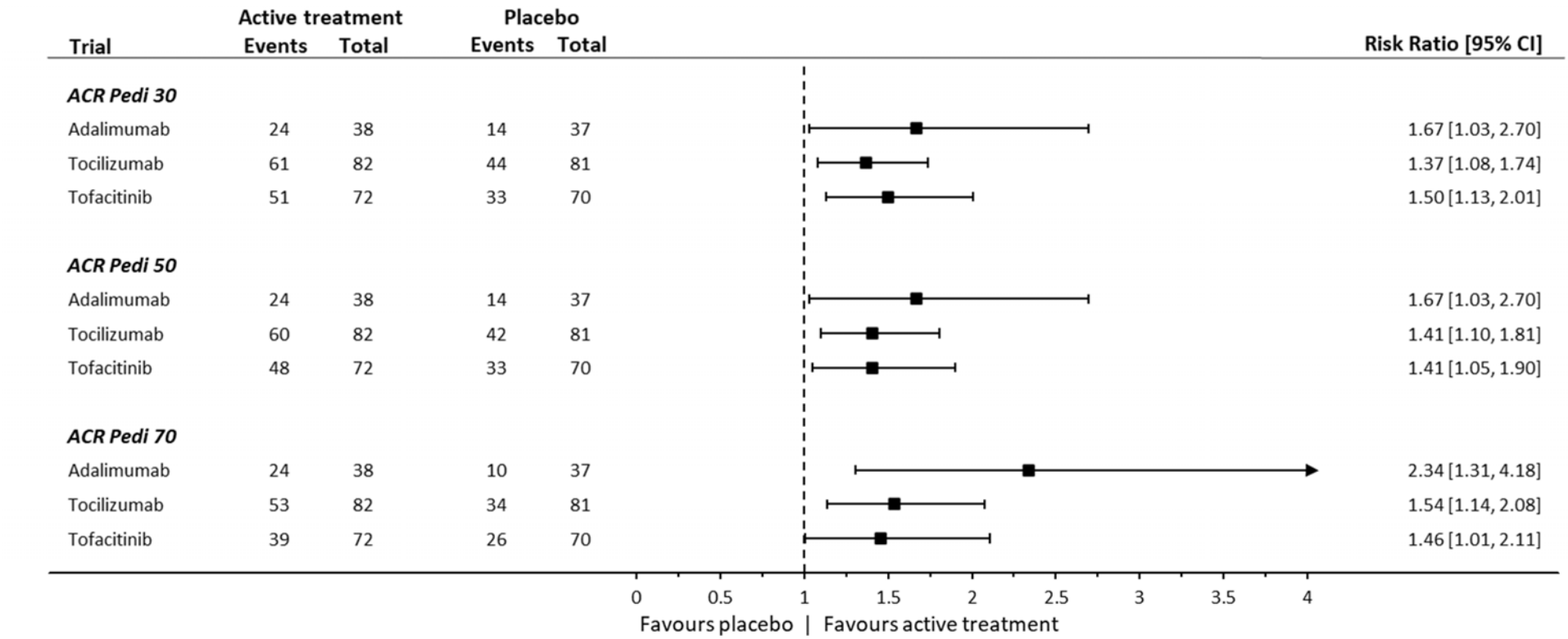


Figure 11 Summary forest plot of active treatment versus placebo for ACR Pedi responses



The results of the Bucher's indirect comparisons for tofacitinib versus the relevant comparators are presented in Figure 12 for disease flares. A value less than one favours tofacitinib and a value greater than one favours the comparator. [redacted]

ACR Pedi 30, 50 and 70 response rates were reported by all three studies included in the ITC analyses (51, 57, 59, 71, 72). The results of these analyses are presented in Figure 13. [redacted].

Figure 12 Risk ratios and summary forest plot of tofacitinib versus comparators for disease flares

Figure 13. Risk ratios and summary forest plot of tofacitinib versus comparators for ACR Pedi responses

An additional ITC was carried out for URTI and also showed that there was no statistically significant difference between tofacitinib and adalimumab and tocilizumab (Appendix D1.2).

B.3.9.3 Sensitivity analyses to address uncertainties in the indirect comparisons

Due to the limited data informing the indirect comparison analyses, no sensitivity analyses were performed.

B.3.9.4 Uncertainties in the indirect and mixed treatment comparisons

The ITCs were conducted using a well-known, transparent methodology (70), similarly to TA373. However, as well as in TA373 there are several limitations and uncertainties regarding the evidence used in the analysis. Only one study informed each pairwise treatment comparison and it was not possible to conduct sensitivity analyses due to limited data. The trial sample sizes were also generally small, ranging from 75 (adalimumab trial, methotrexate stratum (59)) to 173 (tofacitinib trial (57)).

The studies included in the ITCs all included an open-label, lead-in phase followed by a randomised withdrawal phase, as is common for studies in this patient population, followed by an open-label extension phase. All studies informing the ITCs required that patients experience at least an ACR Pedi 30 response for inclusion in the randomised trial phase. The majority of patients across all studies included in the ITCs went on to enter the randomised withdrawal phase (study range: 77%-88%). Therefore, the patient population included in the ITCs have already achieved a response using active treatment, similarly to the population included in the ITC in TA373.

There were differences across the included studies in terms of trial duration. The lead-in phase ranged from 16 weeks (tocilizumab and adalimumab trials (51, 57, 59, 71)) to 18 weeks (tofacitinib trial (57)) and the randomised withdrawal phase ranged from 24 weeks (tocilizumab trial (51, 57, 59, 71)) to 32 weeks (adalimumab trial (59)). It is possible treatment duration may impact time dependent outcomes, such as disease flares and some safety data (11).

There was some heterogeneity across studies in terms of baseline patient characteristics:

- **Age**: Age at the start of the randomised phase was fairly homogenous across the trials included in the ITCs. The mean age across study arms ranged from 10.8 years old (DE038 trial (59); placebo + MTX arm) to 11.9 years old (Brunner 2019 (61) [CSR: Table 14]; both trial arms)(71, 72)

- **Gender**: The majority of patients were female across all study arms (range: 75%-81%).

- **Duration of JIA**: The mean duration of JIA (in years) ranged from [redacted]) to 4.3 (DE038 (59); adalimumab + MTX arm) across the study arms included in the ITCs.

- **Previous biologic DMARD therapy**: Approximately one-third of patients had previous biologic DMARD therapy in the tofacitinib trial (61) (lead-in: 37.8% [CSR: Table 8]) and the tocilizumab trial (51) (lead-in: 32%). However, in the adalimumab study (59) prior biologic DMARD use was an exclusion criterion. Although there is some heterogeneity across studies in terms of proportion of patients who received previous biologic DMARD treatment, it is unclear whether this would impact the efficacy or safety of subsequent treatments (11).

- **Methotrexate use**: There was heterogeneity across the studies in terms of concomitant methotrexate use. All studies allowed methotrexate use during the trial. The proportion of patients who used methotrexate ranged from 65.9% (Brunner 2019 (61) [double-blind phase: tofacitinib arm; CSR: Table 10]) to 100% (DE038 (59), methotrexate stratum) across study arms.

It is important to note that the heterogeneities amongst trials were similar to the uncertainties already identified during the assessment of TA373 and were not introduced by the addition of tofacitinib to the network. The methodology that Pfizer follows in the current assessment is the same as that the Assessment Group followed in TA373 and what the NICE appraisal committee has accepted as sufficient evidence base for decision making.

B.3.10 Adverse reactions

Key messages

- Tofacitinib has an established safety profile in adult patients with rheumatoid arthritis, psoriatic arthritis and ulcerative colitis
- Treatment of paediatric patients with JIA in Study A3921104 raised no new safety concerns related either to treatment of JIA with tofacitinib or the overall tofacitinib safety profile
- The proportion of patients with treatment-emergent AEs (TEAEs) was similar between tofacitinib and placebo in the double-blind phase
- Fewer patients in the tofacitinib group discontinued during the double-blind phase because of condition-aggravated AEs, i.e. worsening disease (14 [15.9%] vs 27 [31.8%] in the placebo group]
- There were no deaths during the study
- Most treatment emergent adverse events were mild to moderate in severity. Fewer patients had TEAEs in the tofacitinib group than in the placebo group
- Changes in laboratory parameters were consistent with the expected effects of tofacitinib

B.3.10.1 Summary of AEs

Safety analyses were carried out on the OLFAS and DBSAS and therefore included patients with ERA and PsA as well as those with pcJIA.

Table 18 shows a summary of treatment-emergent AEs (TEAEs) and AEs of special interest in Study A3921104.

Table 18 Summary of AEs

	Number (%) of patients			
	Open-label run-in (OLFAS)	Double-blind phase (DBSAS)		Entire tofacitinib exposure period
	Tofacitinib 5 mg BID (n = 225)	Tofacitinib 5 mg BID (n = 88)	Placebo (n = 85)	Tofacitinib 5 mg BID (n = 225)
At least 1 AE	153 (68.0)	68 (77.3)	63 (74.1)	176 (78.2)
At least 1 SAE	7 (3.1)	1 (1.1)	2 (2.4)	8 (3.6)
Discontinuation due to AEs	26 (11.6)	16 (18.2)	29 (34.1)	42 (18.7)
Temporary dose reduction or discontinuation due to AEs	20 (8.9)	9 (10.2)	8 (9.4)	25 (11.1)
Most common AEs (≥5% in any treatment group				
URTI	24 (10.7)	13 (14.8)	9 (10.6)	34 (15.1)
Headache	16 (7.1)	2 (2.3)	6 (7.1)	18 (8.0)
Nasopharyngitis	10 (4.4)	7 (8.0)	3 (3.5)	15 (6.7)
Nausea	13 (5.8)	1 (1.1)	1 (1.2)	14 (6.2)
Pyrexia	11 (4.9)	4 (4.5)	1 (1.2)	14 (6.2)
Disease progression	5 (2.2)	8 (9.1)	13 (15.3)	13 (5.8)
Vomiting	13 (5.8)	0 (0.0)	4 (4.7)	13 (5.8)
JIA	6 (2.7)	3 (3.4)	12 (14.1)	9 (4.0)
AEs of special interest				
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	Number (%) of patients			
	Open-label run-in (OLFAS)	Double-blind phase (DBSAS)		Entire tofacitinib exposure period
	Tofacitinib 5 mg BID (n = 225)	Tofacitinib 5 mg BID (n = 88)	Placebo (n = 85)	Tofacitinib 5 mg BID (n = 225)
GI perforation[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic events[a]	3 (1.3)	0 (0.0)	0 (0.0)	3 (1.3)
Herpes zoster	2 (0.9)	0 (0.0)	0 (0.0)	2 (0.9)
Interstitial lung disease[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MACE[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malignancy (including NMSC) [a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MAS[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Opportunistic infection[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious infection	3 (1.3)	1 (1.1)[b]	1 (1.2)	4 (1.8)[b]
Thrombotic event (DVT, PE[a] or ATE)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tuberculosis[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a]Adjudicated events; [b]One SAE of pilonidal cyst repair was coded to surgical procedures instead of infection and was inadvertently not identified as a serious infection. Following adjudication, it was determined that the SAE did not meet opportunistic infection criteria; it is also included in the table as a serious infection

AE, adverse event; ATE, arterial thromboembolism; BID, twice-daily; DBSAS, double-blind safety analysis set; DVT, deep vein thrombosis; GI, gastrointestinal; JIA, juvenile idiopathic arthritis; MACE, major adverse cardiovascular event; MAS, macrophage activation syndrome; NMSC, non-melanoma skin cancer; OLFAS, open-label full analysis set; PE, pulmonary embolism; SAE, serious adverse event; URTI, upper respiratory tract infection

Source: Brunner et al, 2019 (57)

B.3.10.2 Treatment-emergent AEs (TEAEs)

During the open-label run-in, the most frequently reported TEAEs were URTI, headache, nausea and vomiting (Table 18). Most TEAEs were mild to moderate in severity. Overall, 64 patients (28.4%) had TEAEs that were considered to be related to treatment. These included URTI (10 patients; 4.4%), headache (7 patients; 3.1%), nausea (6 patients; 2.7%) and abdominal pain (5 patients; 2.2%).

During the double-blind phase, the most frequently reported TEAEs in the tofacitinib group were URTI, disease progression and sinusitis. In the placebo group, the most frequently reported TEAEs were disease progression, TEAEs related to the underlying JIA disease and URTI (Table 19). Most TEAEs were mild to moderate in severity. Twenty-two patients (25%) in the tofacitinib group had TEAEs, compared with 33 (38.8%) in the placebo group; the most common treatment-related TEAEs are shown in Table 19.

Table 19 Treatment-related TEAEs occurring in ≥2% of patients during the double-blind phase (DBSAS)

	Number (%) of patients	
	Tofacitinib 5 mg BID (n = 88)	**Placebo (n = 85)**
URTI	3 (3.4)	4 (4.7)
JIA	3 (3.4)	7 (8.2)
Disease progression	2 (2.3)	8 (9.4)
Pyrexia	2 (2.3)	0 (0.0)
Sinusitis	2 (2.3)	1 (1.2)
ALT increased	1 (1.1)	2 (2.4)
Urinary tract infection	1 (1.1)	3 (3.5)
Headache	0 (0.0)	3 (3.5)

ALT, alanine aminotransferase; BID, twice-daily; DBSAS, double-blind safety analysis set; JIA, juvenile idiopathic arthritis; URTI, upper respiratory tract infection
Source: Study A3921104 clinical study report (61)

The incidence of all AEs that were reported by ≥2% of patients during the study is shown in Appendix F.

B.3.10.3 Discontinuations due to AEs

During the open-label run-in, 26 patients (11.6%) discontinued because of AEs. Of these, 16 discontinued because of condition aggravated AEs (i.e. worsening disease).

During the double-blind phase, 16 patients (18.2%) in the tofacitinib group and 29 (34%) in the placebo group discontinued because of AEs. TEAEs leading to discontinuation during the double-blind phase are summarised in Table 20. Fewer patients in the tofacitinib group discontinued because of worsening disease compared with the placebo group (14 [15.9%] vs. 27 [31.8%]).

Table 20 AEs leading to discontinuation during the double-blind phase (DBSAS)

	Number (%) of patients	
	Tofacitinib 5 mg BID (n = 88)	**Placebo (n = 85)**
Disease progression	8 (9.1)	10 (11.8)
JIA	3 (3.4)	12 (14.1)
Condition aggravated	2 (2.3)	2 (2.4)
Arthritis	1 (1.1)	3 (3.5)
Pilonidal sinus repair	1 (1.1)	0 (0.0)
Tooth impacted	1 (1.1)	0 (0.0)
Appendicitis	0 (0.0)	1 (1.2)
Haemoglobin decreased	0 (0.0)	1 (1.2)
Intussusception	0 (0.0)	1 (1.2)

BID, twice-daily; DBSAS, double-blind safety analysis set; JIA, juvenile idiopathic arthritis
Source: Study A3921104 clinical study report (61)

During the open-label run-in, 20 patients (8.9%) had their dose reduced or temporarily discontinued because of AEs. During the double-blind phase, AEs led to dose reduction or temporary discontinuation in 9 patients (10.2%) in the tofacitinib group and 8 (9.4%) in the placebo group.

B.3.10.4 Serious AEs

During the open-label run-in, 7 patients reported a total of 10 treatment emergent SAEs: appendicitis, condition aggravated, Crohn's disease, diarrhoea, epidural empyema, JIA, pneumonia, sinusitis, subperiosteal abscess and vomiting.

During the double-blind phase, 1 patient in the tofacitinib group reported an SAE of pilonidal cyst. In the placebo group, 2 patients reported 3 SAEs: appendicitis, intussusception and JIA.

B.3.10.5 AEs of special interest

Death

There were no deaths during the study.

Uveitis

There were no cases of uveitis during the open-label run-in. During the double-blind phase,1 patient in the placebo group had a mild case of active uveitis.

B.3.10.6 Safety conclusions

Tofacitinib has an established safety profile in adult patients with RA (73, 74), PsA (75) and ulcerative colitis (76, 77). During Study A3921104, no new safety signals or issues related either to treatment of JIA patients with tofacitinib or the overall tofacitinib safety profile were detected.

Injection site reactions, such as redness, swelling and pain are among the most commonly occurring AEs with adalimumab (78) and can be bothersome for the patient. As an oral preparation, tofacitinib avoids these issues.

Infections are considered one of the most relevant safety concerns for biologic treatments (79). However, it was not possible to conduct an ITC using infection data as proportion of patients who experienced an infection was not reported for either the adalimumab or tocilizumab trials (51, 57, 59, 71). URTI was selected for specific comparison as it was frequently reported in the trials included in the ITC analysis. The risk of URTI compared with tofacitinib varies widely across competitors, but the CIs were wide and none of the comparisons shown statistically significant difference.

B.3.11 Conclusions about comparable health benefits and safety

The ITC (Section B.3.9) showed no statistically significant differences between tofacitinib and the chosen comparators (adalimumab and tocilizumab) in terms of risk of disease flare and JIA ACR responses. Therefore, tofacitinib can be considered similarly clinically effective to the currently available biologics with respect to these

outcomes in the treatment of pcJIA. No major sources of heterogeneity were identified in the trials informing the ITCs (Section B.3.9).

Tofacitinib has an established safety profile in other indications and during Study A3921104, no new safety signals or issues related either to treatment of JIA patients with tofacitinib or the overall tofacitinib safety profile were detected.

In TA373, risk of disease flare was a key driver of cost-effectiveness and the main clinical outcome included in the economic model (see section B.2.1). The Committee considered that including disease flare in the model was appropriate, but that it did not reflect all benefits of biological treatments. The Committee considered that the effect of the 4 technologies on controlling disease activity and duration (including flare, response and remission) was an important benefit, but that the Assessment Group's model did not fully capture this. The additional possible clinical benefits of the technologies were expected to reduce the ICERs had they been included.

B.3.11.1 Uncertainties in the evidence

The ITCs were conducted using a well-known, transparent methodology (70). However, there are several limitations and uncertainties regarding the evidence used in this analysis; these are discussed in detail in Section B.3.9. Briefly, only one study informed each pairwise treatment comparison, precluding the conduct of any sensitivity analyses due to limited data. The sample sizes of studies included in the ITC analyses were relatively small, ranging from 75 to 173 patients, and the patient population included in the ITCs comprised those who had already achieved a response on active treatment during the open-label lead-in phase. There were differences across the studies in terms of duration, baseline characteristics and concomitant methotrexate use.

During TA373 the Assessment group identified similar uncertainties in the evidence base and the Appraisal Committee acknowledged that a robust comparison of the technologies with each other was not possible given the differences between the trials. It concluded, however, that all technologies were clinically effective for polyarticular JIA (as measured by disease flare rate and ACR Pedi responses), and there was no evidence to suggest that abatacept, adalimumab, etanercept and

tocilizumab for polyarticular JIA are different from each other in terms of clinical effectiveness.

B.3.12 Ongoing studies

A summary of the ongoing studies assessing tofacitinib in JIA is presented in Table 21.

Table 21. Ongoing studies assessing tofacitinib in juvenile idiopathic arthritis

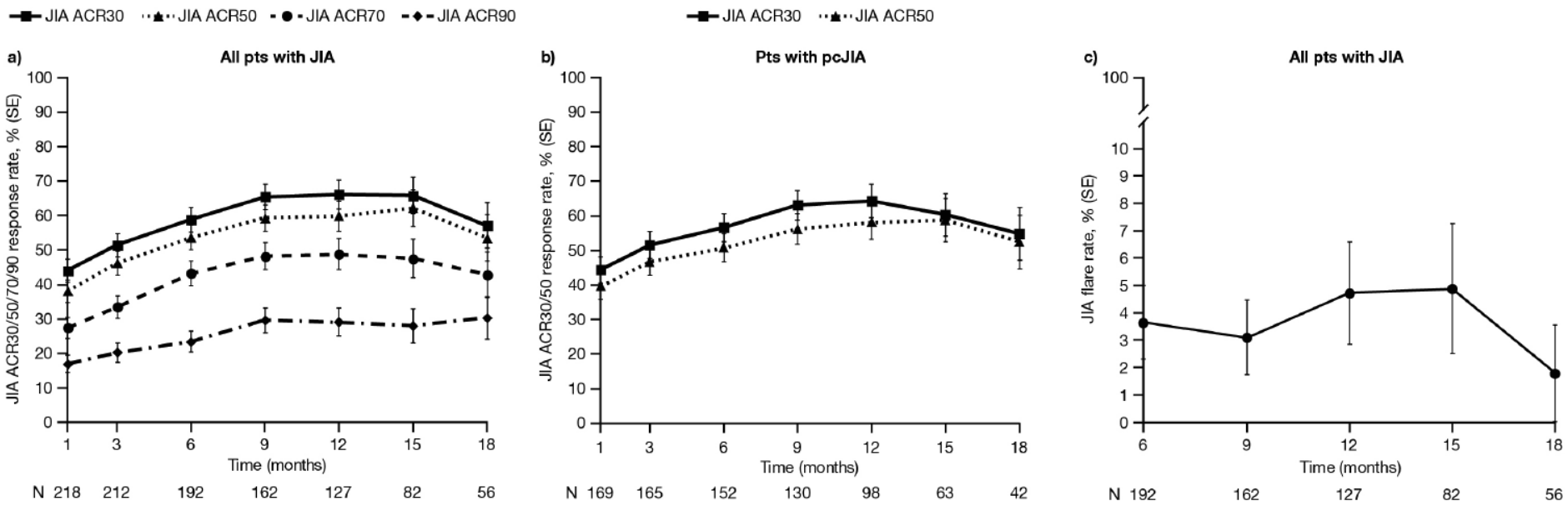
Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.
Study A3921145 long-term open-label, non-comparative extension study	Tofacitinib	Patients aged 2 to 18 who have previously participated in the previous Phase 1 and Phase 3 studies of tofacitinib in JIA The study included patients with pcJIA, ERA and PsA.	To determine the long-term safety and tolerability of tofacitinib for treatment of JIA	Brunner 2020
Study A3921165	Tofacitinib	Patients aged 2 to 18 who have active sJIA disease according to ILAR criteria for at least 6 weeks before screening	To determine the efficacy, safety, tolerability and pharmacokinetics of tofacitinib for treatment of sJIA with active systemic features in children and young people.	NCT03000439 (80)

B.3.12.1 Interim results from the long-term extension study (Study A3921145)

Interim results from the open-label extension study are available for up to 66 months (64). The interim analysis was performed on a data cut from June 4, 2019. The dosing regimen of tofacitinib was the same as in Study A39211104 (5 mg BID or equivalent weight-based dose). Safety endpoints, reported up to 66 months, were AEs and active uveitis. Efficacy endpoints, reported through 18 months, included JIA ACR 30/50/70/90 response rates, JIA ACR 30/50 response rates for patients with pcJIA, JIA ACR clinical remission (i.e. inactive disease for 6 months continuously), JIA flare rate, mean JADAS-27 CRP, JADAS-27 CRP minimal disease activity (scores ≤3.8 and ≤2 in patients with >4 and ≤4 active joints, respectively) rate and mean CHAQ DI.

The results of the interim analysis were similar to those of Study A3921104. There were no new safety findings and clinical efficacy was maintained over 18 months (Figure 14).

Figure 14 Results of the interim analysis of Study A3921165: a) JIA ACR 30/50/70/90 response rates through Month 18 in all patients, b) JIA ACR 30/50 response rates in pcJIA patients, c) JIA flare rate in all patients



Missing values were not imputed. Baseline values for determining JIA ACR 30/50/70/90 response rates were those of the qualifying index study, except for patients who enrolled more than 14 days after the end of study visit of the qualifying index study, whose baseline values were those of the long-tern extension study. As such Month 1 was the first time point at which it was possible to calculate response rates for all patients with available data. Baseline values for determining flare rate were those of the Month 3 visit of the long-term extension study. As such, Month 6 was the first time point at which it was possible to calculate flare rate.

ACR, American College of Rheumatology; JIA, juvenile idiopathic arthritis; pcJIA, polyaticular course JIA; pts, patients; SE, standard error

Source: Brunner et al, 2020 (64)

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Tofacitinib is the first orally administered treatment, that will be available for patients with pcJIA. All currently available biological treatment options, including the comparators of this appraisal, adalimumab and tocilizumab, are administered parenterally, either as subcutaneous (SC) injection or intravenous (IV) formulation.

Patients receiving their treatment as an IV infusion need to visit an appropriate facility to have the treatment delivered by a consultant paediatric rheumatologist. Besides, a proportion of patients who receives the treatment as a SC injection also require assistance with administering the injection due to fear of needles or needle phobia, as discussed in section B.1.3.5. These patients often need to visit an appropriate facility to have the treatment administered by a community nurse, which has cost implications to the NHS. The proportion of patients who require community nurse assistance with administering SC injection can be as high as 30-50% (3). Consequently, the introduction of tofacitinib into secondary care is expected to improve service provision and decrease resource use by making obsolete the need for a healthcare professional to administer the treatment.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

Cost inputs considered in the base-case analysis comprised of drug acquisition costs and administration costs. Only direct medical costs were included in the model. Unit costs were sourced from the 2018/19 NHS reference costs(56), the Monthly Index of Medical Specialties (MIMS)(81). The analyses also included the PAS applicable for tofacitinib. In the case of adalimumab, the lowest per mg cost biosimilar was considered in the calculations.

Costs were calculated for ages 2-18 year old patients to cover the full scope of licensed dose until the maximum dose of tocilizumab is reached (18 years). Separate results were also presented for 11-year old and 16-year old patients to account for differences in costs according to changes in dosing. In the economic

model for TA373, the starting age of the modelled population was 11 years (to reflect the average age of the clinical trials) and [redacted].

Aggregated results were also calculated for patients aged 11-18 years old, with drug and administration costs accrued every three months. This time horizon was considered long enough to capture the difference in costs of treatment for patients with pcJIA. Future costs were discounted at 3.5% in the base case, in line with the NICE reference case. The impact of no discounting (0%) was explored in scenario analysis.

B.4.2.2 Intervention and comparators' acquisition costs

Unit costs for each comparator are summarised in Table 22 for tofacitinib, adalimumab and tocilizumab. The dose and posology of each treatment were taken from the Summary of Product Characteristics (SmPC). The dosage of all treatment options is based on the patient's body weight. The dose of adalimumab between 20-30kg is 20mg every other week; for patients weighting 30kg or above the dose is 40mg every other week. The dose for tocilizumab SC injection is 162mg once every 3 weeks in patients weighing less than 30kg and 162mg once in every 2 weeks in patients weighing greater than or equal to 30kg. The dose of tocilizumab IV infusion is 10mg/kg once every 4 weeks in patients weighing less than 30kg and 8mg/kg once every 4 weeks in patients 30kg or above.

Tofacitinib is available either as an oral solution or tablet. The SmPC suggests that [redacted]. The base case analysis assumed that [redacted]. Based on clinical advice, it was assumed that patients would use the whole bottle or box before opening the new prescription package and thus no wastage for oral tofacitinib was considered in the model (3).

To capture the dose increase, age and weight data from the Royal College of Paediatrics and Child Health for boys and girls between 2-18 years old(82) (Table

23) were digitised and used. To estimate the quarterly cost for each treatment, linear interpolation was applied to bi-annual estimates of age and height.

To estimate the quarterly cost of adalimumab SC, and tocilizumab SC and IV, the acquisition cost of each administration was multiplied by the number of administrations in a three-month period. In the base case analysis it was assumed that any unused medication in an opened vial would be thrown away. This meant minimal vial wastage for adalimumab because it is available in 20mg and 40mg pre-filled syringes or pens. Tofacitinib SC is also administered in full 162mg pre-filled syringes or pens, however tofacitinib IV is administered in a mg/kg dose and available in 80, 200 and 400 mg vials.

Table 22 Acquisition costs of the intervention and comparator technologies

	Tofacitinib	Adalimumab	Tocilizumab
Pharmaceutical formulation	• 240 ml bottle of 1mg/ml solution • 5 mg tablets in 56 tablets pack	1x20 mg or 2x40 mg solution for injection in pre-filled syringe or pre-filled pen	4x162 mg/0.9ml in prefilled syringe or pre-filled pen or 80 mg or 200 mg or 400 mg solution for infusion
(Anticipated) care setting	Secondary care	Secondary care	Secondary care
Acquisition cost (excluding VAT)	[redacted] or [redacted] (PAS prices)	£158.40 or £633.60 (list prices) *	£913.12 or £102.40 or £256.00 or £512.00 (list prices) *
Method of administration	Oral solution or oral tablets	SC injection	SC injection or IV infusion (assuming 80% of patients uses SC and 20% IV)
Dose	10 to <20kg: 3.2 mg BID (as 3.2 mL oral solution) 20 to <40kg: 4 mg BID (as 4 mL oral solution) ≥40kg: 5 mg BID (as one 5 mg tablet or 5 mL oral solution)	10 kg to < 30 kg 20 mg every other week ≥ 30 kg 40 mg every other week	SC tocilizumab: 162 mg once every 2 weeks in patients ≥30kg or 162 mg once every 3 weeks in patients weighing <30 kg. IV tocilizumab: 8 mg/kg once every 4 weeks in patients ≥30kg or 10 mg/kg once every 4 weeks in patients weighing <30 kg.
Dosing frequency	Twice daily	Every 2 weeks	**SC**: <30kg every 3 weeks; ≥30kg every 2 weeks **IV**: Every 4 weeks
Dose adjustments	N/A	N/A	N/A
Average length of a course of treatment	Long term	Long term	Long term
Average cost of 1 year of treatment (acquisition costs only)	Variable by age. Indicative: average cost over 1 year: 11 y/o patient : [redacted] 16 y/o patient :	Variable by age. Indicative: average cost over 1 year: 11 y/o patient : £8,237 16 y/o patient : £8,237	Variable by age. Indicative: average cost over 1 year: 11 y/o patient : £5,946 16 y/o patient : £6,346

	Tofacitinib	Adalimumab	Tocilizumab
(Anticipated) average interval between courses of treatment	N/A	N/A	N/A
(Anticipated) number of repeat courses of treatment	Continuous treatment	Continuous treatment	Continuous treatment

IV, intravenous; N/A, not applicable; PAS, patient access scheme; SC, subcutaneous, y/o, year old
*Cheapest available prices were used from the Monthly Index of Medical Specialties (81)

Table 23 Median weight and height used in the model

	Weight (median value in kg)		Height (median value in cm)	
Age	**Boys**	**Girls**	**Boys**	**Girls**
2.0	12.20	11.30	87.14	86.04
2.5	13.30	12.50	91.81	90.90
3.0	14.50	13.80	96.04	95.34
3.5	15.50	14.80	99.78	99.31
4.0	16.40	15.90	102.64	101.59
4.5	17.80	17.30	106.10	105.20
5.0	18.80	18.30	109.67	108.98
5.5	19.90	19.40	112.90	112.34
6.0	20.10	20.40	116.02	115.41
6.5	22.10	21.70	119.00	118.35
7.0	23.40	23.00	121.92	121.30
7.5	24.70	24.50	124.97	124.50
8.0	26.00	25.90	127.89	127.00
8.5	27.40	27.20	130.75	130.20
9.0	28.80	28.60	133.29	132.95
9.5	29.80	30.40	135.80	135.69
10.0	31.30	32.20	138.36	138.56
10.5	33.00	34.00	140.98	141.37
11.0	34.50	35.90	143.27	144.11
11.5	36.20	37.90	145.62	147.10
12.0	38.00	40.10	148.29	149.97
12.5	40.50	42.60	151.13	152.78
13.0	42.90	45.10	154.52	155.56
13.5	46.00	47.60	158.35	157.84
14.0	49.20	49.80	162.12	160.00
14.5	52.40	51.70	165.68	161.23
15.0	55.30	53.40	168.74	162.30
15.5	58.10	54.30	171.19	162.94
16.0	60.50	55.30	173.10	163.28
16.5	62.70	56.10	174.51	163.49
17.0	64.50	56.70	175.71	163.55

17.5	65.70	57.10	176.35	163.58
18.0	66.80	57.40	176.77	163.64

B.4.2.3 Intervention and comparators' healthcare resource use and associated costs

An SLR was conducted to identify studies reporting resource use and cost data for patients with pcJIA. Overall, 36 studies were identified, including 14 full-text papers (3 UK studies and 10 non-UK) and 22 abstracts (1 UK-based and 21 non-UK). The search found no new studies that were published since the publication of TA373, that would report on resource use estimations for JIA. Thornton et al. 2008(54) was still the most relevant study for resource use assumptions, which assumed the same resource use across all biological therapies (also see section B.2.2). The identification of relevant cost and healthcare resource data for England and the methods of the SLR is described in detail in Appendix G.

The frequency of administration for each treatment is presented in Table 22. Tofacitinib is given orally and requires no resources for training or administration. Adalimumab is administered as an SC injection while tocilizumab has SC and IV infusion formulation.

Intravenous infusions were assumed to be administered by a health care professional with the cost of IV administration assumed to be equal to the cost of an outpatient visit, based on the mean of a consultant-led, non-admitted, face-to-face follow-up and non-admitted, face-to-face, first appointment. Unit costs were taken from the 2018-19 NHS Reference Cost values(56) and estimated to be £241.47 per administration. Unit costs and calculations are detailed in Table 24.

Regarding SC injection administrations, clinical expert advice suggested that a proportion (between 30-50%) of patients would still require assistance from a healthcare professional to administer the treatment. Mulligan et al. 2013 reported that approximately 25% of patients almost always feel anxious about SC injections(41). Therefore, in the base case analysis it was assumed that 25% of patients would require assistance from a community care nurse. The unit cost of this visit was estimated at £67.27. The proportion of patients who required assistance

with SC administration was varied in sensitivity analysis between no cost and a higher proportion of 62.5% reporting anxiety sometimes, from Mulligan et al. 2013(41).

Table 24 Treatment administration costs

Currency Code	No. of attendances	National Average Unit Cost	Source/assumptions
Intravenous infusion			
Consultant led (CL) - Non-Admitted Face-to-Face Attendance, Follow-up	25,487	£216.72	NHS Reference Cost 2018-19(56), CL WF01A (Paediatric rheumatology)
Consultant led (CL) - Non-Admitted Face-to-Face Attendance, Follow-up	2,005	£114.24	NHS Reference Cost 2018-19(56), CL WF01C (Paediatric rheumatology)
Consultant led (CL) - Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	4,417	£267.73	NHS Reference Cost 2018-19(56), CL WF02A (Paediatric rheumatology)
Consultant led (CL) - Non-Admitted Face-to-Face Attendance, First	7,838	£329.67	NHS Reference Cost 2018-19(56), CL WF01B (Paediatric rheumatology)
Consultant led (NCL) - Non-Admitted Face-to-Face Attendance, First	135	£90.42	NHS Reference Cost 2018-19(56), CL WF01D (Paediatric rheumatology)
Consultant led (CL) - Multiprofessional Non-Admitted Face-to-Face Attendance, First	1,305	£317.28	NHS Reference Cost 2018-19(56), CL WF02B (Paediatric rheumatology)
Cost per intravenous administration	£241.47 (£90.42 to £329.67)		NHS Reference Cost 2018-19(56), weighted average of the number of attendances and the unit cost of CL WF01A, WF01B, WF01C, WF01D, WF02A, WF02B The range of values was determined by the lowest and highest limit of the CL costs.
Subcutaneous injection			
Specialist Nursing, Arthritis Nursing/Liaison, Child, Face to face	970	£67.27 (£27.33 to £107.21)	NHS Reference Cost 2018-19(56), N07CF The higher limit of the range was based on the unit cost of NURS N12 and the lower limit on the difference between the higher limit and the mean value

CL, consultant led; NHS, National Health Service.

No additional treatment-related monitoring costs for tofacitinib were assumed(83). Healthcare resource use and associated costs for each treatment are presented in Table 25.

Table 25 Resource costs of the intervention and comparator technologies

	Tofacitinib	Tocilizumab	Adalimumab
Administration cost			
Unit cost			
Cost (£), price year 2018/19	£0	Tocilizumab SC: £13.45 per administration (80% of patients, 25% of patients require help with administering SC injection due to fear of needles or needle phobia) Tocilizumab IV: £48.29 per administration (20% of patients)	£16.82 per administration (25% of patients require help with administering SC injection due to fear of needles or needle phobia)
Source reference	N/A	NHS Reference Costs 2018/19(56)	NHS Reference Costs 2018/19(56)
Rationale for source	N/A	Latest NHS costs associated with the administration of treatment.	Latest NHS costs associated with the administration of treatment
Units per course of treatment			
Number of units	N/A	Tocilizumab SC <30 kgs: 4.3 administrations every 3 months Tocilizumab SC ≥30 kgs: 6.5 administrations every 3 months Tocilizumab IV: 3.25 administrations every 3 months	6.5 administrations every 3 months
Source reference	SmPC(5)	SmPC for SC(84) and IV(85)	SmPC(86)
Rationale for source	In line with the marketing authorisation of the treatment	In line with the marketing authorisation of the treatment	In line with the marketing authorisation of the treatment
Total cost of administration			
Per course of treatment (3 months cost)	11 y/o patient: £0	11 y/o patient: £244.40	11 y/o patient: £109.31
Over the full time-horizon **(undiscounted)**	£0	£28,698	£13,226

IV, intravenous; N/A; not applicable; NHS, National Health Service; SC, subcutaneous; SmPC, Summary of Product Characteristics.

B.4.2.4 Adverse reaction unit costs and resource use

As there was no statistically significant difference in the adverse event rates from the indirect treatment comparison, adverse event costs were not included in the cost comparison (see section B.3.10 Adverse reactions).

B.4.2.5 Miscellaneous unit costs and resource use

None that are relevant.

B.4.2.6 Clinical expert validation

One clinical expert was interviewed in November 2020 and validated the following aspects of the submission (3):

- Relevant comparators
- Similarity of efficacy between treatments
- Similarity of safety profile between treatments
- Similarity of resource use between treatments
- The frequency of use of tocilizumab SC and IV formulations
- No wastage to be assumed for tofacitinib
- Differences in administration costs and the use of community care for a proportion of patients that require SC injections (25%)
- Market share of comparators

B.4.2.7 Sensitivity and scenario analyses

One-way sensitivity analysis (OWSA) was carried out, varying the relevant inputs between upper and lower values.

- Community care use was varied between 0% to 62.5% assuming no need for community care and a higher proportion (62.5%) based on patients reporting anxiety sometimes, informed by the study from Mulligan et al. 2013(41).
- Community care cost for administration of SC injection was varied between £27.33 to £107.21, informed by the lower and upper limits of the unit cost described in Table 24.
- The IV administration unit cost was varied from £90.42 to £329.67, informed by the lower and upper limit of the unit cost described in Table 24.

In addition, a number of scenario analyses were conducted to test the influence of the model assumptions in the base-case results. The scenarios explored were:

- No discounting of future costs (0%)
- Changing the percentage of tocilizumab SC and IV use and assuming 100% SC tocilizumab use
- Inclusion of background drug acquisition and administration costs of methotrexate.

Changing the percentage of tocilizumab SC and IV use

In the base case, following clinical advice it was assumed that 80% of patients would use SC injections and 20% IV infusions of tocilizumab. In this scenario analysis the impact of changing the percentage of IV and SC use was varied. The first assumption was 100% SC use, in line with current NICE recommendation on switching IV treatments to SC form if possible (30) (see section B.1.3.5 Unmet need). The second assumption was 40% IV and 60% SC tocilizumab use.

Background treatment with methotrexate

All technologies considered in this submission can be used in combination with methotrexate, however our base case assumption was that adding the costs of concomitant methotrexate use would not lead to cost differences between the technologies. Concomitant methotrexate use for adalimumab and tocilizumab was informed from two clinical trials(49, 51) and for tofacitinib from the pivotal trial A3921104(87). The proportion of patients receiving methotrexate in the clinical trials was different amongst trials as it is presented in Table 26 Concomitant drug and methotrexate use. In scenario A it was assumed that 80% of patients would receive concomitant methotrexate with all technologies (tofacitinib, adalimumab and tocilizumab). In scenario B it was assumed that 70% of patients would receive concomitant methotrexate with tofacitinib and 80% of patients with adalimumab and tocilizumab.

Table 26 Concomitant drug and methotrexate use

Trial	Treatment	Number of randomised patients	Proportion using methotrexate

Brunner 2014 (CHERISH)(51)	Placebo	81	79%
Brunner 2014 (CHERISH)(51)	Tocilizumab (8 mg/kg Q4W or 10 mg/kg Q4W)	82	79%
Lovell 2008 (DE038)(49)	Placebo plus methotrexate (≥10 mg/m^2/week)	37	100%
Lovell 2008 (DE038)(49)	Adalimumab (24 mg/m^2 Q2W) plus methotrexate (≥10 mg/m^2/week)	38	100%
Lovell 2008 (DE038)(49)	Placebo	28	0%
Lovell 2008 (DE038)(49)	Adalimumab (24 mg/m^2 Q2W)	30	0%
Brunner 2019 (Study A3921104) (87)	Placebo	85	68%
Brunner 2019 (Study A3921104)(87)	Tofacitinib (2 mg - 5 mg)	88	66%

Q2W, every two weeks, Q4W, every four weeks.

The unit cost for methotrexate was derived from the online version of MIMS(81) and is summarised in Table 27 Methotrexate unit cost The patient body surface area (BSA), required for the calculation of the methotrexate dose, was estimated using the Du Bois formula (BSA = 0.007184 * Height^0.725 * Weight^0.425)(88) with weight and height data derived from the Royal College of Paediatrics and Child Health(82).

Methotrexate was assumed to be administered as an oral solution or subcutaneously. The percentage use of subcutaneous formulations was informed by a UK study by Mulligan et al. 2013(41) which explored the prevalence and extent of difficulties and side effects associated with the use of methotrexate and the impact on quality of life. In this study, 32.2% of patients reported using the oral solution(41), and in our model the value of 67.8% (complement) was therefore used for SC injection use.

Table 27 Methotrexate unit cost

Drug	Pack size	Strength (g/mg)	Pack cost	Cost per dose
Methotrexate	28	2.5 mg	£2.56	£0.04
Methotrexate	100	10 mg	£54.19	£0.05
Methofil	1	7.5	£10.86	£1.45
Metoject	1	7.5	£12.87	£1.72
Nordimet/Zlatal	1	7.5	£13.37	£1.78
Methofil	1	10.0	£11.25	£1.13
Metoject	1	10.0	£13.26	£1.33
Nordimet/Zlatal	1	10.0	£13.77	£1.38
Methofil	1	12.5	£12.34	£0.99
Metoject	1	12.5	£14.35	£1.15
Nordimet/Zlatal	1	12.5	£14.85	£1.19
Methofil	1	15.0	£12.40	£0.83
Metoject	1	15.0	£14.41	£0.96
Nordimet/Zlatal	1	15.0	£14.92	£0.99
Methofil	1	17.5	£13.24	£0.76

Drug	Pack size	Strength (g/mg)	Pack cost	Cost per dose
Metoject	1	17.5	£15.25	£0.87
Nordimet/Zlatal	1	17.5	£15.75	£0.90
Methofil	1	20.0	£13.55	£0.68
Metoject	1	20.0	£15.56	£0.78
Nordimet/Zlatal	1	20.0	£16.06	£0.80

Methotrexate SC was assumed to be administered every week as per the SmPC. For tocilizumab IV, it was assumed that patients will receive methotrexate weekly as well as during the IV administration. Results of the scenario analyses with 80% methotrexate use for all treatments and 70% for tofacitinib only are presented in Table 34.

B.4.3 Base-case results

Annual costs for an 11-year-old and 16-year-old patient as well as aggregate discounted results for 11-18 years old age group are presented in Table 28. Table 29 presents the annual costs for each age group between 2-18 years of age.

Table 28 Base-case results

Technologies	Acquisition costs (£)	Administration costs (£)	Total costs (£)	Incremental costs (Tofacitinib - comparator)
Base-case results for an 11-year-old patient				
Tofacitinib	[redacted]	£0	[redacted]	N/A
Tocilizumab	£5,946	£978	£6,924	[redacted]
Adalimumab	£8,237	£437	£8,674	[redacted]
Base-case results for a 16-year-old patient				
Tofacitinib	[redacted]	£0	[redacted]	N/A
Tocilizumab	£6,346	£978	£7,323	[redacted]
Adalimumab	£8,237	£437	£8,674	[redacted]
Base-case aggregated, discounted results for 11-18 years olds				
Tofacitinib	[redacted]	£0	[redacted]	N/A
Tocilizumab	£31,779	£5,038	£36,817	[redacted]
Adalimumab	£42,448	£2,253	£44,702	[redacted]

N/A, not applicable

Table 29 Base-case results for age categories between 2-18 years of age

Age	Tofacitinib	Adalimumab	Tocilizumab
2	[redacted]	£4,556	£4,559
3	[redacted]	£4,556	£4,559
4	[redacted]	£4,556	£4,692
5	[redacted]	£4,556	£4,692
6	[redacted]	£4,556	£4,825
7	[redacted]	£4,556	£4,892
8	[redacted]	£4,556	£4,958
9	[redacted]	£6,615	£5,941
10	[redacted]	£8,674	£6,658
11	[redacted]	£8,674	£6,924
12	[redacted]	£8,674	£6,924
13	[redacted]	£8,674	£7,024
14	[redacted]	£8,674	£7,157
15	[redacted]	£8,674	£7,257
16	[redacted]	£8,674	£7,323
17	[redacted]	£8,674	£7,323
18	[redacted]	£8,674	£7,323

Total 3-monthly costs for each drug and for each age group are presented in Figure 15. Tofacitinib is cheaper than tocilizumab and adalimumab for all age groups.

Figure 15 Total cost comparison for adalimumab, tocilizumab and tofacitinib, undiscounted results

B.4.4 Sensitivity and scenario analyses

B.4.4.1 Sensitivity analysis

Table 30 presents the results of the one-way sensitivity analyses, aggregated for 11-18 year olds. For both comparisons with adalimumab and tocilizumab, the analysis was minimally sensitive to changes in assumptions around the community care use for the administration of SC injections, the unit cost of the SC administration by a community nurse and the unit cost of IV administration.

Table 30 Results of the one-way sensitivity analysis (compared to Tofacitinib)

	Tofacitinib vs Tocilizumab		Tofacitinib vs Adalimumab	
Model parameter	**Low value**	**High value**	**Low value**	**High value**
Community care nurse use	[redacted]	[redacted]	[redacted]	[redacted]
Community care nurse cost	[redacted]	[redacted]	[redacted]	[redacted]
IV administration costs	[redacted]	[redacted]	N/A	N/A

IV, intravenous; vs, versus; N/A, not applicable

B.4.4.2 Scenario analyses

B.4.4.2.1 No future costs discounting (0%)

Aggregate undiscounted results are presented in Table 31. The results showed that the incremental costs [redacted] if no discounting is applied.

Table 31 Undiscounted aggregate results

Technologies	Acquisition costs (£)	Administration costs (£)	Total costs (£)	Incremental costs (Tofacitinib comparator)
Tofacitinib	[redacted]	£0	[redacted]	N/A
Tocilizumab	£49,434	£7,821	£57,255	[redacted]
Adalimumab	£65,894	£3,498	£69,392	[redacted]

N/A, not applicable.

B.4.4.2.2 Changing the percentage of tocilizumab SC and IV use

The results demonstrated in Table 32 show that

[redacted]

Table 32 Results with assuming 100% tocilizumab SC use

Technologies	Acquisition costs (£)	Administration costs (£)	Total costs (£)	Incremental costs (Tofacitinib comparator)
Tofacitinib	[redacted]	£0	[redacted]	N/A
Tocilizumab	£30,587	£2,253	£32,841	[redacted]
Adalimumab	£42,448	£2,253	£44,702	[redacted]

N/A, not applicable.

Table 333 Results with assuming 40% tocilizumab IV use and 60% tocilizumab SC

Technologies	Acquisition costs (£)	Administration costs (£)	Total costs(£)	Incremental costs (Tofacitinib comparator)
Tofacitinib	[redacted]	£0	[redacted]	N/A
Tocilizumab	£32,971	£7,823	£40,794	[redacted]
Adalimumab	£42,448	£2,253	£44,702	[redacted]

n/a, not applicable

B.4.4.2.3 Background treatment with methotrexate

Table 34 Results of scenario with background use of methotrexate

Technologies	Acquisition costs (£)	Administration costs (£)	Total costs (£)	Incremental costs (Tofacitinib comparator)
80% methotrexate use for all treatments				
Tofacitinib	[redacted]	£2,444	[redacted]	N/A
Tocilizumab	£33,804	£6,382	£40,186	[redacted]
Adalimumab	£44,473	£3,475	£47,948	[redacted]
80% methotrexate use for adalimumab and tocilizumab and 70% use for tofacitinib				
Tofacitinib	[redacted]	£2,139	[redacted]	N/A
Tocilizumab	£33,804	£6,382	£40,186	[redacted]
Adalimumab	£44,473	£3,475	£47,948	[redacted]

N/A, not applicable.

B.4.5 Subgroup analysis

No subgroup analyses were conducted.

B.4.6 Interpretation and conclusions of economic evidence

A cost-comparison analysis was developed for the economic evaluation of tofacitinib versus adalimumab and tocilizumab. Given the similarities in efficacy and safety between the comparators, only acquisition and administration costs were considered in the analyses. As the Assessment Group in TA373 concluded, the differences in

cost-effectiveness of the biologic DMARDs are primarily the effect of the differences in the drug acquisition cost(4).

The resource use assumptions for the administration of treatments followed the analysis conducted by the Assessment Group during NICE TA373(4), and was validated by a clinical expert on the use of community nurse support for SC injections (3).

The results considered the confidential PAS of tofacitinib and list price for the comparators. The results showed that overall, tofacitinib [redacted]

compared to adalimumab or to tocilizumab, aggregated for the age group of 11-18 years and annually for each age group between 2-18 years old patients. Deterministic sensitivity and scenario analyses showed that tofacitinib [redacted]

[redacted] for these patients, despite changes to the inputs and assumptions.

In summary, it can be concluded that tofacitinib would provide [redacted] for the NHS in the treatment of patients with pcJIA.

Tofacitinib has further benefits that were not parameterised in the cost-minimisation analysis. These relate to the oral administration of the treatment, preventing adverse events such as injection site reactions and especially benefiting patients with needle fear or needle phobia. It also allows minimising the number of in-person clinic visits and increase remote/virtual patient management, which has been a trend in the NHS as a result of the current pandemic.

B.5 References

1. Ramanan A, Dick A, Jones A, McKay A, Williamson P, Compeyrot-Lacassagne S, et al. Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis. New England journal of medicine [Internet]. 2017; 376(17):[1637-46 pp.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01372331/full https://www.nejm.org/doi/pdf/10.1056/NEJMoa1614160?articleTools=true.

2. Kearsley-Fleet L, Heaf E, Davies R, Baildam E, Beresford MW, Foster HE, et al. Frequency of biologic switching and the outcomes of switching in children and young people with juvenile idiopathic arthritis: a national cohort study. Lancet Rheumatol. 2020;2(4):e217-e26.

3. Pfizer Ltd. Clinical expert interview. 2020.

4. National Institute for Health and Care Excellence. Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis. Technology appraisal guidance TA373. 2015.

5. Pfizer. Xeljanz 5 mg film-coated tablets. Summary of product characteristics (DRAFT). 2020.

6. Hodge JA, Kawabata TT, Krishnaswami S, Clark JD, Telliez JB, Dowty ME, et al. The mechanism of action of tofacitinib - an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. Clinical and experimental rheumatology. 2016;34(2):318-28.

7. Murray PJ. The JAK-STAT signaling pathway: input and output integration. Journal of immunology (Baltimore, Md : 1950). 2007;178(5):2623-9.

8. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31(2):390-2.

9. Umławska W, Prusek-Dudkiewicz A. Growth retardation and delayed puberty in children and adolescents with juvenile idiopathic arthritis. Archives of medical science : AMS. 2010;6(1):19-23.

10. Versus Arthritis. Juvenile idiopathic arthritis (JIA) 2018 [Available from: https://www.versusarthritis.org/about-arthritis/conditions/juvenile-idiopathic-arthritis/.

11. Shepherd J, Cooper K, Harris P, Picot J, Rose M. The clinical effectiveness and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2016;20(34).

12. Moorthy LN, Peterson MG, Hassett AL, Lehman TJ. Burden of childhood-onset arthritis. Pediatric rheumatology online journal. 2010;8:20.

13. Patient Info. Juvenile idiopathic arthritis 2015 [Available from: patient.info/doctor/juvenile-idiopathic-arthritis-pro.

14. Mayo Clinic. Juvenile idiopathic arthritis 2017 [Available from: https://www.mayoclinic.org/diseases-conditions/juvenile-idiopathic-arthritis/symptoms-causes/syc-20374082.

15. Amine B, Rostom S, Benbouazza K, Abouqal R, Hajjaj-Hassouni N. Health related quality of life survey about children and adolescents with juvenile idiopathic arthritis. Rheumatol Int. 2009;29(3):275-9.

16. Angelis A, Kanavos P, López-Bastida J, Linertová R, Serrano-Aguilar P. Socioeconomic costs and health-related quality of life in juvenile idiopathic arthritis: a cost-of-illness study in the United Kingdom. BMC musculoskeletal disorders. 2016;17:321.

17. Bruns A, Hilário MO, Jennings F, Silva CA, Natour J. Quality of life and impact of the disease on primary caregivers of juvenile idiopathic arthritis patients. Joint bone spine. 2008;75(2):149-54.

18. Grande SW, Longacre MR, Palmblad K, Montan MV, Berquist RP, Hager A, et al. Empowering Young People Living With Juvenile Idiopathic Arthritis to Better Communicate With Families and Care Teams: Content Analysis of Semistructured Interviews. JMIR mHealth and uHealth. 2019;7(2):e10401.

19. Haverman L, Grootenhuis MA, van den Berg JM, van Veenendaal M, Dolman KM, Swart JF, et al. Predictors of health-related quality of life in children and adolescents with juvenile idiopathic arthritis: results from a Web-based survey. Arthritis Care Res (Hoboken). 2012;64(5):694-703.

20. Müller-Godeffroy E, Lehmann H, Küster RM, Thyen U. [Quality of life and psychosocial adaptation in children and adolescents with juvenile idiopathic arthritis and reactive arthritis]. Z Rheumatol. 2005;64(3):177-87.

21. Tong A, Jones J, Craig JC, Singh-Grewal D. Children's experiences of living with juvenile idiopathic arthritis: a thematic synthesis of qualitative studies. Arthritis care & research. 2012;64(9):1392-404.

22. Webb K, Wedderburn LR. Advances in the treatment of polyarticular juvenile idiopathic arthritis. Current opinion in rheumatology. 2015;27(5):505-10.

23. Oberle EJ, Harris JG, Verbsky JW. Polyarticular juvenile idiopathic arthritis - epidemiology and management approaches. Clin Epidemiol. 2014;6:379-93.

24. Children's Chronic Arthritis Association. About juvenile idiopathic arthritis 2020 [Available from: https://www.ccaa.org.uk/about-jia/.

25. Office for National Statistics. Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid 2019, using April 2020 local authority district codes 2020 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland.

26. Costello R, McDonagh J, Dixon W, Hyrich K, Humphreys J. P01 Incidence of juvenile idiopathic arthritis in the United Kingdom: estimates from a national primary care dataset. Rheumatology. 2019;58(Supplement_4).

27. Magni-Manzoni S, Pistorio A, Labo E, Viola S, Garcia-Munitis P, Panigada S, et al. A longitudinal analysis of physical functional disability over the course of juvenile idiopathic arthritis. Ann Rheum Dis. 2008;67(8):1159-64.

28. Lelieveld OT, Armbrust W, van Leeuwen MA, Duppen N, Geertzen JH, Sauer PJ, et al. Physical activity in adolescents with juvenile idiopathic arthritis. Arthritis Rheum. 2008;59(10):1379-84.

29. Bloom BJ, Owens JA, McGuinn M, Nobile C, Schaeffer L, Alario AJ. Sleep and its relationship to pain, dysfunction, and disease activity in juvenile rheumatoid arthritis. J Rheumatol. 2002;29(1):169-73.

30. Butbul Aviel Y, Stremler R, Benseler SM, Cameron B, Laxer RM, Ota S, et al. Sleep and fatigue and the relationship to pain, disease activity and quality of life in juvenile idiopathic arthritis and juvenile dermatomyositis. Rheumatology (Oxford). 2011;50(11):2051-60.

31. Hanns L, Cordingley L, Galloway J, Norton S, Carvalho LA, Christie D, et al. Depressive symptoms, pain and disability for adolescent patients with juvenile idiopathic arthritis: results from the Childhood Arthritis Prospective Study. Rheumatology (Oxford). 2018;57(8):1381-9.

32. Mullick MS, Nahar JS, Haq SA. Psychiatric morbidity, stressors, impact, and burden in juvenile idiopathic arthritis. J Health Popul Nutr. 2005;23(2):142-9.

33. British Association of Dermatologists. Guidelines for biologic therapy for psoriasis. Methods, evidence and recommendations.; 2017.

34. Martin G, Young M, Aldredge L. Recommendations for Initiating Systemic Therapy in Patients with Psoriasis. J Clin Aesthet Dermatol. 2019;12(4):13-26.

35. Rasu RS, Cline SK, Shaw JW, Hayes O, Agbor Bawa W, Cifaldi MA. Impact of JIA on parents' work absences. Rheumatology (Oxford). 2015;54(7):1177-85.

36. Torres-Made MD, Pelaez-Ballestas I, Garcia-Rodriguez F, Villarreal-Trevino AV, Fortuna-Reyna BJ, de la OCME, et al. Development and validation of the CAREGIVERS questionnaire: multi-assessing the impact of juvenile idiopathic arthritis on caregivers. Pediatr Rheumatol Online J. 2020;18(1):3.

37. Jacobse J, Ten Voorde W, Rissmann R, Burggraaf J, Ten Cate R, Schrier L. The effect of repeated methotrexate injections on the quality of life of children with rheumatic diseases. European journal of pediatrics. 2019;178(1):17-20.

38. Orenius T, Saila H, Mikola K, Ristolainen L. Fear of injections and needle phobia among children and adolescents: an overview of psychological, behavioural, and contextual factors. SAGE Open Nursing. 2018;4:1-8.

39. McLenon J, Rogers MAM. The fear of needles: A systematic review and meta-analysis. Journal of advanced nursing. 2019;75(1):30-42.

40. Collins K, Wren A, Lee T. Injection fear in juvenile idiopathic arthritis patients using injectable medications. Arthritis Rheumatol. 2019;71 (suppl 10).

41. Mulligan K, Kassoumeri L, Etheridge A, Moncrieffe H, Wedderburn LR, Newman S. Mothers' reports of the difficulties that their children experience in taking methotrexate for Juvenile Idiopathic Arthritis and how these impact on quality of life. Pediatr Rheumatol Online J. 2013;11(1):23.

42. NHS England. Clinical commissioning policy statement: biologic therapies for the treatment of juvenile idiopathic arthritis (JIA). 2015.

43. Garcês S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Annals of the rheumatic diseases. 2013;72(12):1947-55.

44. Maneiro JR, Salgado E, Gomez-Reino JJ. Immunogenicity of monoclonal antibodies against tumor necrosis factor used in chronic immune-mediated Inflammatory conditions: systematic review and meta-analysis. JAMA internal medicine. 2013;173(15):1416-28.

45. Zisapel M, Zisman D, Madar-Balakirski N, Arad U, Padova H, Matz H, et al. Prevalence of TNF-α blocker immunogenicity in psoriatic arthritis. J Rheumatol. 2015;42(1):73-8.

46. Doeleman MJH, van Maarseveen EM, Swart JF. Immunogenicity of biologic agents in juvenile idiopathic arthritis: a systematic review and meta-analysis. Rheumatology (Oxford, England). 2019;58(10):1839-49.

47. National Institute for Health and Care Excellence. COVID-19 rapid guideline: rheumatological autoimmune, inflammatory and metabolic bone disorders (NG167). 2020.

48. Lovell D, Giannini E, Reiff A, Cawkwell G, Silverman E, Nocton J, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. New England journal of medicine [Internet]. 2000; 342(11):[763-9 pp.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00275805/full https://www.nejm.org/doi/pdf/10.1056/NEJM200003163421103?articleTools=true.

49. Lovell D, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. New England journal of medicine [Internet]. 2008; 359(8):[810-20 pp.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00650630/full https://www.nejm.org/doi/pdf/10.1056/NEJMoa0706290?articleTools=true.

50. Ruperto N, Lovell D, Quartier P, Paz E, Rubio-Pérez N, Silva C, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet (london, england) [Internet]. 2008; 372(9636):[383-91 pp.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00640638/full https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(08)60998-8/fulltext.

51. Brunner H, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Annals of the rheumatic diseases [Internet]. 2014; 74(6):[1110-7 pp.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01083253/full https://ard.bmj.com/content/annrheumdis/74/6/1110.full.pdf.

52. Tynjälä P, Vähäsalo P, Honkanen V, Lahdenne P. Drug survival of the first and second course of anti-tumour necrosis factor agents in juvenile idiopathic arthritis. Ann Rheum Dis. 2009;68(4):552-7.

53. Prince FH, de Bekker-Grob EW, Twilt M, van Rossum MA, Hoppenreijs EP, ten Cate R, et al. An analysis of the costs and treatment success of etanercept in juvenile idiopathic arthritis: results from the Dutch Arthritis and Biologicals in Children register. Rheumatology (Oxford). 2011;50(6):1131-6.

54. Thornton J, Lunt M, Ashcroft DM, Baildam E, Foster H, Davidson J, et al. Costing juvenile idiopathic arthritis: Examining patient-based costs during the first year after diagnosis. Rheumatology. 2008;47(7):985-90.

55. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2014. 2014.

56. NHS Improvement. 2018/19 National Cost Collection data 2019 [Available from: https://improvement.nhs.uk/resources/national-cost-collection/.

57. Brunner H, Synoverska O, Ting T, Mendoza CA, Spindler A, Vyzhga Y, et al. Tofacitinib for the treatment of polyarticular course juvenile idiopathic arthritis: results of a phase 3 randomized, double-blind, placebo-controlled withdrawal study. ACR/ARP Annual Meeting; Atlanta, Georgia, USA2019.

58. Burgos-Vargas R, Tse SML, Horneff G, Pangan AL, Kalabic J, Goss S, et al. A randomized, double-blind, placebo-controlled multicenter study of adalimumab in pediatric patients with enthesitis-related arthritis. Arthritis Care and Research. 2015;67(11):1503-12.

59. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. New England Journal of Medicine [Internet]. 2008; 359(8):[810-20 pp.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00650630/full https://www.nejm.org/doi/pdf/10.1056/NEJMoa0706290?articleTools=true.

60. Quartier P, Baptiste A, Despert V, Allain-Launay E, Kone-Paut I, Belot A, et al. ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis. Annals of the Rheumatic Diseases. 2018;77(7):1003-11.

61. Pfizer. Data on file: Efficacy, safety, and tolerability of tofacitinib for treatment of polyarticular course juvenile idiopathic arthritis (JIA) in children and adolescent subjects (Study A3921104 clinical study report). Clinical Study Report. Pfizer Inc.; 2019.

62. Ruperto N, Synoverska O, Ting T, Abud-Mendoza C, Spindler A, Vyzhga Y, et al. Tofacitinib for the treatment of polyarticular course juvenile idiopathic arthritis: results of a phase 3, randomised, double-blind, placebo-controlled withdrawal study. Ann Rheum Dis. 2020;79 (suppl 1):180-1.

63. European Medicines Agency. Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006. Xeljanz.; 2020.

64. Brunner HI, Akikusa J, Al-Abadi E, Bohnsack J, Boteanu AL, Kobusinka K, et al. Tofacitinib for the treatment of patients with juveile idiopathic arthritis: an interim analysis of

data up to 5.5 years from an open-label long-term extension study. Arthritis & Rheumatology. 2020;72(S20).

65. Brunner HI, Lovell DJ, Finck BK, Giannini EH. Preliminary definition of disease flare in juvenile rheumatoid arthritis. J Rheumatol. 2002;29(5):1058-64.

66. Consolaro A, Ruperto N, Bazso A, Pistorio A, Magni-Manzoni S, Filocamo G, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis and rheumatism. 2009;61(5):658-66.

67. Consolaro A, Bracciolini G, Ruperto N, Pistorio A, Magni-Manzoni S, Malattia C, et al. Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis: defining criteria based on the juvenile arthritis disease activity score. Arthritis and rheumatism. 2012;64(7):2366-74.

68. Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis and rheumatism. 1994;37(12):1761-9.

69. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

70. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of clinical epidemiology. 1997;50(6):683-91.

71. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton J, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. New England Journal of Medicine [Internet]. 2000; 342(11):[763-9 pp.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00275805/full https://www.nejm.org/doi/pdf/10.1056/NEJM200003163421103?articleTools=true.

72. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet [Internet]. 2008; 372(9636):[383-91 pp.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00640638/full https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(08)60998-8/fulltext.

73. Cohen S, Curtis JR, DeMasi R, Chen Y, Fan H, Soonasra A, et al. Worldwide, 3-Year, Post-Marketing Surveillance Experience with Tofacitinib in Rheumatoid Arthritis. Rheumatology and therapy. 2018;5(1):283-91.

74. Cohen SB, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P, et al. Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. Annals of the rheumatic diseases. 2017;76(7):1253-62.

75. Burmester GR, Curtis JR, Yun H, FitzGerald O, Winthrop KL, Azevedo VF, et al. An Integrated Analysis of the Safety of Tofacitinib in Psoriatic Arthritis across Phase III and Long-Term Extension Studies with Comparison to Real-World Observational Data. Drug safety. 2020;43(4):379-92.

76. D'Amico F, Parigi TL, Fiorino G, Peyrin-Biroulet L, Danese S. Tofacitinib in the treatment of ulcerative colitis: efficacy and safety from clinical trials to real-world experience. Therapeutic advances in gastroenterology. 2019;12:1756284819848631.

77. Sandborn WJ, Panés J, D'Haens GR, Sands BE, Su C, Moscariello M, et al. Safety of Tofacitinib for Treatment of Ulcerative Colitis, Based on 4.4 Years of Data From Global Clinical Trials. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2019;17(8):1541-50.

78. Henderson Berg MH, Carrasco D. Injection Site Reactions to Biologic Agents Used in Psoriasis and Psoriatic Arthritis. Journal of drugs in dermatology : JDD. 2017;16(7):695-8.

79. Swart J, Giancane G, Horneff G, Magnusson B, Hofer M, Alexeeva E, et al. Pharmacovigilance in juvenile idiopathic arthritis patients treated with biologic or synthetic drugs: combined data of more than 15,000 patients from Pharmachild and national registries. Arthritis research & therapy. 2018;20(1):285.

80. ClinicalTrials.gov. A safety, efficacy and pharmacokinetics study of tofacitinib in pediatirc patients with sJIA2020. Available from: https://clinicaltrials.gov/ct2/show/NCT03000439.

81. Monthly Index of Medical Specialities. [Available from: https://www.mims.co.uk/.

82. Royal College of Paediatrics and Child Health. Royal College of Paediatrics and Child Health's School age growth charts 2019 [Available from: https://www.rcpch.ac.uk/resources/uk-who-growth-charts-2-18-years.

83. National Institute for Health and Care Excellence. Tofacitinib for moderately to severly active ulcerative colitis. Technology appraisal guidance TA547. 2018.

84. Electronic medicines compendium. RoActemra 162 mg Solution for Injection in Pre-Filled Pen 2020 [Available from: https://www.medicines.org.uk/emc/product/9086/smpc.

85. Electronic medicines compendium. RoActemra 20mg/ml Concentrate for Solution for Infusion 2020 [Available from: https://www.medicines.org.uk/emc/product/6673/smpc.

86. Electronic medicines compendium. Amgevita 20 mg solution for injection in pre-filled syringe 2020 [Available from: https://www.medicines.org.uk/emc/product/9547/smpc.

87. Hermine Brunner, Olga Synoverska, Tracy Ting, Mendoza CA, Spindler A, Vyzhga Y, et al. Tofacitinib for the Treatment of Polyarticular Course Juvenile Idiopathic Arthritis: Results of a Phase 3 Randomized, Double-blind, Placebo-controlled Withdrawal Study. American College of Rheumatology2019.

88. Du Bois Delafield DBE. Clinical calorimetry: tenth paper a formula to estimate the approximate surface area if height and weight be known. Archives of Internal Medicine. 1916;XVII(6_2):863-71.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Fast Track appraisal: cost-comparison case

Tofacitinib for treating juvenile idiopathic arthritis [ID2718]

Clarification questions

March 2021

File name	Version	Contains confidential information	Date
ID2718 tofacitinib for pcJIA ERG clarification letter company response Pfizer	1.0	Yes	26 March 2021

Section A: Clarification on effectiveness data

Current treatment pathway

A1. PRIORITY QUESTION: Please give a source for the current UK treatment pathway for JIA shown in figure 2 (page 24, Document B). Please comment on the relationship between this pathway and existing guidance, particularly the short period (6 weeks) from methotrexate to first biologic agent. For example, NHS England clinical commissioning policy states "Biologics should not be used unless a patient is intolerant to, or has failed optimised treatment with MTX; this is defined as 15mg/m2 given subcutaneously once-weekly for at least 3 months**"** **(https://www.england.nhs.uk/wp-content/uploads/2018/08/Biologic-therapies-for-the-treatment-of-juvenile-idiopathic-arthritis.pdf)**

Pfizer response:

Thank you for flagging this discrepancy, this was a typographical error in reproducing the diagram. The 6 weeks in the text should be corrected to at least 3 months. The reference for the treatment pathway was reference nr. 42. NHS England. *Clinical commissioning policy statement: biologic therapies for the treatment of juvenile idiopathic arthritis (JIA)*. 2015.

Systematic Literature Review (SLR)

A2. An SLR was conducted to identify non-RCT evidence regarding the efficacy and safety of tofacitinib that could supplement the evidence identified from the SLR of the RCTs. Please clarify the purpose of these searches and why they were not conducted for the comparators?

Pfizer response:

The non-RCT SLR for tofacitinib was conducted to supplement the RCT evidence and to support the development of the cost-comparison model in line with NICE's requirements. A non-RCT SLR was not conducted for the comparators because RCTs were identified for all comparators and as this is the highest quality of

evidence and preferred by NICE to inform evidence synthesis, it was not needed to supplement this evidence with non-randomised studies.

This is aligned with Section 2.2 of the NICE STA user guide for company evidence submission template, where it is stated "NICE prefers RCTs that directly compare the technology with 1 or more relevant comparators. However, such evidence may not always be available and may not be sufficient to quantify the effect of treatment over the course of the disease. Therefore, data from non-randomised and non-controlled studies may be needed to supplement RCT data.

A3. The search strategies in the following sections of the appendices contain a study design search filter to limit retrieval to randomised controlled trials:

- Table 1 Embase (lines 24-36), p .9, Appendix D

- Table 2 Medline (lines 24-36), p. 10-11, Appendix D

Please provide a source for the filters and confirm whether they have been validated.

Pfizer response:

The study design search filters used in the Embase and Medline search strategies follow the Scottish intercollegiate Guidelines Network (SIGN) guidance. The SIGN filters are pre-tested to enable the retrieval of medical studies that are most likely to match SIGN's methodological criteria.

Specific terms that did not meet the methodological criteria of this this review were adapted or removed, such as SIGN’s filter for identifying crossover trials (removed), as the crossover study design was not of specific interest in this review. Additionally, some search field options were edited to be more inclusive that those developed by SIGN. E.g. SIGN restricts with “.tw.” which restricts to matching results in the title, abstract or drug trade name only. This review uses the end .mp. which is less restrictive, including matching results in the title, abstract, subject heading, author keywords, amongst others.

Reference: Scottish Intercollegiate Guidelines Network (SIGN). Search filters [internet]. Edinburgh: SIGN; 2020. https://www.sign.ac.uk/assets/search-filters-randomised-controlled-trials.docx (accessed 18 Sept 2020)

A4. The search strategies in Appendix G contain terms for pcJIA and study design terms only. However, the search strategies are described on page 128 of Appendix G as also containing the interventions of interest – is this an error in the description? Please clarify.

Pfizer response:

Thank you for flagging this discrepancy, this was an error. The description should not include any reference to the interventions of interest being searched.

A5. PRIORITY QUESTION: Several biosimilar drugs are missing in the search strategies in Appendix D: Table 1, Embase, p. 9 and Table 2, Medline. p.11. Both strategies are missing the biosimilars of adalimumab – Amsparity, Cyltezo, Halimatoz, Kromeya, Solymbic, Yuflyma and biosimilars of etanercept – Nepexto and Lifmior.

a) Please explain the reasons for this.

Pfizer response:

The adalimumab and etanercept biosimilars listed above are either not licensed in the UK for the treatment of pJIA, were not licensed at the time the searches were conducted or are licensed but not launched in the UK. Full details for each biosimilar are as follows:

- Adalimumab
  - Amsparity: licensed but not launched in UK (https://www.sps.nhs.uk/medicines/adalimumab/, accessed 19th March 2021)
  - Cyltezo: withdrawal of the marketing authorisation in the EU (https://www.ema.europa.eu/en/medicines/human/EPAR/cyltezo, accessed 19th March 2021)

- Halimatoz: withdrawal of the marketing authorisation in the EU (https://www.ema.europa.eu/en/medicines/human/EPAR/halimato, accessed 19th March 2021)

- Kromeya: withdrawal of the marketing authorisation in the EU (https://www.ema.europa.eu/en/medicines/human/EPAR/kromeya, accessed 19th March 2021)

- Solymbic: withdrawal of the marketing authorisation in the EU (https://www.ema.europa.eu/en/medicines/human/EPAR/solymbic, accessed 19th March 2021)

- Yuflyma: not licensed at the time the searches were conducted, marketing authorisation was approved in February 2021 (https://www.ema.europa.eu/en/documents/overview/yuflyma-epar-medicine-overview_en.pdf, accessed 19th March 2021)

• Etanercept:

- Nepexto: licensed but not launched in UK (https://www.sps.nhs.uk/medicines/etanercept/, accessed 19th March 2021)

- Lifmior: no longer authorised in EU (https://www.ema.europa.eu/en/medicines/human/EPAR/lifmior, accessed 19th March 2021)

For other treatments in the searches, tocilizumab and abatacept, there are no biosimilars currently available.

b) Please also detail how the company ensured all relevant biosimilars were included in the searches.

Pfizer response:

A review of the Monthly Index of Medical Specialities (MIMS) website and the British National Formulary (BNF) was conducted to ensure biosimilars relevant to the UK market were included in the searches.

Clinical evidence

A6. The long-term extension study A3921145 had a data cut in April 2019, when will the next data cut be available?

Pfizer response:

The next available data cut from study A3921145 will be [redacted].

A7. Please provide baseline characteristics for the double blind pcJIA analysis set (DBJAS) as provided in Table 11 for the double-blind full analysis set (DBFAS)

Pfizer response:

Please see the baseline patient characteristics of patients in the double blind pcJIA analysis set (DBJAS) in Tables 1680.8 and 1680.15-1680.17 of Appendix 5 (please note, data reported in the appendices are academic-in-confidence).

A8. Was there a washout period before the open-label phase of A3921104? Please confirm there was no washout period between the open-label and double-blind phases of A3921104.

Pfizer response:

The Clinical Study protocol required that any experimental or prohibited therapy must be discontinued for at least 4 weeks or 5 half-lives (whichever is longer) prior to the first dose of study drug in the open label phase.

There was no washout period between the open-label phase and double-blind phase of study A3921104. This is consistent with pivotal clinical trial protocols in this disease area.

A9. Please explain the scale for the outcomes presented in Figures 7-10 in Appendix D. For example, Fig 7 is titled ‘occurrence of flare’ which is a dichotomous outcome, yet the relative treatment effect is presented as “difference” – what scale is this difference in? Similarly, for Figures 8-10 which represent different ACR cut-offs.

Pfizer response:

Figure 7 in the appendices represents the difference in the proportion (%) of patients who experienced a disease flare between the study arms, tofacitinib and placebo at week 44. Figure 8, 9 and 10 are presenting the difference in the proportion of patients who experienced a respective ACR response between the study arms.

A10. PRIORITY QUESTION: Please provide effectiveness and safety data for the full analysis set and the pcJIA analysis set for the following subgroups in trial A3921104:

a) Prior biologic DMARD use (biologic naïve; 1 prior bDMARD; 2 prior bDMARDs and ≥ 3 prior bDMARDs). Please also provide details of which biologic DMARDs were used in prior therapy.

Pfizer response:

Please see below the subgroup analysis by prior bDMARD use for the double-blind pcJIA analysis set (DBJAS) for study A3921104. The list of previously used bDMARDs are listed in Table 8 of the clinical study report. These were:

[redacted] According to the study protocol, continued use of bDMARDs during the study was not allowed, therefore treatment with these biologics had to be discontinued, for at least 4 weeks or 5 half-lives (whichever is longer), before the first dose of study drug.

The results for the full analysis set (DBFAS) are not available and would require further data analysis. However, we believe they would add limited value to the assessment as they include JIA subgroups that

[redacted]

.

Table 1: Subgroup analysis by prior bDMARD use (DBJAS)

			Presence		Tofacitinib - Placebo			
Previous biologic DMARDs received	Treatment	N	n (%)	SE	Diff	SE	95% CI	P-value
bDMARD naïve	Tofacitinib 5mg BID DB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Placebo	[redacted]						
bDMARD experienced (all)	Tofacitinib 5mg BID DB	[redacted]						
	Placebo	[redacted]						
1 prior bDMARD	Tofacitinib 5mg BID DB	[redacted]						
	Placebo	[redacted]						
>=2 prior bDMARD	Tofacitinib 5mg BID DB	[redacted]						
	Placebo	[redacted]						

b) Uveitis prior to start of trial and during trial with / without concomitant methotrexate.

Pfizer response:

No patients in the study had uveitis prior to start of trial, as active uveitis within 3 months of enrolment was an exclusion criterion. One patient experienced uveitis during the trial, at week 24. This patient was randomised to the placebo arm and was taking concomitant methotrexate. D

c) Subcutaneous / oral methotrexate.

Pfizer response:

Patients enrolled in the clinical trial who took concomitant methotrexate were required to be on a stable dose for at least 3 months. Patients were given the formulation that was recommended by local guidelines. Efficacy and safety data was not available for this criterion, but it was collected in study A3921104. Please see results of the post-hoc subgroup analysis based on administration route of methotrexate in Tables 1680.10-14 of Appendix 5 (please note, data reported in the appendices are academic-in-confidence).

A11. PRIORITY QUESTION: Please provide all the tables referenced in section 14 and the contents of Appendix 16 (including the final study protocol and amendments) of the A3921104 clinical study report.

Pfizer response:

The Clinical Study Protocol and the Clinical Study Report Errata for A3921104 were uploaded to NICE docs and were provided alongside the first version of the clarification response on March 26, 2021.

The selected tables and figures, specified by the ERG, from Section 14 of the A3921104 clinical study report are presented in Clarification response Appendix 3

and 4. The selected tables from Appendix 16 of the clinical study report are presented in Clarification response Appendix 4 (please note, data reported in the appendices are academic-in-confidence).

A12. PRIORITY QUESTION: Please report available JIA ACR90 and ACR100 results for study A3921104 (over the entire study period, and at week 44 of the double-blind phase) and for the open-label extension study A3921145.

Pfizer response:

Available and published ACR90 and ACR100 data for study A3921104 were reported in Table 15 Appendix D of the submission for tofacitinib at week 44 and also for the comparators.

Results for the entire study period are provided in Table 14.2.5.1 in Clarification response Appendix 2 (please note, data reported in the appendices are academic-in-confidence).

Results for the open-label extension study A3921145 are presented below.

Figure 1 JIA ACR90 responses (%) (±SE) - FAS

Figure 2 JIA ACR 100 Responses (%) ((±SE) - FAS

A13. PRIORITY QUESTION: Please provide an indirect comparison of ACR90 and 100 data for tofacitinib and its comparators. Please ensure all data used in the calculations are presented clearly so that the analyses can be reproduced.

Pfizer response:

An indirect treatment comparison was conducted based on results published in Table 15 of Appendix D, for the DBJAS population which included all participants randomised to the double-blind phase, received at least 1 dose of study medication in the double-blind phase and had polyarticular course JIA. Please note, the table included an error in the number of patients reaching ACR90 in the placebo arm of the CHERISH trial, this should read as 19 patients (previously reported as 10 patients).

The studies used in the base case ITCs are summarised in Table 16 of the submission and described in detail in Appendix D. In line with the ITCs in the submission, adalimumab and tocilizumab are considered relevant comparators.

ACR90 was reported for tofacitinib (Brunner 2019), adalimumab (DE038) and tocilizumab (CHERISH). For tofacitinib and adalimumab, only the percentage of patients reaching ACR90 was reported; therefore, the number of patients was calculated by multiplying these percentages by the total number of patients in each trial arm.

The ACR90 data used for the Bucher's indirect treatment comparisons are summarised in the table below.

Table 2 ACR 90 response for tofacitinib and comparators

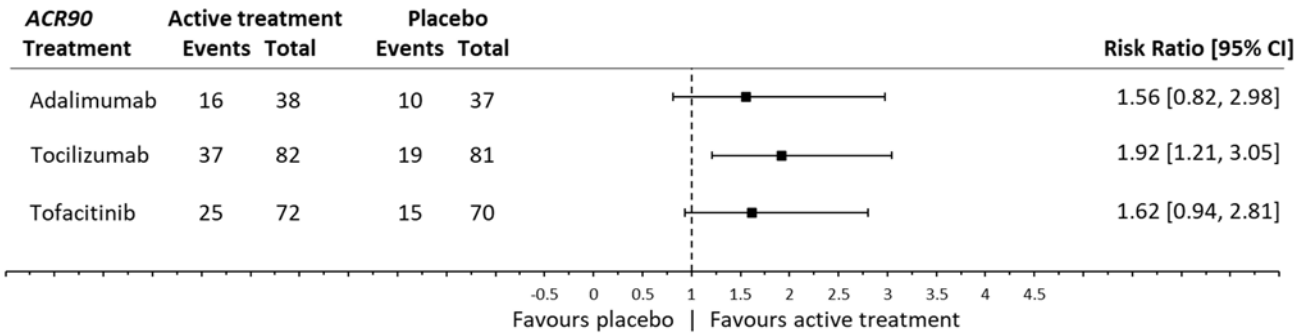
Trial	Drug	N (total patients)	n (number of patients reaching ACR90)
Brunner 2019	Placebo	70	[redacted]
	Tofacitinib	72	[redacted]
DE038	Placebo + methotrexate	37	*10*[1]
	Adalimumab + methotrexate	38	*16*[1]
CHERISH	Placebo	81	19
	Tocilizumab	82	37
[1] The number of patients reaching ACR90 (n) has been estimated using percentage of responders			

Simple Bucher's indirect treatment comparisons were conducted as all relevant included trials compared active treatment to placebo, and none of the pairwise comparisons were informed by more than one trial. This analysis followed the same approach as was used in TA373 and in the submission.

A summary forest plot showing active treatment versus placebo is presented below for proportion of patients achieving ACR90 in the 3 trials. These data are taken directly from the corresponding trial publications and are not calculated using ITC analysis.

[redacted]

Figure 3: Forest plot of active treatment versus placebo for JIA ACR 90 responses



The results of the Bucher's ITC for tofacitinib versus the relevant comparators are presented below for ACR90. A value less than one favours the comparator and a value greater than one favours tofacitinib.

[redacted]

Figure 4: Forest plot for tofacitinib versus comparators for JIA 90 response

[redacted]

ACR100 was only reported for the tofacitinib study (Table 15, Appendix D); therefore, no indirect comparison could be carried out for this outcome.

A14. Table 12 in Document B states that [redacted] of patients received immunosuppressants in A3921104 OLFAS. The ERG cannot find the corresponding value in the clinical study report or EMA assessment report.

a) Please clarify the source of this information

b) Please clarify which medications were classified as immunosuppressant and the proportion of participants receiving each type of immunosuppressant.

Pfizer response:

Thank you for flagging this discrepancy, this was a typographical error. The [redacted] in the table refers to patients who had prior medication with folate. Overall, [redacted]) patients had DMARD (91.6% csDMARD, 37.8% bDMARD), corticosteroid (49.3%), or immunosuppressant exposure prior to the study A3921104 (OLFAS), as reported in Table 8 of the clinical study report. The specific immunosuppressants used were azathioprine ([redacted] and ciclosporin ([redacted]).

A15. Was any imputation carried out for week 44 disease flare or JIA ACR outcome data (e.g. observations carried forward from previous visits)? Please provide details.

Pfizer response:

In the double-blind phase of study A3921104, the last observation carried forward (LOCF) method was used to impute any missing component of flare and JIA ACR 30, 50, 70, 90, 100 responses. LOCF was also used for the missing binary endpoints of flare, JIA ACR 30, 50, 70, 90, 100 responses, JADAS minimum disease activity, JADAS inactive disease, and JIA ACR inactive disease for the visits prior to study treatment discontinuation. Subjects who discontinued from double-blind study treatment for any reason were considered as having a flare/nonresponse/active disease for all the endpoints listed above, as of their study double-blind treatment discontinuation visit through Week 44, except subjects who met JIA ACR defined clinical remission criteria (ie, inactive disease for at least 24 weeks) at the time of study treatment discontinuation. Subjects who discontinued study treatment while in clinical remission were to have their LOCF from that visit onward through Week 44. Please see section 11.1.3.2 of the CSR for further details on handling missing data.

A16. Please provide the sensitivity and tipping point analyses for the disease flare, JIA ACR, and CHAQ outcomes mentioned in section 11.1 of the clinical study report.

Pfizer response:

Sensitivity and tipping point analyses for disease flare, JIA ACR and CHAQ outcomes, as requested by the ERG, are presented in Tables 14.2.1.6, 14.2.1.7, 14.2.2.1.6, 14.2.2.2.6 in Clarification response Appendix 2 and in Figures presented in Clarification response Appendix 3 (please note, data reported in the appendices are academic-in-confidence).

A17. PRIORITY QUESTION: Clinical advice to the ERG is that the benefits of having an oral solution can be substantial for younger patients but only if the taste is tolerable and patients do not suffer nausea after taking the medication.

a) Please provide all available data on taste acceptability for Tofacitinib oral solution. Some data are in the CSR (Table 23) and also appear to be in a Table in section 16 (Appendix) which is missing.

b) Please provide any additional data on taste acceptability.

Pfizer response:

Table 28 reports [redacted] in the open label period (all causalities). [redacted] of nausea were considered treatment related in the open label period (CSR Table 30), however treatment formulation and timing of the event is not specified.

Regarding taste acceptability, as reported in Table 23 of the CSR most patients either liked the taste of the oral solution “very much” (34 [40.00%]) or “a little” (32 [37.65%]). There were few patients who disliked the taste “a little” (8 [9.41%]) or “very much” (4 [4.71%]).

Besides these results from study A3921104, a pharmacokinetic, phase 1, open-label, multicentre study (NCT01513902) has assessed the taste acceptability of the grape-flavoured oral solution. The results of 18 patients who received the oral solution confirmed the taste was acceptable, on day 5 only 1 rated the taste as “dislike very much” (2 on day 1) and 4 (2 on day 1) patients as “dislike a little”.

Reference: Table 3 in Ruperto et al. 2017 *Pharmacokinetic and safety profile of tofacitinib in children with polyarticular course juvenile idiopathic arthritis: results of a phase 1, open-label, multicentre study.* Pediatric Rheumatology (2017) 15:86. Pharmacokinetic and safety profile of tofacitinib in children with polyarticular course juvenile idiopathic arthritis: results of a phase 1, open-label, multicenter study (nih.gov)

A18. PRIORITY QUESTION: Please provide data on the timing of nausea events relative to dosing schedule (for both tofacitinib and methotrexate).

Pfizer response:

No data on the timing of nausea events relative to dosing schedule is available from study A3921104, as specific timing of taking tofacitinib within a day was not collected.

A19. Discontinuation due to adverse events (AEs) in study A3921104 is reported in Tables 17, 18 and 20 of Document B. However, the number of patients who discontinued due to adverse events differs across all three tables. Please explain these differences and confirm the correct proportion of patients that discontinue due to AEs in each arm**.**

Pfizer response:

Table 17 in Document B of the submission summarises heterogeneity in discontinuation reporting across the included studies for tofacitinib and the comparators. Here, the number of discontinuations due to adverse events for study A3921104 is reported in 2 patients for each trial arm, as reported in the CSR (Figure 2). This corresponds to discontinuation due to adverse events excluding all pcJIA-specific events (disease progression, JIA, condition aggravated and arthritis).
For the tofacitinib arm, when excluding these categories from the 16 discontinuations listed in Table 20, 2 events remain (1 discontinuation due to pilonidal sinus repair and 1 who discontinuation due to tooth impacted). For the placebo arm, when excluding these categories from the 30 discontinuations we obtain 3 events remain, however this accounts for 2 patients (1 discontinuation due to appendicitis, 1 discontinuation due to haemoglobin decreased and discontinuation due to

intussusception). The reason for this discrepancy is that one patient on the placebo arm has had 2 events.
Table 18 reports the total number of discontinuations due to adverse events amounting to 16 patients for the tofacitinib group, and 29 patients for the placebo group.

A20. Please clarify the number of cases of uveitis identified in study A3921104 as there appear to be slight inconsistencies within and between documents. From the submission appendix:

- P.81 “The tofacitinib study (Brunner 2019 (13)) reported that no patients had active uveitis at the end of the randomised trial period.”
- Table 21 indicates 2 cases of uveitis in the placebo arm.

From the clinical study report:

- Table 29 (p.156) [redacted] uveitis in placebo group during double blind phase (DBSAS)
- Section 12.5.2.2 No uveitis cases during the open-label run-in phase. 1 case uveitis in placebo group at week 24 of double-blind phase (DBSAS)

Pfizer response:

During the double-blind phase of the study, there were 2 cases reported for uveitis in the placebo arm, when these cases were investigated, only 1 met the definition of uveitis as described in the clinical study protocol (section 7.2.3) This 1 case resolved by week 44, therefore at the end of the randomised trial period, no patients had active uveitis.

Section B: Clarification on cost-effectiveness data

B1. PRIORITY QUESTION: Please provide information on the current market share in the UK of each comparator in the scope.

Pfizer response:

Unfortunately, it is not possible to obtain market share data, specific to the pcJIA population, because all market share data consider pcJIA and systemic JIA together as one group. Therefore, we consulted registry data and an England based clinical expert on utilisation of different technologies.

As explained in the submission (section B.1.1.2) according to UK registry data between 2004 and 2019 most patients with pcJIA who required a biologic initiated treatment with a TNFi (91%) as a first line treatment. According to the clinical expert consulted, currently the most commonly initiated TNFi is adalimumab. Etanercept is less frequently initiated as the first TNFi. The most commonly used non-TNFi is tocilizumab and abatacept is less frequently used ([redacted]) (please see clinical expert interview summary provided).

B2. PRIORITY QUESTION: Please describe the monitoring requirements for a patient receiving tofacitinib, with and without concomitant methotrexate, and compare this to the monitoring requirements of the other comparators in the analysis.

Pfizer response:

It is expected that the monitoring requirements would be similar across all comparators. This is in line with the approach that the Assessment Group had taken in TA373, where it was assumed that the monitoring costs amongst technologies would be the same based on clinical expert advice and data from Thornton et al. 2008. This was also confirmed by our clinical expert (please see clinical expert interview summary provided). Therefore, costs of monitoring was not taken into account in the economic analysis.

The monitoring requirement for tofacitinib is expected to be the same as for other bDMARDs. Regular blood monitoring is required for MTX and biologics as part of routine care. A lipid test between 4-8 weeks is also recommended for tofacitinib which is in line with tocilizumab monitoring requirements.

B3. PRIORITY QUESTION: For the pcJIA population of the OLFAS dataset of A3921104,

a) Please provide the following information on patient bodyweight: the proportion who are i) 10 to 20 kg, ii) 20 to 40 kg, iii) 40 kg and above, iv) under 30 kg, v) over 30 kg, and iv) 10 to 30kg.

b) Please comment on whether this distribution is generalisable to the bodyweight distribution of patients with pcJIA in the UK population.

c) If you have access to registry data or another relevant real-world dataset recruiting patients from the UK pcJIA population, please also provide the corresponding evidence on bodyweight for comparison.

d) Please explain why the company's base case includes a population aged between 11 and 18 years, [redacted]?

Pfizer response:

a) Results on the proportion of patients in different weight categories, specified by the ERG are presented in Table 1680.7 of Clarification response Appendix 1 (please note, data reported in the appendices are academic-in-confidence).

b) The weight distribution reported in the pivotal clinical trial, A3921104 is generalisable to the UK patient population with pcJIA. Most trial publications report the age distributions of patients with JIA only, because weight is strongly correlated with age. The age distribution reported in the clinical trials of the comparators and in TA373 is similar to what has been reported in study A3921104. This is also emphasised by the fact that the mean age of patients in the tofacitinib trial was similar to ([redacted]) what was reported in the clinical trial data for the comparators (CHERISH and DE038), as well as to the model in TA373 (11 years).

c) No registry data or real-world evidence was identified, that reported on the weight distribution of patients with pcJIA in detail. Publications from UK

registers assess age as a variable due to the high correlation with weight. Different sub-types of JIA may be associated with different age groups. A 2016 publication by Kearsley-Fleet et al. *Factors associated with choice of biologic among children with Juvenile Idiopathic Arthritis: results from two UK paediatric biologic registers*, indicates the median age of patients starting biologics was 11 years this included all ILAR subtypes.

Reference: Kearsley-Fleet et al. 2016 Factors associated with choice of biologic among children with Juvenile Idiopathic Arthritis: results from two UK paediatric biologic registers. Rheumatology (Oxford). 2016 Sep;55(9):1556-65. doi: 10.1093/rheumatology/kev429. Epub 2016 Jan 4.

d) The population of patients aged between 11-18 represent the average cohort of patients who would be most likely to receive tofacitinib in UK clinical practice. This is consistent in the clinical trial data for the comparators (CHERISH and DE038), where the mean age of patients was 11 years, as well as the model used in TA373, where the starting age of the modelled population was 11 years (to reflect the average age of the clinical trials). The [redacted]. Patients then are followed on until adulthood (18 years of age).

   Annual costs for each age group between 2-18 years of age are also presented in the base case, in Table 29 of Document B of the submission.

B4. PRIORITY QUESTION: For the pcJIA population of the open label analysis set and the double blind pcJIA analysis set (DBJAS) of A3921104, please provide the following information for patients who received dose adjustments with tofacitinib:

a) The number of patients who discontinued due to non-compliance, and the most common reasons for doing so,

b) The proportion that were less than 80% or more than 110% compliant,

c) The mean dose of tofacitinib received,

d) Please include a scenario in the cost consequence model where any dose adjustments for tofacitinib are accounted for.

e) Please include a scenario where dose adjustments for tocilizumab and adalimumab are also accounted for.

Pfizer response:

a) – b) Please see results on compliance presented in Tables 1680.1-1680.4 Clarification response Appendix 1 (please note, data reported in the appendices are academic-in-confidence).

c) Please see data on the mean dose of tofacitinib received presented in Clarification response Appendix 1, in Tables 1680.5-6 (please note, data reported in the appendices are academic-in-confidence).

d) As indicated in tables in Clarification response Appendix 1, a good level of compliance was achieved for tofacitinib in study A3921104, both in the open-label and in the double-blind phase of the study, for the maximum dose of tofacitinib (5mg BID=10mg). Only one patient in the tofacitinib arm received lower dose than the prescribed one for two or more consecutive visits while no overcompliance occurred for two or more consecutive visits (Table 1680.4).

The additional scenario analysis presents the base-case (100%) compliance and adjustments related to the compliance rate observed in the trial according to mean dose (8.84 mg) and median dose (9.58mg).

The analysis is based on the same assumptions as the base case analysis presented in the submission (with 80% use of tocilizumab SC, undiscounted annual results (Table 3) and discounted aggregate results (Table 4)).

As compliance results were presented for the 5mg BID dose of tofacitinib, scenario analyses are presented for a 16-year old age group only. The weight in this age group equals or exceeds 40 kg, therefore patients require the maximum dose of tofacitinib (5mg BID=10mg). In the calculation of the aggregate results (11-18 years), the dose adjustment was applied in patient ages 12.25 years and above, where the estimated weight is equal or exceeds 40 kg, (maximum dose for tofacitinib); for ages 11-12.25 full dose of 4mg was assumed.

Table 3 Undiscounted annual results for a 16-year-old patient

Technologies	Acquisition costs (£)	Administration costs (£)	Total costs (£)	Incremental costs (Tofacitinib - comparator)
No adjustment				
Tofacitinib	[redacted]	£0	[redacted]	N/A
Tocilizumab	£6,346	£978	£7,323	[redacted]
Adalimumab	£8,237	£437	£8,674	[redacted]
Dose adjustment (8.84mg)				
Tofacitinib	[redacted]	£0	[redacted]	N/A
Tocilizumab	£6,346	£978	£7,323	[redacted]
Adalimumab	£8,237	£437	£8,674	[redacted]
Dose adjustment (9.58mg)				
Tofacitinib	[redacted]	£0	[redacted]	N/A
Tocilizumab	£6,346	£978	£7,323	[redacted]
Adalimumab	£8,237	£437	£8,674	[redacted]

N/A, not applicable

Table 4 Aggregate discounted results for 11-18 years old; dose intensity duration over time horizon

Technologies	Acquisition costs (£)	Administration costs (£)	Total costs (£)	Incremental costs (Tofacitinib - comparator)
No adjustment				
Tofacitinib	[redacted]	£0	[redacted]	N/A
Tocilizumab	£43,312	£6,866	£50,178	[redacted]
Adalimumab	£57,853	£3,071	£60,924	[redacted]
Dose adjustment (8.84mg)				
Tofacitinib	[redacted]	£0	[redacted]	N/A
Tocilizumab	£43,312	£6,866	£50,178	[redacted]
Adalimumab	£57,853	£3,071	£60,924	[redacted]
Dose adjustment (9.58mg)				
Tofacitinib	[redacted]	£0	[redacted]	N/A
Tocilizumab	£43,312	£6,866	£50,178	[redacted]
Adalimumab	£57,853	£3,071	£60,924	[redacted]

N/A, not applicable

e) The literature did not provide evidence on dose adjustments or the dose intensity for tocilizumab or adalimumab. Pfizer is not aware of any dose adjustments for these treatments.

B5. The majority of evidence comparing the clinical benefit of tofacitinib to tocilizumab and adalimumab consists of the patients' response to treatment within approximately the first year.

a) Please provide a comparison on the long-term efficacy for each comparator, particularly commenting on whether there are any differences in long-term treatment discontinuation rates.

b) Please describe what the implications would be on treatment costs, should there be differences in mean treatment duration.

Pfizer response:

The systematic literature review did not provide any comparable long-term efficacy evidence for the comparators. We note that in the absence of such evidence in TA373, it was also assumed that all treatments have the same long-term efficacy, or discontinuation rate (Tynjala et al.,2008). This was supported by feedback received

in the clinical expert interview (please see clinical expert interview summary provided).

Reference: Tynjala P, Vahasalo P, Honkanen V, Lahdenne P. 2009 *Drug survival of the first and second course of anti-tumour necrosis factor agents in juvenile idiopathic arthritis*. Ann.Rheum.Dis. 2009;68:552-7.

B6. The Company's submission notes that the risk of upper respiratory tract infection (URTI) varies widely across competitors, although the ERG acknowledges that a statistically significant difference was not demonstrated.

a) Please provide an additional scenario analysis that incorporates the cost of treating URTI, plus any other Grade 3+ adverse events that may be significant.

b) Please justify the reasons for the choice of adverse events used in response to a).

Pfizer response:

a) We note that the ITC presented in the submission referred to the randomised-controlled phase of the clinical trials. For consistency, we used this evidence to derive the baseline risk of URTI (Table 21 of Appendix D). The mean duration of tofacitinib treatment was [redacted] days and during this period [redacted] URTI events occurred, of which [redacted] severity. Information about the severity of URTIs for adalimumab and tocilizumab is not reported within the respective publications and thus data on the severity were not directly comparable. Our base case analysis for adalimumab and tocilizumab assumed the same proportion of severity of URTI events to that of tofacitinib.

   To calculate the 3-month baseline probability of a URTI, the observed risk during the time of tofacitinib exposure was used (Table 5). The risk for adalimumab and tocilizumab was calculated using the relative risks derived from the ITC analysis.

Table 5 Calculation of three-month probability for experiencing an URTI

Treatment	N	Exposure (days)	URTI (events)	3-month probability

		Mean	SD	Mild	Moderate	Mild%	
Tofacitinib (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab							[redacted]
Tocilizumab							[redacted]

Abbreviations: RR, relative risk; URTI, upper respiratory tract infection

In the base case analysis it was assumed that mild URTIs do not incur any costs while URTIs of moderate severity are associated with a visit to a general practitioner (GP). The analysis also assumed that URTIs would resolve within 3 months.

General practitioner costs were obtained from the Personal Social Services Research Unit (PSSRU) and were calculated as the average of GP costs with and without qualifications (including direct care staff costs) and estimated at £36.21. The lower limit was informed from the unit cost without qualification while the upper limit from the unit cost with qualification, estimated at £33.19 and £39.23, respectively.

A number of sensitivity and scenario analyses were conducted to test the influence of the above assumptions to the AE-related results. Sensitivity analysis was conducted on:

- the lower and higher limits of the mean duration on treatment for the baseline URTI risk ([redacted]
- the lower and higher limits of the RRs for adalimumab ([redacted]) and tocilizumab ([redacted])
- the lower and higher limits of the GP visit cost (£33.19 to £39.23)

The following scenarios were explored:

- Instead of assuming [redacted] URTI events required a GP visit, this scenario assumed that all URTI events required a GP visit,

- Instead of assuming that the events occurred only in the first 3 months, this scenario assumed that URTIs recur throughout the duration of treatment (same 3-month risk was used)

AE analysis results

Annual costs for an 11-year-old and 16-year-old patient as well as aggregate discounted results for 11-18 years old age group are presented in Table 6. Table 7 presents the annual costs for each age group between 2-18 years of age. The analysis take into consideration the patient access scheme for tofacitinib, and the list price of the comparators.

Table 6 Results of analysis with inclusion of AEs

Technologies	Acquisition costs (£)	Administration costs (£)	Adverse event costs (£)	Total costs (£)	Incremental costs (tofacitinib - comparator)
Undiscounted results for an 11-year-old patient					
Tofacitinib	[redacted]	£0	[redacted]	[redacted]	N/A
Tocilizumab	£5,946	£978	[redacted]	£6,925	[redacted]
Adalimumab	£8,237	£437	[redacted]	£8,674	[redacted]
Undiscounted results for a 16-year-old patient					
Tofacitinib	[redacted]	£0	[redacted]	[redacted]	N/A
Tocilizumab	£6,346	£978	[redacted]	£7,324	[redacted]
Adalimumab	£8,237	£437	[redacted]	£8,674	[redacted]
Base-case aggregated, discounted results for 11-18 years olds					
Tofacitinib	[redacted]	£0	[redacted]	[redacted]	N/A
Tocilizumab	£43,312	£6,866	[redacted]	£50,179	[redacted]
Adalimumab	£57,853	£3,071	[redacted]	£60,924	[redacted]

N/A, not applicable

Table 7 AE analysis results for age categories between 2-18 years of age

Age	Tofacitinib	Adalimumab	Tocilizumab
2	[redacted]	£4,556	£4,560
3	[redacted]	£4,556	£4,560
4	[redacted]	£4,556	£4,693
5	[redacted]	£4,556	£4,693
6	[redacted]	£4,556	£4,826
7	[redacted]	£4,556	£4,893
8	[redacted]	£4,556	£4,959
9	[redacted]	£6,615	£5,942
10	[redacted]	£8,674	£6,658
11	[redacted]	£8,674	£6,925

Age	Tofacitinib	Adalimumab	Tocilizumab
12	[redacted]	£8,674	£6,925
13	[redacted]	£8,674	£7,025
14	[redacted]	£8,674	£7,158
15	[redacted]	£8,674	£7,257
16	[redacted]	£8,674	£7,324
17	[redacted]	£8,674	£7,324
18	[redacted]	£8,674	£7,324

Total 3-monthly costs for each drug and each age group are presented in Figure 5. The inclusion of AEs does not alter the direction of results which indicate that tofacitinib [redacted].

Figure 5 Total cost comparison for adalimumab, tocilizumab and tofacitinib, undiscounted results

Sensitivity analyses

1. **Change of the mean duration on treatment for the baseline URTI risk**

Table 8 Aggregate discounted results for different duration of treatment exposure

Technologies	Acquisition costs (£)	Administration costs (£)	Adverse event costs (£)	Total costs (£)	Incremental costs (tofacitinib comparator)
Mean duration of treatment equal to [redacted] days					
Tofacitinib	[redacted]	£0	[redacted]	[redacted]	N/A
Tocilizumab	£43,312	£6,866	[redacted]	£50,180	[redacted]
Adalimumab	£57,853	£3,071	[redacted]	£60,925	[redacted]
Mean duration of treatment equal to [redacted] days					
Tofacitinib	[redacted]	£0	[redacted]	[redacted]	N/A
Tocilizumab	£43,312	£6,866	[redacted]	£50,179	[redacted]
Adalimumab	£57,853	£3,071	[redacted]	£60,924	[redacted]

N/A, not applicable.

2. Change of RRs for adalimumab and tocilizumab

Table 9 Aggregate discounted results varying the RRs of treatments

Technologies	Acquisition costs (£)	Administration costs (£)	Adverse event costs (£)	Total costs (£)	Incremental costs (Tofacitinib comparator)
Use of lower limit for adalimumab ([redacted]) and tocilizumab ([redacted])					
Tofacitinib	[redacted]	£0	[redacted]	[redacted]	N/A
Tocilizumab	£43,312	£6,866	[redacted]	£50,183	[redacted]
Adalimumab	£57,853	£3,071	[redacted]	£60,925	[redacted]
Use of higher limit for adalimumab ([redacted]) and tocilizumab ([redacted])					
Tofacitinib	[redacted]	£0	[redacted]	[redacted]	N/A
Tocilizumab	£43,312	£6,866	[redacted]	£50,178	[redacted]
Adalimumab	£57,853	£3,071	[redacted]	£60,924	[redacted]

N/A, not applicable.

3. Change of GP visit unit cost

Table 10 Aggregate discounted results varying the unit cost of GP visit

Technologies	Acquisition costs (£)	Administration costs (£)	Adverse event costs (£)	Total costs (£)	Incremental costs (Tofacitinib comparator)
Use of lower limit (£33.19)					
Tofacitinib	[redacted]	£0	[redacted]	[redacted]	N/A
Tocilizumab	£43,312	£6,866	[redacted]	£50,179	[redacted]
Adalimumab	£57,853	£3,071	[redacted]	£60,924	[redacted]
Use of higher limit (£39.23)					
Tofacitinib	[redacted]	£0	[redacted]	[redacted]	N/A
Tocilizumab	£43,312	£6,866	[redacted]	£50,179	[redacted]
Adalimumab	£57,853	£3,071	[redacted]	£60,924	[redacted]

N/A, not applicable.

Further scenario analyses

1. Inclusion of GP costs for all URTI events

Aggregate discounted results are presented in Table 11, for 11-18 year olds. Results show that URTI costs for tofacitinib increase slightly but the incremental costs are [redacted].

Table 11 Aggregate discounted results assuming GP costs irrespective of severity

Technologies	Acquisition costs (£)	Administration costs (£)	Adverse event costs (£)	Total costs (£)	Incremental costs (Tofacitinib comparator)
Tofacitinib	[redacted]	£0	[redacted]	[redacted]	N/A
Tocilizumab	£43,312	£6,866	[redacted]	£50,183	[redacted]
Adalimumab	£57,853	£3,071	[redacted]	£60,927	[redacted]

N/A, not applicable.

2. Upper respiratory tract infections recur throughout the treatment duration

Aggregate discounted results are presented in Table 12, for 11-18 year olds.

Table 12 Aggregate discounted results assuming URTIs recur throughout treatment duration

Technologies	Acquisition costs (£)	Administration costs (£)	Adverse event costs (£)	Total costs (£)	Incremental costs (Tofacitinib comparator)
Tofacitinib	[redacted]	£0	[redacted]	[redacted]	N/A
Tocilizumab	£43,312	£6,866	[redacted]	£50,200	[redacted]
Adalimumab	£57,853	£3,071	[redacted]	£60,936	[redacted]

N/A, not applicable.

b) During the double-blind phase of the trial and across the trials included in the ITC analyses, URTIs were the most frequently reported AE and were selected as a supporting analysis. For overall infections it was not possible to perform ITC analyses as this was not reported for the adalimumab and tocilizumab trials. No further events were mutually and consistently reported across the clinical trials.

Section C: Textual clarification and additional points

C1. An EndNote library was included with the submission containing 274 references (File name: pJIA combined EN library_deduplicated_15Feb). Some but not all of the references are cited in Document B. Please explain the contents of the endnote library (x274 records) and how they relate to the submission (Document A, Document B and Appendices)

Pfizer response:

An updated library has been provided with two sub-groups [one for the main submission document (Document B) and one for the Appendices]. Please note that two duplicate references were identified in the reference list of Document B, which are listed below. Therefore, the total number of references in the library is less than in the reference list. Apologies for this discrepancy.

“ Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. New England Journal of Medicine [Internet]. 2008; 359(8):[810-20 pp.]. “

“Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet [Internet]. 2008; 372(9636):[383-91 pp.].”

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Evidence Review Group's Report
Fast Track Appraisal – cost comparison

Tofacitinib for treating juvenile idiopathic arthritis

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
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Declared competing interests of the authors

None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Rodgers M, Sharif S, Walton M, Harden M, Dias S, Claxton L. Tofacitinib for treating juvenile idiopathic arthritis: A Fast Track Appraisal. CRD and CHE Technology Assessment Group, University of York, 2021.

Contributions of authors

Mark Rodgers and Sahar Sharif wrote the critique of the clinical effectiveness evidence submitted and conducted additional indirect treatment comparisons. Lindsay Claxton and Matthew Walton wrote the critique of the economic evidence submitted and conducted additional scenario analyses. Melissa Harden critiqued the company search strategies and provided information support. Sofia Dias led the project, provided advice, commented on drafts of the report, and takes overall responsibility for the report.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

Copyright statement

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List of abbreviations

ACR	American College of Rheumatology
ADA	Adalimumab
AE	Adverse event
bDMARD	Biologic DMARD
BID	Twice daily
BNF	British National Formulary
BSA	Body surface area
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence/credible interval
CRP	C-reactive protein
CS	Company submission
CSR	Clinical study report
DBFAS	Double blind full analysis set
DBJAS	Double blind pcJIA analysis set
DMARD	Disease modifying anti-rheumatic drug
ERA	Enthesitis related arthritis
ERG	Evidence review group
FD	Fixed dose
FTA	Fast track appraisal
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
IV	Intravenous
JAK	Janus kinase
JIA	Juvenile idiopathic arthritis
MIMS	Monthly Index of Medical Specialities
MTA	Multiple technology appraisal
MTX	Methotrexate
NC	Not calculable
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drug
OLE	Open label extension
PAS	Patient access scheme
pcJIA	Polyarticular course juvenile idiopathic arthritis
PsA	Psoriatic arthritis
RCT	Randomised controlled trial
RF	Rheumatoid factor
RR	Relative risk
SAE	Serious adverse event
SC	Subcutaneous
sJIA	Systemic juvenile idiopathic arthritis
SLR	Systematic literature review
SmPC	Summary of product characteristics
TCZ	Tocilizumab
TEAE	Treatment emergent adverse event

TNF	Tumour necrosis factor
TNFi	TNF inhibitor
URTI	Upper respiratory tract infection

EVIDENCE REVIEW GROUP REPORT: FAST TRACK APPRAISAL – COST COMPARISON

1 SUMMARY OF THE ERG'S VIEW OF THE COMPANY'S FTA CASE

1.1 Appropriateness of selected comparators

1.1.1 Correct decision problem

The company submission (CS) covers the expected marketing authorisation for tofacitinib, which is [redacted]

The licensed indications for the two chosen comparators (adalimumab and tocilizumab) also cover this population. This is different to the population in the NICE scope which includes all people aged 2 and older with juvenile idiopathic arthritis (JIA).

Tofacitinib and the selected comparators are likely to be used in the same place in the treatment pathway.

1.1.2 Appropriate comparators

Clinical advice to the evidence review group (ERG) was that the company's choice of comparators is appropriate. The comparators selected by the company were adalimumab and tocilizumab due to adalimumab being the most frequently used biologic disease modifying anti-rheumatic drug (DMARD) and tocilizumab representing an alternative mode of action to tumour necrosis factor (TNF) inhibitors. It is important to note that clinical advice to the ERG was that abatacept is commonly used as a second line treatment and etanercept is also frequently used in clinical practice.

1.2 Similarity of costs across interventions

The company's case for a fast track appraisal (FTA) cost-comparison was based upon the assumption of equivalence in clinical effectiveness and safety outcomes across tofacitinib, adalimumab, and tocilizumab.

The ERG was satisfied that the exclusion of background management and adverse event (AE) treatment costs would not bias the results. However, it remains unclear whether uveitis control on tofacitinib will be equivalent to that on adalimumab.

There were several key issues in the intervention costs used in the company's analysis. Whilst the individual effect of each issue is not substantial, they consistently act to skew the predicted costs in

favour of tofacitinib. The ERG therefore proposed an alternative base-case, comprising the following modifications:

- The company presented results for different age groups, using a relationship between bodyweight and age to estimate the expected dose for each age. The ERG proposed comparing total drug costs for each bodyweight category, using data on weight distribution in the tofacitinib trial to estimate a weighted average annual drug cost per patient for the pcJIA population (see section 4.2.1).
- The ERG considered it inappropriate to apply an administration cost for subcutaneous injection of tocilizumab and adalimumab. This cost was removed from the ERG's preferred base-case (see section 4.2.3)
- The ERG did not agree that intravenous infusions of tocilizumab are administered directly by a consultant paediatric rheumatologist. The ERG instead applied a more appropriate unit cost from NHS Reference Costs, which was more consistent with that used in TA373 and other rheumatology appraisals (TA375; see section 4.2.3).

In the ERG's alternative base-case analysis, tofacitinib remained less costly than tocilizumab and adalimumab. However, this was no longer the case when accounting for nationally available commercial access arrangements for adalimumab biosimilars, and the confidential patient access scheme discount for tocilizumab. Since it was not possible to account for dose adjustments and interruptions for each comparator, the true difference in costs may not be fully captured.

1.3 Non-inferiority relative to selected comparators

The ERG considered non-inferiority plausible on the basis of the evidence presented, albeit caveated by a number of uncertainties.

The CS presented indirect treatment comparisons (ITCs) that showed [redacted] between tofacitinib and tocilizumab or adalimumab (with 100% concomitant methotrexate) on disease flare or ACR30/50/70 response outcomes. The ERG's independently conducted ITCs confirmed the results for these comparisons. In additional analyses, the ERG found [redacted] between tofacitinib and adalimumab (with 0% or 56% concomitant methotrexate), etanercept or abatacept. While there was clinical heterogeneity between the few included trials, and confidence intervals were wide for all comparisons, similarly uncertain ITC results in TA373 were considered adequate to demonstrate similar efficacy across treatments.

ITCs of additional ACR Pedi 90 and inactive disease thresholds [redacted] between tofacitinib and the biologic DMARD (bDMARD) comparators.

1.4 Long term efficacy: area of uncertainty

Due to the limited length of follow up of tofacitinib and the lack of data for disease flare or ACR 70 response in patients with pcJIA, there is uncertainty regarding whether its long-term efficacy is comparable to adalimumab and tocilizumab. The different mechanism of action and route of administration of tofacitinib increases this uncertainty. Interim efficacy results from the open-label, long-term extension study (A3921145) are available for up to 18 months.[1] The proportion of patients achieving ACR 30 and 50 response decreases after 15 months, which suggests uncertainty in the long-term efficacy of tofacitinib.

The cost comparison assumes that tofacitinib has similar long-term efficacy to its comparators adalimumab and tocilizumab, for which there are more substantial long-term data suggesting that long term treatment responses are maintained through to week 104 and week 312, for tocilizumab[2] and adalimumab,[3] respectively (Section 3.4). However, due to its different mechanism of action and route of administration, the validity of extending this assumption to tofacitinib is uncertain.

1.5 Adverse events: area of uncertainty

The ERG agrees that no new safety concerns were raised by study A3921104, with the proportion of patients with treatment-emergent AEs (TEAEs) being similar between tofacitinib and placebo in the double-blind phase, and most TEAEs being of mild to moderate severity. However, the sample size of study A3921104 is insufficient to identify rare adverse events.

AE data are available from an ongoing tofacitinib open label extension (OLE) study, that recruited participants primarily from study A3921104.[4] At the time of reporting, only a few pcJIA participants had received medium- to long-term tofacitinib treatment thus, the possible medium- and longer-term adverse effects of tofacitinib in children with pcJIA are highly uncertain or unknown.

1.6 Long-term discontinuation: area of uncertainty

The cost comparison assumes that discontinuation rates are equivalent for tofacitinib and the comparators adalimumab and tocilizumab. However, only discontinuation due to AEs is reported for tofacitinib up to 72 weeks of follow up (Section 3.4.1).

Adalimumab studies report discontinuation rates up to 6.9 years of follow up, which are in line with other long-term extension studies of abatacept and etanercept. As tofacitinib is administered orally, twice daily it may have different levels of adherence than its comparators (Section 3.3). Therefore, the lack of data on long-term discontinuation rates for tofacitinib results in uncertainty in whether discontinuation can be assumed to be equivalent to comparators adalimumab and tocilizumab.

1.7 Other issues for consideration

The availability of an oral treatment option will undoubtedly be very welcome to clinicians and patients, particularly given the well-noted issue of needle phobia affecting adherence to biologics. However, nausea may present a new barrier to treatment adherence in many patients, and missed doses may have a potentially larger impact upon efficacy due to the relatively short biological half-life of tofacitinib. Poor taste acceptability of tofacitinib in oral solution for some patients could also contribute to the risk of poor adherence and reduced long-term efficacy. However, the net effect of these issues upon relative rates of adherence on tofacitinib and biologics remains unclear. Further uncertainty may be introduced by the use of biosimilar adalimumab, as these reportedly more painful injections could result in reduced adherence relative to the proprietary product.

A further issue for consideration concerns the effectiveness of tofacitinib for controlling extra-articular manifestations of JIA. Adalimumab has demonstrable superiority to other biologics for inducing and maintaining clinical remission of uveitis. No equivalent data exists for tofacitinib, which may be a consideration for treatment selection in JIA patients with a clinical history of uveitis, particularly those with poor adherence to methotrexate. This could also affect the relative cost-effectiveness of tofacitinib in practice.

2 CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY'S SUBMISSION

The decision problem assesses the use of [redacted] This is different to the population in the NICE scope which includes all people aged 2 and older with juvenile idiopathic arthritis (JIA). [redacted]

Clinical advice to the ERG was that the company's choice of comparators is appropriate. The position of tofacitinib in the treatment pathway is for people whose disease has responded inadequately to or who are intolerant to one or more disease modifying antirheumatic drugs (DMARD). Therefore, methotrexate, which is included in the NICE scope, is not a relevant comparator. The comparators selected by the company were adalimumab and tocilizumab. Whilst the company acknowledged that abatacept and etanercept were also relevant comparators, they stated that adalimumab is the most frequently used biologic DMARD and tocilizumab represents an alternative mode of action to tumour necrosis factor (TNF) inhibitors (TNFi). However, clinical advice to the ERG was that abatacept is commonly used as a second line treatment and etanercept is also frequently used in clinical practice due to only requiring a once weekly dose and having a smaller vial, which suits younger children.

The NICE scope also included infliximab, rituximab and anakinra as comparators. However, these were not included in the company's decision problem as infliximab and rituximab do not have marketing authorisations for JIA and anakinra has a marketing authorisation for sJIA, which is outside the expected marketing authorisation for tofacitinib.

The two comparators adequately represent the NICE recommended treatment options. According to UK registry data,[5] the majority of patients with pcJIA who required a biologic initiated treatment with a TNFi (91%) as a first line treatment, of which the most commonly initiated is adalimumab. The most commonly used non-TNFi is tocilizumab. Clinical advice to the company and ERG on the relative use of different agents slightly differed [redacted] ; ERG clinical advisors: 50-60% adalimumab, 10% etanercept, 30-40% tocilizumab).

The company's decision problem does not include four of the outcomes stated in the NICE scope: joint damage, corticosteroid sparing, JIA specific outcomes and body weight and height. Joint damage was not collected in the tofacitinib trial A3921104. This was included as an outcome in the previous multiple technology appraisal (MTA) TA373, however it was not used in the economic model. The ERG is satisfied with the justification for not collecting the other three outcomes, which are stated in Table 1 of the CS.

The company's decision problem includes subgroups by JIA, which matches the NICE scope. Additional subgroups included were baseline C-reactive protein (CRP), geographical region, baseline body weight and age group.

3 SUMMARY OF THE ERG'S CRITIQUE OF CLINICAL EFFECTIVENESS EVIDENCE SUBMITTED

3.1 Points for clarification

After receiving the CS, the ERG submitted several points for clarification to the company. Any additional or corrected data provided by the company have been incorporated into the analyses and discussion of this ERG report where appropriate.

3.2 Systematic literature review

3.2.1 Searches

The searches to identify randomised controlled trials (RCTs) of tofacitinib or relevant comparators to treat juvenile idiopathic arthritis were reported in Appendix D of the CS.

The search strategies presented were generally appropriate, however some weaknesses were identified by the ERG: an incorrect restriction to RCTs was applied to the search of the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (CDSR); health technology assessment databases were not searched; and several synonyms for children were missing from the search strategies. The search strategies for conference abstracts and clinical trial registers were not reported.

Several biosimilar drugs were missing from the search strategies, however the company clarified that they were either not licensed in the UK for the treatment of pcJIA, were not licensed at the time the searches were conducted or are licensed but not launched in the UK. The biosimilars included in the search strategies were those relevant to the UK, identified through a review of the Monthly Index of Medical Specialities (MIMS) website and the British National Formulary (BNF).

3.2.2 Included studies

The systematic literature review (SLR) identified 12 RCTs, however only five were relevant to the decision problem. One of these was a trial of tofacitinib, A3921104,[4] which informed the clinical effectiveness evidence of the CS. Three studies of adalimumab[6-8] and one of tocilizumab[9] were also identified and assessed for inclusion in the ITC. Reasons for including and excluding the studies are listed in Tables 5 and 6 in Appendix D of the CS. A second SLR was conducted to identify non-RCT evidence on the efficacy and safety of tofacitinib; no additional studies were identified.

3.3 Clinical effectiveness evidence of tofacitinib

Study A3921104 is a phase 3, randomised, double-blind, placebo-controlled, 44-week trial, which provides evidence on the efficacy and safety of tofacitinib in patients aged 2 to 18 years old with pcJIA. The trial also included patients with PsA and ERA, however these patients were excluded from the results presented in the CS [redacted] .

225 patients entered into the 18-week open-label run-in phase, during which they received tofacitinib. Of these, 173 patients achieved a JIA American College of Rheumatology (ACR) 30 response and were randomised 1:1 to treatment with tofacitinib (n =88) or placebo (n=85) for the 26-week double blind phase. The [redacted] , 75% were female and most had polyarthritis rheumatoid factor (RF) negative disease. The characteristics of the double-blind period pcJIA analysis set (DBJAS) appear similar to the full analysis set (DBFAS). Of the patients who entered the open label run in phase, 37.8% had received previous biologic DMARDs and most had used methotrexate (90.7%). The majority of patients in the double-blind phase had not received a previous biological DMARD (68% in the tofacitinib arm and 71% in the placebo arm).

Clinical advice to the ERG was that the baseline characteristics of the tofacitinib trial are largely representative of patients eligible for tofacitinib in the UK. The full baseline characteristics are reported in Table 11 of the CS. The quality assessment of study A3921104 is presented in Table 15 of the CS, which was conducted using the Cochrane risk of bias tool. All domains were judged to have a low risk of bias. The ERG checked the full study protocol, which was requested from the company, and agrees with the company's assessment.

Section B.3.6 summarises the key efficacy outcomes of study A3921104. At week 44, significantly fewer patients experienced disease flare with tofacitinib (29.2%) than with placebo (52.9%) (Figure 6 of the CS). During the double-blind phase, significantly more patients achieved JIA ACR 30, 50 and 70 responses with tofacitinib than with placebo (Figure 7 of the CS). This difference was statistically significant from week 24 for JIA ACR 30 and 50 responses and from week 32 for JIA ACR 70 response. Clinical advice to the ERG is that an ACR 70 response is clinically meaningful but often clinicians aim for an ACR 90 response. The proportion of patients achieving ACR 90 ([redacted] in the tofacitinib arm and [redacted] in the placebo arm) and 100 response ([redacted] in the tofacitinib arm and [redacted] in the placebo arm) at week 44 was reported in Appendix D of the CS (Table 15). Some of the ACR response results may be sensitive to imputation assumptions (e.g. one less ACR 70 responder for tofacitinib at week 44 would result in a non-significant difference between treatment arms), but the proportion of data imputed at week 44 was not made available. Tipping-point analyses provided in response to clarifications indicated that the disease flare results were more robust to a range of imputation assumptions.

The ERG requested effectiveness and safety data for patients who were biologic naïve and patients with prior biologic DMARD use, as clinical advice to the ERG was that prior biologic use can affect response to treatment. These were provided by the company at the clarification stage (see Table 1). Only [redacted] patients ([redacted] %) had received one prior biologic DMARD and [redacted] patients ([redacted] %) had received two or more biologic DMARDs. [redacted] (Table 1). However, the trial was not powered to detect subgroup differences.

Table 1 Subgroup analysis by prior bDMARD use (DBJAS)

			Number of patients		**Tofacitinib - Placebo**			
Previous biologic DMARDs received	Treatment	N	n (%)	SE	Difference (%)	SE	95% CI	P-value
bDMARD naïve	Tofacitinib 5mg BID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

bDMARD experienced (all)	Tofacitinib 5mg BID	[redacted]						
	Placebo	[redacted]						
1 prior bDMARD	Tofacitinib 5mg BID	[redacted]						
	Placebo	[redacted]						
≥ 2 prior bDMARD	Tofacitinib 5mg BID	[redacted]						
	Placebo	[redacted]						

DMARD: disease modifying anti-rheumatic drugs, bDMARD: biologic disease modifying anti-rheumatic drugs, BID: twice daily, CI: confidence interval; SE: standard error

3.3.1 Oral administration of tofacitinib

Since biological treatments for JIA are widely considered to be equivalent in efficacy, the choice of treatment takes into account patient preference after a discussion with the patient and carers about how, and how often, the drugs are administered.[10] There may be a number of reasons why adherence to medication varies, including for safety and for patient preference reasons.

Clinical advice to the ERG was that the oral administration of tofacitinib may be beneficial for younger patients who often experience needle phobia. They highlighted that tofacitinib is easier to administrate than injections and may reduce treatment administration pain which could potentially increase adherence. However, there are a number of factors which may instead reduce adherence. Administration at home, taste acceptability and nausea can all significantly impact adherence.

The CS did not include taste acceptability as an outcome, however, taste acceptability of the tofacitinib oral solution on day 14 of the open-label phase was reported in the clinical study report (CSR). [redacted]. The ERG requested further data on taste acceptability. The company stated that these were the only results from study A3921104, however results from a phase 1, open-label, multicentre study (NCT01513902)[11] of 18 patients who received the oral solution confirmed the taste was acceptable.

Additionally, nausea may have a greater impact on adherence with an oral therapy than with subcutaneous administration. The CSR reports [redacted] of nausea in the open-label run-in phase of the tofacitinib study. However, there no data are available on the timing of nausea events relative to dosing schedule. Nausea appears to be a large barrier to adherence, which is particularly present with methotrexate.[12]

Adherence issues may be further compounded in adolescent patients, in whom poor adherence to regular medication for conditions ranging from diabetes to leukaemia is well documented.[13-17] Indeed, studies in JIA have shown adherence to oral non-steroidal anti-inflammatory drugs (NSAIDs) to be as low as 52%.[18-20] Coupled with the short half-life of tofacitinib, missed doses due to poor treatment adherence may reduce the long-term efficacy of tofacitinib.

However, the net effect of the above issues upon relative rates of adherence on tofacitinib and other biologics remains unclear. Further uncertainty may be introduced by the use of biosimilar adalimumab, as these reportedly more painful injections could lead to reduced adherence relative to the proprietary product. The summary of product characteristics (SmPC) for tocilizumab states that adjustments may be made for patients with liver enzyme abnormalities, or low absolute neutrophil or platelet count, and that treatment should be interrupted in the case of serious infection. Clinical advice to the ERG noted that doses may be omitted, rather than adjusted, in the case of neutropenia, especially since it is more difficult to adjust doses administered via subcutaneous (SC) injection.

3.3.2 Indirect treatment comparisons

Indirect treatment comparisons (ITC) were carried out to compare tofacitinib to adalimumab and tocilizumab and are summarised in section B.3.9 of the CS, with additional details in Appendix D. The ITC uses the same method (described by Bucher et al[21]) as was used in TA373.

3.3.2.1 Identification and selection of studies

The identification and selection of relevant RCT evidence is summarised in sections B.3.1 and B.3.9.1. Appendix D1.1.1. describes the study selection criteria and processes and key characteristics of included and ongoing studies. Despite the weaknesses in the search strategy identified in Section 3.2, the submission is likely to have identified all currently available RCT evidence relevant to the decision problem.

Of the twelve RCTs evaluating tofacitinib, etanercept, adalimumab, tocilizumab and abatacept, three were considered suitable for inclusion in the ITC. The remaining nine RCTs were excluded "because they presented substantial heterogeneity in study design or patient baseline characteristics compared with Brunner 2019[4] (the tofacitinib trial), or because they included a comparator not of interest for this assessment (etanercept or abatacept)". Several of these studies were appropriately excluded from the ITC because they did not use a withdrawal design, and so were incompatible with the tofacitinib trial,[4] and/or were substantially shorter in duration (Appendix D1.2). See section 3.3.2.6 of this report for comment on the exclusion of evidence on etanercept and abatacept.

3.3.2.2 Selection of outcomes

The effectiveness outcomes selected for the ITCs (proportion of patients experiencing a disease flare; ACR Pedi 30, 50 and/or 70 response) were appropriate and matched those used for the ITCs in TA373. However, the ERG's clinical advisors considered ACR Pedi 90 or 100 to be a more desirable treatment goal in the population covered by this assessment. The ERG therefore requested and/or conducted additional ITCs for the higher ACR Pedi thresholds where data were available (see section 3.3.2.6).

Small numbers of observed events and inconsistencies in the handling of disease flare/discontinuation between trials precluded ITC analyses for serious adverse events (SAEs) and treatment discontinuation, respectively. Inconsistencies in reporting of total infections meant that upper respiratory tract infection (URTI) was the only adverse event included in the ITCs. These decisions appear to be justified, given the available evidence.

3.3.2.3 Consistency and similarity of studies included in the ITC

Section B.3.9 states that trials were generally comparable in terms of study design and patient population: all included an open-label lead-in phase (16-18 weeks) followed by a placebo-controlled randomised withdrawal phase (24-32 weeks), and a subsequent open-label extension phase. The included adalimumab[7] and tocilizumab[9] studies had previously been included in the ITC conducted for TA373.[10]

The adalimumab study[7] contained a methotrexate stratum and a non-methotrexate stratum where all or none of the patients received concomitant methotrexate, respectively. The methotrexate stratum was selected by the company for the ITC because the majority of patients in the other studies included in the ITC used concomitant methotrexate. While this approach was not unreasonable, the ERG explored the impact of combining the two adalimumab strata – see section 3.3.2.6.

Section B.3.9.4 of the CS appropriately noted heterogeneity across included studies in terms of baseline participant characteristics, particularly differences in prior bDMARD therapy and concomitant MTX use. However, the submission did not report differences in placebo response rates across the included studies: this information is therefore presented in Table 2 for all comparators included in the CS and ERG's ITCs. Each of these sources of heterogeneity, along with the small number of studies with small sample sizes and differing durations, add further uncertainty to the ITC results.

As stated in Appendix D1.2 of the CS, it was not possible to statistically assess the consistency of the ITCs as no relevant evidence directly comparing active treatments was available.

Table 2:Prior bDMARD use, concomitant MTX use, and placebo response rates in trials included in ITCs of effectiveness

Treatment	Prior bDMARD use (%)	Concomitant MTX (%)	Outcome	Placebo response rate
Abatacept[22]	17*	77	Disease flare	0.53
			ACR30	0.69
			ACR50	0.52
			ACR70	0.31
Adalimumab MTX[7]	0	100	Disease flare	0.65
			ACR30	0.38
			ACR50	0.38
			ACR70	0.27
Adalimumab no MTX[7]	0	0	Disease flare	0.71
			ACR30	0.32
			ACR50	0.32
			ACR70	0.29
Adalimumab combined[7]	0	56	Disease flare	0.68
			ACR30	0.35
			ACR50	0.35
			ACR70	0.28
Etanercept[23]	0	0	Disease flare	0.81
			ACR30	0.35
			ACR50	0.23
			ACR70	0.19
Tocilizumab[9]	32	80	Disease flare	0.37
			ACR30	0.54
			ACR50	0.52
			ACR70	0.42
Tofacitinib[4]	[redacted]	[redacted]	Disease flare	[redacted]
			ACR30	[redacted]
			ACR50	[redacted]
			ACR70	[redacted]

* "Previous anti-TNF therapy discontinued"

3.3.2.4 Validity of studies included in the ITC

Appendix D.1.1.1 of the CS provides an assessment of the risk of bias for all RCTs identified in the SLR, including those included in the CS and ERG's ITCs. Studies included in the ITCs used a broadly similar methodology, though inadequate reporting of randomisation, allocation concealment, and blinding procedures precluded the company from making a definitive judgement about risk of bias for some studies. Apart from some matters of interpretation, the ERG's risk of bias assessment agreed with that presented in the CS (see Appendix Table 10).

3.3.2.5 Results of the indirect treatment comparisons presented in the company submission

The ITC results are reported in section B.3.9.2 of the CS. These show [redacted] between tofacitinib and adalimumab or tocilizumab on disease flare or ACR response outcomes. The ERG's independently conducted ITCs found identical results for these comparisons (see section 3.3.2.6).

3.3.2.6 Additional indirect treatment comparison analyses by the ERG

Concomitant methotrexate use

The CS selected the stratum of the adalimumab trial (DE038)[7] in which all participants received concomitant methotrexate for the ITC analysis. This was justified based on a majority of patients ([redacted])in the other included studies using concomitant methotrexate. An alternative approach would have been to combine the two adalimumab arms of DE038, resulting in a group in which 56.4% of patients received concomitant methotrexate.

Table 3 shows the results of ITCs for tofacitinib versus the different adalimumab/methotrexate strata from DE038 (methotrexate stratum, no methotrexate stratum, combined strata) for disease flare and available ACR Pedi outcome data (ACR Pedi 30, 50, 70, and inactive disease). For most outcomes, the indirect estimates of effect [redacted]

Additional comparators from TA373

The CS included only adalimumab and tocilizumab as comparators in the ITC, as justified in section B.1.1.2 of the CS. The ERG's clinical advisors were satisfied with the selection of comparators given the requirements of an FTA. However, they also stated that abatacept is commonly used as a second line treatment and etanercept is frequently used in clinical practice due to only requiring a once weekly dose and having a smaller vial, which can suit younger children. These comparators were therefore included in the ERG's ITC analysis. Data from one etanercept study (Lovell 2000)[23] and one abatacept study (Ruperto 2008)[22] informed this analysis; these same two studies informed the ITC conducted in TA373 (these studies are summarised in table 7 of the CS appendices). None of the additional etanercept or abatacept studies identified by the SLR in the CS were eligible for inclusion.

Table 3 shows the results of the indirect treatment comparison for tofacitinib versus etanercept and abatacept for disease flare and ACR Pedi outcomes. [redacted]

Table 3 Indirect treatment comparison of tofacitinib vs all comparators from TA373

Comparison	Disease flare RR (95% CI)	ACR Pedi 30 RR (95% CI)	ACR Pedi 50 RR (95% CI)	ACR Pedi 70 RR (95% CI)	ACR Pedi 90 RR (95% CI)	JIA ACR inactive disease RR (95% CI)
Tofacitinib vs adalimumab, 100% concomitant MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib vs adalimumab, 0% concomitant MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib vs adalimumab, 56.4% concomitant MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib vs tocilizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib vs abatacept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib vs etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

RR=risk ratio; CI=confidence interval; NC=not calculable (no reported comparator data)

3.4 Long-term efficacy

There is limited data on the long-term efficacy of tofacitinib. Interim results on efficacy from the open-label, long-term extension study (A3921145) are available for up to 18 months.[1] In patients with pcJIA, the proportion of patients achieving ACR 30 response increased until month 12, after which it decreased. Similarly, the proportion of patients who achieved an ACR 50 response increased up until 15 months and then decreased (Figure 14 in the CS). ACR 70 or 90 response was not reported for patients with pcJIA. In the full analysis set, which includes patients with ERA and PsA disease, ACR 70, 90 and 100 responses increase slightly up until 12 months and ACR 70 response then starts to decrease. The company provided further data for ACR 90 and 100 responses, which slightly increase up to 24 months. However, the number of patients beyond this point is very low. The downward trend of ACR 30 and 50 response after 12 months suggests uncertainty in the long-term efficacy of tofacitinib. Additionally, clinical advice to the ERG is that an ACR 70 response is the most clinically meaningful, for which there is currently no long-term data in the pcJIA cohort. It is important to note that there were small patient numbers at 18 months.

The cost comparison assumes that tofacitinib has similar long-term efficacy to its comparators, adalimumab and tocilizumab, for which there is more substantial long-term data. The open label extension (OLE) for the CHERISH study[2] reports efficacy data of tocilizumab for up to two years. Only patients who completed the double blind RCT phase or had a JIA flare were eligible to enter the OLE. 160 (96%) eligible participants entered the OLE and 155 of these (97%) completed 104 weeks of follow-up (16-week open label + 24 weeks double-blind RCT + 64 weeks OLE). For patients who received continuous tocilizumab throughout the study (n=82) the proportion who achieved an ACR response of 30 and 50 decreased slightly, whereas the proportion who achieved a response of 70, 90

and who had inactive disease was higher at week 104 compared with week 40 (Table 4). An additional study reports long term efficacy of tocilizumab up to a further 24 weeks after the 104 weeks of the comparative study[24]. This study included 41 patients who had completed the 104 weeks on tocilizumab treatment and achieved an ACR 70 response. The proportion of patients with ACR 30, 50 and 70 response at week 128 (week 104 + 24) was very similar to the proportion at baseline (week 104). The proportion of patients with ACR 90 response and with inactive disease increased slightly from baseline to week 128. This suggests that long term treatment response was sustained with tocilizumab.

The long-term efficacy of adalimumab is reported for up to 6.9 years, which follows on from the DE038 study.[3] Patients completing the double-blind period were eligible to enter into the 2-part long-term extension, in which patients received open-label adalimumab based on body surface area (BSA) for up to 44–136 weeks, and then fixed-dose (FD) adalimumab for up to 224 weeks. There were 128 patients who entered the OLE, with 106 (62%) completing the first phase at 104 weeks and 62 (36%) completing the second phase at 312 weeks. There were 94 patients included in the observed analysis, which excluded patients who were lost to follow up, withdrew consent and had protocol violations. The majority of patients achieved JIA ACR 30, 50, 70 and 90 responses (non-responder imputation analysis: 36% to 53%) at week 104 (Table 4). The response rates were generally maintained through to week 312. These results include both patients who received adalimumab and placebo in the randomised phase. It is also important to note that only 71/128 (58%) of this group received methotrexate during the open-label and double-blind phases of the study.

Due to the limited length of follow up of tofacitinib and the lack of data for disease flare or ACR 70 response in patients with pcJIA, there is uncertainty regarding whether its long-term efficacy is comparable to adalimumab and tocilizumab. Having comparable short-term efficacy does not necessarily equate to comparable long-term efficacy. The company have provided no wider evidence supporting equivalent durability of response between small molecule JAK inhibitors and biologics. This issue has been raised in prior appraisals of small molecule inhibitors in the context of established biological therapies;[25, 26] however, long-term data is yet to be presented in support of this assumption. The ERG does note that the assumption of equivalence in long-term discontinuation was accepted in the appraisal of tofacitinib for PsA, in which data provided to the ERG suggested that such an assumption was valid. However, the ERG also notes that in the absence of explicit response-based stopping rules in JIA, the drivers of discontinuation may differ between adult and paediatric populations. Therefore, this is a key area of uncertainty when considering the cost-comparison analysis.

Table 4 Open-label extension results for adalimumab and tocilizumab

Study (follow-up), Outcome	Intervention (at end of RCT phase)		Intervention (at end of OLE)
Adalimumab (104 weeks)			
ACR Pedi, n (%)	**ADA + MTX (n=38)**	**ADA alone (n=30)**	**ADA (n=128) at week 104[a]**
ACR Pedi 30	24 (63%)	17 (57%)	90/94 (96%)
ACR Pedi 50	24 (63%)	16 (53%)	88/94 (94%)
ACR Pedi 70	24 (63%)	14 (47%)	84/94 (89%)
ACR Pedi 90	16 (42%)	9 (30%)	62/94 (66%)
ACR Pedi 100	NR	NR	NR
Tocilizumab (104 weeks)			
ACR Pedi, n (%)	**TCZ (n=82) at week 40**		**TCZ (n= 82) at week 104**
ACR Pedi 30	80 (97.6%)		78 (95.1%)
ACR Pedi 50	78 (95.1%)		74 (90.2%)
ACR Pedi 70	65 (79.3%)		71 (86.6%)
ACR Pedi 90	41 (50.0%)		58 (70.7%)
Proportion with inactive disease	33 (40.2)		52 (63.4%)

[a] 94 patients were included in the patients-observed analysis and included patients who received both placebo and adalimumab in the randomised phase.

3.4.1 Discontinuation

The cost comparison assumes that discontinuation rates are equivalent for tofacitinib and comparators adalimumab and tocilizumab. In the initial open-label run-in phase of the tofacitinib trial, 40 patients (17.8%) discontinued, of which 16 (7.1%) were due to worsening disease. However, these included patients with PsA and ERA sub-types. The discontinuation rates in the open-label run in of the phase 3, double blind, placebo-controlled studies of adalimumab (DE038)[7] and tocilizumab (CHERISH),[9] which were included in the ITC were similar to the rates in the open-label run in of the tofacitinib trial (Table 5).

The number of patients who discontinued (all-cause) in the randomised phase of the tofacitinib trial was 27 (31%) in the tofacitinib arm and 47 (55%) in the placebo arm. The majority of these were due to lack of efficacy (81% in the tofacitinib arm and 94% in the placebo arm) (Table 5). Clinical advice to the ERG is that in practice, patients who experience a flare would not immediately discontinue treatment. Steroids are used to manage flares and patients tend to continue on the same treatment unless they experience multiple flares, in which case the patient would switch to a different medication. Thus, having a flare should not be conflated with loss of response. In the adalimumab (DE038) and tocilizumab (CHERISH) trials included in the ITC, all cause discontinuation in the randomised phase was much lower than in the tofacitinib trial, which may be due to patients

experiencing a flare not being counted as discontinuations, thus resulting in discontinuation values that are more reflective of clinical practice (Table 5).

In the OLE study of tofacitinib, 13 (5.8%) patients had discontinued due to AEs at 72 weeks of follow up. However, all-cause discontinuation was not reported. The tocilizumab study had a similar length of follow up and comparable rate of discontinuation (Table 5). In the longer OLE of the adalimumab trial, 66 patients (51%) had discontinued at the end of the 6.9 year follow up. The majority were due to withdrawal of consent (n=18), lost to follow up (n=13) and 19 were stated as other, a smaller number were due to AEs (n=6) or lack of efficacy (n=7). Discontinuation in the adalimumab study seems to be in line with other long-term JIA extension studies; 36% of patients completed a 7-year abatacept trial[27] and 38% completed 7 years in an etanercept study[28].

As discussed further in Section 3.5, the adverse event profile of tofacitinib appeared generally consistent with the selected comparators. Rates of discontinuation due to treatment emergent AEs would therefore not be expected to differ substantially on this basis. However, as a BID oral therapy, nausea may present a greater barrier to adherence on tofacitinib than on subcutaneous biologics. Coupled with the short half-life of tofacitinib, missed doses due to poor treatment adherence may have a greater effect upon the long-term efficacy of tofacitinib.

Due to the lack of evidence on long-term discontinuation rates for tofacitinib, it is uncertain whether retention will be comparable to adalimumab and tocilizumab. Therefore, this represents a key area of uncertainty.

Table 5 Discontinuation rates for tofacitinib, adalimumab and tocilizumab

Study, Outcome	Intervention		Comparator	
Tofacitinib [a]				
Discontinuation during open label run in (18 weeks) n (%)	40 (17.8%)			
Discontinuation during DB period (26 weeks) n (%)	**Placebo**		**Tofacitinib**	
	47/85 (55%) [b]		27/88 (31%) [b]	
Discontinuation due to AEs during OLE phase (72 weeks)	13 (5.8%)			
Adalimumab				
Discontinuation during open label run in (16 weeks) n (%)	**ADA (+MTX)**		**ADA (-MTX)**	
	2/85 (2%) [c]		9/86 (10.5%) [c]	
Discontinuation during DB period (32 weeks) n (%)	**Placebo + MTX**	**Ada +MTX**	**Placebo**	**Ada**
	0/28 (0%)	1/30 (3%) [d]	1/37 (3%) [d]	3/38 (8%) [d]
Discontinuation during OLE phase (8.9 years)	66/128 (51%)			
Tocilizumab				
Discontinuation during open label run in (16 weeks) n (%)	22/188 (12%) [e]			
Discontinuation during DB period (24 weeks) n (%)	**Placebo**		**Tocilizumab**	
	2/84 (2%) [f]		3/82 (4%) [g]	
Discontinuation during OLE phase (64 weeks)	5/160 (3%) [h]			

[a] All discontinuation data for tofacitinib includes patients with ERA and PsA [b] 3/88 (3%) in the tofacitinib arm and 5/85 (6%) in the placebo arm were due to AEs, including arthritis [c] A further 27 (16%) patients discontinued after completing the open label run in phase and prior to randomisation. [d] None were due to lack of efficacy or AEs. [e] 15 were due to lack of efficacy, 3 due to AEs and 3 withdrew [f] One patient discontinued due to AEs and one due to insufficient clinical response. [g] One patient discontinued due to AEs, one due to insufficient clinical response and one withdrew. [h] 188 patients entered into the open label run in phase and 155 completed the OLE at 104 weeks (17.5%).

3.5 Safety/Adverse events

3.5.1 Data from Study A3921104

Section B.3.10 and Appendix F of the CS presented safety/adverse event data for tofacitinib in paediatric patients with JIA. With the exception of upper respiratory tract infection, which was compared between tofacitinib, adalimumab and tocilizumab in an indirect comparison, all adverse event data were drawn from the OLFAS and DBSAS analysis sets of Study A3921104 (see tables 18 and 19 of the CS).

The CS concluded that no new safety concerns were raised by Study A3921104, with the proportion of patients with treatment-emergent AEs (TEAEs) being similar between tofacitinib and placebo in the double-blind phase, and most TEAEs being of mild to moderate severity. This conclusion seems appropriate based on the available data.

While total adverse events were numerically greater in the placebo arm, this difference was partly due to the greater number of "JIA" and "disease progression" events classified as AEs (see table 19, section B.3.10.2). Similarly, the larger number of AEs leading to discontinuation in the placebo group appears to be driven by reasons possibly related to lack of efficacy ("disease progression"; "JIA"; "Condition aggravated"; "Arthritis"; see table 20, section B.3.10.3).

3.5.1.1 Uveitis

Uveitis is a common extra-articular manifestation of JIA, involving inflammation of the middle layers of the eye. Uveitis can lead to visual impairment and permanent vision loss if improperly managed, and is a major burden to those affected. Control of active uveitis is typically established using corticosteroids, with ongoing use of methotrexate recommended to suppress relapse.[29, 30] Prevalence and form vary by JIA subtype, but estimates range between 11.6 – 30% of patients with a JIA diagnosis.[31] Uveitis control is an important consideration for clinicians selecting a biologic for JIA treatment, as there is RCT and observational evidence supporting the superiority of adalimumab over methotrexate (HR 0.27, 95% CI 0.13 – 0.52) and other biologics for inducing and maintaining remission of uveitis.[31]

Patients with active uveitis were excluded from enrolment in the A3921104 trial, and during the study there were just two reported cases in the placebo arm, of which only one met the study definition of uveitis and which resolved by the end of the randomised trial period. It is unclear whether the inhibition of the JAK-STAT signalling pathway using tofacitinib will have an independently suppressive effect upon uveitis. TNF-α has been shown to play an important role in the pathogenesis of uveitis in human and animal models, which has been translated into its successful treatment and suppression using TNF inhibitors. It is therefore uncertain whether the efficacy of tofacitinib could be considered equivalent to adalimumab in the treatment of extra-articular manifestations of JIA. This may be a consideration for treatment selection in patients with a clinical history of uveitis, and may be more of a concern for those with poor methotrexate adherence.

3.5.1.2 Laboratory parameters

The CS states that laboratory parameters "were consistent with the expected effects of tofacitinib", but data on laboratory parameters were not available in the CS or appendices.

3.5.1.3 Open label extension

The CS did not present AE data from the tofacitinib open label extension (OLE) study. The ERG therefore extracted this information from published data[1] and presents it in Appendix Table 11. The OLE included participants from study A3921104 and an earlier phase 1 study (NCT01513902).[11] There appears to have been less than a month between the final study visit for A3921104 ([redacted] and the data cut-off for the reported OLE data (4th June 2019). Consequently, of the

223 participants recruited to the OLE, just 127 participants (57%) received tofacitinib for 12 months and 20 participants (9%) received it for two years. While the study included up to 66 months of observation, the median exposure to tofacitinib was 347 days. Although these data did not indicate any additional safety concerns about tofacitinib, given the diminishingly small number of participants observed beyond a year of exposure, medium- and longer-term adverse events are highly uncertain or unknown.

3.5.2 Adverse events across comparators

Due to inconsistencies in reporting across trials, upper urinary tract infection (URTI) was the only AE compared between tofacitinib, adalimumab and tocilizumab. Figure 5 of Appendix D.1.2 shows the results of an indirect comparison, which found [redacted]. Confidence intervals were very wide due to the small number of observed events.

Though the CS commented that the oral route of administration for tofacitinib avoided the injection site reactions associated with adalimumab, the CS did not present any AE data for adalimumab or tocilizumab. The ERG therefore have collated available AE data for the comparators of interest..

Appendix Table 12 and Table 13 show AEs reported in the double blind phases from RCTs that were used in the CS indirect treatment comparisons of tofacitinib, adalimumab and tocilizumab. Table 12 brings together the available data on total adverse events, SAEs, and adverse events leading to drug discontinuation, harmonising the classification and units of measurement where possible. Table 13 provides a fuller list of AEs from the trials, retaining the differences in reporting.

While AEs were reported differently across trials, the available data do not suggest any notable differences in safety between the three comparators during the double-blind study phases. However, it should be noted that the sample sizes of these trials might be too small to detect rare AEs.

Differences in reporting and follow-up across studies preclude meaningful comparison of AEs for the different treatments during study run-in and extension periods.

4 SUMMARY OF THE ERG'S CRITIQUE OF COST EVIDENCE SUBMITTED

Whether it is appropriate for the assessment to proceed as a cost comparison FTA rests primarily on the clinical effectiveness and the appropriateness of assuming equal efficacy of tofacitinib to at least one relevant comparator. The ERG critique of the cost comparison evidence assumes that it is appropriate for the assessment to proceed as a cost comparison FTA, and seeks to answer under what circumstances tofacitinib is likely to be cost saving or equivalent in cost to the comparators.

4.1 Company cost comparison

4.1.1 Summary of costs and assumptions

The company presents the formal cost comparison of tofacitinib against adalimumab and tocilizumab. It is assumed that these three treatments have response rates that can be considered statistically equivalent, as estimated by the company's ITC (Section 3.3.2). Both adalimumab and tocilizumab were previously appraised by NICE in a multiple technology comparison of treatments for JIA (TA373[10]).

The primary costs considered in the company's cost comparison comprise drug acquisition costs and drug administration costs. These were estimated on a 3-monthly cycle basis. In addition to the intervention being considered, a proportion of patients were assumed to receive concomitant methotrexate in a scenario analysis.

The results of the company's cost comparison reflect the application of the tofacitinib patient access scheme (PAS), which comprises a simple discount of [redacted] to the list price of tofacitinib. Tocilizumab also has a confidential PAS and the price of adalimumab biosimilars is also commercially confidential. The drug acquisition costs and results reported in this document do not reflect the application of the tocilizumab PAS and adalimumab biosimilar costs; these are applied in a confidential appendix separate to this report.

The unit costs and assumptions regarding resource use in the cost comparison analysis are summarised in Table 6. Dosing assumptions were from the respective SmPCs, and drug acquisition costs were from MIMs.[32-35]

Table 6 Summary of unit costs and resource use assumptions

	Tofacitinib	Tocilizumab	Adalimumab
Dose (based on body weight, in kg)	10 to <20 kg: 3.2mg BID 20 to <40 kg: 4mg BID ≥40 kg: 5mg BID	< 30 kg: 10 mg/kg every 4 weeks (IV) or 162 mg every 3 weeks (SC) ≥30 kg: 8 mg/kg every 4 weeks (IV) or 162 mg every 2 weeks (SC)	10–29 kg: 20 mg every 2 weeks ≥30 kg: 40 mg every 2 weeks
Mode of administration	Oral (tablet or solution)	By subcutaneous injection (SC) or by intravenous infusion (IV) Assume 80% will receive toci via SC and 20% via IV.	By subcutaneous injection
Administrations per cycle (3 months)	182.625	SC: 6.5 (under 30 kg) or 4.33 (over 30 kg) IV: 3.25	6.5
Drug acquisition cost	Oral solution (240 ml) [redacted] (list price), [redacted] (discounted price) Tablets (5mg, pack of 56): [redacted] (list price), [redacted] (discounted price)	RoActemra (162mg/0.9ml in prefilled syringe, pack of four): £913.12 RoActema (80mg/4ml, for IV infusion): £102.40	Amgevita (20mg/0.4ml solution for injection in pre-filled syringe, pack of one): £158.40 Amgevita (40mg/0.8ml solution for injection in pre-filled syringe, pack of two): £633.60
Drug acquisition cost per cycle (3 months)	10 to <20 kg: [redacted] 20 to <40 kg: [redacted] 40 kg and over: [redacted]	Under 30 kg: £989.21 (SC), £1,497.60 (IV for 30kg patient) 30 kg and over: £1,483.82 (SC), £1,830.40 (IV for 50kg patient)	10–29 kg: £1,029.60 >30 kg: £2,059.20
Administration cost	£0	Unit cost for administration by IV: £241.47 [Source: NHS ref cost 2018-2019. Weighted average of WF01A, WF01B, WF01C, WF01D (Consultant led)] [36] Assume 25% of patients with SC require administration by community nurse. Unit cost of community nurse: £67.27 [Source: NHS Ref Cost 2018-2019. Community health services (N12)].[36]	Assume 25% of patients with SC require administration by community nurse. Unit cost of community nurse: £67.27 [Source: NHS Ref Cost 2018-2019. Community health services (N12)].[36]
Administration cost per cycle (3 months)	£0	Under 30 kg: £215.25 30 kg and over: £244.40	£109.31
Concomitant MTX	0%	0%	0%
BID, twice daily; IV, intravenous; SC, subcutaneous; MTX, methotrexate			

Key assumptions in the company analysis included:

- No difference in AE profile between interventions, and costs of treating AEs were not applied.
- No concomitant methotrexate use was considered in the base-case analysis; in a scenario analysis, 80% concomitant methotrexate usage for each intervention was considered, based on

clinical expert opinion, and differential rates of methotrexate usage based on trial evidence for each comparator (70% for tofacitinib[4] and 80% for tocilizumab[2] and adalimumab[7]).

- The dose for each age was estimated from the median body weight of the general population for that age (Table 23 of CS),[37] adjusted for gender in the pcJIA population (74% female[38]).
- Administration by IV would be by a consultant rheumatologist in an outpatient setting. Due to anxiety about SC injections, a proportion of SC administrations would require assistance from a community care nurse.[12]
- Health state costs and monitoring were assumed to be the same between interventions, on the basis of clinical expert opinion and previous assumptions made in TA373.[10, 39] A lipid test between 4-8 weeks is recommended for tofacitinib, which is in line with tocilizumab monitoring requirements. Therefore, these costs were not applied in the analysis.
- No drug wastage with tofacitinib; for adalimumab and tocilizumab, any unused medication in an opened vial (due to the required dose, based on bodyweight, being lower than the total in the vial) would be thrown away.
- Discontinuation rates and dose adjustments, either due to a loss of efficacy of AEs, were not considered.

4.1.2 Results

The company presented mean annual costs for each age group, particularly highlighting annual costs for 11-year old and 16-year old patients to account for differences in costs according to changes in dosing (Table 1 and Figure 1 in company submission erratum). Additionally, aggregate results for the 11-18 years old age group were presented, where future costs were discounted at an annual rate of 3.5%, as these were thought to represent the average cohort of patients who would be most likely to receive tofacitinib, given the [redacted].

Under the company's assumptions and using the list price for tocilizumab and adalimumab, tofacitinib [redacted] than tocilizumab and adalimumab for all age groups. Tofacitinib is associated with [redacted] drug acquisition costs and [redacted] administration costs than both comparators.

The company presented a number of one-way sensitivity analyses, displaying the impact on total aggregated discounted costs for 11- to 18-year olds by varying key parameters in the analysis. Deterministic sensitivity and scenario analyses showed that tofacitinib [redacted] for these patients, despite changes to the inputs and assumptions (see Table 14 in Appendix for details).

4.2 ERG critique of the company submission

The ERG conducted a technical validation of the executable model, by cross-checking values against the submission and auditing formulae. At the clarification stage, the company identified an error in how future costs were discounted, when estimated aggregated costs over the ages of 11 to 16 years. Updated results were provided in an erratum to the submission, and the tables in this report reflect the corrected results. The ERG detected no further errors in the economic model.

The ERG critique centres on the following aspects of the analysis:

- Body weight,
- Dose adjustment,
- Administration,
- Adverse events,
- Long-term efficacy.

Following the critique, the ERG has proposed an alternative base-case analysis, exploring alternative assumptions to those used in the company analysis.

4.2.1 Dose-based body weight

The company approach to presenting results for each age relied on assuming that there is a relationship between patient age and patient body weight, as per Table 23 in the CS,[37] which was used to estimate the intervention dose size. There is not thought to be any registry data or real-world evidence that reported on the weight distribution of patients with pcJIA in detail, and therefore it is not possible to comment on whether the weight distribution of the general population is similar to that of the pcJIA population. The ERG considered an alternative approach which compares total costs for each body weight category, and avoids the need to make judgements on the age-weight relationship. The proportion of patients in each weight category was provided by the company for the pcJIA population of Study A3921104, and was used by the ERG to present the weighted average cost per patient for the pcJIA population.

4.2.2 Dose adjustment

The company analysis did not incorporate the impact of dose interruptions or adjustments for any of the comparators to the cost of providing treatment (Section 3.3.1).

At the clarification stage, the company provided additional information on adherence of patients on tofacitinib in the pcJIA population of the A3921104 trial. Adherence to tofacitinib (DBJAS phase) appeared high: [redacted] patients in the tofacitinib arm received a lower dose (defined as <80% of planned dose, for two or more consecutive visits), and there were [redacted] instances of overcompliance.

In a scenario analysis, the observed mean daily dose ([redacted]) and median dose ([redacted]) in the double-blind phase of the trial were applied to those eligible for the 5mg BID dose of tofacitinib (i.e. over 40kg in bodyweight). For those not eligible for the 5mg BID dose, the company assumed the full dose in the scenario analysis, stating that the mean daily dose was not available. As a result of the company's assumptions, the total annual cost for a patient over 40kg (approximately 10 years of age) on tofacitinib decreased by [redacted] and [redacted] (approximately [redacted] and [redacted] respectively) in each scenario, relative to the company's base case assumptions. However, the ERG is concerned that the evidence on mean daily dose may have been misinterpreted by the company and that it in fact reflects all patients in the DBJAS tofacitinib arm, not just those eligible for the 5mg BID dose of tofacitinib. The CS notes that all patients in the DBJAS tofacitinib arm are listed as "tofacitinib 5mg BID" regardless of the dose they received, and the number of patients in the tofacitinib arm of the trial corresponds to the number of patients providing points of data to estimate mean daily dose. In this case, applying the mean daily dose to those over 40kgs will overestimate the impact on adherence and underestimate the associated costs. As such, the ERG does not consider it appropriate to incorporate the evidence on dose adjustment for tofacitinib into the base-case analysis.

Neither the company or the ERG are aware of any evidence on dose adjustments or interruptions for adalimumab or tocilizumab for this population in the literature, and so it was not possible to include a cost scenario where dose adjustments were applied for these comparators.

4.2.3 Administration costs

There are two aspects of the company model that lead to an overestimation of the administration cost of adalimumab and tocilizumab: i) the application of a cost for SC administration is inappropriate, and ii) an inappropriate cost for IV administration was applied.

The ERG considers that there should be no administration cost associated with SC administration. This was not considered in the MTA of treatments for JIA (TA373) and our clinical experts did not consider that this was the model of care in the UK. Some competitor companies offer the self-injection training service to patients for free, while others also offer a free homecare service for those unable to self-inject. Moreover, the study cited by the company describes patients who have difficulties with MTX treatment, including nausea and vomiting after MTX, anticipatory nausea and fear of injections or blood tests; not all of which are associated with SC biologic treatment and do not indicate the requirement for administration assistance.

The company stated that IV-administered treatment would be delivered by a consultant paediatric rheumatologist (Section B.4.1 of CS), and applied the associated cost from NHS Reference Costs (Table 24 of CS), estimated as £241.47 per administration. However, clinical advice to the ERG asserted that a rheumatologist would not be directly involved with the administration of treatment.

The ERG considers the unit cost for a "Non-admitted Face to Face Attendance, Follow-up" in paediatric rheumatology is more appropriate, which is £114 per administration. This is more consistent with the cost applied in previous NICE appraisals in JIA (TA373)[10] and other rheumatology appraisals (TA375).[40]

4.2.4 Adverse events

While these may not be considered to have a substantial impact on differences between discontinuation rates, any differences in AE profiles may lead to different associated costs between comparators. The company notes that the risk of URTI varies widely across competitors, although the ERG acknowledges that [redacted] (see section 3.5.2 of this report). Injection site reactions are among the most commonly occurring AEs with adalimumab but are not associated with tofacitinib as an orally administered treatment.

At the clarification stage, the company provided a number of scenario analyses that incorporates the cost of treating URTI. During the exposure period, the majority of URTIs were of mild severity, which were assumed not to have an associated treatment cost. The remaining URTIs were of moderate severity and were assumed to be associated with a visit to a general practitioner at a cost of £36.21 per visit.[41] The results of the analyses found that the inclusion of URTI costs made a negligible impact in the majority of scenarios. A similar conclusion was made in TA373, which considered the wider category of serious adverse events and found very small differences in total SAE costs.

As such, the ERG is satisfied that the exclusion of AE costs in the analyses does not bias the results and that differences in safety profile between comparators, which may be important when considering patient experience, are not a driver of the cost analysis. However, the ERG notes that in TA373, uveitis control was considered a factor that could decrease the incremental cost-effectiveness ratio (ICER) for biologics in practice, but was not captured in the model. As described in Section 3.5.1.1, it is unclear whether the efficacy of tofacitinib will be equivalent to adalimumab in the suppression of uveitis. This could have implications for the cost-effectiveness of tofacitinib in practice.

4.2.5 Long-term efficacy and treatment discontinuation

The company's cost-comparison analysis necessarily assumes that treatment discontinuation occurs at an equal rate for patients on tofacitinib and the selected comparators. The primary driver of treatment discontinuation in the JIA trials and in practice is ineffectiveness,[5] through either a failure to achieve an adequate response, or due to a loss of an established response. As discussed in Section 3.4, evidence on the long-term efficacy of tofacitinib is sparse in JIA, whilst data on adalimumab and tocilizumab are more complete. As patients in the randomised phase of the tofacitinib trial

discontinued upon experiencing disease flare, the rates observed cannot be directly compared to the corresponding rates in the comparator trials.

Whilst not addressed directly in the submission, the assumption of continuing equivalence in efficacy is based upon that adopted in TA373, wherein the same discontinuation rate was applied across the biologics. This approach was necessary due to the lack of long-term data on most of the comparators, and the plausibility of such an assumption based on the similarity of the respective mechanisms of action. Indeed, data since generated on all-cause discontinuation at 7 years on abatacept, etanercept, and adalimumab appear comparable in JIA (see Section 3.4). However, due to its different mechanism of action and route of administration, the validity of extending this assumption to tofacitinib is uncertain.

In light of issues raised in Section 3.4, the ERG considers there to be a non-negligible risk that the long-term efficacy of tofacitinib may not be equivalent to the selected comparators. However, in the absence of comparative data, the direction and magnitude of any effects upon the cost-effectiveness of tofacitinib remains uncertain.

4.3 ERG exploratory scenarios

The ERG presents an analysis that incorporates the following alternative assumptions:

- No administration cost associated with SC injections,
- An alternative unit cost for an intravenous infusion.

The total annual costs per age predicted by the ERG analysis are presented in Table 7 and Figure 1.

Table 8 presents the average cost per patient for each comparator, using the proportion of patients in the pcJIA cohort in each bodyweight category and the cost per each bodyweight category to estimate a weighted mean cost. Table 9 presents the results of the equivalent analysis under the company's base case assumptions, for completeness.

The impact of the ERG's alternative assumptions is upon adalimumab and tocilizumab; total costs for tofacitinib remain unchanged from the company's analysis. Using the list price for tocilizumab and adalimumab, tofacitinib remains [redacted] than tocilizumab and adalimumab for all age groups, being associated with [redacted] drug acquisition costs. However, since it was not possible to account for dose adjustments and interruptions for each comparator, the true difference in costs may not be fully captured.

Table 7 Results of the ERG alternative base-case analysis

Technologies	Acquisition costs	Administration costs	Total costs	Incremental costs (Tofacitinib - comparator)
Annual costs for an 11-year-old patient				
Tofacitinib	[redacted]	£0	[redacted]	-
Tocilizumab	£5,946	£296	£6,243	[redacted]
Adalimumab	£8,237	£0	£8,237	[redacted]
Annual costs for a 16-year-old patient				
Tofacitinib	[redacted]	£0	[redacted]	-
Tocilizumab	£6,346	£296	£6,642	[redacted]
Adalimumab	£8,237	£0	£8,237	[redacted]
Aggregated, discounted results for 11-18 years olds				
Tofacitinib	[redacted]	£0	[redacted]	-
Tocilizumab	£43,312	£2,082	£45,394	[redacted]
Adalimumab	£57,853	£0	£57,853	[redacted]

Figure 1 Results of the ERG alternative base-case analysis: cost per age

Table 8 Results of the ERG alternative base-case analysis: Weighted average cost per patient

Body weight category	Proportion of patients	Total cost	Weighted cost per patient	Incremental costs (Tofacitinib - comparator)
Annual cost of adalimumab				
Under 30kg	[redacted]	£4,118	£7,118	[redacted]
Over 30kg	[redacted]	£8,237		
Annual cost of tocilizumab [1]				
Under 20kg	[redacted]	£3,994	£5,853	[redacted]
20-30kg	[redacted]	£4,394		
30-40kg	[redacted]	£6,243		
Over 40kg	[redacted]	£6,509		
Annual cost of tofacitinib				
Under 20kg	[redacted]	[redacted]	[redacted]	-
20-40kg	[redacted]	[redacted]		
Over 40kg	[redacted]	[redacted]		
[1] Weight based on mid-point of band				

Table 9 Results of the base-case analysis under company's base-case assumptions: Weighted average cost per patient

Body weight category	Proportion of patients	Total cost	Weighted cost per patient	Incremental costs (Tofacitinib - comparator)
Annual cost of adalimumab				
Under 30kg	[redacted]	£4,556	[redacted]	[redacted]
Over 30kg	[redacted]	£8,674		
Annual cost of tocilizumab [1]				
Under 20kg	[redacted]	£4,559	[redacted]	[redacted]
20-30kg	[redacted]	£4,958		
30-40kg	[redacted]	£6,924		
Over 40kg	[redacted]	£7,190		
Annual cost of tofacitinib				
Under 20kg	[redacted]	[redacted]	[redacted]	-
20-40kg	[redacted]	[redacted]		
Over 40kg	[redacted]	[redacted]		
[1] Weight based on mid-point of band				

5 ERG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

5.1 Strengths

5.1.1 Clinical evidence:

- The company's choice of comparators appropriately represents the NICE recommended treatment options. Adalimumab is the most frequently used biologic DMARD and tocilizumab represents an alternative mode of action to TNF inhibitors.
- The availability of an oral treatment option will be welcomed by clinicians and patients, particularly given the well noted issue of needle phobia affecting adherence to biologics. However, there is little available evidence on the potential advantages of oral delivery to inform the assessment.

5.1.2 Economic evidence:

- The company provided a number of re-analyses of data Study A3921104 that allowed for the exploration of scenarios specific to the population in the decision problem.
- The electronic model is simple and transparently presented, and no errors were detected.

5.2 Weaknesses and areas of uncertainty

5.2.1 Clinical evidence:

- There was clinical heterogeneity between the few trials included in indirect comparisons of tofacitinib, adalimumab and tocilizumab, with wide confidence intervals for all comparisons. However, similarly uncertain results in TA373 were considered adequate to demonstrate similar efficacy across treatments.
- The cost comparison assumes that tofacitinib has similar long-term efficacy to its comparators adalimumab and tocilizumab, for which there are more substantial data suggesting that long-term treatment responses are maintained (Section 3.5). However, due to its different mechanism of action and route of administration, the long-term efficacy of tofacitinib is uncertain.
- At the time of reporting, only a few pcJIA participants had received medium- to long-term tofacitinib treatment thus, possible medium- and longer-term adverse effects of tofacitinib in children with pcJIA are highly uncertain or unknown.
- The cost comparison assumes that discontinuation rates are equivalent for tofacitinib and the comparators adalimumab and tocilizumab. However, only discontinuation due to adverse

events is reported for tofacitinib up to 72 weeks of follow up (Section 3.5.1), with more substantial data reported for adalimumab. As tofacitinib is administered orally, twice daily, it may have different levels of adherence than its comparators (Section 3.3). Therefore, the long-term discontinuation of tofacitinib is a key area of uncertainty.

- Due to the oral administration of tofacitinib, nausea may present a new barrier to treatment adherence in many patients, and missed doses may have a potentially larger impact upon efficacy due to the relatively short biological half-life of tofacitinib. Poor taste acceptability of tofacitinib in oral solution for some patients might also influence adherence. However, there is little available evidence on the potential disadvantages of oral delivery to inform the assessment.

5.2.2 Economic evidence:

- The cost-effectiveness of tofacitinib is largely dependent upon the assumption that tofacitinib will have equal rates of long-term efficacy and discontinuation to the comparators. Due to its different mechanism of action and route of administration, the validity of this assumption cannot be assessed without longer-term data.
- There may be aspects of tofacitinib's cost-effectiveness profile (e.g. uveitis control) that are not captured in the cost-comparison analysis. This could have implications for the relative cost-effectiveness of tofacitinib in practice.
- Insufficient data on dose adjustments and interruptions for tocilizumab and adalimumab were available in a pcJIA population, so comparisons to tofacitinib could not be drawn. Potential differences between adherence to biosimilar and proprietary adalimumab introduce further uncertainty.
- The net effect of issues affecting treatment adherence on biologics and oral tofacitinib remains unclear, but dose interruptions may have a greater impact upon the efficacy of tofacitinib.

6 REFERENCES

1. Brunner HI, Akikusa J, Al-Abadi E, Bohnsack J, Boteanu AL, Kobusinka K, et al. Tofacitinib for the treatment of patients with juveile idiopathic arthritis: an interim analysis of data up to 5.5 years from an open-label long-term extension study. *Arthritis Rheumatol* 2020;**72(Suppl 10)**:1495.

2. Brunner H, Ruperto N, Zuber Z, Cuttica RJ, Xavier R, Calvo I, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: 2-year data from CHERISH. *Arthritis Rheumatol* 2014;**66**:S5-S6.

3. Lovell DJ, Brunner HI, Reiff AO, Jung L, Jarosova K, Němcová D, et al. Long-term outcomes in patients with polyarticular juvenile idiopathic arthritis receiving adalimumab with or without methotrexate. *RMD Open* 2020;**6**:e001208.

4. Brunner H, Synoverska O, Ting T, Mendoza CA, Spindler A, Vyzhga Y, et al. *Tofacitinib for the treatment of polyarticular course juvenile idiopathic arthritis: results of a phase 3 randomized, double-blind, placebo-controlled withdrawal study*. In: ACR/ARP Annual Meeting. Atlanta, Georgia, USA; 2019.

5. Kearsley-Fleet L, Heaf E, Davies R, Baildam E, Beresford MW, Foster HE, et al. Frequency of biologic switching and the outcomes of switching in children and young people with juvenile idiopathic arthritis: a national cohort study. *Lancet Rheumatol* 2020;**2**:e217-e26.

6. Quartier P, Baptiste A, Despert V, Allain-Launay E, Kone-Paut I, Belot A, et al. ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis. *Ann Rheum Dis* 2018;**77**:1003-11.

7. Lovell D, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med* 2008;**359**:810-20.

8. Burgos-Vargas R, Tse SML, Horneff G, Pangan AL, Kalabic J, Goss S, et al. A randomized, double-blind, placebo-controlled multicenter study of adalimumab in pediatric patients with enthesitis-related arthritis. *Arthritis Care Res* 2015;**67**:1503-12.

9. Brunner H, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. *Ann Rheum Dis* 2014;**74**:1110-7.

10. National Institute for Health and Care Excellence. *Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis. Technology appraisal guidance TA373*: NICE; 2015.

11. Ruperto N, Brunner HI, Zuber Z, Tzaribachev N, Kingsbury DJ, Foeldvari I, et al. Pharmacokinetic and safety profile of tofacitinib in children with polyarticular course juvenile idiopathic arthritis: results of a phase 1, open-label, multicenter study. *Pediatr Rheumatol Online J* 2017;**15**:86.

12. Mulligan K, Kassoumeri L, Etheridge A, Moncrieffe H, Wedderburn LR, Newman S. Mothers' reports of the difficulties that their children experience in taking methotrexate for Juvenile Idiopathic Arthritis and how these impact on quality of life. *Pediatr Rheumatol Online J* 2013;**11**:23.

13. Ingerski LM, Baldassano RN, Denson LA, Hommel KA. Barriers to oral medication adherence for adolescents with inflammatory bowel disease. *J Pediatr Psychol* 2010;**35**:683-91.

14. Goh XT, Tan YB, Thirumoorthy T, Kwan YH. A systematic review of factors that influence treatment adherence in paediatric oncology patients. *J Clin Pharm Ther* 2017;**42**:1-7.

15. Wu YP, Stenehjem DD, Linder LA, Yu B, Parsons BG, Mooney R, et al. Adherence to oral medications during maintenance therapy among children and adolescents with acute lymphoblastic leukemia: a medication refill analysis. *J Pediatr Oncol Nurs* 2018;**35**:86-93.

16. Taddeo D, Egedy M, Frappier JY. Adherence to treatment in adolescents. *Paediatr Child Health* 2008;**13**:19-24.

17. Venditti EM, Tan K, Chang N, Laffel L, McGinley G, Miranda N, et al. Barriers and strategies for oral medication adherence among children and adolescents with Type 2 diabetes. *Diabetes Res Clin Pract* 2018;**139**:24-31.

18. Favier LA, Taylor J, Loiselle Rich K, Jones KB, Vora SS, Harris JG, et al. Barriers to adherence in juvenile idiopathic arthritis: a multicenter collaborative experience and preliminary results. *J Rheumatol* 2018;**45**:690-6.

19. Rapoff MA, Belmont JM, Lindsley CB, Olson NY. Electronically monitored adherence to medications by newly diagnosed patients with juvenile rheumatoid arthritis. *Arthritis Rheum* 2005;**53**:905-10.

20. Ringold S, Grant S, Girdish C, Wallace CA, Sullivan SD. Methotrexate and injectable tumor necrosis factor-α inhibitor adherence and persistence in children with rheumatic diseases. *J Rheumatol* 2013;**40**:80-6.

21. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;**50**:683-91.

22. Ruperto N, Lovell D, Quartier P, Paz E, Rubio-Pérez N, Silva C, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet* 2008;**372**:383-91.

23. Lovell D, Giannini E, Reiff A, Cawkwell G, Silverman E, Nocton J, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Engl J Med* 2000;**342**:763-9.

24. Opoka-Winiarska V, Żuber Z, Alexeeva E, Chasnyk V, Nikishina I, Dębowska G, et al. Long-term, interventional, open-label extension study evaluating the safety of tocilizumab treatment in patients with polyarticular-course juvenile idiopathic arthritis from Poland and Russia who completed the global, international CHERISH trial. *Clin Rheumatol* 2018;**37**:1807-16.

25. National Institute for Health and Care Excellence. *Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs. Technology appraisal guidance [TA543]*. NICE; 2018. Available from: https://www.nice.org.uk/guidance/ta543 [accessed 15th April 2021].

26. National Institute for Health and Care Excellence. *Baricitinib for moderate to severe rheumatoid arthritis. Technology appraisal guidance [TA466]*. NICE; 2017. Available from: https://www.nice.org.uk/guidance/ta466 [accessed 15th April 2021].

27. Lovell DJ, Ruperto N, Mouy R, Paz E, Rubio-Pérez N, Silva CA, et al. Long-term safety, efficacy, and quality of life in patients with juvenile idiopathic arthritis treated with intravenous abatacept for up to seven years. *Arthritis Rheumatol* 2015;**67**:2759-70.

28. Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, et al. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. *Arthritis Rheum* 2008;**58**:1496-504.

29. *Uveitis*. Clinical Knowledge Summaries, National Institute for Health and Care Excellence; 2019. Available from: https://cks.nice.org.uk/topics/uveitis/ [accessed 15th April 2021].

30. Bou R, Adán A, Borrás F, Bravo B, Calvo I, De Inocencio J, et al. Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus. *Rheumatol Int* 2015;**35**:777-85.

31. Clarke SL, Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. *Pediatr Rheumatol Online J* 2016;**14**:27.

32. Electronic medicines compendium. *RoActemra 162 mg Solution for Injection in Pre-Filled Pen*. 2020. Available from: https://www.medicines.org.uk/emc/product/9086/smpc [accessed 2020].

33. Electronic medicines compendium. *RoActemra 20mg/ml Concentrate for Solution for Infusion*. 2020. Available from: https://www.medicines.org.uk/emc/product/6673/smpc [accessed 2020].

34. Electronic medicines compendium. *Amgevita 20 mg solution for injection in pre-filled syringe*. 2020. Available from: https://www.medicines.org.uk/emc/product/9547/smpc [accessed 2020].

35. *Monthly Index of Medical Specialities (MIMS)*. Haymarket Media Group Ltd.; Available from: https://www.mims.co.uk/ [accessed 15th April 2021].

36. NHS Improvement. *2018/19 National Cost Collection data* 2019. Available from: https://improvement.nhs.uk/resources/national-cost-collection/ [accessed 15th April 2021].

37. Royal College of Paediatrics and Child Health. *Royal College of Paediatrics and Child Health's School age growth charts*. 2019. Available from: https://www.rcpch.ac.uk/resources/uk-who-growth-charts-2-18-years [accessed 15th April 2021].

38. Davies R, Carrasco R, Foster HE, Baildam EM, Chieng SEA, Davidson JE, et al. Treatment prescribing patterns in patients with juvenile idiopathic arthritis (JIA): Analysis from the UK Childhood Arthritis Prospective Study (CAPS). *Semin Arthritis Rheum* 2016;**46**:190-5.

39. Thornton J, Lunt M, Ashcroft DM, Baildam E, Foster H, Davidson J, et al. Costing juvenile idiopathic arthritis: examining patient-based costs during the first year after diagnosis. *Rheumatology* 2008;**47**:985-90.

40. National Institute for Health and Care Excellence. *Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. Technology appraisal guidance [TA375]*. NICE; 2016. Available from: https://www.nice.org.uk/guidance/ta375 [accessed 15th April 2021].

41. Personal Social Services Research Unit. *Unit Costs of Health and Social Care 2014*. Kent: Personal Social Services Research Unit, University of Kent; 2014.

APPENDICES

Clinical evidence

Table 10 Cochrane risk of bias assessment for studies included in the CS/ERG indirect treatment comparisons (adapted from Table 22 of CS appendix)

Study, publication	Was the randomisation method adequate?	Was the allocation adequately concealed?	Were participants and investigators blind to exposure and comparison?	Were outcomes assessors blinded?	Were drop-outs between groups adequately explained? Were unexpected imbalances adjusted for?	Were all outcomes adequately reported?	Did study appear free from other sources of bias?
ABATACEPT							
Ruperto 2008 [22]	Yes	Yes	Unclear[1]	Unclear	Yes (HRQoL:No)	Yes	Yes
ADALIMUMAB							
DE038 [7]	Unclear	Unclear	Yes	Yes	Yes	Yes	No[2]
ETANERCEPT							
Lovell 2000 [23]	Yes[3]	Unclear	Yes	Unclear	Yes	Yes	Unclear
TOCILIZUMAB							
CHERISH [9]	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes
TOFACITINIB							
Brunner 2019 [4]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

HRQoL, health-related quality of life
Yes, no risk of bias; No, high risk of bias; Unclear, unclear risk of bias
[1]CS statement: "…described as "double-blind"; however, these studies did not report specifically who was blinded and so were assigned an unclear risk of performance bias". Ruperto 2008 article: "A solution that was identical in appearance to abatacept (either 5% dextrose in water or normal saline) was administered to patients in the control group in the same way as abatacept treatment. Solutions were prepared in the hospital pharmacies and trial administrators did not have access to the preparation phase." May be considered adequate.
[2]CS statement: "Study was slightly underpowered (28 placebo patients instead of the 29 minimum patients required"
[3]CS: "did not report whether the randomisation sequences were computer-generated but did include a blocked, stratified randomisation scheme that was deemed to be sufficient to suggest a low risk of bias". Though an appropriate randomisation method seems likely to have been used, "Unclear" may be a more appropriate judgement

Table 11 Adverse event data from tofacitinib open label extension study

Tofacitinib (n=223*; 265.8 PY; data cut at 66 months; Mean (median; range) exposure 401.4 (347; 20-1983) days)[1]	
	Pts with events, n (%)
AEs	160 (71.7)
SAEs	15 (6.7)
Permanent discontinuations due to AES	13 (5.8)
Dose reductions or temporary discontinuations due to AEs	43 (19.3)
Most common AEs (25% occurrence, by MedDRA preferred term)	
Upper respiratory tract infection	36 (16.1)
JIA exacerbation	19 (8.5)
Nasopharyngitis	19 (8.5)
Arthralgia	16 (7.2)
Viral infection	14 (6.3)
Headache	14 (6.3)
Sinusitis	12 (5.4)
Vomiting	12 (5.4)
AEs of special interest	
Death	0
Gastrointestinal perforation	0
Hepatic event	0
Herpes Zoster (non-serious and serious)[b]	2 (0.9)
Interstitial lung disease	0
Major adverse cardiovascular event	0
Malignancy (including non-melanoma Skin cancer)	0
Macrophage activation syndrome[c]	0
Opportunistic infections (excluding tuberculosis)[d]	1 (0.4)
Serious infection	5 (2.2)
Thrombotic event[e]	0
Tuberculosis	0
Uveitis	1 (0.4)
Pts with laboratory test abnormalities, n (%)[f]	
Haemoglobin	
<0.8x LLN	4 (18)
Lymphocytes	
<0.8x LLN	6 (2.7)
>1.2x ULN	1 (0.5)
Aspartate aminotransferase	
>3x ULN	0
Alanine aminotransferase	
>3.0x ULN	1 (0.5)
Cholesterol	
>1.3x ULN	0

Safety events were assessed from baseline through the data cut-off date.
*pcJIA n=172. [a]Tofacitinib 5 mg BID or equivalent weight-based lower dose in pts <40kg; [b]one serious case, one non-serious case; [C]Applicable to pts with systemic JIA without active systemic features only (N=11); [d]The serious herpes zoster case was an opportunistic infection; [e]Includes deep vein thrombosis, pulmonary embolism, and arterial thromboembolism; [f]220 pts were evaluated for laboratory abnormalities, except cholesterol which was evaluated in 204 pts
LLN, lower limit of normal; MedDRA, Medical Dictionary for Regulatory Activities; N, number of pts evaluated; n, number of pts with event; pts, patients; SAE, serious AE; ULN upper limit of normal

Table 12: Total adverse events, serious adverse events, and adverse events leading to drug discontinuation across included trials: double blind treatment period

	Tofacitinib		Tocilizumab		Adalimumab			
	Tofacitinib 5 mg BID (N=88)	**Placebo (N=85)**	**TCZ (n=82)**	**PBO (n=81)**	**ADA (+MTX) (n=37; 15 Patient-yrs)**	**Placebo (+MTX) (n=38; 18.3 Patient-yrs)**	**ADA (-MTX) (n=30; 14.4 Patient-yrs)**	**Placebo (-MTX) (n=28; 10.6 Patient-yrs)**
Total number of AEs	[redacted]	[redacted]	147	141	234	155	171	153
Participants (%) with at least 1 AE	[redacted]	[redacted]	58 (70.7)	60 (74.1)	NR	NR	NR	NR
SAEs	1 (1.1) - pilonidal cyst[a]	2 (2.4) - 1 intussusception, 1 appendicitis, 1 JIA (3 SAEs in 2 ptps)[a]	3 (3.7) - pneumonia, upper limb fracture, psychosomatic disease[a]	3 (3.7) - uveitis, enterocolitis, complicated migraine[a]	0[b]	1 (0.1) – Gastroduodenitis[b]	0[b]	0[b]
AEs leading to the discontinuation of the drug	[redacted]impacted tooth, pilonidal sinus repair	[redacted][c] Intussusception, appendicitis, haemoglobin decreased[d]	1 (1.2) Increased blood bilirubin level	1 (1.2) Gastroenteritis	0	0	0	0

[a]Participants with at least 1 SAE

[b]Serious AEs, possibly related to study drug. Further SAEs were reported (in 1 patient each, except where noted), but not considered to be possibly related to the study drug: abdominal pain, abortion, adenoidal and tonsillar hypertrophy (2 patients), arthritis (2 patients), appendicitis (2 patients), diabetic ketoacidosis, femur fracture, unspecified injury, malabsorption, joint contracture, joint dislocation, juvenile rheumatoid arthritis disease flare (12 patients), osteoarthritis, speech disorder, retinal detachment, urinary tract infection, and vomiting. These events were not reported by treatment group

[c]Discontinuation due to adverse events excluding all pcJIA-specific events (disease progression, JIA, condition aggravated and arthritis)

[d]3 events in 2 participants

NR: Not reported

Table 13 All reported AEs for the included trials: double blind treatment period

Tofacitinib			**Tocilizumab**			**Adalimumab**				
TEAEs occurring in 2% of patients during the double-blind phase (DBSAS)	**Tofacitinib 5 mg BID (N=88)**	**Placebo (N=85)**	**SAEs and AEs occurring ≥5% of patients, n (%)**	**TCZ (n=82)**	**PBO (n=81)**	**Adverse Events, no. of events (no. of events per patient-year)**	**ADA (+MTX) (n=37; 15 Patient-yrs)**	**Placebo (+MTX) (n=38; 18.3 Patient-yrs)**	**ADA (-MTX) (n=30; 14.4 Patient-yrs)**	**Placebo (-MTX) (n=28; 10.6 Patient-yrs)**
Infection and infestations	[redacted]	[redacted]	Duration in study (years)	32.33	27.41	**Any AE**	234 (12.8)	155 (10.3)	171 (11.9)	153(14.4)
URTI	[redacted]	[redacted]	**Patients with ≥1 AE**	58 (70.7)	60 (74.1)	**Most frequently reported AEs**				
Nasopharyngitis	[redacted]	[redacted]	**Total no. of AEs**	147	141	Related to injection-site reaction	73 (4.0)	57 (3.8)	71 (4.9)	20 (1.9)
Sinusitis	[redacted]	[redacted]	Rate of AEs per 100 patient-years	454.7	514.4	Contusion	12 (0.7)	7 (0.5)	2 (0.1)	5 (0.5)
Influenza	[redacted]	[redacted]	**Most frequent AEs**			Nasopharyngitis	5 (0.3)	6 (0.4)	0	5 (0.5)
RTI	[redacted]	[redacted]	Nasopharyngitis	14 (17.1)	9 (11.1)	Upper respiratory tract infection	6 (0.3)	5 (0.3)	6 (0.4)	6 (0.6)
Gastroenteritis	[redacted]	[redacted]	Headache	3 (3.7)	0	Viral infection	7 (0.4)	3 (0.2)	8 (0.6)	4 (0.4)
Pharyngitis	[redacted]	[redacted]	Upper respiratory infection	4 (4.9)	2 (2.5)	Vomiting	4 (0.2)	2 (0.1)	0	1 (0.1)
Pharyngitis streptococcal	[redacted]	[redacted]	Cough	2 (2.4)	1 (1.2)	Excoriation	10 (0.6)	1 (0.1)	6 (0.4)	2 (0.2)
Rhinitis	[redacted]	[redacted]	Pharyngitis	3 (3.7)	3 (3.7)					
Viral infection	[redacted]	[redacted]	Nausea	2 (2.4)	2 (2.5)	**Serious AEs, possibly related to study drug**	0	1 (0.1) - Gastroduodenitis	0	0
Respiratory tract infection viral	[redacted]	[redacted]	Diarrhoea	2 (2.4)	3 (3.7)					
Tonsillitis	[redacted]	[redacted]	Rhinitis	2 (2.4)	1 (1.2)	**AEs leading to the discontinuation of the drug**	0	0	0	0
Urinary tract infection	[redacted]	[redacted]	Vomiting	3 (3.7)	1 (1.2)					
General disorders and administration site conditions	[redacted]	[redacted]	Abdominal pain	2 (2.4)	2 (2.5)					
Disease progression	[redacted]	[redacted]	Oropharyngeal pain	1 (1.2)	5 (6.2)					
Pyrexia	[redacted]	[redacted]	Rash	4 (4.9)	1 (1.2)					

Tofacitinib			**Tocilizumab**			**Adalimumab**
Condition aggravated	[redacted]	[redacted]	**SAEs**			
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	Patients with ≥1 SAE	3 (3.7)	3 (3.7)	
Rash	[redacted]	[redacted]	Rate of SAEs per 100 patient-years	9.3	10.9	
GI disorders	[redacted]	[redacted]	Patients with ≥1 infectious SAE	1 (1.2)	0	
Dyspepsia	[redacted]	[redacted]	Rates of infectious SAEs per 100 patient-years	3.1	0	
Diarrhoea	[redacted]	[redacted]	Pneumonia	1 (1.2)	0	
Abdominal pain	[redacted]	[redacted]	Upper limb fracture	1 (1.2)	0	
Vomiting	[redacted]	[redacted]	Uveitis	0	1 (1.2)	
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	Psychosomatic disease	1 (1.2)	0	
Back pain	[redacted]	[redacted]	Enterocolitis	0	1 (1.2)	
JIA	[redacted]	[redacted]	Complicated migraine	0	1 (1.2)	
Arthralgia	[redacted]	[redacted]	**AEs leading to study drug discontinuation**			
Arthritis	[redacted]	[redacted]	Increased blood bilirubin level	1 (1.2)		
Pain in extremity	[redacted]	[redacted]	Gastroenteritis		1 (1.2)	
Investigations	[redacted]	[redacted]				
AST increased	[redacted]	[redacted]				
ALT increased	[redacted]	[redacted]				
Blood creatinine phosphokinase increased	[redacted]	[redacted]				
CRP increased	[redacted]	[redacted]				
Haemoglobin decreased	[redacted]	[redacted]				
WBC count decreased	[redacted]	[redacted]				
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]				
Epistaxis	[redacted]	[redacted]				
Cough	[redacted]	[redacted]				
Nasal congestion	[redacted]	[redacted]				
Oropharyngeal pain	[redacted]	[redacted]				
Blood and lymphatic system disorders	[redacted]	[redacted]				

Tofacitinib					**Tocilizumab**	**Adalimumab**
Lymphadenitis	[redacted]		[redacted]			
Leukopenia	[redacted]		[redacted]			
Ear and labyrinth disorders	[redacted]		[redacted]			
Ear pain	[redacted]		[redacted]			
Eye disorders	[redacted]		[redacted]			
Uveitis	[redacted]		[redacted]			
Nervous system disorders	[redacted]		[redacted]			
Headache	[redacted]		[redacted]			

Economics

Table 14 Results of the company's sensitivity and scenario analyses

Model parameter	Tofacitinib vs Tocilizumab		Tofacitinib vs Adalimumab	
	Low value	High value	Low value	High value
Base case	[redacted]		[redacted]	
Community care nurse use	[redacted]	[redacted]	[redacted]	[redacted]
Community care nurse cost	[redacted]	[redacted]	[redacted]	[redacted]
IV administration costs	[redacted]	[redacted]	[redacted]	-
No future costs discounting	[redacted]		[redacted]	
100% tocilizumab SC use	[redacted]		[redacted]	
40% tocilizumab IV use and 60% tocilizumab SC	[redacted]		[redacted]	
80% methotrexate use for all treatments	[redacted]		[redacted]	
80% methotrexate use for adalimumab and tocilizumab and 70% use for tofacitinib	[redacted]		[redacted]	

IV, intravenous; vs, versus

These results were corrected at the clarification stage and provided by the company in an erratum to their submission

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Tofacitinib for treating juvenile idiopathic arthritis [ID2718]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 17 May 2021** using the below 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.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Typographical error, long-term extension study number

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The study number for the long-term extension study has been incorrectly quoted in the ERG report (pages 10 and 20).	Please correct the study number from A3921165 to A3921145 on pages 10 and 20.	The study number of the long-term extension study for tofactinib in pcJIA is A3921145. A3921165 is an ongoing Phase III study aiming to determine the efficacy, safety and pharmacokinetics of tofacitinib in patients with systemic JIA with active systemic features.	These typographical errors have been corrected.

Issue 2 Typographical error in Table 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Table 5 (p.24), the headings for the adalimumab trial (DE038) double-blind period have been inverted for the two strata compared to the heading of the open label run in phase just above: the MTX headings are in the non-MTX stratum, and vice versa.	The headings for the adalimumab trial, double-blind period, should be amended so that they appear in the following order: Placebo + MTX; Ada + MTX; Placebo; Ada.	In the current version of Table 5, DE038 trial discontinuation rates during the double-blind period are erroneously matched across the four trial arms.	This typographical error has been corrected.

Issue 3 Long-term efficacy of comparators incorrect assessment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG assessed tofacitinib long-term efficacy by qualitatively comparing the results of study A3921145 (the open-label extension of A3921104) with the results of the open-label extension phases of DE038 (adalimumab) and CHERISH (tocilizumab). A formal quantitative synthesis of these data could not be performed (p. 20-22). Based on efficacy trends from the three trials, the ERG highlighted a downward trend in tofacitinib efficacy outcomes (p.20-22), and inferred a "*non-negligible risk that the long-term efficacy of tofacitinib may not be equivalent to the selected comparators*" in the economic section (p. 33). This assessment is purely speculative and was not based on a formal quantitative assessment. The validity of this inference is therefore questionable.	It is proposed that the wording "non-negligible risk that the long-term efficacy of tofacitinib may not be equivalent to the selected comparators" in the economic section (p. 33) be removed.	Heterogeneity in clinical trial design may limit the validity of comparing the long-term efficacy of the three drugs. This includes heterogeneity related to open-label extension treatment regimen. Data from the tofacitinib trial are immature in comparison to the older trials. In A3921145 (the tofacitinib trial), the interim analysis was performed on a data cut of 18 months, whereas later timepoints were available in DE038 (up to 6.9 years) and CHERISH (up to 2 years). This limits the validity of visually comparing trends across these three trials. An exclusively qualitative assessment of data trends from observational, open-label studies is not sufficient to dismiss equivalency in long-term efficacy between tofacitinib, adalimumab and tocilizumab; therefore, the approach used in TA373, wherein the same discontinuation rate was applied across drugs, was also applied in this submission.	Not a factual error. Highlighting uncertainties and potential areas of risk is not equivalent to 'dismiss[ing] equivalency'. This was not the conclusion of the ERG's discussion of discontinuation rates. The company has not presented sufficient evidence to demonstrate long-term equivalence in discontinuation between tofacitinib and its comparators. By definition, this remains an area of uncertainty. There are a number of factors described in Sections 3.4.1 and 4.2.5 of the ERG report which may contribute to potential differences in discontinuation rates. The report states that thus uncertainty means there is a risk of lower long-term efficacy on tofacitinib. However, the report makes no conclusions on whether there is equivalence or not.

Issue 4 Tocilizumab and adalimumab trials are unlikely to be more reflective of clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states that "*In the adalimumab (DE038) and tocilizumab (CHERISH) trials included in the ITC, all cause discontinuation in the randomised phase was much lower than in the tofacitinib trial, which may be due to patients not discontinuing after experiencing a flare and is more reflective of clinical practice (Table 5).*" (page 22-23). However, in the CHERISH trial patients did discontinue part 2 (the randomised, double-blind phase) if they experienced a flare, as stated in Brunner 2014: "*Patients continued in part 2 until week 40, unless they experienced JIA-flare*". Additionally, in DE038, adalimumab or placebo were administered in the double-blind phase until completion or flare of disease.	The proposed amendment is to remove the inference that all-cause discontinuation is lower in the randomised phase for the tocilizumab and adalimumab trials due to patients not discontinuing the randomised phase after experiencing a flare. The conclusion that these findings are more reflective of clinical practice should also be removed, as it is based on an incorrect inference.	The CHERISH trial primary publication (Brunner 2014) states that patients did discontinue the randomised trial phase if they experienced a flare. The DE038 CT.gov entry states that adalimumab or placebo were administered in the double-blind phase until completion or flare of disease. Differences in all-cause discontinuation rates between the tofacitinib trial and comparator trials may be due to how discontinuation due to flare is defined. As the number of patients who experienced a flare in the comparator trials is much higher than those who discontinued, despite both comparator trials stating that patients discontinued the randomised phase if they experienced a flare, it is likely that flare-related discontinuation from the randomised trial phase was not reported or defined as discontinuation in the tocilizumab or adalimumab trials.	Not a factual error. Unlike trial A3921104, the published subject disposition data for the randomised phases of the tocilizumab (CHERISH) and adalimumab (DE038) trials did not report participants with disease flare as discontinuations. Consequently, the reported rates of discontinuation were much lower for these studies. As stated in section 3.4.1, clinical advice to the ERG was that patients who experience a flare would not immediately discontinue treatment, so discontinuation rates excluding flare (as reported by CHERISH and DE038 publications) may be more reflective of clinical practice. However, given ambiguities around the collection and reporting of discontinuation

			data within and between CHERISH and DE038 sources, we have amended the wording of the text for clarity. This now reads: *"In the adalimumab (DE038) and tocilizumab (CHERISH) trials included in the ITC, all cause discontinuation in the randomised phase was much lower than in the tofacitinib trial, which may be due to patients experiencing a flare not being counted as discontinuations, thus resulting in discontinuation values that are more reflective of clinical practice"*

Issue 5 IV administration cost underestimated

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
At pages 31-32 in the ERG report, the ERG suggests a unit costs for the administration of intravenous infusions (IV) equal to a "Non-admitted Face to Face Attendance, Follow-up" visit which has a unit cost of £114. According to the ERG, this is consistent with	The unit cost of £114 for an IV infusion is an underestimation of what has been used in previous appraisals. In TA373 the IV administration cost was equal to £154. Similarly, in TA375 the assessment group used a value of £154 for the administration of the IV infusions informed by TA247 in which the final appraisal determination stated that 'the manufacturer's	A unit cost of £114 does not reflect the economic impact of IV administration costs to the NHS. Using ERGs assumptions but higher IV administration cost (£154) increases costs for tocilizumab from £5,853 to £5,957. Compared to tofacitinib the incremental cost	This is a typographical error, and referred to the magnitude of the administration cost. Text on Page 32 of the report has been amended to the following: "The ERG considers the unit cost for a "Non-admitted Face to Face Attendance, Follow-up"

previous NICE appraisals in JIA (TA373) and other rheumatology appraisals (TA375). It is unclear why the ERG claim the value of non-admitted face to face attendance is consistent with previous appraisals.	revised estimate of £154 was acceptable'. Based on the above evidence the unit cost of IV administration should be at least £154.	increases from [redacted] to [redacted] in favour of tofacitinib.	in paediatric rheumatology is more appropriate, which is £114 per administration. This is more consistent with the cost applied in previous NICE appraisals in JIA (TA373) and other rheumatology appraisals (TA375). The summary text on Page 9 has also been amended to better reflect this point. The estimates of £154/£158 applied in previous RA and JIA appraisals was based on inflating unsourced administration costs from TA36 (cost year 2000). The costs applied by the ERG in the present appraisal are taken directly from 2018-19 NHS Reference costs, which represent 'current costs', and so don't require adjustment. 2018-19 reference costs were used by the company elsewhere in the model. On the basis of expert advice, the ERG considered the most relevant costing for an IV infusion to be for a non-consultant led face-to-face attendance in Paediatric Rheumatology. This appears

			the more relevant cost source.

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Page 11: section 2; Critique of the decision problem in the company's submission, first sentence	The wording of the proposed marketing authorisation is confidential until the publication of CHMP opinion.	The decision problem assesses the use of tofacitinib [redacted]	This text has been marked as requested
Page 13: section 3.3, second paragraph, penultimate row	The mean age of patients in study A3921104 remains confidential until publication.	The [redacted] 75% were female and most had polyarthritis rheumatoid factor (RF) negative disease.	This text has been marked as requested
Page 14: section 3.3, third paragraph, third sentence	The proportion of patients achieving ACR 90 and 100 response is academic in confidence. There has been an error in the marking of this data in appendix D, but this information is not in the public domain currently. Please correct this in the ERG report.	The proportion of patients achieving ACR 90 [redacted] in the tofacitinib arm and [redacted] in the placebo arm) and 100 response [redacted] in the tofacitinib arm and [redacted] in the placebo arm) at week 44 was reported in Appendix D of the CS (Table 15).	This text has been marked as requested

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Fast track appraisal: cost-comparison case

Tofacitinib for treating juvenile idiopathic arthritis [ID2718]

Company evidence submission addendum for the juvenile psoriatic arthritis indication

Pfizer Ltd. confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

July 2021

File name	Version	Contains confidential information	Date

ID2718 Tofacitinib for JIA – Addendum	1.0	Yes	20.07.2021

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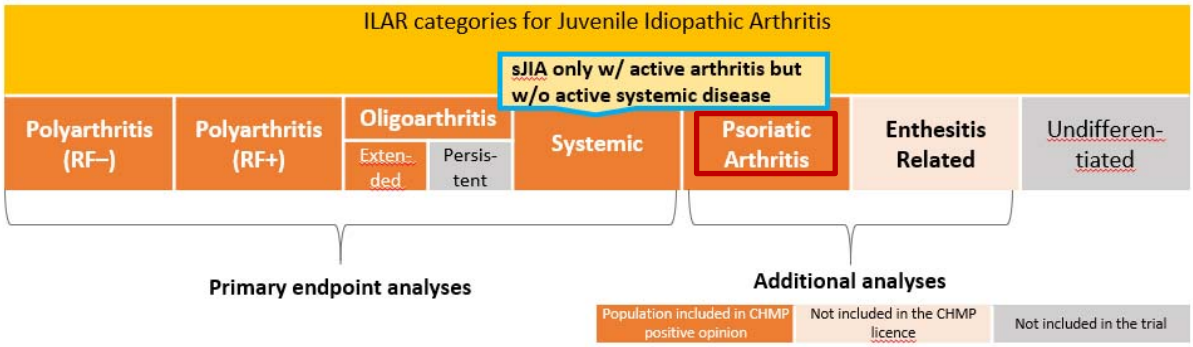
Introduction

The focus of this Addendum is to provide additional data and evidence for the juvenile psoriatic arthritis (jPsA) indication for tofacitnib.

The Committee for Medicinal Products for Human Use (CHMP) has published a positive opinion for tofacitinib (Xeljanz©) on the 25th June 2021. The indication is *for the treatment of active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive or negative polyarthritis and extended oligoarthritis), and juvenile psoriatic arthritis (PsA) in patients 2 years of age and older, who have responded inadequately to previous therapy with DMARDs. Tofacitinib can be given in combination with methotrexate (MTX) or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate*.(1)
Pfizer's original evidence submission was focused on the polyarticular juvenile idiopathic arthritis population (pJIA). However, the final CHMP indication is broader and includes jPsA, therefore NICE has requested the company to submit additional evidence in line with the final indication. Pfizer is following the European Commission Decision Reliance Procedure (ECDRP) for marketing authorisation application with the MHRA, therefore this is the relevant indication for Great Britain as well.
This addendum provides additional data and evidence for the jPsA indication for the committee to appraise the full licensed population. All other information provided in the main submission (ID2718 Company evidence submission Document B) holds for this subpopulation in terms of comparators, treatment pathway and burden of disease for patients and carers.

Juvenile PsA is a subtype of JIA (Figure 1) and accounts for a small proportion (approximately 6%) of all cases of JIA (approximately 12,000 patients).(2, 3) This equates to 759 patients with jPsA in total. The treatment pathway for patients with jPsA is the same as for pJIA, except that the only licensed biological DMARD is etanercept. This leads to a higher unmet need in this patient population as the treatment options are more limited. The proportion of patients with JIA receiving biological disease modifying (bDMARD) treatments is around 38%, which equates to approximately 288 patients in the jPsA population eligible for bDMARDs (the same proportion in the pJIA population equates to 1300 patients).(2) Pfizer's expectation is that the same uptake will be applicable for the jPsA subpopulation as for the pJIA population. Therefore, in the first 5 years [redacted] (for more details on market share expectations, please see Pfizer's Budget Impact submission).

Figure 1: ILAR categories for JIA



Population for which evidence was not included in the original evidence submission and submitted in this addendum.
CHMP, Committee for Medicinal Products for Human Use; ILAR, International League of Associations for Rheumatology; MA, marketing authorisation; RF, rheumatoid factor; sJIA, systemic juvenile idiopathic arthritis

Clinical effectiveness of tofacitinib in juvenile PsA

Evidence for the clinical effectiveness of tofacitinib in juvenile PsA is available from Study A3921104.(4) Study A3921104 was a phase 3 randomised withdrawal, double-blind, placebo controlled, 44-week study to assess the efficacy, safety and tolerability of tofacitinib in paediatric patients with JIA. Full details of the study protocol, methodology and results can be found in Document B section B3.3-3.7.(5)

Exploratory objective and end points in patients with jPsA was to [redacted]

- [redacted]
- [redacted]

[redacted]

Study A3921104 included [redacted] patients ([redacted] patients enrolled into the open-label phase) with jPsA in the open label run in phase. In the double-blind phase (DBPsA analysis set), [redacted] out of 173 patients in the double-blind phase) patients continued with jPsA. [redacted] out of 88 patients on the tofacitinib arm in DBFAS) patients were randomised on the tofacitinib arm and [redacted] out of 85 patients on the placebo arm in DBFAS) on the placebo arm.

Occurrence of disease flare in the jPsA population

[redacted] **Error! Reference source not found. Error! Reference source not found.** [redacted]

[redacted]

Table 1 Occurrence of disease flare in Open-Label Run-in phase (OLPsA)

			Presence	
Visit	Treatment	N	n (%)	SE
[redacted]				

NC=not calculated. SE was not calculated when the % was 0% or 100%
Source: Study A3921104 clinical study report (4)

Table 2 Occurrence of disease flare in Double-Blind Phase - DBPsA

			Presence	
Visit	Treatment	N	n (%)	SE
[redacted]				

NC=not calculated. SE was not calculated when the % was 0% or 100%
Source: Study A3921104 clinical study report (4)

ACR results in the jPsA population

The ACR results shown improvement across all ACR endpoints in the open-label run-in phase and on the tofacitinib arm, versus placebo in the double-blind phase (**Error! Reference source not found.**, **Error! Reference source not found.**). At Week 44 more patients achieved ACR 30, 50, 70, 90 and 100 responses with tofacitinib than with placebo.

Table 3 JIA ACR Responses in Open-Label Run-in Phase (OLPsA)

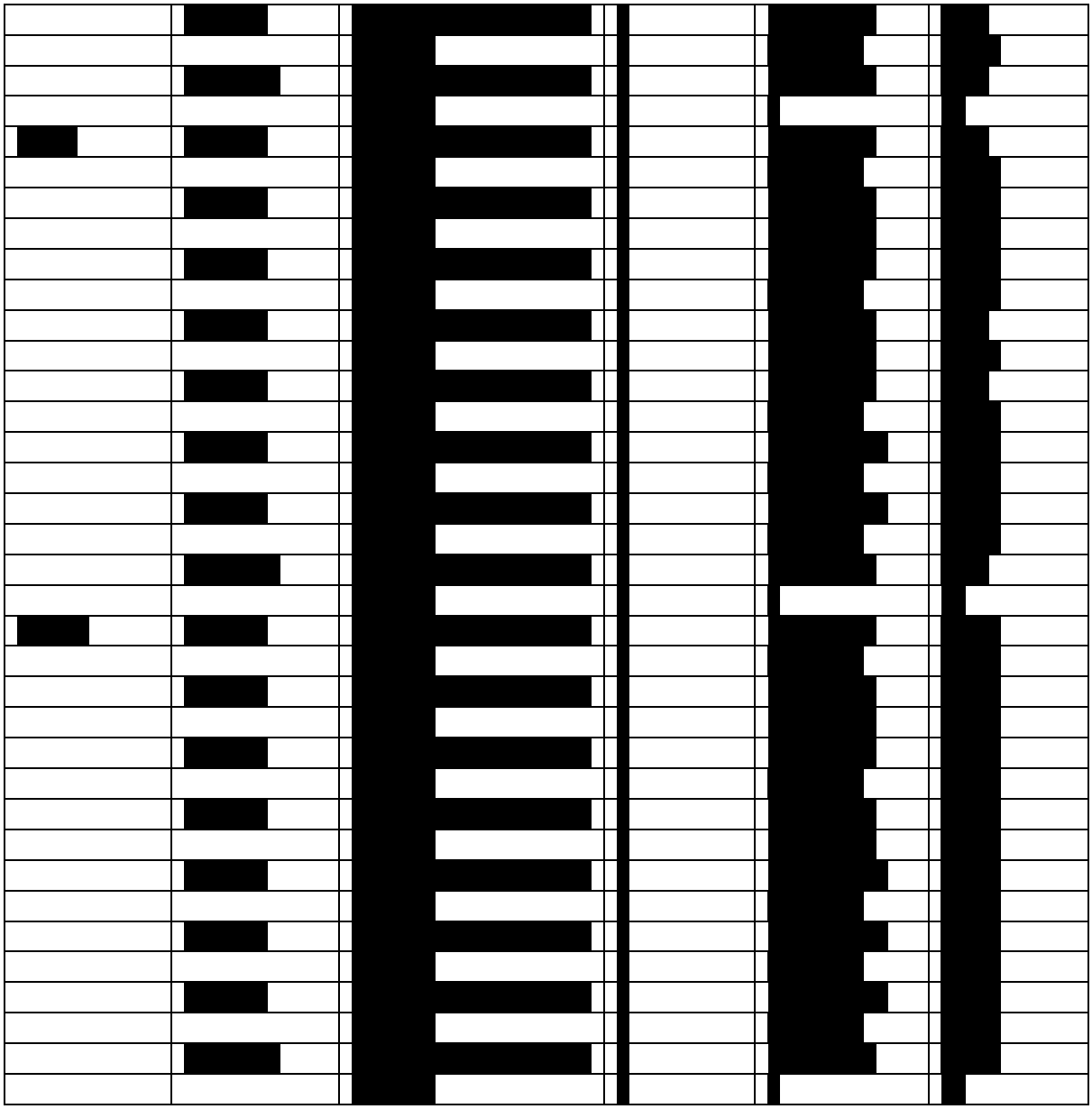
				Response	
ACR Response	Visit	Treatment	N	n (%)	SE
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NC=not calculated. SE was not calculated when the % was 0% or 100%
Source: Study A3921104 clinical study report (4)

Table 4 JIA ACR Responses in Double-Blind Phase - DBPsA

				Response	
ACR response	Visit	Treatment	N	n (%)	SE
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



NC=not calculated. SE was not calculated when the % was 0% or 100%.
Response is calculated relative to the Open-Label baseline.
Source: Study A3921104 clinical study report (4)

CHAQ results in the jPsA population

The results of the Child Health Assessment Questionnaire (CHAQ) showed greater improvements in disability index throughout the double-blind phase on the tofacitinib arm compared to placebo in relation to the open-label baseline **Error! Reference source not found.**.

Table 5 Descriptive Statistics of Change from Open-Label Run-in Baseline in CHAQ - Disability Index in Double-Blind Phase - DBPsA

Visit	Treatment	n	Mean	SD	SE	Min	Q1	Median	Q3	Max

Response is calculated relative to the Open-Label baseline.
Source: Study A3921104 clinical study report (4)

Results for BSA affected with psoriasis and PGA of psoriasis assessment

The results showed that in patients with jPsA,

.

Figure 2 Mean Change From Open-Label Run-In Baseline in the BSA (%) affected with psoriasis (OLPsA)

Error bars are ±SE. Open-label run-in phase baseline of Day 1 was used is the study period before randomization day (Week 18). Missing data were not imputed. BSA, body surface area
Source: Study A3921104 clinical study report (24)

Figure 3 Mean Change From Open-Label Run-In Baseline in the PGA of Psoriasis Assessments in the Open-Label Run-In Phase (OLPsA)

Error bars are ±SE. Open-label run-in phase baseline of Day 1 was used is the study period before randomization day (Week 18). Higher PGA of overall disease activity means more JIA disease activity. Missing data were not imputed. PGA, Physician's Global Assessment
Source: Study A3921104 clinical study report (24)

Figure 4 Mean change from double-blind baseline in the BSA (%) affected with psoriasis (DBPsA)

Error bars are ±SE. Double-blind baseline was taken as Week 18. Missing data were not imputed. BSA, body surface area
Source: Study A3921104 clinical study report (4)

Figure 5 Mean change from double-blind baseline in PGA of psoriasis assessments (DBPsA)

Error bars are ±SE. Double-blind baseline was taken as Week 18. Higher PGA of overall disease activity means more JIA disease activity. Missing data were not imputed. PGA, Physician's Global Assessment.
Source: Study A3921104 clinical study report (4)

Summary of the consideration of jPsA in previous NICE guidance

In order to support decision making, please see a summary of how the jPsA population was considered in the previous NICE guidance on polyarticular JIA (TA373)(6).

Out of the 4 technologies considered in TA373, only etanercept has a marketing authorisation for juvenile PsA in people aged 12 years and over whose disease has responded inadequately to, or who are intolerant of, methotrexate. Therefore, the guidance only recommends etanercept for jPsA.
The evidence submitted by the manufacturer was limited to data from a single-arm, open-label trial, the CLIPPER trial. The trial included 29 children and young people with PsA, between 12-17 years. Other inclusion criteria were; 2 or more active joints (swollen or limited motion with pain or tenderness) and a history of intolerance or unsatisfactory disease response to at least a 3-month course of 1 or more DMARDs. Patients with uveitis, other rheumatic diseases, or who had received a previous biological treatment were excluded. Patients in the trial could have 1 DMARD, 1 oral corticosteroid and 1 NSAID at the same time as etanercept. Etanercept was given at a dosage of 0.8 mg/kg once weekly (maximum dose 50 mg/kg). The primary outcome at week 12 was ACR Pedi 30, which was seen in 93% of patients with PsA. The proportion with inactive disease at week 12 was 7% in the PsA group. All subtypes showed improvement from baseline in the Child Health Assessment Questionnaire (CHAQ, a measure of quality of life), degree of pain and number of active joints. Patients with PsA had an improvement in the BSA covered by psoriasis (48.2% improvement) and in the PGA (39.6% improvement). The Assessment Group could not develop a model for modelling the cost-effectiveness of etanercept in jPsA, because it did not have sufficient evidence to model jPsA separately.

During the committee meeting, the appraisal committee heard from the clinical experts that it was possible to generalise results for the effectiveness of etanercept for treating adult forms of PsA to psoriatic JIA (we note that psoriatic JIA refers to the same indication as jPsA), because the immunological effect of these treatments would be expected to be the same in adults and children. Besides the clinical experts also confirmed that there was no evidence to suggest that etanercept would be any less effective in reducing disease activity in people with juvenile PsA, than when using these technologies for polyarticular JIA (see section 4.43 of FAD)(6)
The conclusion of the appraisal committee was that the results of the economic model were generalisable to people with psoriatic JIA (jPsA) because it heard from clinical experts that the biological treatments indicated for these JIA subtypes are similarly effective across all subtypes of JIA (section 4.44 of FAD)(6).

Conclusions

Tofacitinib has shown numerical improvement in patients with jPsA across all key endpoint, including occurrence of disease flare, ACR responses, changes from baseline in the BSA affected with psoriasis and PGA of psoriasis assessments, and CHAQ-disability index endpoints. Although the small patient numbers do not allow definitive conclusions to be drawn, the results suggest tofacitinib is a clinically and cost-effective treatment option for patients with jPsA.

Although Pfizer did not submit evidence for the comparison with etanercept (the only licensed bDMARD for jPsA), the ERG provided this analysis for disease flare and ACR response and concluded that there was no statistically significant difference between tofacitinib and etanercept in clinical effectiveness in the pJIA population (see section 3.4.1.6 and Table 3 of the ERG report (7)). Besides, it was concluded by the Appraisal Committee in TA373, that the results from the overall polyarticular JIA population can be generalisable for the jPsA population both in terms of clinical- and cost-effectiveness. The committee in TA373 also concluded that results from the adult indication of PsA can be generalisable to the jPsA indication. Tofacitinib has been considered clinically and cost effective in the adult indication of PsA in TA543, and the NICE appraisal committee has concluded that it works as well as other recommended treatments for PsA. (8)

In summary, Pfizer believes that including the jPsA sub population in the consideration within pJIA is a low-risk and straightforward decision. Despite the evidence base specific for the jPsA sub population is limited, given the real world prevalence of this sub population the uncertainty is inherent, the results presented in the document show it to be a efficacious treatment across all key endpoints and there is precedent that the NICE committee has dealt with this uncertainty pragmatically where jPsA was considered alongside the full JIA population.

References

1. Agency EM. Committee for Medicinal Products for Human Use. Summary of opinion (post authorisation). 2021.
2. Davies R, Carrasco R, Foster HE, Baildam EM, Chieng SEA, Davidson JE, et al. Treatment prescribing patterns in patients with juvenile idiopathic arthritis (JIA): Analysis from the UK Childhood Arthritis Prospective Study (CAPS). Seminars in arthritis and rheumatism. 2016;46(2):190-5.
3. Costello R, McDonagh J, Dixon W, Hyrich K, Humphreys J. P01 Incidence of juvenile idiopathic arthritis in the United Kingdom: estimates from a national primary care dataset. Rheumatology. 2019;58(Supplement_4).
4. Pfizer. Data on file: Efficacy, safety, and tolerability of tofacitinib for treatment of polyarticular course juvenile idiopathic arthritis (JIA) in children and adolescent subjects (Study A3921104 clinical study report). Clinical Study Report. Pfizer Inc.; 2019.
5. Pfizer. Tofacitinib for treating juvenile idiopathic arthritis [ID2718] Company evidence submission Document B for National Institute for Health and Care Excellence. 2021.
6. National Institute for Health and Care Excellence. Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis. Technology appraisal guidance TA373. 2015.
7. Rodgers M SS, Walton M, Harden M, Dias S, Claxton L. Tofacitinib for treating juvenile idiopathic arthritis: A Fast Track Appraisal. CRD and CHE Technology Assessment Group, University of York. 2021.
8. National Institute for Health and Care Excellence. Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs. Technology appraisal guidance [TA543]. 2018.

NICE National Institute for Health and Care Excellence

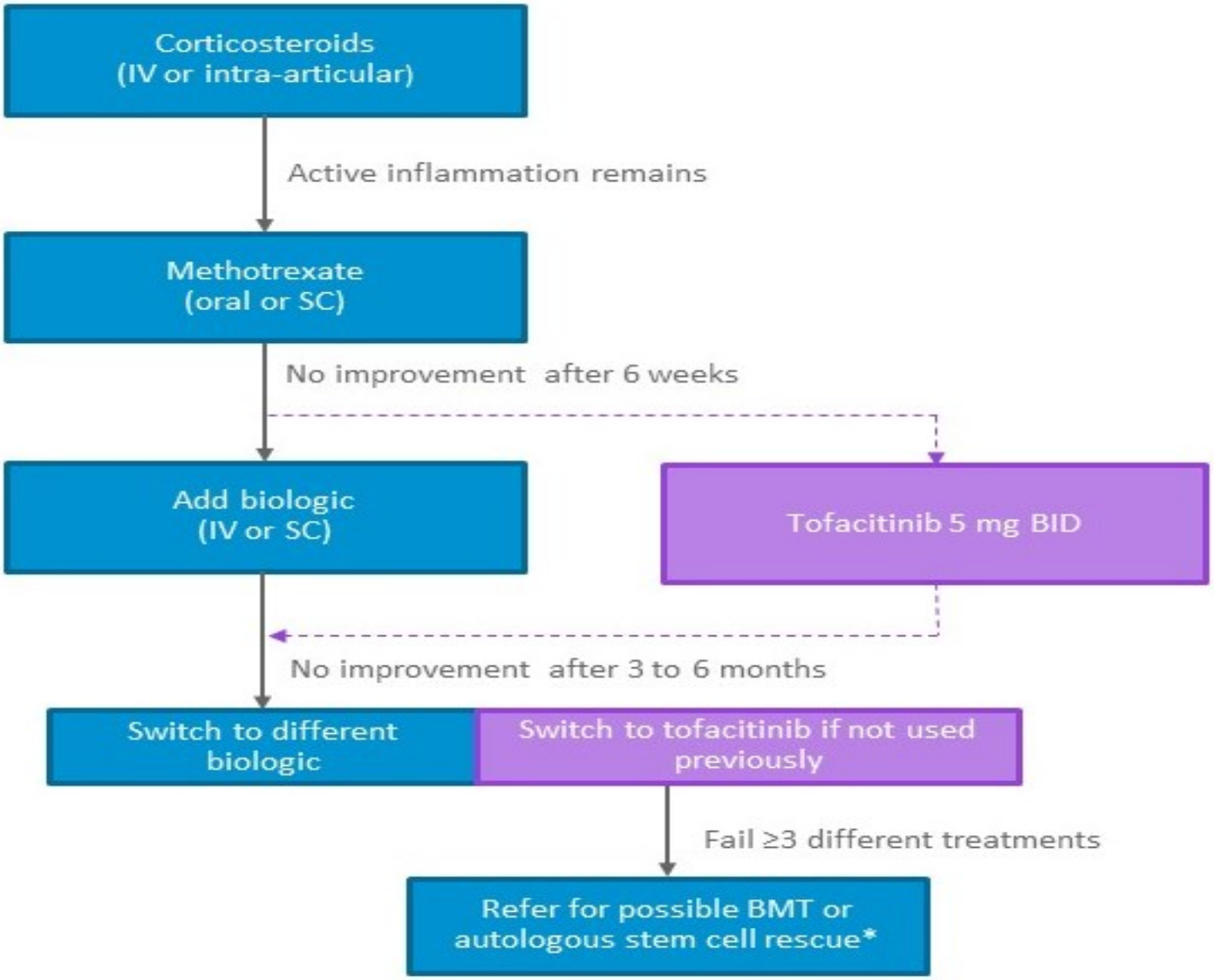
Tofacitinib for treating juvenile idiopathic arthritis (JIA)

Fast track appraisal

Technical briefing

Tofacitinib

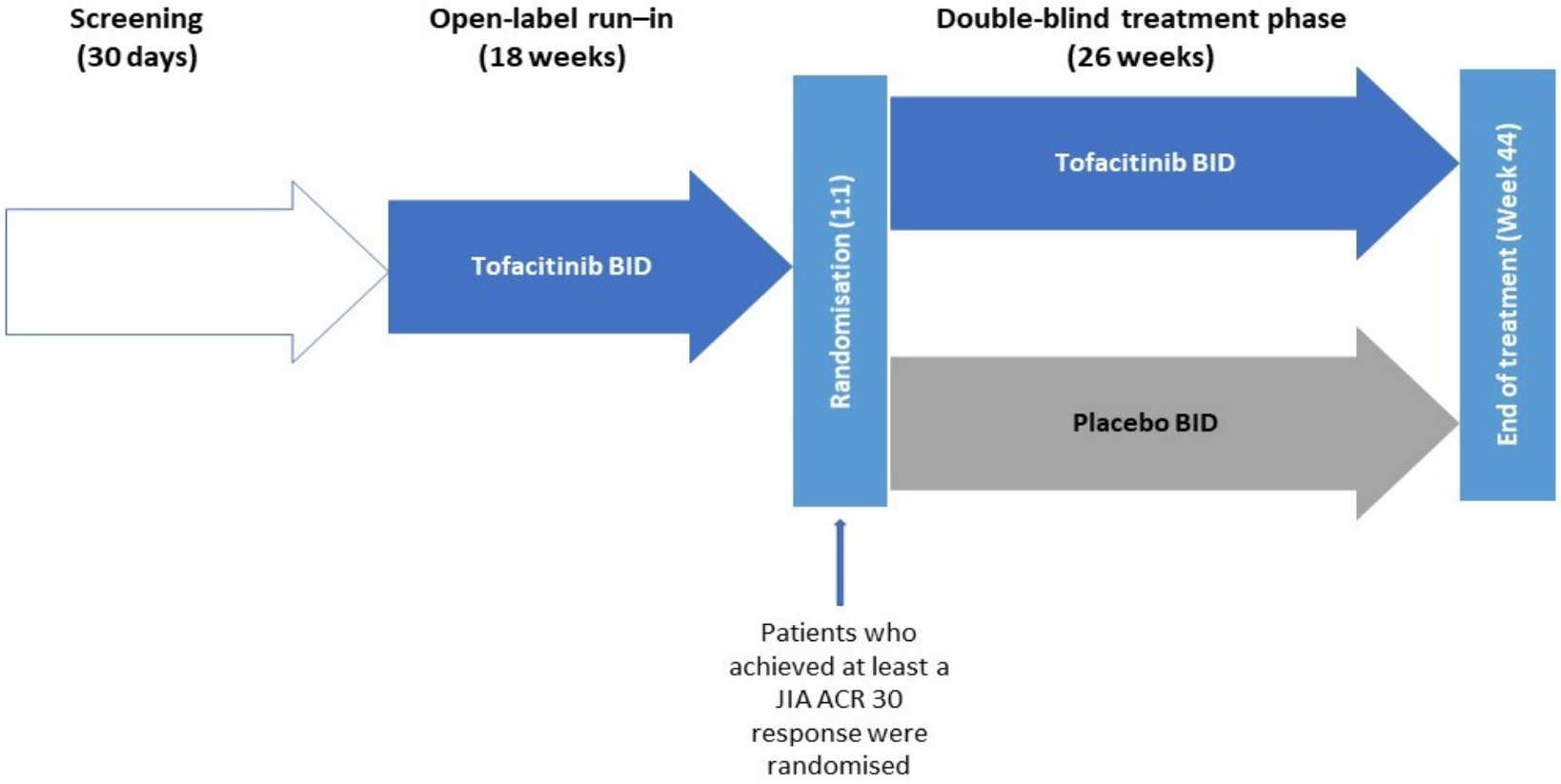
Marketing authorisation (CHMP granted July 2021)	Active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive or negative polyarthritis and extended oligoarthritis), and juvenile psoriatic arthritis (PsA) in patients 2 years of age and older, who have responded inadequately to previous therapy with DMARDs. Tofacitinib can be given in combination with methotrexate (MTX) or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate
Mechanism of action	Janus kinase (JAK) inhibitor. It preferentially inhibits signalling by cytokine receptors that associate with JAK3 and/or JAK1.
Administration	Oral
Price	List - £690.43 per 28 day pack. Annual cost ~£8,995 PAS – XXXX per 28-day pack. Annual cost ~XXXXX


Corticosteroids
(IV or intra-articular)
Active inflammation remains
Methotrexate
(oral or SC)
No improvement after 6 weeks
Add biologic
(IV or SC)
Tofacitinib 5 mg BID
No improvement after 3 to 6 months
Switch to different biologic
Switch to tofacitinib if not used previously
Fail ≥3 different treatments
Refer for possible BMT or autologous stem cell rescue*

Fast track submission

- Company submitted a cost-comparison against adalimumab and tocilizumab (both recommended in TA373)
- Rationale for choice of comparators:
  - adalimumab, a TNF inhibitor is most frequently initiated in JIA
  - tocilizumab, an IL-6 inhibitor is the most frequently used technology with an alternative mode of action to TNF inhibitors
- Estimates of market share:
  - company advisers: adalimumab XX tocilizumab XX
  - ERG clinical advisers: adalimumab 50-60%, tocilizumab 30-40%
- Scrutiny panel view – chosen comparators appropriately represent the NICE recommended treatment options and current clinical practice.

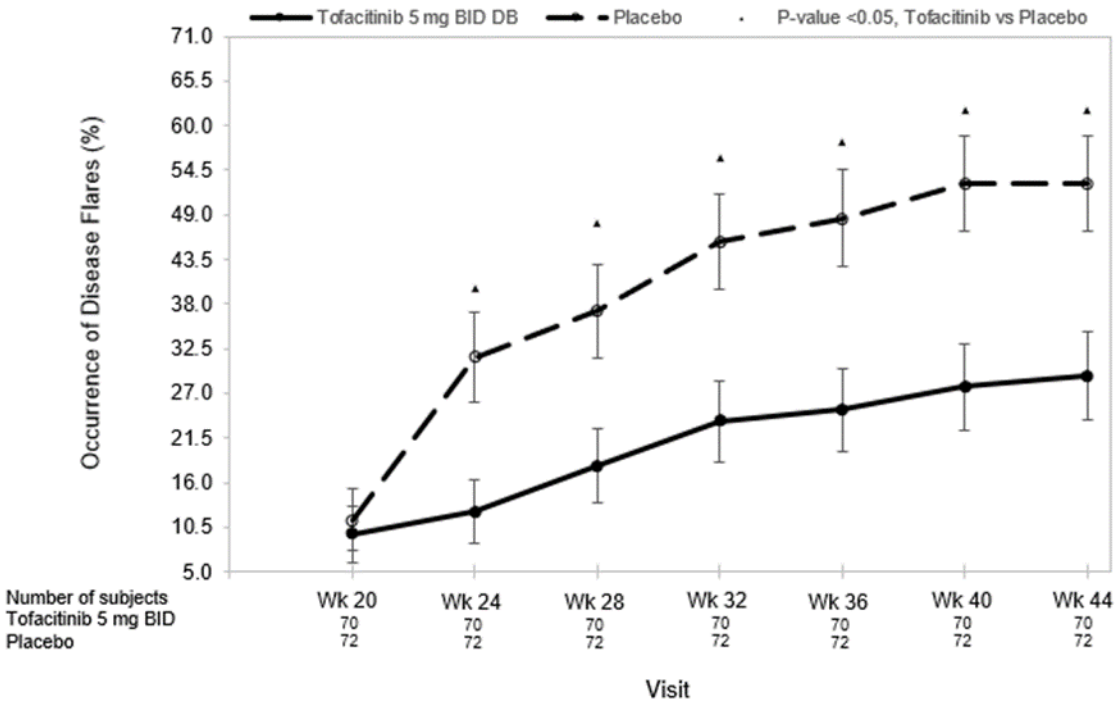
Clinical trial evidence – study A3921104

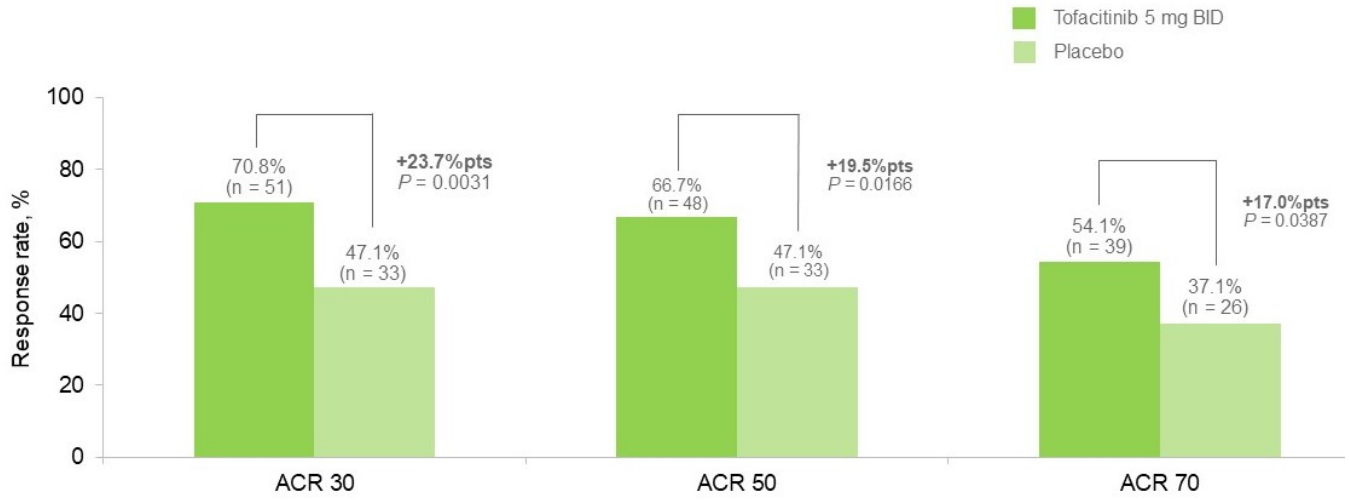


	Tofacitinib 5 mg (n =88)	Placebo (n= 85)
Extended oligoarthritis	8 (9.1)	10 (11.8)
Polyarthritis RF+	14 (15.9)	14 (16.5)
Polyarthritis RF-	45 (51.1)	42 (49.4)
sJIA with active arthritis but no active syst features	5 (5.7)	4 (4.7)
PsA	7 (8.0)	8 (9.4)
ERA	9 (10.2)	7 (8.2)

Previous treatments	Tofacitinib 5 mg
bDMARDs	37.8%
csDMARDs	91.6%

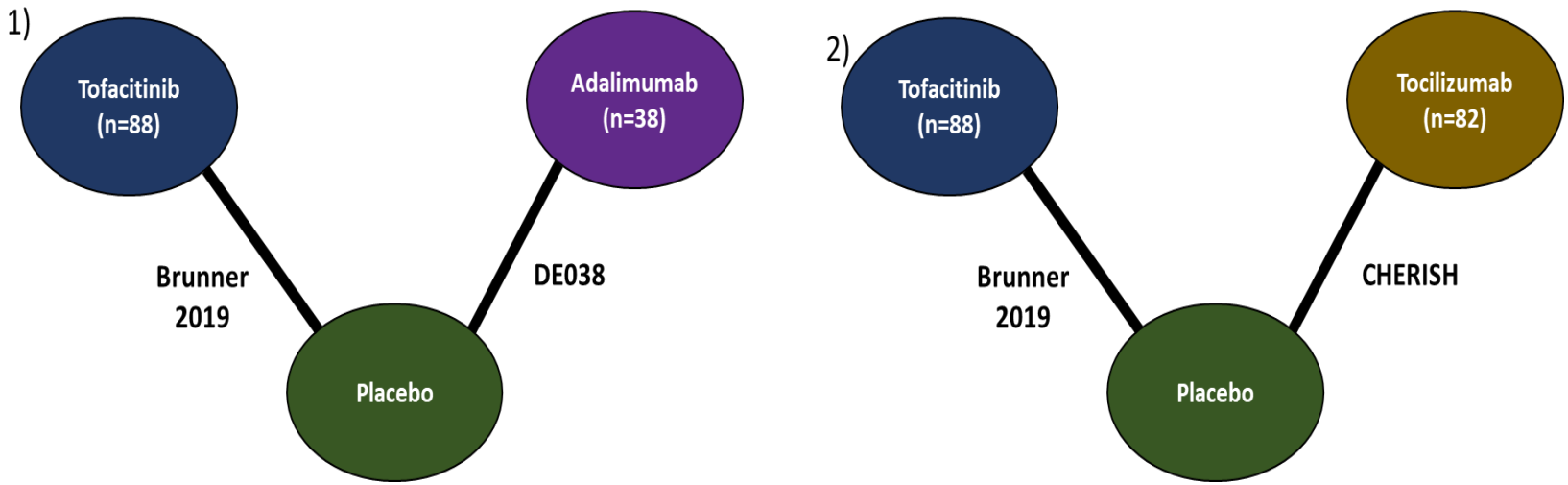
Trial results – pcJIA cohort, week 44





NICE

Indirect treatment comparisons



Evidence on clinical similarity

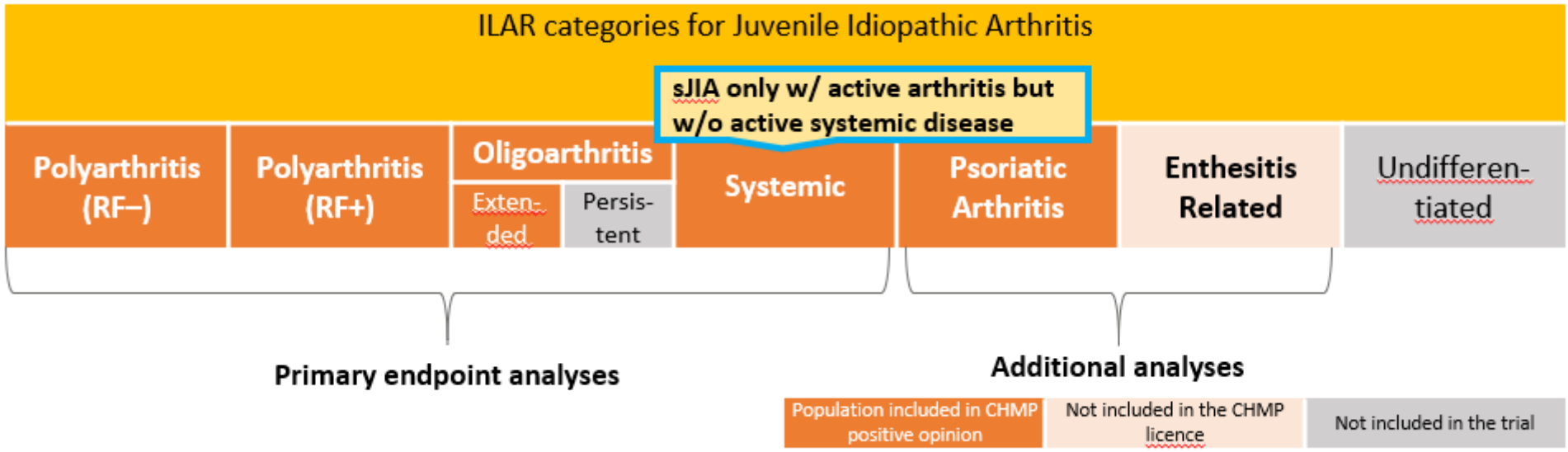
- Indirect evidence suggests XXXXXXXXX between technologies on disease flare or ACR response outcomes

Evidence on clinical similarity

- ERG considers non-inferiority plausible based on the evidence presented, albeit caveated by a number of uncertainties:
  - the % of patients achieving ACR 30 and 50 response decreases after 15 months, suggesting uncertainty in the long-term efficacy
  - long term evidence for tocilizumab and adalimumab shows the treatment effect is maintained at week 104 and 312 respectively
  - extending this longer-term effect to tofacitinib is uncertain due to the different mode of administration and mechanism of action.
- Similar conclusions on effectiveness across drug classes have been drawn in the RA appraisals
- The British Society for Rheumatology (BSR), endorsed by the Royal College of Physicians (RCP), supported a cost-comparison
- Scrutiny panel considered tofacitinib likely to have similar clinical effectiveness as adalimumab and tocilizumab, despite uncertainties

Update to indication

- Company original evidence submission was focused on the polyarticular juvenile idiopathic arthritis population (pJIA), but the final CHMP indication is broader and includes juvenile psoriatic arthritis (jPsA)
  - jPsA accounts for 6% of cases
  - treatment pathway is the same as for pJIA, but the only licensed biological DMARD is etanercept



Trial results for jPsA

- [redacted] of 88 patients) patients were randomised on the tofacitinib arm and [redacted] out of 85 patients) on the placebo arm had jPsA
- At week 44, [redacted] had a disease flare vs. [redacted] in placebo results are similar to those observed in the pJIA population (29.2% on the tofacitinib versus 52.9% on the placebo arm)
- Results also favoured tofacitinib for ACR response and BSA affected by psoriasis → figure

Considerations on jPsA efficacy

- No data available comparing with active treatments
- Etanercept is recommended in TA373 (only treatment with MA)
  - only evidence available was from a single-arm, open-label trial with 29 patients
  - AG could not develop a model for etanercept in jPsA
  - committee heard from the clinical experts that it was possible to generalise results for the effectiveness of etanercept for treating adult forms of PsA to psoriatic JIA
  - clinical experts also confirmed that there was no evidence to suggest that etanercept would be any less effective in reducing disease activity in people with jPsA, than when using for pcJIA

Evidence on similarity of costs

- The acquisition cost is [redacted]

ERG base case				
Technologies	**Acquisition costs**	**Administration costs**	**Total costs**	**Incremental costs: Tofacitinib - comparator**
Aggregated, discounted results for 11-18 year olds				
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]	N/A
Tocilizumab	[redacted]	[redacted]	[redacted]	[redacted]

- This indication is for a relatively small population, which means consequences of decision error is low
- [redacted]

Scrutiny panel conclusion

- Cost-comparison appropriate methodology because tofacitinib is likely to be similarly clinically effective compared with comparators
- Tofacitinib has higher costs than main comparator, adalimumab
- Suggested it may be more appropriate for the company to position tofacitinib as an option when adalimumab has failed or is unsuitable
  - tocilizumab would be appropriate comparator here (clinical experts: tocilizumab mostly used after 1st line adalimumab)
  - tofacitinib has similar costs compared with tocilizumab

Potential recommendation?

- Tofacitinib is recommended as an option for treating active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive or negative polyarthritis and extended oligoarthritis), and juvenile psoriatic arthritis (PsA) in patients 2 years of age and older, who have responded inadequately to previous therapy with DMARDs, only if:
  - TNF-alpha inhibitors are unsuitable or do not control the condition well enough
  - the company provides tofacitinib according to the commercial arrangement
- If patients and their clinicians consider tofacitinib to be 1 of a range of suitable treatments, including tocilizumab, choose the least expensive (taking into account administration costs and commercial arrangements).
  - Similar recommendation reached by committee A for recent secukinumab for spondyloarthritis appraisal