NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Filgotinib for treating moderate to severe rheumatoid arthritis [ID1632]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Filgotinib for treating moderate to severe rheumatoid arthritis [ID1632]

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 **Gilead Sciences**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. National Rheumatoid Arthritis Society - NRAS

4. **Expert personal perspectives** from:
   a. Professor Maya H Buch – clinical expert, nominated by Gilead Sciences
   b. Teresa Shakespeare-Smith – patient expert, nominated by National Rheumatoid Arthritis Society (NRAS)

5. **Evidence Review Group report** prepared by **Kleijnen Systematic Reviews Ltd**

6. **Evidence Review Group report – factual accuracy check**

7. **Technical engagement response** from **Gilead Sciences**

8. **Technical engagement responses from experts:**
   a. Professor Maya H Buch – clinical expert, nominated by Gilead Sciences
   b. Teresa Shakespeare-Smith – patient expert, nominated by National Rheumatoid Arthritis Society (NRAS)

9. **Technical engagement response from consultees and commentators:**
   a. National Rheumatoid Arthritis Society – NRAS
   b. British Society for Rheumatology
      - *Royal College of Physicians endorses the submission by the British Society for Rheumatology*
   c. AbbVie
   d. Pfizer

10. **Evidence Review Group critique of company response to technical engagement** prepared by **Kleijnen Systematic Reviews Ltd**

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

Single technology appraisal

Filgotinib for treating moderate-to-severe rheumatoid arthritis [ID1632]

Document B

Company evidence submission

File name	Version	Contains confidential information	Date
ID1632_Filgotinib_STA_Document B_v6.0_Redacted	6.0	Yes	June 29th, 2020

Contents

Tables and figures

List of abbreviations

Abbreviation	Definition
ABA	Abatacept
ACPA	Anti-citrullinated protein antibodies
ACR	American College of Rheumatology
ADA	Adalimumab
AIMS	Arthritis Impact Measurement Scales
ATP	Adenosine triphosphate
BAR	Baricitinib
bDMARD	Biological disease modifying antirheumatic drugs
CCP	Cyclic citrullinated peptide
CDAI	Clinical disease activity index
CI	Confidence interval
CSA	Clinically suspect arthralgia
cDMARDs	Conventional disease modifying antirheumatic drugs
CVD	Cardiovascular disease
CZP	Certolizumab pegol
DALY	Disability-adjusted life years
DAS	Disease Activity Score
DMARD	Disease modifying antirheumatic drugs
EQ-5D	EuroQol five dimension
EMEA	Europe, Middle East and Africa
ERAN	Early rheumatoid arthritis network
ESR	Erythrocyte sedimentation rate
ET	Early termination
ETA	Etanercept
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy
GOL	Golimumab
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire Disability Index
HRQoL	Health-related quality of life
IC50	Half maximal inhibitory concentration
IFX	Infliximab
JAK	Janus kinase
MACE	Major adverse cardiovascular events
MCS	Mental component of the SF-36 survey
MTX	Methotrexate
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

Abbreviation	Definition
PCS	Physical component of the SF-36 survey
PDUS	Power Doppler ultrasound
PSS	Personal Social Services
SDAI	Simplified Disease Activity Index
tsDMARDs	Targeted synthetic DMARDs
QALY	Quality-adjusted life years
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RTX	Rituximab
SF-36	36-item Short Form Survey
SLR	Systematic literature review
SmPC	Summary of product characteristics
STATs	Signal transducers and activators of transcription
TA	Technology Appraisal
TOC	Tocilizumab
TOF	Tofacitinib
UK	United Kingdom
US	United States
ULN	Upper limit of normal

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

B.1.1 Decision problem

The Marketing Authorisation application for filgotinib was submitted to the European Medicines Agency (EMA) in [redacted] and is currently under review.

Filgotinib is a targeted synthetic disease modifying antirheumatic drug (tsDMARD) and, together with biological DMARDs (bDMARDs), is considered an advanced therapy for rheumatoid arthritis (RA).

The Marketing Authorisation for filgotinib is expected to be as monotherapy or in combination with methotrexate (MTX) for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to, or who are intolerant to, one or more (DMARDs), including conventional or biological DMARDs.

This submission covers filgotinib's full anticipated Marketing Authorisation, including the following populations:

Two populations in moderately active RA:

1a. As monotherapy after two or more cDMARD failures in patients who are MTX ineligible

1b. As combination therapy with MTX after two or more cDMARD failures in patients who are MTX eligible

Four populations in severely active RA, for patients who are MTX eligible:

2b. As combination therapy with MTX as first-line advanced therapy[1]

[1] Advanced therapy refers to bDMARDs and targeted DMARDs (tsDMARDs) and is used throughout this document to refer to these treatments as one group

3b. As combination therapy with MTX, after failure of first-line advanced therapy in patients who are RTX ineligible or intolerant

4. As combination therapy with MTX, after first-line advanced therapy failure in patients who are RTX eligible

5. As combination therapy with MTX, after failure of RTX in combination with MTX

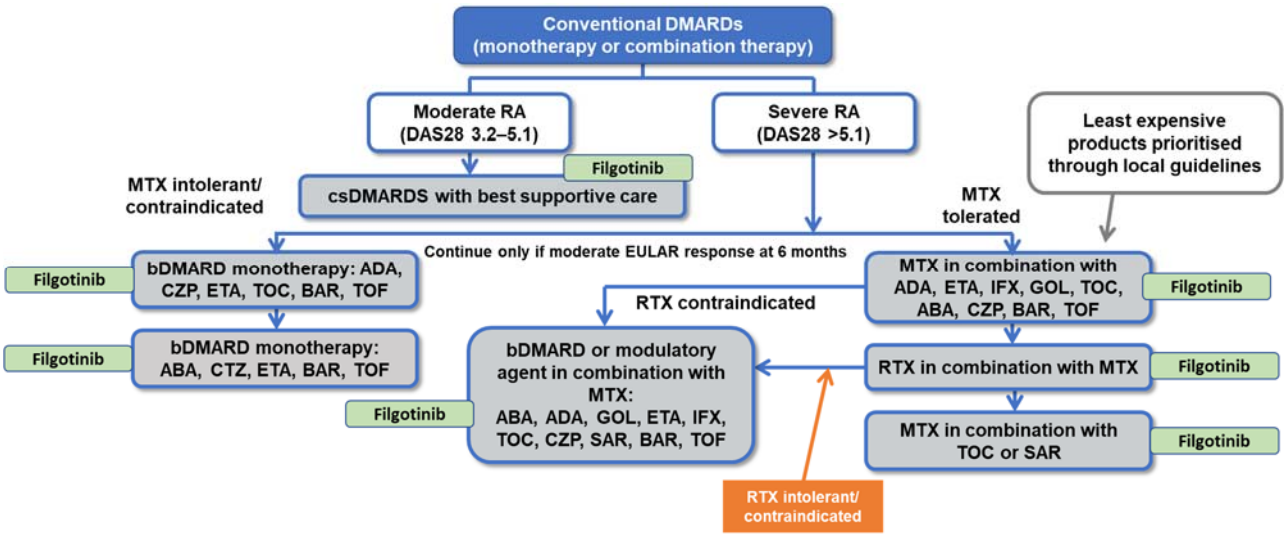
Two populations in severely active RA, for patients who are MTX ineligible:

2a. As monotherapy, used as first-line advanced therapy

3a. As monotherapy, after failure of first-line advanced therapy

The expected position of filgotinib within the current treatment pathway is represented in Figure 1.

Figure 1. Positioning of filgotinib within current NICE treatment pathway



ADA=adalimumab; ABA=abatacept; BAR=baricitinib; CZP=certolizumab pegol; DAS=Disease Activity Score; DMARD=Synthetic disease modifying antirheumatic drugs; ETA=etanercept; GOL=golimumab; IFX=infliximab; MTX=Methotrexate; RA=Rheumatoid arthritis; RTX=Rituximab; TOC=tocilizumab; TOF=tofacitinib;

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

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderately to severely active rheumatoid arthritis who have had an inadequate response to, or who are intolerant of one or more DMARDs, including conventional or biological DMARDs	Adults with moderately to severely active, active RA whose disease has responded inadequately to two or more cDMARDs, or who are intolerant to DMARDs, including conventional or biologic DMARDs. The specific populations modelled in the cost-effectiveness analysis are: Filgotinib for moderately active RA: 1a. As monotherapy after two or more cDMARD failures in patients who are MTX ineligible 1b. As combination therapy with MTX after two or more cDMARD failures in patients who are MTX eligible Filgotinib in combination with MTX for severely active RA, for patients who are MTX eligible: 2b. As combination therapy with MTX as first-line advanced therapy[2] 3b. As combination therapy with MTX, after failure of first-line advanced therapy in patients who are RTX ineligible or intolerant	The populations included within the submission is within the NICE scope. However, in the moderately active RA population the company submission is limited to patients following two or more cDMARD failures, this restriction is applied on the basis of clinical opinion and expected cost-effectiveness.

[2] Advanced therapy refers to bDMARDs and targeted DMARDs (tsDMARDs) and is used throughout this document to refer to these treatments as one group

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		4. As combination therapy with MTX, after first-line advanced therapy failure in patients who are RTX eligible 5. As combination therapy with MTX, after failure of RTX in combination with MTX Filgotinib for severely active RA, for patients who are MTX ineligible: 2a. As monotherapy, used as first-line advanced therapy 3a. As monotherapy, after failure of first-line advanced therapy	
Intervention	Filgotinib (as monotherapy or in combination with other conventional DMARDs, including methotrexate)	Aligned with NICE scope	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Comparator(s)	For moderately active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs: • Combination of two or more conventional DMARDs (including methotrexate and at least one other DMARD, such as sulfasalazine and leflunomide) • Conventional DMARD monotherapy with dose escalation • Best supportive care For severely active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs: • Biological DMARDs in combination with methotrexate (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept or sarilumab) • Adalimumab, etanercept, certolizumab pegol, tocilizumab or sarilumab (each as monotherapy) • Tofacitinib, baricitinib or upadacitinib (each as monotherapy or in combination with methotrexate) For severely active rheumatoid arthritis that has not responded adequately to therapy with DMARDs including at least one TNF inhibitor: • Rituximab in combination with methotrexate	For moderately active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs: • Best supportive care For severely active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs: MTX intolerant patients: • Adalimumab, etanercept, tocilizumab or baricitinib (each as monotherapy) MTX tolerant patients: • Biological DMARDs in combination with methotrexate (adalimumab, etanercept, baricitinib) For severely active rheumatoid arthritis that has not responded adequately to therapy with bDMARDs including at least one TNF inhibitor: When rituximab is contraindicated or withdrawn due to adverse events, MTX is not tolerated or is contraindicated: • Abatacept, baricitinib or tofacitinib (each as monotherapy) When rituximab is contraindicated or withdrawn due to adverse events, MTX tolerated and is not contraindicated: • Abatacept, baricitinib or tofacitinib in combination with methotrexate When rituximab is tolerated, MTX is tolerated:	Comparators in the model were applied based on currently reimbursed treatments and availability of evidence to inform comparisons, comparisons are consistent with previous Technology Appraisals. Real-world data and expert opinion, in conjunction with NICE guidance for the treatment of RA, were used to inform treatment sequences, which are reflective of current clinical practice.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	When rituximab is contraindicated or withdrawn due to adverse events: • Adalimumab, etanercept, infliximab, abatacept tocilizumab, certolizumab pegol, golimumab or sarilumab (each in combination with methotrexate) • Tofacitinib, baricitinib, or upadacitinib (each in combination with methotrexate) When methotrexate is contraindicated or withdrawn due to adverse events: • Adalimumab, etanercept, certolizumab pegol or sarilumab (each as monotherapy) • Tofacitinib, baricitinib, or upadacitinib (each as monotherapy) When the disease has not responded adequately to therapy with rituximab in combination with methotrexate: • Tocilizumab, sarilumab (each in combination with methotrexate) • Upadacitinib (in combination with methotrexate)	• Rituximab in combination with MTX When the disease has not responded adequately to therapy with rituximab in combination with methotrexate: • Tocilizumab or sarilumab, both in combination with MTX	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • disease activity • physical function • joint damage, pain • mortality • fatigue • radiological progression • extra-articular manifestations of disease • adverse effects of treatment • health-related quality of life.	Aligned with final NICE scope (except where noted). Outcome measures considered in the analysis: • disease activity (American College of Rheumatology - ACR20, ACR50, ACR70, European League Against Rheumatism (EULAR) response, Disease Activity Score (DAS28) • physical function (HAQ-DI) • pain, fatigue • mortality • radiological progression • adverse effects of treatment • health-related quality of life.	Extra-articular manifestations of disease were not captured in the FINCH trial programme and therefore could not be included within this submission. In line with previous economic models with RA appraised by NICE, including MTA375, fatigue was not modelled in the economic analysis.
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	Aligned with NICE scope	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator technologies and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar products should be taken into account.		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • moderate disease activity (DAS28 between 3.2 and 5.1) • severe active disease (DAS28 greater than 5.1)	Aligned with NICE scope	NA

NICE=National Institute for Health and Care Excellence; NA=Not applicable; DMARD=Synthetic disease modifying antirheumatic drugs; ACR=American College of Rheumatology; European League Against Rheumatism HAQ=Health Assessment Questionnaire; HAQ-DI=Health Assessment Questionnaire Disability Index; FACIT-F=Functional Assessment of Chronic Illness Therapy; DAS=Disease Activity Score; QALY=Quality-adjusted life years;

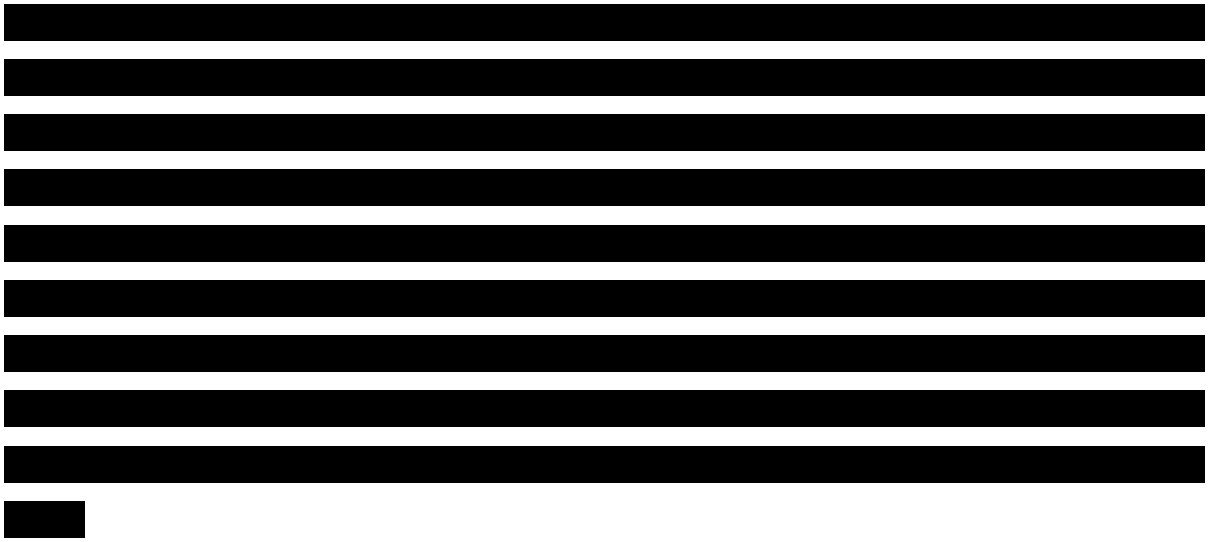
B.1.2 Description of the technology being appraised

The main characteristics of filgotinib are summarised in Table 2. For the full draft summary of product characteristics (SmPC) (1), see Appendix C.

B.1.2.1 Mechanism of action

Filgotinib is a potent reversible JAK inhibitor with a selectivity for JAK1. Cytokines associated with JAK1 are involved in the inflammatory signalling pathway that drives RA progression. Targeted inhibition of JAK1 could reduce dominant inflammatory cytokine signalling involved in RA, whilst limiting impact on normal physiological function. Filgotinib and its active metabolite contribute to its pharmacodynamic effects, with similar JAK1 selectivity.

Filgotinib modulates the signalling pathway by preventing the phosphorylation and activation of STATs by JAKs, thereby supressing immune cell activity and pro-inflammatory cytokine signalling (1). In addition, neither filgotinib nor its active metabolite induce or inhibit cytochrome P450 enzymes or inhibit critical drug transporter enzymes, including P-glycoprotein (2). Therefore, the potential for drug-drug interactions is low, which means filgotinib can be administered with commonly used RA drugs without the need for dose adjustments (2).



B.1.2.2 Technology being appraised

Table 2. Technology being appraised

UK approved name and brand name	Filgotinib (brand name to be confirmed)
Mechanism of action	Filgotinib is a potent, selective ATP-competitive and reversible inhibitor of JAK1. It modulates the cytokine signalling pathway by preventing the phosphorylation and activation of STATs by JAK. For a detailed overview of the mechanism of action, see section B.1.2.1.
Marketing Authorisation/CE mark status	The Marketing Authorisation application for filgotinib in the treatment of adults with RA was submitted to the European Medicines Agency in [redacted]. The anticipated date of regulatory approval is [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Filgotinib is indicated as monotherapy or in combination with MTX for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to, or who are intolerant to, one or more disease-modifying antirheumatic drugs (DMARDs). Contraindications: • Hypersensitivity to the active substance or to any of the excipients • Pregnancy For the full draft SmPC, see Appendix C.
Method of administration and dosage	The recommended dose is one 200mg tablet once a day. A dose of 100mg of filgotinib once daily is recommended for patients with severe renal impairment (Creatinine clearance 15 to 30 mL/min). Filgotinib may be used as monotherapy or in combination with MTX.

Additional tests or investigations	No additional investigations outside of routine clinical management of RA. For the full SmPC, see Appendix C.
List price and average cost of a course of treatment	£863.10 per bottle of 30 200mg tablets Equivalent to £10,508.24 per year
Patient access scheme (if applicable)	[redacted]

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

B.1.3.1 Disease overview

Signs and symptoms

Rheumatoid arthritis is a common autoimmune disease that is associated with progressive disability, systemic complications, early death, and socioeconomic costs (3). Swelling and tenderness of the joints and degradation of synovial tissue (4, 5) leading to joint damage is an important manifestation of RA. However, RA does not exclusively affect the joints. Extra-articular systemic manifestations can include: ocular, pulmonary, skin, cardiac, vascular, renal, haematological, neurological, gastrointestinal. These manifestations also worsen as disease progresses.

Although at early stages of the disease there is no evidence of joint destruction, RA has an impact even at this stage: the main symptoms of early RA are pain and fatigue. Without adequate treatment the disease is associated with progressive joint damage and disability, both of which are irreversible (3). However, even at the moderately active stage of disease, patients' burden is significant, with joint damage and disability accumulating over time if no remission or low disease activity can be achieved. These patients also experience reduced quality of life and represent a substantial burden to healthcare systems.

As a progressive disease, the burden of RA increases with time, with worsening symptoms and increasingly irreversible joint damage. As a systemic disease, multiple organs of the body are typically affected, adding to the clinical burden.

RA also leads to a variety of complications, many of which are related to the chronic inflammation associated with the disease (6).

Diagnosis

The European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) criteria are widely used by rheumatologists to confirm the diagnosis (4, 7).

These criteria include assessment of joint damage or impairment, levels of serum markers, anti-citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF), acute phase reactants: C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (4, 7), and duration of symptoms.

Stratification by severity

Disease activity is classified by composite scoring systems. DAS28 is primarily used in UK, and includes the following variables:

- In 28 specified joints
- Tender joint count (TJC)
- Swollen joint count (SJC)
- High sensitive C reactive Protein (hsCRP) or erythrocyte sedimentation rate (ESR) value
- Patient global health assessment on a 0-100 visual analogue scale

DAS28 cut-off points used for stratifying disease by severity are presented in Table 3 (8).

Table 3. DAS28 cut off points for disease activity categories

DAS28 score	Disease activity
DAS28 <2.6	Remission
DAS28 <3.2	Low disease activity (LDA)
DAS28 3.2 - 5.1	Moderate disease activity (MDA)
DAS28 >5.1	High disease activity / Severe disease (HDA)

DAS, Disease Activity Score; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity.

Source: Fransen et al, 2004 (8)

B.1.3.2 Epidemiology

Prevalence

RA is the most common inflammatory arthritis (9), with an estimated global prevalence of 0.24% (10). It develops more frequently in women (estimated global prevalence of 0.35%) than in men (estimated global prevalence of 0.13%) (10). Prevalence estimates for the UK have been reported as 1.16% in women and 0.44% in men (11),

yielding an overall population-level estimate of 0.81%. Based on current population figures (12), this equates to approximately 400,000 prevalent adult patients in England and Wales.

A 2016 report suggests that in the in UK, 87% of the total RA population is diagnosed, and the percentage of diagnosed patients being treated is 76% (13), putting the estimated number of diagnosed and treated patients at approximately 300,000.

Incidence

The UK-specific incidence rate of RA has been reported to be 40 per 100,000 persons per year in a report published in 2013 (14), with a markedly higher (54 per 100,000 persons, 95% confidence interval [CI]: 44.5 to 64.7) incidence in women than in men (25 per 100,000 persons, 95% CI: 18.1 to 32.4) (14). Using the above rates and latest population figures (12), approximately 20,000 new adult patients are estimated to be diagnosed with RA each year in England and Wales.

Moderately to severely active patients

Out of the total RA patient pool, market research suggests 39% are estimated to have moderately active disease (or around 120,000 in England and Wales), while the proportion of severely active RA patients are estimated to be 29% (approximately 90,000) (15). A study of UK patients in the Early RA Network (ERAN), a cohort of newly diagnosed RA patients receiving cDMARDs, showed the rate of patients progressing from moderately to severely active disease was 19% over a two-year period (16), which translates to approximately 12,000 patients in England and Wales a year who progress to severely active disease.

B.1.3.3 Disease burden

Clinical burden

The clinical burden of RA is substantial. Improvements made in therapies in recent years led to reduced disease severity overall; a study by Diffin et al (17), studying patients from Norfolk Arthritis Register (NOAR), found a significant association

between year of presentation and lower DAS scores[3]. However, a substantial proportion of RA patients have moderately to severely active disease activity. RA can progressively lead to irreversible joint damage and disability (18, 19). As a progressive disease, the burden of RA increases with time, with worsening symptoms and increasingly irreversible joint damage. As a systemic disease, multiple organs of the body are typically affected, adding to the clinical burden.

Disease progression

As detailed above, a study of patients in the ERAN patient network showed the rate of patients progressing from moderately to severely active disease to be 19% over a two-year period (16). A recent UK multi-centre, retrospective non-interventional study concluded that many patients with moderately active RA had received multiple cDMARDs, suggesting there may be a lack of suitable, effective treatments following failure of cDMARDs (20).

EULAR guidelines identify key prognostic factors that may be used to identify patients more likely to progress to severe disease activity. According to the guidelines (21), these include persistently moderate or high disease activity despite cDMARDs, failure of two or more cDMARDs, high levels of RF/ACPA, high disease activity, early joint damage, and high swollen joint count. A recent retrospective single centre study from the UK, involving 207 patients (22), aimed to identify moderately active RA patients with poor functional outcomes found that baseline Health Assessment Questionnaire – Disability Index (HAQ-DI) score was the dominant predictor of 12-month HAQ-DI, implying those who had more significant disability at baseline remained so during the full period– suggesting a need among moderately active RA patients for additional treatments that effectively treat their disease (22). The poor functional outcomes of patients assessed in the study also highlight the fact that even moderately active RA is associated with substantial joint destruction and disability – which is exacerbated with progression of disease.

[3] In the study, calendar year of presentation to NOAR was significantly associated with lower DAS28 scores over time [Y = 4.51 + (–0.56 x year) + (0.44 x year2)]

Disease complications and comorbidities

RA is a multisystem disease that can affect several organ systems, leading to a variety of complications, many of which are related to the chronic inflammation associated with the disease (6). These comorbidities, particularly cardiovascular disease (CVD), can lead to serious clinical events, reduced health related quality of life (HRQoL), and death (23). The 2014 COMORA study (6) evaluated the prevalence of comorbidities in RA patients and found that hypertension and dyslipidaemia were most prevalent. Other comorbidities that have been found to occur with greater frequency in patients with RA compared with the general population include depression, lung cancer, lymphoma, infections, and the RA-related complications osteoporosis and osteoporotic fractures.

Other potentially serious non-CV related comorbidities prevalent in RA patients include anaemia, psychiatric disorders, malignancies, and diabetes (6).

Mortality

RA patients are at an increased risk of mortality, partly due to the increased rate of comorbidities described previously, and partly due to the interplay between inflammation and disease activity (23-25). A 2016 study by Michaud et al (24) reported age- and sex-standardised mortality incidence rates (per 100 person-years) from RA registries; finding a UK mortality incidence rate of 0.8 per 100 person-years. Within the same UK RA registry, cardiovascular mortality was 0.2 per 100 person-years (24), highlighting RA patients' high risk for CV-related mortality.

Humanistic burden

In addition to its clinical burden, RA is also associated with a substantial humanistic burden, reducing the HRQoL of patients as measured using a range of disease-specific and generic assessments. A 2014 literature review (26),which included 31 studies (including two from the UK) with a total of 22,335 patients, investigated the effects of RA on HRQoL as measured by the 36-item Short Form survey (SF-36) questionnaire. Results of this study show worse mean scores for the physical component (PCS) of the survey than the mental component (MCS), the mean pooled

HRQoL score for PCS was 34.1 (95% CI: 22.0, 46.1) and the mean score for MCS was 45.6 (95% CI: 30.3, 60.8) (100 represents best possible QoL) (26).

Another study highlighting the high burden of RA was published in 2019 by Safiri et al (27). In it, the authors analysed RA-specific data from the 2017 Global Burden of Disease study. The age-standardised rate of RA disability-adjusted years (DALYs) per 100,000 population was 43.3 (95% CI 33.0 to 54.5) globally, underscoring that RA leads to a substantial number of healthy life years lost (27).

Economic burden

The economic burden of RA is substantial, estimated by Lundkvist et al in 2008 to be up to €45.3 billion across all European countries, including direct, indirect and informal care costs (28). Overall, the mean annual cost per patient was estimated at around €13,500 in Europe, of which medical costs and medications represent approximately one third. The remaining two thirds are from outside the healthcare sector (production losses contribute 32%, informal care 19% and non-medical costs 14%) (32). UK-specific cost estimates from this study showed a total cost of €16,502 (£11,116 at 2007 exchange rates (29) the cost year reported from the study), with 61% (£6,793) representing direct costs and 39% (£4,323) indirect costs.

B.1.3.4 Current treatment guidelines

Recommendations for the management of RA are available from international guidelines such as EULAR (21), as well as national guidelines for England, published by NICE (30).

EULAR guidelines

The 2019 update to the EULAR guidelines was published in early 2020 (21). At diagnosis, the guidelines first recommend methotrexate, as first-line treatment, unless contraindicated to use other cDMARDs (combined with short-term glucocorticoids). If at three months there is an improvement, treatment is recommended to be continued.

For patients not responding to treatment or achieving target, recommendations are stratified by the presence or absence of poor prognostic factors. If the treatment target is not achieved after six months, a change to another bDMARD or JAK inhibitor is recommended, from the same class or a different one.

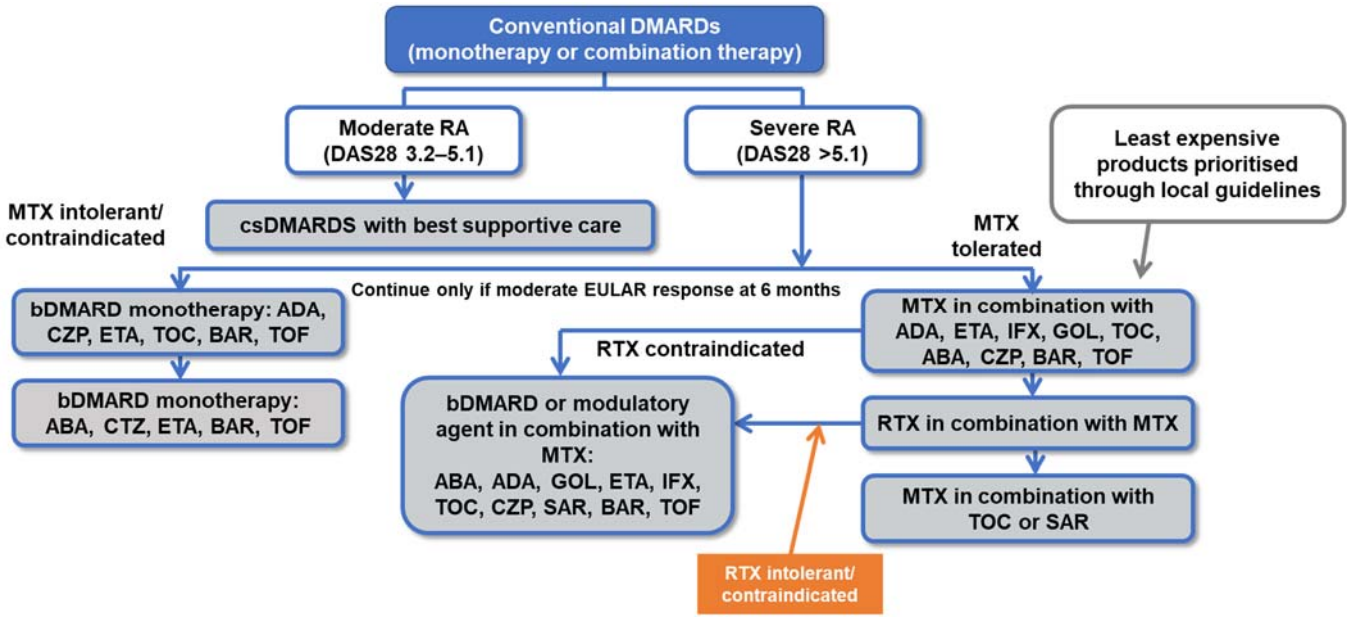
A notable difference between EULAR guidelines and NICE guidelines is that, in addition to severely active RA patients, they recommend considering advanced therapies in moderate disease activity, following failure of two cDMARDs, or after one cDMARD in patients with poor prognostic factors (detailed earlier in section B.1.3.3 on Disease burden).

NICE guidelines

The NICE clinical guidance [NG100] for the management of RA in adults was published in 2009 and most recently updated in 2018 (30). The current version provides guidance on pharmacotherapy options as well as exercise and physical and occupational therapy (30).

The clinical pathway of pharmacological care, recommended by the NICE guidelines, is presented in Figure 2.

Figure 2. Current NICE treatment guidance on treatment of moderately to severely active RA



ADA=adalimumab; ABA=abatacept; BAR=baricitinib; CZP=certolizumab pegol; DAS=Disease Activity Score; DMARD=Synthetic disease modifying antirheumatic drugs; ETA=etanercept; GOL=golimumab; IFX=infliximab; MTX=Methotrexate; RA=Rheumatoid arthritis; RTX=Rituximab; TOC=tocilizumab; TOF=tofacitinib;

Source: NICE 2009 clinical guideline: 2018 update [NG100] (30)

Newly diagnosed and moderately active patients

For newly diagnosed patients, cDMARDs (preferably MTX, or alternatively leflunomide or sulfasalazine) as monotherapy are the recommended first-line treatments, ideally within three months of onset of persistent symptoms. For those who do not respond to this treatment, treatment dose is escalated, or a combination therapy is given with another cDMARD, preferably including MTX. Alternatively, leflunomide, sulfasalazine

or hydroxychloroquine should be offered in combination in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved despite dose escalation. From this point, current recommendations differentiate between moderately active (DAS28 score of 3.2-5.1) and severely active (DAS28 score greater than 5.1) RA patients, with the recommended treatments dependent upon this classification.

For moderately active RA patients, NICE guidelines currently recommend further cDMARDs (oral MTX, leflunomide, sulfasalazine or hydroxychloroquine) in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved despite dose escalation.

Where combination therapies are not appropriate (in the case of comorbidities or pregnancy), cDMARD monotherapy is recommended.

After the failure of two cDMARDs, there is a notable lack of clinical options with current NICE guidance, presenting an unmet need for additional therapeutic options, particularly as a subset of these patients are at risk of progressing to severely active disease. The only remaining treatment option is best supportive care, comprising of cDMARDs that patients have already received, administered at lower doses.

Severely active RA

For severely active RA patients in whom disease has not responded to intensive combination therapy with cDMARDs, NICE guidance recommends bDMARDs (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept and sarilumab) or tsDMARDs/JAK inhibitors (baricitinib and tofacitinib) in combination with MTX, unless intolerant or contraindicated. For those who are intolerant or for whom MTX is contraindicated, adalimumab, etanercept, certolizumab pegol, tocilizumab, baricitinib, sarilumab or tofacitinib are recommended, as monotherapy.

Where severely active RA patients do not show adequate response to advanced treatments, a combination of RTX and MTX is recommended.

Where RTX is contraindicated or withdrawn because of adverse events, advanced therapies (adalimumab, etanercept, infliximab, abatacept, golimumab, tocilizumab, certolizumab pegol, sarilumab, tofacitinib and baricitinib) are recommended, in combination with MTX.

For those who are not eligible for MTX and have failed first-line advanced therapy, advanced therapies are recommended to be used as monotherapy (adalimumab, etanercept, certolizumab pegol, sarilumab, tocilizumab, tofacitinib and baricitinib).

Finally, for those patients who have not responded to treatment with RTX and MTX, tocilizumab and sarilumab, in combination with MTX, are recommended by NICE guidance.

Key differences between NICE and EULAR Guidelines

NICE currently only recommends the use of advanced therapies in severely active RA patients, following failure of intensive combination therapy or at least two cDMARDs. In contrast, the recently updated EULAR guidelines recommend advanced therapies for moderately or severely active patients, following failure of two cDMARDs, or after one cDMARD in patients with other poor prognostic factors detailed earlier in section the Disease burden section (see B.1.3.3).

Related NICE Technology Appraisals

A summary of all related NICE Technology Appraisals (TAs) is presented in Table 4.

Table 4. Summary of related NICE Technology Appraisals

Technology and indication	Year
Published Technology Appraisals	
Sarilumab for moderately to severely active rheumatoid arthritis (NICE TA485) (31)	2017
Tofacitinib for moderately to severely active rheumatoid arthritis (NICE TA480) (32)	2017
Baricitinib for moderately to severely active rheumatoid arthritis (NICE TA466) (33)	2017
Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor (NICE TA415) (34)	2016 (reviewed in 2019)
Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (NICE MTA375 (previously TA130, TA186 and TA280) (35)	2016

Technology and indication	Year
Tocilizumab for the treatment of rheumatoid arthritis (NICE TA247) (36)	2012
Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease modifying anti-rheumatic drugs (NICE TA225) (37)	2011
Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (NICE TA195) (38)	2010
Appraisals in development	
Upadacitinib for treating moderately to severely active rheumatoid arthritis (NICE TA guidance [ID1400]) (39)	Expected 2020
Sirukumab for previously treated moderately to severely active rheumatoid arthritis (NICE TA guidance [ID1002]) (40)	Suspended appraisal
Rituximab for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs (NICE TA guidance [ID333]) (41)	Suspended appraisal

DMARD=Synthetic disease modifying antirheumatic drug; NICE= National Institute for Health and Care Excellence; TA= Technology Appraisal

B.1.3.5 Unmet need with current treatments

The unmet need of patients with RA includes issues such as: efficacy, safety and tolerability, patient preference, and treatment options for patients with moderately active disease.

Efficacy issues

The aim of RA treatment is to achieve remission, or, alternatively, to remain in a low disease activity state. Therefore, it is crucial that patients have adequate and timely response to their treatments, but treatment failure (defined as lack of response) is among the main challenges with current treatments for a considerable number of patients. Though the advent of bDMARDs has brought options with improved efficacy to the treatment of RA, many patients still either do not achieve response or lose response to therapy over time. A study of 13,502 UK RA patients (42), published in 2018, investigated biologic refractory disease among patients in the British Society for Rheumatology Biologics Register. Data showed that 6.4% of all RA patients were classified as bDMARD refractory (defined as being exposed to at least three different classes of bDMARD), a substantial portion of patients (38%) reported lack of efficacy.

Safety and tolerability issues

Currently available treatments in RA have notable safety and tolerability issues. Firstly, infections are among the common side effects of both corticosteroids and biologic treatments. This is in addition to the underlying immune disfunction due to the disease

process itself (i.e. immunological alteration), disability and immobility, and the perioperative infection risk associated with joint surgery (43, 44). For example, currently available JAK inhibitors are associated with an increased rate of herpes zoster infection (45).

Exposure to cDMARDs, bDMARDs and currently available JAK inhibitors is associated with AEs such as serious infections, malignancies, deep vein thrombosis (DVT) and pulmonary embolism (PE) (46-52). In addition, current treatment strategies may worsen patients' existing comorbidities or extra-articular manifestations (51-56).

Patients with RA have a higher risk of cardiovascular complications, including heart failure, myocardial infarction, stroke, DVT and PE than those without the disease, which is thought to be linked to the inflammatory disease process (53-55). This risk may be worsened by treatment with non-selective JAK inhibitors, for example baricitinib carries a special warning for risk of venous thromboembolism (VTE) and PE (51), and a post-marketing study of tofacitinib found a statistically significantly increased risk of PE in patients treated with tofacitinib (56).

A recent analysis found that AEs were the cause of discontinuation for 8% to 22% of patients who stopped bDMARD therapy (57, 58). In a 2017 study by Li et al (57), involving 572 RA patients from the UK, France, and Germany, adverse effects were the reason for stopping etanercept treatment in 21.6% of patients. Furthermore, among the reasons for choosing a second biologic treatment, tolerability was named frequently among patients choosing TNF inhibitors (15.2%), and non-TNF biologics alike (22.5%) (57).

Patient preference

Patient preference presents challenges with some of the current RA treatment options: oral therapy is preferable to an injection for a substantial portion of RA patients (59, 60). A 2013 survey of 1,400 patients with RA in France, the UK, Germany, Italy, Spain, Belgium, Sweden and the Netherlands found that 79% would prefer to take a tablet twice daily over an IV infusion or a subcutaneous injection (53).

A common reason for patients preferring oral treatments is needle phobia, which currently presents challenges for some patients. A survey of 250 RA patients from the US, published in 2015, indicated that a considerable portion (6.8%) of patients who discontinued their treatments (etanercept, adalimumab, certolizumab, or golimumab) pointed to fear of needles as the primary reason (61).

Lack of treatment options in moderately active RA

A considerable unmet need exists within the current RA treatment landscape in the UK for moderately active RA patients. Current NICE recommendations (30), as outlined previously in section B.1.3.4, do not provide any further therapeutic options for moderately active RA patients who fail cDMARDs, the only option remaining is best supportive care, which is considered to provide little therapeutic benefit to patients. Only patients who have severely active disease are currently eligible for advanced treatments to control their disease progression, with disease progression carrying an increased risk of a range of comorbidities and increasing disease burden - clinical, humanistic and economic alike, as detailed previously in section B.1.3.3.

In the UK the majority of moderately active RA patients do not achieve a satisfactory clinical response with currently available therapies. Sustained clinical remission is only achieved by 20%-40% of patients and long-term remission (>1 year) is only achieved by 3% to 14% of patients (62, 63). Sustained inflammation contributes to cartilage damage and bone erosion, affecting up to 80% of patients within one year of diagnosis (3, 64). Patients with persistent moderately active disease have also been shown to experience functional decline (as measured by HAQ-DI), suggesting that these patients could benefit from more advanced therapy (3, 64).

At present, in the UK, advanced therapies are licensed by EMA but not recommended by NICE for treatment of patients with moderately active RA. The current lack of flexibility to allow clinicians to tailor the use of advanced therapy to the needs of patients may result in poorer long-term outcomes (65), with patients remaining on cDMARDs rather than switching to more effective treatment strategies leaving them at greater risk of disease progression (66).

Filgotinib is a potent reversible JAK inhibitor with a selectivity for JAK1. Cytokines associated with JAK1 are involved in the inflammatory signalling pathway that drives RA progression. Targeted inhibition of JAK1 could reduce dominant inflammatory cytokine signalling involved in RA, whilst limiting impact on normal physiological function. Filgotinib and its active metabolite contribute to its pharmacodynamic effects, with similar JAK1 selectivity.

B.1.3.6 Positioning of filgotinib within current the clinical pathway

As described in section B1.1. Filgotinib is a tsDMARD and can be used after failure of cDMARDs in moderately to severely active RA patients. Its oral method of administration is also preferred by patients, as well as avoiding the need for training for administration or refrigerated storage associated with IV or SC treatments.

B.1.4 Equality considerations

No equality issues were identified in relation to filgotinib.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

Two systematic literature reviews (SLRs) were conducted to determine the clinical efficacy of existing interventions for the treatment of moderately to severely active RA for:

- Patients who had intolerance or inadequate response to prior conventional synthetic disease-modifying antirheumatic drugs (cDMARDs) including MTX.
- Patients who had intolerance or inadequate response to previous biologic disease modifying anti-rheumatic drugs (bDMARD-IR).

Comprehensive literature searches were undertaken in electronic databases (MEDLINE, Embase and The Cochrane Library) for studies published between 1st January 1999 and 8th of August 2018, as well as conference proceedings and websites of national reimbursement and Health technology assessment organisations. An update searched these databases from 08 August 2018 to 18 September 2019. Data from eligible studies was extracted and assessed for methodological quality and applicability.

In total, the reviews identified 191 publications describing 139 trials that met review inclusion criteria for clinical effectiveness of interventions for the treatment of moderately to severely active RA. Among these, four trials and five publications were related to filgotinib.

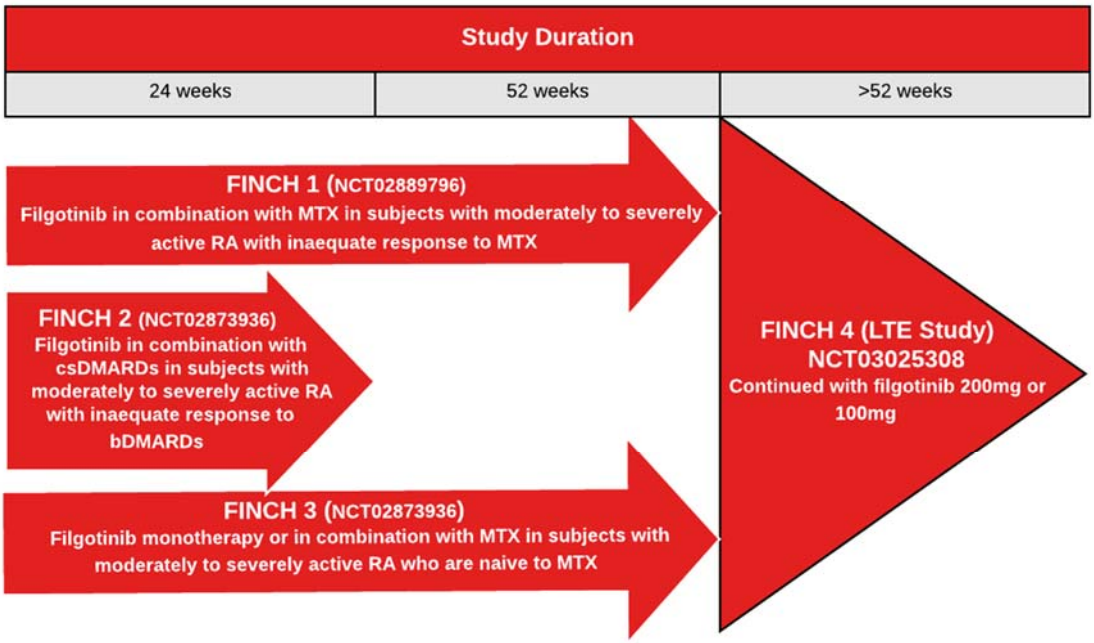
See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

Filgotinib (both in combination with MTX and as monotherapy) has been well-studied and characterised through an extensive clinical trial programme. Three Phase 3 studies, FINCH 1, 2 and 3 inform the safety and efficacy in three distinct populations. The clinical effectiveness evidence from the three FINCH trials is detailed in Table 5.

A long-term extension (LTE) study (FINCH 4) to characterise the long-term safety and efficacy of filgotinib is currently underway, further details are provided in section B.2.11. An overview of the filgotinib phase 3 clinical trial programme can be found in Figure 3.

Figure 3. Overview of the filgotinib clinical trial programme



DMARDs, disease modifying anti-rheumatic drugs; bDMARDs, biologic DMARDs, csDMARDs, conventional synthetic DMARDS; LTE, long-term extension; MTX, methotrexate; RA, rheumatoid arthritis

The primary endpoint for both FINCH 1 and FINCH 2 was the proportion of subjects achieving a 20% improvement in American College of Rheumatology response (ACR20) at week 12. The primary endpoint in FINCH 3 was the proportion of subjects achieving an ACR20 response at week 24.

The results of FINCH 3 were included in the Marketing Authorisation application for filgotinib to the European Medicine Agency (EMA) and are therefore presented in sections 2.2 to 2.6. FINCH 3 was not included in the economic model because participants in this trial were naïve to MTX and therefore were not within the scope of this submission.

Table 5. Clinical effectiveness evidence: FINCH 1, FINCH 2 and FINCH 3

Study	FINCH 1, (NCT02889796) (67)	FINCH 2, (NCT02873936) (68)	FINCH 3, (NCT02886728) (69)
Study design	Randomised, double-blind, placebo- and active-controlled, multicentre, parallel assignment, 52-week Phase 3 trial	Randomised, double-blind, placebo-controlled, multicentre, parallel assignment, 24-week Phase 3 trial	Randomised, double-blind, placebo- and active-controlled, multicentre, parallel assignment, 52-week, Phase 3 trial
Population	Adults with moderately to severely active RA who have inadequate response to ongoing stable MTX dose	Adults with moderately to severely active RA despite ongoing therapy with 1 or 2 cDMARD(s) and who have had an inadequate response or are intolerant to at least one biologic DMARD (bDMARD).	Adults with moderately to severely active RA who were MTX-naïve
Intervention(s)	**Filgotinib 200mg** • Filgotinib 200mg once daily • Placebo-to-match (PTM) filgotinib 100mg once daily • PTM adalimumab -subcutaneous injection every 2 weeks **Filgotinib 100mg** • Filgotinib 100mg once daily • PTM filgotinib 200mg once daily • PTM adalimumab subcutaneous injection every 2 weeks	**Filgotinib 200mg** • Filgotinib 200mg tablet • PTM filgotinib 100mg tablet administered orally, once daily **Filgotinib 100mg**: • Filgotinib 100mg tablet • PTM filgotinib 200mg tablet, administered orally, once daily	**Filgotinib 200mg + MTX** • Filgotinib 200mg once daily • PTM filgotinib 100mg once daily + MTX up to 20 mg once weekly **Filgotinib 100mg + MTX** • Filgotinib 100mg once daily • PTM filgotinib 200mg once daily + MTX up to 20 mg once weekly **Filgotinib 200mg monotherapy** • Filgotinib 200mg once daily • PTM filgotinib 100mg once daily • PTM MTX once weekly
Comparator(s)	**Active comparator** • Adalimumab 40 mg subcutaneous injection every 2 weeks • PTM filgotinib 200mg once daily • PTM filgotinib 100mg once daily **Placebo**	**Placebo** • PTM filgotinib 200mg tablet • PTM filgotinib 100mg tablet, administered orally, once daily	**MTX monotherapy** • PTM filgotinib 200mg once daily • PTM filgotinib 100mg once daily • MTX up to 20 mg once weekly

	• PTM filgotinib 200mg once daily • PTM filgotinib 100mg once daily • PTM adalimumab subcutaneous injection every 2 weeks		
Background treatment	Subjects must have had ongoing treatment with a stable dose of MTX as described below: • Use of oral MTX on a continuous basis for at least 12 weeks prior to Day 1 and on a stable prescribed dose of 7.5 mg to 25 mg/weekly for at least 4 weeks prior to Day 1. • Stable doses of <7.5 mg/week were allowed only in the presence of intolerance or toxicity to higher doses or where higher doses were prohibited by the local label or local clinical practice. • Doses >25 mg weekly were not permitted during the study.	All subjects continued to receive a stable dose of a permitted protocol-specified cDMARD (MTX, hydroxychloroquine, sulfasalazine, or leflunomide).	Less than 3 months with conventional synthetic disease modifying antirheumatic drugs (cDMARDs) other than MTX or hydroxychloroquine.
Trial supports application for Marketing Authorisation?	Yes	Yes	Yes
Trial used in the economic model?	Yes	Yes	No
Rationale for use/non-use in the model	Pivotal trial in relevant patient population	Pivotal trial in relevant patient population	Patients naïve to MTX, are out of the scope of this appraisal.
Reported outcomes specified in the decision problem	• Disease activity (American College of Rheumatology - ACR20, ACR50, ACR70, • **European League Against Rheumatism (EULAR) response,** • **Disease Activity Score (DAS28)**	• Disease activity (American College of Rheumatology - ACR20, ACR50, ACR70, • **European League Against Rheumatism (EULAR) response,** • **Disease Activity Score (DAS28)**	• Disease activity (American College of Rheumatology - ACR20, ACR50, ACR70, • **European League Against Rheumatism (EULAR) response,** • **Disease Activity Score (DAS28)**

	• **physical function (HAQ-DI)** • pain • mortality • fatigue (FACIT-F) • radiological progression (mTSS) • adverse effects of treatment • health-related quality of life.	• **physical function (HAQ-DI)** • pain • mortality • fatigue (FACIT-F) • radiological progression (mTSS) • adverse effects of treatment • health-related quality of life.	• **physical function (HAQ-DI)** • pain • mortality • fatigue (FACIT-F) • radiological progression (mTSS) • adverse effects of treatment • health-related quality of life.
All other reported outcomes	Additional endpoints included changes in individual ACR components, other composite measures of disease activity (e.g., ACR-N% improvement [ACR-N], Clinical Disease Activity Index [CDAI], Simplified Disease Activity Index [SDAI]), and additional patient reported outcomes, including measures of health-related quality of life: • SF-36 • EQ-5D • WPAI-RA at day 1 and at weeks 4, 12, 24, 36, and 52, or at ET (if applicable)	Additional endpoints included changes in individual ACR components, other composite measures of disease activity (e.g., ACR-N% improvement [ACR-N], Clinical Disease Activity Index [CDAI], Simplified Disease Activity Index [SDAI]), and additional patient reported outcomes, including measures of health-related quality of life: • SF-36 • EQ-5D • WPAI-RA at day 1 and at weeks 4 (Treatment satisfaction questionnaire for medication excluded), 12, 24, at ET (if applicable)	Additional endpoints included changes in individual ACR components, the ACR N% improvement (ACR-N) response, change from baseline in Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI), low disease activity (LDA) per CDAI and SDAI criteria, remission per CDAI and SDAI criteria, Boolean remission per TJC28 criteria, the proportion of subjects with no radiographic progression from baseline, and additional patient-reported outcomes, including measures of health-related quality of life: • SF-36 • WPAI-RA • EQ-5D on day 1 and at weeks 4, 12, 24, 36, and 52, and at ET (if applicable).

ACR, American College of Rheumatology; CDAI, clinical disease activity index; DAS, disease activity score; DMARDs, disease modifying anti-rheumatic drugs; bDMARDs, biologic DMARDs, cDMARDs, conventional DMARDS; EQ-5D, EuroQol five dimension; ET, early termination; EULAR, European League Against Rheumatism; FACIT-F, functional assessment of chronic illness therapy-fatigue; HAQ-DI, health assessment questionnaire disability index; LDA, low disease activity; mTSS, modified Total Sharp Score; MTX, methotrexate; NA, not applicable; PTM, placebo-to-match; RA, rheumatoid arthritis; SDAI, simplified disease activity index; SF-36, 36-item short form survey; WPAI, work productivity and activity impairment.

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

A summary of the methods used in the three pivotal FINCH trials is provided in Table 6 below.

Table 6. Comparative summary of trial methodology

Trial no. (acronym)	NCT02889796 (FINCH 1) (67)	NCT02873936 (FINCH 2) (68)	NCT02886728 (FINCH 3) (69)
Trial design	52-week randomised, double-blind, placebo- and active-controlled, multicentre, Phase 3 study. Patients were randomised in a 3:3:2:3 ratio to receive MTX and: • Filgotinib (200mg) or • Filgotinib (100mg) or • Adalimumab (40mg) or • Placebo Randomisation was stratified by geographic region, prior exposure to bDMARDs and presence of RF or anti-CCP antibodies at screening and was carried out using a computerised interactive web response system. Treatment assignments should have remained blinded unless that knowledge was necessary to determine emergency medical care for the subject. The rationale for unblinding must have been clearly explained in source documentation and on the Case Report Form (CRF), along with the date on which the treatment assignment was unblinded.	24-week randomised, double-blind, placebo-controlled, multicentre, Phase 3 study. Patients were randomised in a 1:1:1 ratio to receive a stable dose of cDMARD (MTX, hydroxychloroquine, sulfasalazine, or leflunomide) and: • Filgotinib (200mg) or • Filgotinib (100mg) or • Placebo Randomisation was stratified by geographic region, number of bDMARDs previously exposed to (<3 or ≥3), and the presence of RF or anti-CCP antibody at screening and was carried out using a computerised IXRS system. Treatment assignments should have remained blinded unless that knowledge was necessary to determine emergency medical care for the subject. The rationale for unblinding must have been clearly explained in source documentation and on the Case Report Form (CRF),	52-week randomised, double-blind, placebo- and active-controlled, multicentre, Phase 3 study. Patients were randomised using a 2:1:1:2 ratio to receive: • Filgotinib (200mg) + MTX (up to 20mg) or • Filgotinib (100mg) + MTX (up to 20mg) or • Filgotinib (200mg) or • MTX (up to 20mg) Randomisation was stratified by geographic region and presence of either RF or anti-CCP antibody at screening and was carried out using an interactive web response system. Treatment assignments should have remained blinded unless that knowledge was necessary to determine emergency medical care for the subject. The rationale for unblinding must have been clearly explained in source documentation and on the Case Report Form (CRF), along with the date on which the treatment assignment was unblinded. The investigator was requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

Trial no. (acronym)	NCT02889796 (FINCH 1) (67)	NCT02873936 (FINCH 2) (68)	NCT02886728 (FINCH 3) (69)
	The investigator was requested to contact the Gilead medical monitor promptly in case of any treatment unblinding. At week 14, patients who had not achieved at least 20% improvement from baseline in both Swollen Joint Count (SJC) and Tender Joint Count (TJC) discontinued investigational study drug dosing but continued with study visits and assessments per protocol. All patients meeting this criterion who discontinued from investigational therapy received standard of care treatment for their RA (as determined by the investigator). At week 24, all patients assigned to placebo were reassigned 1:1 to either filgotinib 100mg + MTX or filgotinib 200mg + MTX in a blinded fashion and continued in the study per protocol up to week 52. Subjects previously randomized to filgotinib 100 or 200 mg or adalimumab continued on their original randomization group. All patients who continued on study drug were evaluated for loss of therapeutic response from week 30 through week 52. Patients failing to maintain at least a 20% improvement from baseline in TJC and SJC, (which was confirmed at two consecutive visits), discontinued from	along with the date on which the treatment assignment was unblinded. The investigator was requested to contact the Gilead medical monitor promptly in case of any treatment unblinding. At week 14, patients who had not achieved at least 20% improvement from day 1 in both SJC66 and TJC68 discontinued study drugs, but continued study visits and assessments, and received SoC treatment for RA. All patients who attained responder status at week 14 continued on their assigned study drugs, in a blinded fashion, to week 24. Upon completion of the 24-week dosing period all patients, regardless of response, who had not discontinued the study drug due to toxicity were given the option to screen for enrolment in a separate long-term extension study (FINCH 4). The Full Analysis Set (FAS) included all subjects who were randomized into the study and received at least 1 dose of study drug. The FAS was the primary analysis set for efficacy analyses. The Safety Analysis Set (SAS) included all subjects who received at	At week 24, patients who had not achieved at least a 20% improvement from day 1 in both SJC and TJC discontinued the investigational study drug dosing but continued with study visits and assessments per protocol. All patients meeting this criterion who discontinued from investigational therapy received standard of care treatment as determined by the investigator. Subjects who achieved at least a 20% improvement in SJC and TJC at Week 24 continued the dosing regimen to which they were randomized and were evaluated for loss of therapeutic response from Week 30 through week 52. Subjects who failed to maintain at least a 20% improvement from Day 1 in TJC and SJC (confirmed at 2 consecutive visits) discontinued investigational study drug dosing to receive standard of care treatment for RA as determined by the investigator, but continued with study visits and assessments per protocol Upon completion of the 52-week treatment period, subjects who had not discontinued assigned study drug or had not met the criteria for loss of therapeutic response had the option to enter a long-term extension (LTE) study (FINCH 4). Subjects who did not enter the LTE study completed the Posttreatment Week 4 visit after the last dose of study drug. The Full Analysis Set (FAS) included all randomized subjects who received at least 1 dose of study drug. The FAS was the primary analysis set for efficacy analyses.

Trial no. (acronym)	NCT02889796 (FINCH 1) (67)	NCT02873936 (FINCH 2) (68)	NCT02886728 (FINCH 3) (69)
	investigational study drug therapy but continued with study visits and assessments per protocol. All patients meeting this criterion who discontinued from investigational study drug dosing received standard of care treatment for their RA as determined by the investigator and were not eligible for enrolment in the separate Long-Term Extension (LTE) study (FINCH 4). At completion of the 52-week dosing period, subjects who had not discontinued assigned study drug dosing, were provided the option to enrol into the LTE Study GS-US-417-0304.(70). The primary analysis set for efficacy analyses was the Full Analysis Set (FAS), which included all randomized subjects who received at least 1 dose of study drug The Safety Analysis Set (SAS) included all subjects who received at least 1 dose of study drug. This was the primary analysis set for safety analyses.	least 1 dose of study drugs. This was the primary analysis set for safety analyses.	The Safety Analysis Set (SAS) included all subjects who received at least 1 dose of study drug. This was the primary analysis set for safety analyses.
Eligibility criteria for participants	• Age ≥18 years (≥20 years in Japan) • Met 2010 ACR/EULAR criteria for RA and were ACR functional class I–III	• Aged ≥18 years • Met 2010 ACR/EULAR criteria for RA and were ACR functional class I-III • Had ≥6 swollen joints and ≥6 tender joints at screening and on Day 1	• Age ≥18 years • Met 2010 ACR/EULAR criteria for RA and were ACR functional class I–III • ≥6 swollen joints and ≥6 tender joints at screening and on Day 1 • Met at least one of the following parameters at screening:

Trial no. (acronym)	NCT02889796 (FINCH 1) (67)	NCT02873936 (FINCH 2) (68)	NCT02886728 (FINCH 3) (69)
	• ≥6 swollen joints and ≥6 tender joints at screening and on Day 1 • At least one of the following parameters at screening: ≥1 documented joint erosion on radiographs of the hands, wrists or feet by central reading and a positive result for RF or anti-CCP antibodies ≥3 documented joint erosions on radiographs of the hands, wrists or feet by central reading if both RT and anti-CCP antibodies were negative Serum CRP ≥6 mg/L Underwent treatment with oral MTX for at least 12 weeks prior to Day 1, at a stably prescribed dose	• Undergoing treatment with 1 or 2 cDMARDs at a stable dose • Prior inadequate response or intolerance to at least one bDMARD	o Positivity for RF or anti-CCP antibodies per central laboratory, or o CRP ≥4 mg/L based on central laboratory value, or o ≥1 document joint erosion of the hands, wrists or feet on radiographs by central reading • Naïve to MTX or have had limited prior treatment with MTX (≤3 doses of MTX ≤25 mg, with the last dose occurring at least 28 days prior to Day 1)
Settings and locations where the data were collected	This study was conducted at 303 study centres in: **Group A:** Australia, Belgium, Germany, Canada, Ireland, Israel, Italy, Netherlands, New Zealand, Republic of Korea, South Africa, Spain, United Kingdom, and the United States	This study was conducted at 114 sites in: **Group A:** Australia, Belgium, France, Germany, Israel, Italy, Netherlands, South Korea, Spain, Switzerland, United Kingdom, and the United States	This study was conducted in over 227 sites in: **Group A:** Australia, Belgium, Canada, France, Germany, Ireland, Israel, Italy, Netherlands, New Zealand, Republic of Korea, Singapore, South Africa, Spain, Sweden, Switzerland, United Kingdom, and the United

Trial no. (acronym)	NCT02889796 (FINCH 1) (67)	NCT02873936 (FINCH 2) (68)	NCT02886728 (FINCH 3) (69)
	Group B: Bulgaria, Czech Republic, Hungary, India, Poland, Romania, Russian Federation, Serbia, Slovakia, Ukraine, **Group C:** Argentina, Mexico **Group D:** Hong Kong, Taiwan, Thailand, **Group E:** Japan	**Group B:** Czech Republic, Hungary, Poland **Group C:** Argentina, Mexico **Group D:** China (originally planned but no subjects were screened or enrolled from China). **Group E:** Japan	States **Group B:** Bulgaria, Croatia, Czech Republic, Estonia, Georgia, Hungary, India, Latvia, Moldova, Poland, Romania, Russian Federation, Serbia, Slovakia, and Ukraine **Group C:** Argentina, Brazil, Chile, Colombia, Mexico, Peru, and Puerto Rico **Group D:** China, Hong Kong, Malaysia, Philippines, Taiwan, Thailand, and Vietnam **Group E:** Japan
Trial drugs	**Interventions:** • Filgotinib 200mg + MTX + placebo (n=477), • Filgotinib 100mg + MTX + placebo (n=480) **Comparators:** • Adalimumab + MTX + placebo (n=325), • placebo + MTX (n=475).	**Interventions:** • Filgotinib 200mg + placebo + cDMARD(s) (n=148), • Filgotinib 100mg + placebo +cDMARD(s) (n=153) **Comparators:** • placebo + cDMARD(s) (n=148).	**Interventions:** • Filgotinib 200mg + placebo + MTX (n=417), • Filgotinib 100mg+ placebo + MTX (n=207), • Filgotinib 200mg + placebo (n=210) **Comparators:** • MTX + placebo (n=418).
Permitted and disallowed concomitant medications	Concomitant therapies taken for treatment of pre-existing conditions continued during the study provided they were in accordance with the inclusion and exclusion criteria. It was preferred that these medications were continued without variation of dose or regimen during the study, as much as possible. All non-RA medication used within 30 days of consent (including any changes) were to be documented in the eCRF. All prior medication(s) used in the treatment for RA were documented in the eCRF Prohibited concomitant medications (and their wash out period as	Concomitant therapies taken for treatment of pre-existing conditions could continue during the study provided they were in accordance with the inclusion and exclusion criteria. It was preferred that these medications were continued without variation of dose or regimen during the study, as much as possible. All non-RA medication used within 30 days of consent (including any changes) were to be documented in the eCRF. All prior medication used for treatment of RA, were to be documented in the eCRF. Prohibited concomitant medications	Concomitant therapies taken for treatment of pre-existing conditions could continue during the study provided they were in accordance with the inclusion and exclusion criteria. It was preferred that these medications were continued without variation of dose or regimen during the study, as much as possible. All non-RA medications used within 30days of consent (including any changes) were to be documented in the eCRF. All prior medications used for treatment of RA were to be documented in the eCRF. Prohibited concomitant medications (and their wash out period as applicable) while on study drug included: • Use of cDMARDs (other than the study-

Trial no. (acronym)	NCT02889796 (FINCH 1) (67)	NCT02873936 (FINCH 2) (68)	NCT02886728 (FINCH 3) (69)
	applicable) while on study drug included: • Use of any DMARDs, other than background MTX and anti-malarial' s • Use of oral or injectable gold within 4weeks prior to Day1 • Use of sulfasalazine within 4weeks prior to Day1 • Use of Azathioprine within 4weeks prior to Day1 • Use of D-penicillamine within 4weeks prior to Day1 • Use of cyclosporine within 4 weeks prior to Day1 • Use of leflunomide within 8 weeks prior to Day1 or a minimum 4weeks prior to Day1 if after 11days of standard cholestyramine therapy. • Use of any cytotoxic agent, including chlorambucil, cyclophosphamide, nitrogen mustard, and other alkylating agents. • Use of any JAK inhibitor or other small molecule immunomodulator • Use of any injectable corticosteroids and receipt of an intra-articular or parenteral corticosteroid injection within 4 weeks prior to day 1 was prohibited.	(and their wash out period as applicable) while on study drugs included: • Any DMARD(s), other than the ones specified above • Oral or injectable gold within 4weeks prior to Day1 • Azathioprine within 4weeks prior to Day1 • D penicillamine within 4weeks prior to Day1 • Cyclosporine within 8weeks prior to Day1 • Any cytotoxic agent, including chlorambucil, cyclophosphamide, nitrogen mustard, and other alkylating agents. • Use of any other JAK inhibitor or other small molecule immunomodulator • Any injectable corticosteroids and receipt of an intra-articular or parenteral corticosteroids injection within 4 weeks prior to Day1 is prohibited. • Potent P-gp inducers (e.g. rifampin, phenytoin, carbamazepine, and St. John's wort) within 3weeks prior to Day1	provided MTX/PTM MTX or ongoing hydroxychloroquine ≤400mg/day or chloroquine≤250mg/day) • Use of any bDMARD • Use of any cytotoxic agent, including chlorambucil, cyclophosphamide, nitrogen mustard, and other alkylating agents • Use of any other JAK inhibitor or other small molecule immunomodulator • Use of any injectable corticosteroids and receipt of an intra-articular or parenteral corticosteroid injection within 4weeks prior to Day1 • Use of potent P-glycoprotein inducers (e.g. rifampin, phenytoin, carbamazepine, and St. John's wort) within 3 weeks prior to Day1

Trial no. (acronym)	NCT02889796 (FINCH 1) (67)	NCT02873936 (FINCH 2) (68)	NCT02886728 (FINCH 3) (69)
	• Use of potent P-glycoprotein inducers (e.g. rifampin, phenytoin, carbamazepine, and St. John's wort) within 3weeks prior to Day1		
Primary outcomes	The primary efficacy endpoint was the proportion of subjects who achieved an ACR20 response at week 12	The primary efficacy endpoint was the proportion of subjects who achieved an ACR20 response at week 12.	The primary efficacy endpoint was the proportion of subjects who achieved an ACR20 response at week 24.
Key secondary outcomes (including scoring methods and timings of assessments)	The key secondary efficacy endpoints were: • Proportion of subjects who achieved DAS28-CRP≤3.2 at week 12 versus placebo and versus adalimumab • Change from baseline in the HAQ-DI score at week 12 versus placebo • Proportion of subjects who achieve DAS28-CRP<2.6 at week 24 versus placebo and adalimumab • Change from baseline in mTSS at week 24 versus placebo	The key secondary efficacy endpoints were: • Proportion of subjects who achieved DAS28-CRP≤3.2 at week 12 • Change from baseline in the HAQ-DI score at week 12	The key secondary efficacy endpoints were: • Change from baseline in the HAQ-DI score at week 24 • Proportion of subjects who achieved DAS28-CRP<2.6 at week24 • Change from baseline in mTSS at week 24
Other secondary outcomes	Other secondary efficacy endpoints included: • Change from baseline in the mTSS at week 52 • The proportion of subjects who achieved an ACR50 and ACR70 response at weeks 4, 12, 24, and 52, an ACR20	Other secondary efficacy endpoints included: • The proportion of subjects who achieved an ACR50 response at weeks 4 and 24, an ACR70 response at weeks 4 and 12, an ACR20 response at weeks 4 and 24,	Other secondary efficacy endpoints included: • Change from baseline in mTSS at week 52 • The proportion of subjects who achieved ACR50 and ACR70 responses at weeks 4, 12, 24, and 52, and ACR20 response at weeks 4, 12, and 52, and ACR20/50/70 responses

Trial no. (acronym)	NCT02889796 (FINCH 1) (67)	NCT02873936 (FINCH 2) (68)	NCT02886728 (FINCH 3) (69)
	response at weeks 4, 24, and 52, and an ACR20/50/70 response over time from day 1 through week 52 • Change from baseline in individual components of the ACR response at weeks 4, 12, 24, and 52, and over time from day 1 through week 52 • The proportion of subjects who achieved change (i.e., decrease) in HAQ-DI of ≥ 0.22 at weeks 4, 12, 24, and 52, and over time from day 1 through week 52 • Change from baseline in DAS28-CRPat weeks 4, 12, 24, and 52, and over time from day 1 through week 52 • The proportion of subjects who achieved DAS28-CRP≤ 3.2 at weeks 4, 24, and 52, and over time from day 1 through week 52 • The proportion of subjects who achieved DAS28-CRP< 2.6 at weeks 4, 12, and 52, and over time from day 1 through week 52 • ACR-N and EULAR response at weeks 4, 12, 24, and 52, and over time from day 1 through week 52 • Change from baseline in CDAI at weeks 4, 12, 24, and 52,	and ACR20/50/70 response rates over time from day 1 through week 2 • Change from baseline in individual components of the ACR response at weeks 4, 12, and 24 and over time from day 1 through week 24 • The proportion of subjects who achieved a decrease in HAQ-DI of ≥ 0.22 at weeks 4, 12 and 24, and over time from day 1 through week 24 • Change from baseline in DAS28-CRPat weeks 4, 12, and 24, and over time from day 1 through week 2 • The proportion of subjects who achieved DAS28-CRP≤ 3.2 at weeks 4 and 24, and over • time from day 1 through week 24The proportion of subjects who achieved DAS28-CRP< 2.6 at weeks 4 and 12, and over • time from day 1 through week 24 ACR-N and EULAR response at weeks 4, 12, and 24, and over time from day 1 through week 24 • Change from baseline in CDAI at weeks 4, 12, and 24, and over time from day 1 through week 24	over time from day 1 through week 52 • Change from baseline in individual components of the ACR response at weeks 4, 12, 24, and 52, and over time from day 1 through week 52 • The proportion of subjects who achieved change (i.e., decrease) in HAQ-DI of ≥ 0.22 at weeks 4, 12, 24, and 52, and over time from day 1 through week 52 • Change from baseline in DAS28-CRPat weeks 4, 12, 24, and 52, and over time from day 1 through week 52 • The proportion of subjects who achieved DAS28-CRP≤ 3.2 at weeks 4, 12, 24, and 52, and over time from day 1 through week 52 • The proportion of subjects who achieved DAS28-CRP< 2.6 at weeks 4, 12, and 52, and over time from day 1 through week 52 • ACR-N and European League Against Rheumatism (EULAR) response at weeks 4, 12, 24 and 52, and over time from day 1 through week 52

Trial no. (acronym)	NCT02889796 (FINCH 1) (67)	NCT02873936 (FINCH 2) (68)	NCT02886728 (FINCH 3) (69)
	and over time from day 1 through week 5 • Change from baseline in SDAI at weeks 4, 12, 24, and 52, and over time from day 1 through week 24 • The proportion of subjects with no radiographic progression from baseline at weeks 24 and absolute value and change from baseline in SF-36, FACIT-Fatigue, and the EQ-5D at weeks 4, 12, 24 (except for SF-36 PCS and FACIT-Fatigue), and 52, and over time from day 1 through week 52 • Absolute value and change from baseline in WPAI-RA at weeks 4, 12, 24, and 52, and over • time from day 1 through week 52	• Change from baseline in SDAI at weeks 4, 12, and 24, and over time from day 1 through week 24 • Absolute value and change from baseline in SF-36, FACIT-Fatigue score, and the EQ-5D over time at weeks 4, 12, and 24 (except for SF-36 PCS and FACIT-Fatigue score), and over time from day 1 through week 24 • Absolute value and change from baseline in WPAI-RA at weeks 4, 12, and 24, and over time from day 1 through week 24	

ACR, American College of Rheumatology; CCP, citric citrullinated peptide; CDAI, clinical disease activity index; CRF, case report form, CRP, C-reactive protein; DAS, disease activity score; DMARDs, disease modifying anti-rheumatic drugs; bDMARDs, biologic DMARDs, cDMARDs, conventional DMARDS; EQ-5D, EuroQol five dimension; ET, early termination; EULAR, European League Against Rheumatism; FACIT-F, functional assessment of chronic illness therapy-fatigue; FAS, full analysis set; HAQ-DI, health assessment questionnaire disability index; IXRS, interactive web response system; JAK, Janus kinase; LDA, low disease activity; mTSS, modified Total Sharp Score; MTX, methotrexate; NA, not applicable; PCS, Physical Component Summary; PTM, placebo-to-match; RA, rheumatoid arthritis; RF, Rheumatoid factor; SDAI, simplified disease activity index; SF-36, 36-item short form survey; SJC, Swollen joint count; SoC, Standard of care; TJC, Tender joint count; WPAI, work productivity and activity impairment.

Table 7 shows the baseline characteristics of study patients for FINCH 1, FINCH 2 and FINCH 3. Within the three studies that constitute the pivotal registrational clinical programme, demographics and other baseline characteristics were well-balanced across the different treatment arms and can be considered broadly generalisable to those of patients seen in NHS clinical practice in England.

The characteristics of the population across each arm of FINCH 1 were well aligned. The main differences between FINCH 1 arms were:

- Sex at birth: 20.2% of patients were male in the filgotinib 200mg arm versus 16.9% in the filgotinib 100mg arm.
- Race: 20.0% of patients were Asian in the adalimumab arm versus 25.7% in the filgotinib 200mg arm. 70.5% were White in the adalimumab arm versus 65.7% in the filgotinib 200mg arm.
- Duration of RA since diagnosis: 8.0 years in the adalimumab group and 7.3 years in the filgotinib 200mg group

Similarly, the characteristics of patients within FINCH 2 and FINCH 3 were well balanced. The main differences were seen in sex at birth; in FINCH 2, 22.2% of patients were male in the filgotinib 100mg arm and 18.2% were male in the placebo arm. In FINCH 3, 21.0% of patients were male versus 25.0% in the MTX monotherapy arm.

Table 7. Baseline characteristics of patients in FINCH 1 (filgotinib + MTX; MTX-IR; SAS), FINCH 2 (filgotinib + cDMARD; bDMARD-IR; SAS) and FINCH 3 (filgotinib + MTX; MTX naïve; SAS)

Baseline characteristic	NCT02889796 (FINCH 1) (67)				NCT02873936 (FINCH 2) (68)			NCT02886728 (FINCH 3) (69)			
	filgotinib 200mg (n=475)200mg	filgotinib 100mg (n=480)100mg	Adalimumab (n=325)	placebo (n=475)	filgotinib 200mg (n=147)	filgotinib 100mg (n=153)	placebo (n=148)	filgotinib 200mg + MTX (n=416)	filgotinib 100mg + MTX (n=207)	filgotinib 200mg monotherapy (n=210)	MTX monotherapy (n=416)
Age, mean (SD)	52 (12.8)	53 (12.6)	53 (12.9)	53 (12.8)	56 (12.5)	55 (12.0)	56 (12.1)	53 (13.8)	54 (12.6)	52 (13.9)	53 (13.7)
Sex at birth, n (%)											
Male	96 (20.2%)	81 (16.9%)	59 (18.2%)	84 (17.7%)	27 (18.4%)	34 (22.2%)	27 (18.2%)	91 (21.9%)	49 (23.7%)	44 (21.0%)	104 (25.0%)
Female	379 (79.8%)	399 (83.1%)	266 (81.8%)	391 (82.3%)	120 (81.6%	119 (77.8%)	121 (81.8%)	325 (78.1%)	158 (76.3%)	166 (79.0%)	312 (75.0%)
Ethnicity											
Hispanic or Latino	67 (14.1%)	71 (14.8)	54 (16.6)	70 (14.7%)	0%	0%	0%	93 (22.4%)	40 (19.3%)	45 (21.4%)	84 (20.2%)
Not Hispanic or Latino	404 (85.1%)	399 (83.1%)	268 (82%)	400 (84.2%)	0%	0%	0%	322 (77.4%)	167 (80.7%)	165 (78.6%)	332 (79.8%)
Not permitted	4 (0.8%)	10 (2.1%)	3 (0.9%)	5 (1.1%)	100%	100%	100%	1 (0.2%)	0	0	0
Race, n (%)											
American Indian or Alaskan Native	27 (5.7%)	27(5.6%)	20 (6.2%)	29 (6.1%)	7 (4.8%)	9 (5.9%)	10 (6.8%)	26 (6.3%)	12 (5.8%)	18 (8.6%)	33 (7.9%)

Asian	122 (25.7%)	115 (24.0%)	65 (20.0%)	109 (22.9%)	15 (10.2%)	20 (13.1%)	15 (10.1%)	90 (21.6%)	51 (24.6%)	47 (22.4%)	85 (20.4%)
Black or African American	6 (1.3%)	7 (1.5%)	10 (3.1%)	12 (2.5%)	14 (9.5%)	12 (7.8%)	21 (14.2%)	15 (3.6%)	8 (3.9%)	8 (3.8%)	14 (3.4%)
Native Hawaiian or Pacific Islander	1 (0.2%)	0	0	2 (0.4%)	NA	NA	NA	1 (0.2%)	0	1 (0.5%)	3 (0.7%)
White	312 (65.7%)	324 (67.5%)	229 (70.5%)	319 (67.2%)	110 (74.8%)	109 (71.2%)	97 (65.5%)	278 (66.8%)	132 (63.8%)	135 (64.3%)	278 (66.8%)
Other	7 (1.5%)	6 (1.3%)	1 (0.3%)	3 (0.6%)	1 (0.7%)	3 (2.0%)	2 (1.4%)	6 (1.4%)	4 (1.9%)	0	3 (0.7%)
*Not permitted**	0	1 (0.2%)	0	1 (0.2%)	0	0	3 (2.0%)	0	0	1 (0.5%)	0
BMI, mean kg/m^2 (SD)	26.7 (5.67)	26.4 (5.80)	26.9 (5.97)	27.0 (5.91)	30.5 (7.89)	30.3 (7.66)	29.8 (7.25)	27.6 (6.35)	27.8 (6.25)	27.5 (6.49)	27.9 (6.54)
Mean duration of RA from diagnosis, years (SD)	7.3 (7.39)	8.5 (8.22)	8.0 (7.40)	7.3 (7.24)	12.6 (9.48)	12.0 (7.74)	12.6 (10.30)	1.9 (3.57)	2.3 (4.71)	2.6 (6.26)	2.3 (5.52)
RF positive, n (%)	352 (74.1%)	362 (75.4%)	241 (74.2%)	365 (76.8%)	104 (70.7)	107 (69.9)	92 (62.2)	282 (67.8%)	141 (68.1%)	137 (65.2%)	288 (69.2%)
Anti-CCP positive, n (%)	380 (80.0%)	381 (79.4%)	253 (77.8%)	378 (79.6%)	99 (67.3%)	113 (73.9%)	105 (70.9%)	287 (69.0%)	143 (69.1%)	133 (63.3%)	292 (70.2%)
RF positive + anti-CCP positive, n (%)	331 (69.7%)	332 (69.2%)	219 (67.4%)	333 (70.1%)	91 (61.9%)	102 (66.7%)	84 (56.8%)	252 (60.6%)	122 (58.9%)	112 (53.3%)	258 (62.0%)
Concurrent oral corticosteroid use on first dose date, n (%)											
No	246 (51.8%)	251 (52.3%)	185 (56.9%)	258 (54.3%)	79 (53.7%)	85 (55.6%)	77 (52.0%)	273 (65.6%)	119 (57.5%)	121 (57.6%)	242 (58.2%)
Yes	229 (48.2%)	229 (47.7%)	140 (43.1%)	217 (45.7%)	68 (46.3%)	68 (44.4%)	71 (48.0%)	143 (34.4%)	88 (42.5%)	89 (42.4%)	174 (41.8%)
Mean dose, mg/day (SD)	6.2 (3.42)	6.1 (2.49)	5.9 (2.22)	5.9 (2.52)	6.4 (2.70)	6.3 (2.58)	6.2 (2.69)	6.6 (2.34)	7.2 (2.86)	6.6 (2.24)	6.5 (2.33)
Concurrent MTX use on first dose date, n (%)											
Mean dose, mg/week (SD)	15.3 (4.94)	15.5 (4.81)	15.4 (4.79)	14.9 (4.52)	15.5 (5.12)	16.2 (5.58)	15.5 (5.02)	NA	NA	NA	NA

Prior exposure to cDMARDs other than MTX, n (%)											
Yes	NA	NA	NA	NA	NA	NA	NA	73 (17.5%)	38 (18.4%)	35 (16.7%)	76 (18.3%)
No	NA	NA	NA	NA	NA	NA	NA	343 (82.5%)	169 (81.6%)	175 (83.3%)	340 (81.7%)
Prior exposure to MTX, n (%)											
Yes	NA	NA	NA	NA	NA	NA	NA	29 (7.0%)	14 (6.8%)	15 (7.1%)	24 (5.8%)
No	NA	NA	NA	NA	NA	NA	NA	387 (93.0%)	193 (93.2%)	195 (92.9%)	392 (94.2%)
SJC 66, mean (SD)	15 (8.5)	15 (8.5)	16 (8.4)	16 (8.5)	18 (12.5)	17 (12.4)	17 (9.7)	16 (9.8)	16 (9.3)	16 (9.7)	16 (9.4)
TJC 68, mean (SD)	25 (13.5)	25 (13.4)	24 (13.2)	24 (13.5)	28 (16.1)	26 (15.4)	27 (15.5)	26 (14.5)	25 (13.9)	26 (13.7)	26 (13.8)
SJC 28, mean (SD)	11 (5.2)	11 (5.2)	11 (5.0)	11 (5.0)	12 (6.3)	12 (6.0)	12 (6.0)	11 (5.6)	11 (5.3)	11 (5.9)	12 (5.6)
TJC 28, mean (SD)	15 (6.4)	15 (6.7)	15 (6.3)	15 (6.4)	16 (7.7)	15 (6.8)	16 (6.9)	15 (6.6)	15 (6.9)	15 (6.8)	15 (6.5)
HAQ-DI total score, mean (SD)	1.59 (0.611)	1.55 (0.625)	1.59 (0.600)	1.63 (0.613)	1.70 (0.656)	1.64 (0.683)	1.65 (0.633)	1.52 (0.622)	1.56 (0.654)	1.56 (0.655)	1.60 (0.625)
DAS28-CRP, mean (SD)	5.8 (0.88)	5.7 (0.95)	5.7 (0.88)	5.7 (0.91)	5.9 (1.03)	5.9 (0.98)	5.9 (0.86)	5.7 (0.99)	5.7 (1.04)	5.8 (0.94)	5.7 (1.00)
FACIT-Fatigue, mean (SD)	27.6 (10.68)	27.8 (10.60)	27.2 (10.20)	26.9 (10.34)	24.2 (11.47)	23.7 (12.30)	25.4 (10.89)	28.3 (10.93)	27.3 (11.92)	27.3 (10.90)	27.1 (10.72)
Patient's Pain Assessment, mean (SD)	65 (20.4)	64 (20.1)	64 (19.5)	66 (19.0)	66 (21.6)	67 (21.7)	68 (19.9)	64 (22.0)	67 (22.1)	67 (18.4)	66 (21.4)
Patient's Global Assessment Disease Activity, mean (SD)	67 (19.2)	65 (19.7)	67 (19.1)	68 (18.7)	68 (20.6)	69 (20.2)	70 (18.0)	65 (21.0)	66 (21.6)	68 (19.2)	66 (21.0)
Physician Global Assessment Disease Activity, mean (SD)	66 (16.0)	65 (16.5)	67 (15.5)	66 (16.2)	69 (17.6)	68 (18.7)	66 (16.7)	66 (17.0)	68 (16.3)	66 (14.4)	67 (16.8)
SDAI, mean, (SD)	41.2 (12.26)	40.2 (12.79)	40.6 (11.88)	41.2 (12.37)	43.4 (14.64)	42.6 (14.16)	43.0 (12.33)	41.3 (13.41)	41.0 (13.53)	41.8 (13.09)	41.9 (13.39)

CDAI, mean (SD)	39.5 (11.85)	38.6 (12.23)	39.2 (11.51)	39.6 (11.66)	41.7 (14.23)	40.4 (13.23)	41.4 (12.00)	39.5 (12.77)	39.2 (12.69)	40.0 (12.63)	40.2 (12.50)
hsCRP, mean mg/L (SD)	16.13 (21.005)	16.74 (22.982)	14.56 (18.003)	16.25 (24.051)	17.21 (18.275)	21.49 (28.206)	16.42 (18.321)	18.04 (25.289)	17.72 (27.419)	17.32 (23.228)	16.86 (24.353)

*Not permitted: local regulators did not allow collection of race or ethnicity information; ACR, American College of Rheumatology; BMI, body mass index; CCP, citric citrullinated peptide; CDAI, clinical disease activity index; CRF, case report form, CRP, C-reactive protein; DAS, disease activity score; DMARDs, disease modifying anti-rheumatic drugs; bDMARDs, biologic DMARDs, cDMARDs, conventional DMARDS; EQ-5D, EuroQol five dimension; ET, early termination; EULAR, European League Against Rheumatism; FACIT-F, functional assessment of chronic illness therapy-fatigue; FAS, full analysis set; HAQ-DI, health assessment questionnaire disability index; IR, inadequate response; IXRS, interactive web response system; JAK, Janus kinase; LDA, low disease activity; mTSS, modified Total Sharp Score; MTX, methotrexate; NA, not applicable; PCS, Physical Component Summary; PTM, placebo-to-match; RA, rheumatoid arthritis; RF, Rheumatoid factor; SAS, safety analysis set; SD, standard deviation; SDAI, simplified disease activity index; SF-36, 36-item short form survey; SJC, Swollen joint count; SoC, Standard of care; TJC, Tender joint count; WPAI, work productivity and activity impairment.

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

The statistical analysis methods and definitions of study groups used in the three pivotal FINCH trials are described in Table 8 below.

Table 8. Summary of statistical analysis in RCTs

Trial no. (acronym)	NCT02889796 (FINCH 1) (67)	NCT02873936 (FINCH 2) (68)	NCT02886728 (FINCH 3) (69)
objective	To evaluate the effects of filgotinib versus placebo for the treatment of signs and symptoms of rheumatoid arthritis (RA) as measured by the proportion of subjects achieving an American College of Rheumatology 20% improvement response (ACR20) at week 12.	To evaluate the effects of filgotinib versus placebo for the treatment of signs and symptoms of rheumatoid arthritis (RA) as measured by the proportion of subjects achieving an American College of Rheumatology 20% improvement (ACR20) response at week 12	To evaluate the effects of filgotinib (GS-6034, formerly GLPG0634) in combination with MTX versus MTX monotherapy for the treatment of signs and symptoms of rheumatoid arthritis (RA) as measured by the proportion of subjects achieving an American College of Rheumatology 20% improvement (ACR20) at week 24
Statistical analysis for primary endpoints	The primary efficacy endpoint was the proportion of subjects who achieved an ACR20 response at week 12. For the primary analysis, the ACR20 response rate at week 12 for filgotinib 200mg was compared with placebo for a superiority test at the 2-sided 0.05-level. A logistic regression analysis with treatment groups and stratification factors in the model was used. Subjects who did not have sufficient measurements to establish efficacy at week 12 were considered non-	The primary endpoint for the study was the proportion of subjects who achieved an ACR20 response at week 12. The primary analyses consisted of a superiority test of filgotinib 200mg compared with placebo based on the primary endpoint. Superiority was tested at the 2-sided 0.05-level. A logistic regression analysis with treatment groups and stratification factors in the model was used. Subjects who did not have sufficient measurements to establish efficacy at week 12 were	The primary efficacy endpoint was the proportion of subjects who achieved an ACR20 response at week24. For the primary analysis, the ACR20 response rate at week 24 for filgotinib200mg+ MTX was compared with MTX monotherapy for a superiority test at the 2-sided 0.05-level. A logistic regression analysis with treatment groups and stratification factors in the model was used. Subjects who did not have sufficient measurements to establish efficacy at week 24 were considered as

Trial no. (acronym)	NCT02889796 (FINCH 1) (67)	NCT02873936 (FINCH 2) (68)	NCT02886728 (FINCH 3) (69)
	responders (i.e., non-responder imputation [NRI]).	considered non-responders (i.e., non-responder imputation [NRI]).	non-responders (i.e., non-responder imputation [NRI]).
Sample size, power calculation	Sample size was determined based on the superiority test of filgotinib 200mg compared with placebo based on the change from baseline in mTSS at week 24. When assuming a difference of 0.4 between the 2 groups and a common standard deviation of 1.85, 450 subjects in each group were required to obtain 90% power at a 2-sided 0.05-level. This sample size provided over 95% power to detect an increase in ACR20 response rate of 45%to 65% between the placebo control group and the filgotinib group, respectively, using a 2-sided 0.05-level test. Based on Liu 2014 (71), 450 subjects in each of the filgotinib 200mg group and placebo group, and 300 subjects in the adalimumab group, the sample size provided over 90% power at a 2-sided 0.05 significance level to demonstrate that filgotinib 200mg preserved more than 50% of the effect of adalimumab with respect to the response rate of DAS28 (CRP)≤3.2 at week 12, assuming both filgotinib 200mg and adalimumab groups have similar response rates of DAS28(CRP)≤3.2. Given this study had a placebo group, assay sensitivity was established through a direct comparison of adalimumab to placebo. The total planned sample size was 1650 (450 each for the filgotinib 200mg, filgotinib 100mg, and	Sample size was determined based on the superiority test of filgotinib compared with placebo on the change from baseline in HAQ-DI at week 12. When assuming a difference of 0.25 between the 2 groups and a common standard deviation of 0.645, 141 subjects in each of the filgotinib groups and placebo control group were required to obtain 90% power at a 2-sided 0.05-level. A sample size of 141 subjects in each of the filgotinib groups and placebo control group provided over 90% power to detect an increase in ACR20 response rate of 25% to 45% between the placebo control group and the filgotinib groups respectively, using a 2-sided 0.05-level test. In summary, the total planned sample size was 423 (141 subjects in each treatment group).	Sample size was determined based on the superiority test of filgotinib200mg+ MTX compared with MTX monotherapy based on the change from baseline in mTSS at week 24. When assuming a difference of 0.62 between the 2 groups on change from baseline in mTSS at week 24 and a common standard deviation (SD) of 2.7, 400subjects in the filgotinib 200mg+MTX group and 400subjects in the MTX monotherapy group were required to obtain 90% power at a 2-sided 0.05-level. The total planned sample size was 1200 subjects (400subjects in the filgotinib200mg+ MTX group, 200 subjects in the filgotinib100mg+ MTX group, 200subjects in the filgotinib200mg monotherapy group, and 400 subjects in the MTX monotherapy group). This sample size provided over 90% power to detect a difference in the ACR20 response rate of 62% to 78% between the MTX monotherapy group and the filgotinib groups, respectively, using a 2-sided 0.05-level test.

Trial no. (acronym)	NCT02889796 (FINCH 1) (67)	NCT02873936 (FINCH 2) (68)	NCT02886728 (FINCH 3) (69)
	placebo groups, and 300 for the active comparator group).		
Data management, patient withdrawals	The Gilead medical monitor was to be consulted prior to discontinuation of study drug when medically feasible. Per protocol subjects were supposed to permanently discontinue study drug in the following instances: • Any opportunistic infection • Any serious infection that required antimicrobial therapy or hospitalization, or any infection that met serious adverse events (SAE) reporting criteria • Complicated herpes zoster infection (with multidermatomal, disseminated, ophthalmic, or central nervous system involvement) • Evidence of active HCV during the study, as evidenced by HCV RNA positivity • Evidence of active HBV during the study, as evidenced by HBV DNA positivity • Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromised the subject's ability to continue study-specific procedures or was considered to not be in the subject's best interest	The Gilead medical monitor was to be consulted prior to discontinuation of study drugs when medically feasible. Subjects could have withdrawn nor have been removed from treatment for any of the following reasons: • Any opportunistic infection • Any serious infection that required antimicrobial therapy or hospitalization, or any infection that met serious adverse event (SAE)reporting criteria. • Complicated herpes zoster infection (with multidermatomal, disseminated, ophthalmic, or CNS involvement) • Evidence of active HCV during the study, as evidenced by HCV RNA positivity • Evidence of active HBV during the study, as evidenced by HBV DNA positivity • Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromised the subject's ability to continue study-specific procedures or	The Gilead medical monitor was to be consulted prior to discontinuation of study drug when medically feasible. Per protocol subjects were supposed to permanently discontinue study drug in the following instances: • Any opportunistic infection • Any serious infection that required antimicrobial therapy or hospitalization, or any infection that met serious adverse events (SAE) reporting criteria • Complicated herpes zoster infection (with multidermatomal, disseminated, ophthalmic, or central nervous system involvement) • Evidence of active HCV during the study, as evidenced by HCV RNA positivity • Evidence of active HBV during the study, as evidenced by HBV DNA positivity • Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromised the subject's ability to continue study-specific procedures or

Trial no. (acronym)	NCT02889796 (FINCH 1) (67)	NCT02873936 (FINCH 2) (68)	NCT02886728 (FINCH 3) (69)
	• Non-responder at week 14 or at 2 consecutive visits after week 30 Subject requested to discontinue for any reason • Subject non-compliance Pregnancy during the study Discontinuation of the study at the request of Gilead, a regulatory agency, or an IRB/IEC • Subject use of prohibited concurrent therapy may have triggered discontinuation of study drug; consultation should have been made with the Gilead medical monitor. • Laboratory criteria: After becoming aware of any of the abnormal laboratory changes occurring at any one time described below, an unscheduled visit (i.e., sequential visit) should have occurred to retest within 3 to 7days (except creatinine, which should have been retested 7-14 days apart). • Two sequential neutrophil counts <750 neutrophils/mm3 (SI: $<0.75x10^9$ cells/L) • Two sequential platelet counts <75,000 platelets/mm3 (SI: $<75.x10^9$ cells/L) • Two sequential AST or ALT elevations >3xULN and ≥1 total bilirubin value >2xULN or accompanied by	was considered to not be in the subject's best interest • Subject request to discontinue for any reason • Subject noncompliance • Pregnancy during the study (see Appendix16.1.1, Section 7.7.2.1and Appendix 5) • Discontinuation of the study at the request of the sponsor, a regulatory agency, an IRB, or an IEC • Subject use of prohibited concurrent therapy could trigger discontinuation of study drugs; consultation was to be made with the Gilead Medical Monitor. • Laboratory criteria: After becoming aware of any of the following abnormal laboratory changes occurring at any 1time, an unscheduled visit (i.e. sequential visit) was to occur to reassess within 3 to 7days (except creatinine, which was to be retested within 7 to14days): • Two sequential neutrophil counts <750neutrophils/mm3 (SI: $<75.x10^9$ cells/L) • Two sequential l platelet counts <75,000platelets/mm3 (SI: $<75x10^9$ cells/L)	was considered to not be in the subject's best interest • Non-responder at week 14 or at 2consecutive visits after Week30 Subject requested to discontinue for any reason • Subject non-compliance Pregnancy during the study Discontinuation of the study at the request of Gilead, a regulatory agency, or an IRB/IEC • Subject use of prohibited concurrent therapy may have triggered discontinuation of study drug; consultation should have been made with the Gilead medical monitor. • Laboratory criteria: After becoming aware of any of the abnormal laboratory changes occurring at any one time described below, an unscheduled visit (i.e., sequential visit) should have occurred to retest within 3 to 7days (except creatinine, which should have been retested 7-14 days apart). • Two sequential neutrophil counts <750 neutrophils/mm3 (SI: $<75x10^9$ cells/L)

Trial no. (acronym)	NCT02889796 (FINCH 1) (67)	NCT02873936 (FINCH 2) (68)	NCT02886728 (FINCH 3) (69)
	symptoms consistent with hepatic injury. • Two sequential AST or ALT elevations >5xULN • Two sequential values for estimated creatinine clearance <35 mL/min based on the Cockroft-Gault formula Handling of dropouts or missing data: In general, missing data were not imputed unless methods for handling missing data were Specified in the sensitivity and supportive analyses.	Handling of dropouts or missing data: In general, missing data were not imputed unless methods for handling missing data were Specified in the sensitivity and supportive analyses.	• Two sequential platelet counts <75,000 platelets/mm3 (SI: <75.x10^9 cells/L) • Two sequential AST or ALT elevations >3xULN and ≥1 total bilirubin value >2xULN or accompanied by symptoms consistent with hepatic injury. • Two sequential AST or ALT elevations >5xULNTwo sequential values for estimated creatinine clearance <35 mL/min based on the Cockroft-Gault formula Handling of dropouts or missing data: In general, missing data were not imputed unless methods for handling missing data were Specified in the sensitivity and supportive analyses.

ACR, American College of Rheumatology; CCP, citric citrullinated peptide; CDAI, clinical disease activity index; CRF, case report form, CRP, C-reactive protein; DAS, disease activity score; DMARDs, disease modifying anti-rheumatic drugs; bDMARDs, biologic DMARDs, cDMARDs, conventional DMARDS; EQ-5D, EuroQol five dimension; ET, early termination; EULAR, European League Against Rheumatism; FACIT-F, functional assessment of chronic illness therapy-fatigue; FAS, full analysis set; HAQ-DI, health assessment questionnaire disability index; IXRS, interactive web response system; JAK, Janus kinase; LDA, low disease activity; mTSS, modified Total Sharp Score; MTX, methotrexate; NA, not applicable; PCS, Physical Component Summary; PTM, placebo-to-match; RA, rheumatoid arthritis; RF, Rheumatoid factor; SDAI, simplified disease activity index; SF-36, 36-item short form survey; SJC, Swollen joint count; SoC, Standard of care; TJC, Tender joint count; WPAI, work productivity and activity impairment.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The quality assessment of the FINCH 1, FINCH 2 and FINCH 3 trials is presented in Table 9. In general, the three pivotal FINCH trials were designed and carried out following a robust methodology. Randomisation was performed so that baseline characteristics of patients were homogeneous across treatment groups. Both patients and investigators remained blinded throughout the studies.

Table 9 Quality assessment results for RCTs

Trial no. (acronym)	**NCT02889796 (FINCH 1)**	**NCT02873936 (FINCH 2)**	**NCT02886728 (FINCH 3)**
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes

B.2.6 Clinical effectiveness results of the relevant trials

2.6.1 FINCH 1

FINCH 1 (67) met its primary endpoint, demonstrating superiority of filgotinib 200mg over placebo measured by proportion of patients achieving ACR20 response at week 12 (76.6% [72.7%, 80.5%] versus 49.9% [45.3%, 54.5%] for placebo) (p<0.001). Filgotinib 200mg + MTX and filgotinib 100mg + MTX also demonstrated statistically significantly better efficacy over placebo for a number of key efficacy endpoints including ACR20, ACR50 and ACR70, change from baseline in HAQ-DI, the proportion of patients achieving DAS28-CRP <2.6 (remission), the proportion of patients achieving DAS28-CRP ≤3.2 (LDA) and change from baseline in mTSS (radiographic progression). Further detail is given in the sections below.

ACR20/50/70 response

At week 12, the proportion of patients who achieved an ACR20 response was statistically significantly higher in the filgotinib 200mg (76.6% [72.7%, 80.5%]) and filgotinib 100mg (69.8%) groups compared with placebo (49.9% [45.3%, 54.5%]) (p<0.001 for both). This was also demonstrated for filgotinib 200mg versus adalimumab (70.5% [65.3%, 75.6] (p=0.046). Similarly, the proportion of patients who achieved an ACR50 response was statistically significantly higher in the filgotinib 200mg (47.2% [42.6%, 51.8%]) and filgotinib 100mg (36.5% [32.0%, 40.9%]) groups compared with placebo (19.8% [16.1%, 23.5%]); (p <0.001 for both). This was also demonstrated for filgotinib 200mg versus adalimumab (35.1% [29.7%, 40.4%]) (p<0.001). Finally, the proportion of patients achieving ACR70 response was also statistically significantly higher in the filgotinib 200mg (26.1% [22.1%, 30.2%]) and filgotinib 100mg (18.5% [15.0%, 22.1%]) groups compared with placebo (6.7% [4.4%, 9.1%]); (p <0.001 for both). This was also demonstrated for filgotinib 200mg versus adalimumab (14.2% [10.2%, 18.1%]) (p<0.001).

At week 24, the proportion of patients who achieved an ACR20 response was statistically significantly higher in the filgotinib 200mg (78.1% [74.3%, 81.9%]) and filgotinib 100mg (77.7% [73.9%, 81.5%]) groups compared with placebo (59.2% [54.6%, 63.7%]) (p <0.001 for both). Compared with adalimumab (74.5% [69.6%,

79.4%]), filgotinib 200mg (78.1% [74.3%, 81.9%]) demonstrated a numerically higher ACR20 response at week 24 (p=0.21). Similarly, the proportion of patients who achieved an ACR50 response was statistically significantly higher in the filgotinib 200mg (57.9% [53.3%, 62.4%]) and filgotinib 100mg (52.7% [48.1%, 57.3%]) groups compared with placebo (33.3%); (p <0.001 for both). Compared with adalimumab (52.3% [46.7%, 57.9%]), filgotinib 200mg (57.9% [53.3%, 62.4%]) demonstrated a numerically higher ACR50 response rate at week 24 (p=0.11). Finally, the proportion of patients achieving ACR70 response was also statistically significantly higher in the filgotinib 200mg (36.2% [31.8%, 40.6%]) and filgotinib 100mg (29.6% [25.4%, 33.8%]) groups compared with placebo (14.9% [11.6%, 18.3%]); (p <0.001 for both). The proportion of patients who achieved an ACR70 response was also statistically significantly higher in the filgotinib 200mg compared with the adalimumab group (29.5% [24.4%, 34.7%]) (p =0.042).

Figure 4, Figure 5 and

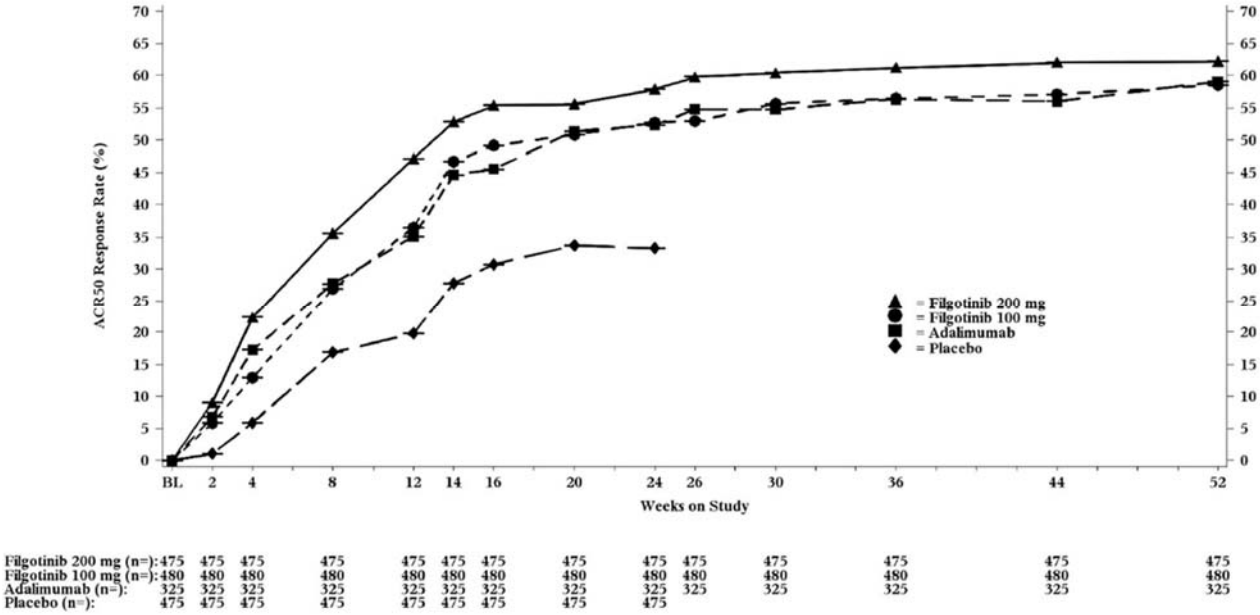
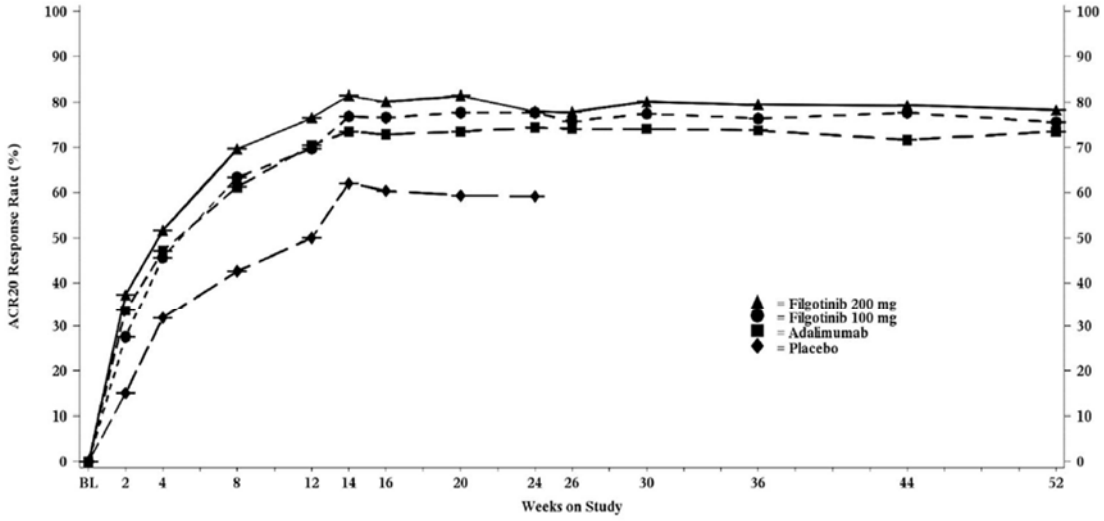


Figure 6 show ACR20, ACR50 and ACR70 over time. These demonstrate filgotinib's rapid onset of action, as well as the maintenance of response across the 52-week study period.

Figure 4. ACR20 response by study visit, FAS



Filgotinib 200 mg (n=):	475	475	475	475	475	475	475	475	475	475	475	475	475	475
Filgotinib 100 mg (n=):	480	480	480	480	480	480	480	480	480	480	480	480	480	480
Adalimumab (n=):	325	325	325	325	325	325	325	325	325	325	325	325	325	325
Placebo (n=):	475	475	475	475	475	475	475	475	475					

Figure 5. ACR50 response by study visit, FAS

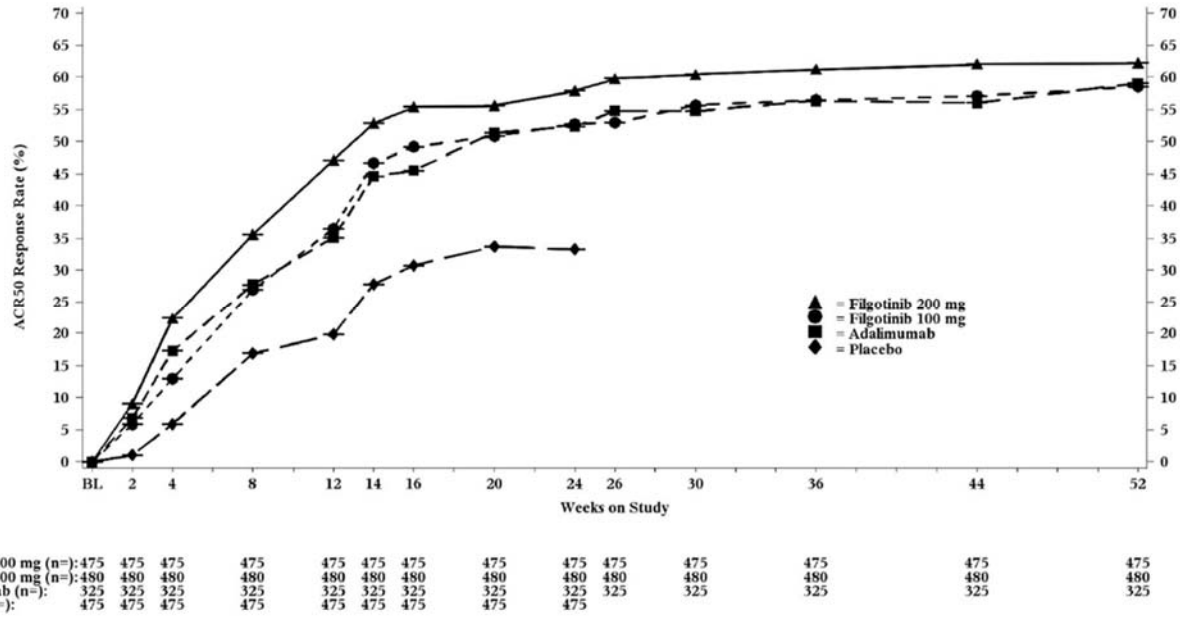
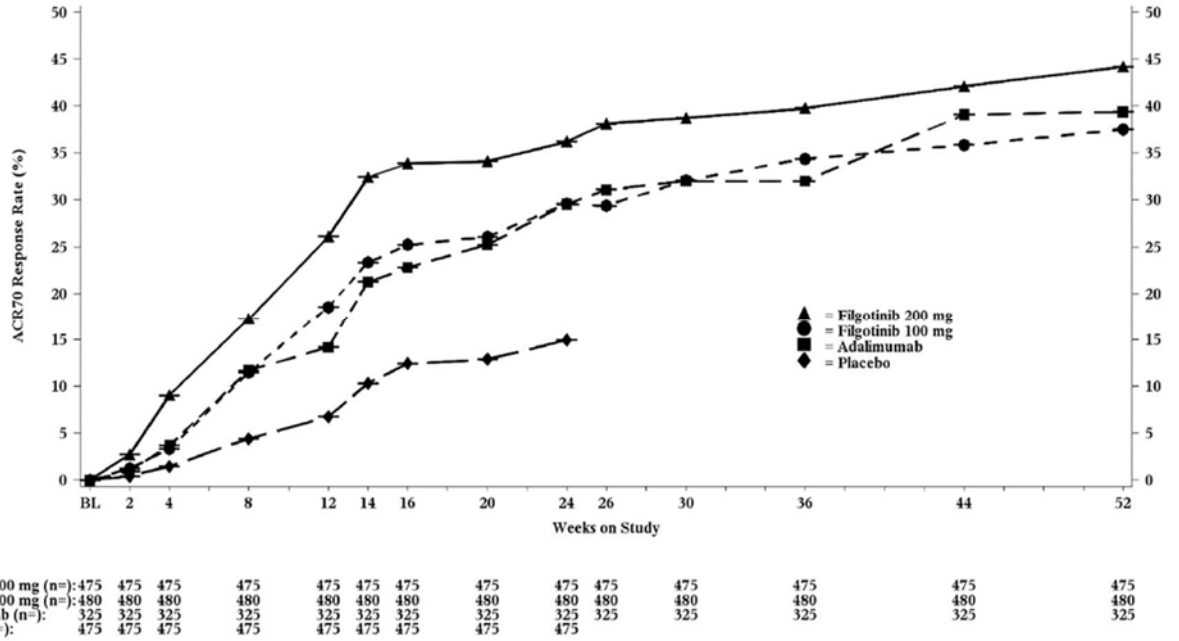


Figure 6. ACR70 response by study visit, FAS



Proportion of subjects who achieved DAS28-CRP <2.6 (remission)

At week 12, the proportion of patients achieving DAS28-CRP <2.6 was statistically significantly higher in the filgotinib 200mg (34.1% [29.7%, 38.5%]) and filgotinib 100mg (23.8% [19.8%, 27.7%]) groups compared with placebo (9.3% [6.6%, 12.0%]) (p <0.001 for both). This was also demonstrated for filgotinib 200mg versus adalimumab (23.7%) (p <0.001).

Similarly, at week 24, the proportion of patients achieving DAS28-CRP <2.6 was statistically significantly higher in the filgotinib 200mg (48.4% [43.8%, 53.0%]) and in the filgotinib 100mg (35.2% [30.8%, 39.6%]) groups compared with placebo (16.2% [12.8%, 19.6%]) (p <0.001 for both). This was also demonstrated for filgotinib 200mg versus adalimumab (35.7% [30.3%, 41.1%]) (p <0.001).

Proportion of subjects who achieved DAS28-CRP ≤3.2 (LDA)

At week 12, the proportion of patients achieving DAS28-CRP ≤3.2 was statistically significantly higher in the filgotinib 200mg (49.7% [45.1%, 54.3%]) and filgotinib 100mg (38.8% [34.3%, 43.2%]) groups compared with placebo (23.4% [19.5%, 27.3%]) (p <0.001 for both). This was also demonstrated for filgotinib 200mg versus adalimumab (43.5% [37.8%, 48.9%]) (p<0.001).

Similarly, at week 24, the proportion of patients achieving DAS28-CRP ≤3.2 was statistically significantly higher in the filgotinib 200mg (60.6%) and filgotinib 100mg (53.1% [48.6%, 57.7%]) groups compared with placebo (33.7% [29.3%, 38.0%]) (p <0.001 for both). This was also demonstrated for filgotinib 200mg versus adalimumab (50.5% [44.9%, 56.1%]) (p <0.001).

EULAR response

At week 12, filgotinib 200mg (51.4%) and filgotinib 100mg (39.2%) demonstrated a higher or comparable percentage of patients achieving a good EULAR response compared with placebo (24.6%) and when compared with adalimumab (44.8%).

At week 24, filgotinib 200mg (68.4%) and filgotinib 100mg (59.7%) demonstrated a higher percentage of patients achieving a good EULAR response compared with placebo (41.8%) and when compared with adalimumab (58.0%).

Change from baseline in HAQ-DI (physical function)

At week 12, a statistically significantly greater mean change from baseline in HAQ-DI was shown in the filgotinib 200mg (−0.69 [-0.77, -0.62]) and filgotinib 100mg (−0.56 [-0.65, -0.50]) groups compared with placebo (−0.42 [-0.48, -0.33]) (p <0.001 for both). This was also demonstrated for filgotinib 200mg versus adalimumab (-0.61[-0.68, -0.52]) (p=0.018). Of note, a reduction of -0.22 is considered a minimum clinically important difference (MCID) for HAQ-DI.

At week 24, a statistically significantly greater mean change from baseline in HAQ-DI was shown in the filgotinib 200mg (−0.82 [-0.90, -0.75]) and filgotinib 100mg (−0.75[-0.82, -0.67]) groups compared with placebo (−0.62 [-0.63, -0.48]) (p <0.001 for both). Compared with adalimumab (-0.78 [-0.85, -0.68]), filgotinib 200mg showed a numerically greater improvement in HAQ-Di at week 24 (p=0.15).

Change from baseline in mTSS (radiographic progression)

At week 24, filgotinib 200mg (0.13 [-0.04, 0.31]) and filgotinib 100mg (0.17 [-0.02, 0.33]) showed significantly less radiographic progression, measured as change from baseline in mTSS, when compared with placebo (0.37 [0.22, 0.59]) (p <0.001 for both). Compared with adalimumab (0.16 [-0.01, 0.38]), filgotinib 200mg showed less radiographic progression (p=0.54).

Results of additional secondary endpoints from FINCH 1 including Quality of Life as measured by SF-36 and additional patient reported outcome measures (pain and fatigue) are presented in Table 10.

Table 10. Summary of secondary efficacy outcomes, FINCH 1

Efficacy assessment	Week	Filgotinib 200 mg + MTX (n=475)	Filgotinib 100 mg + MTX (n=480)	Adalimumab + MTX (n=325)	Placebo + MTX (n=475)
Change from baseline in HAQ-DI, mean [95%CI] (SD)	12	−0.69 ***†# [-0.77, -0.62] (0.613)	−0.56 *** [-0.65, -0.50] (0.564)	−0.61 [0.68, -0.52] (0.559)	−0.42 [-0.48, -0.33] (0.544)
	24	-0.82 (0.632)*** [-0.90, -0.75]	−0.75 (0.597)*** [-0.65, -0.50]	-0.78 (0.632) [-0.85, -0.68]	−0.62 (0.598) [-0.63, -0.48]
EULAR response %	12	51.4%	39.2%	44.8%	24.6%
	24	68.4%	59.7%	58.0%	41.8%
Proportion of patients who achieved DAS28-CRP <2.6, % [95%CI]	12	34.1***†††#a [29.7%, 38.5%]	23.8***††#a [19.8%, 27.7%]	23.7 [19.8%, 27.7%]	9.3 [6.6%, 12.0%]
	24	48.4***#†††#a [43.8%, 53.0%]	35.2***#†††#a [30.8%, 39.6%]	35.7 [30.3%, 41.1%]	16.2 [12.8%, 19.6%]
Proportion of patients who achieved DAS28-CRP ≤3.2, % [95%CI]	12	49.7***#[††††a] [45.1%, 54.3%]	38.8***# [34.3%, 43.2%]	43.4 [37.8%, 48.9%]	23.4 [19.5%, 27.3%]
Change from baseline in mTSS, mean [95%CI] (SD)	24	0.13 *** [-0.04, 0.31] (0.937)	0.17 *** [-0.02, 0.33] (0.905)	0.16 [-0.01, 0.38] (0.948)	0.37 [0.22, 0.59] (1.408)
Change from baseline in SF-36 PCS, mean [95%CI] (SD)	12	9.2 *** # [†#] [8.6, 10.8] (8.10)	8.5 ***# [8.0, 10.2] (7.72)	8.4 [7.4, 9.8] (7.89)	5.8 [4.8, 7.1] (7.10)
Change from baseline in FACIT-Fatigue score, mean [95%CI] (SD)	12	9.2 ***# [-20.0, 38.0] (9.82)	9.1 ***# [-24.0, 39.0] (10.15)	8.8 [-17.0, 33.0] (9.19)	6.8 [-20.0, 40.0] (9.89)
Change from Baseline in Subject's pain assessment mean [95%CI] (SD)	12	-31 *** [-36, -30] (26.9)	-29 *** [-34, -28] (25.3)	-27 [-33, -26] (23.6)	-21 [-24, -18] (26.0)

*P<0.05; **P<0.01; ***P<0.001; versus placebo. †P<0.05; ††P<0.01; †††P<0.001; versus adalimumab. #P value is nominal. Square brackets indicate analyses versus adalimumab. ADA=adalimumab; DAS28-CRP=Disease Activity Score based on 28 joints and C reactive protein value; FACIT=Functional Assessment of Chronic Illness Therapy; FIL=filgotinib; HAQ-DI=Health Assessment Questionnaire-Disability Index; mTSS=modified total Sharp score; MTX=methotrexate; NR=not reported; placebo=placebo; QD=once per day; SD=standard deviation; SF-36 PCS=36-item Short Form Health Survey Physical Component Summary. SOURCE: Gilead Data on File. FINCH 1 CSR. 2019 (67)

2.6.2 FINCH 2

FINCH 2 (68) met its primary endpoint, superiority of filgotinib 200mg compared to placebo as measured by the proportion of patients achieving ACR20 response at week 12 (66.0% [58.0%, 74.0%] and 31.1% [23.3%, 38.9%] ; (p<0.001)). Filgotinib 200mg and filgotinib 100mg also demonstrated statistically significantly better efficacy over

placebo for several key efficacy endpoints including ACR20, ACR50 an ACR70, change from baseline in HAQ-DI (physical function), as well as proportion of patients achieving remission and LDA as measured by DAS28-CRP <2.6 and DAS28-CRP ≤3.2 respectively. Further details are provided in the sections below.

ACR20/50/70 response

At week 12, the proportion of patients who achieved an ACR20 response was statistically significantly higher in the filgotinib 200mg (66.0% [58.0%, 74.0%]) and filgotinib 100mg (57.5% [49.4%, 65.7%]) groups compared with placebo (31.1% [23.3%, 38.9%]) (p<0.001 for both). Similarly, the proportion of patients who achieved an ACR50 response was statistically significantly higher in the filgotinib 200mg (42.9% [34.5%, 51.2%]) and filgotinib 100mg (32.0% [24.3%, 39.7%]) groups compared with placebo (14.9%); (p <0.001 for both). Finally, the proportion of patients who achieved an ACR70 response was statistically significantly higher in the filgotinib 200mg (21.8% [14.8%, 28.8%]) and filgotinib 100mg (14.4% [8.5%, 20.3%]) groups compared with placebo (6.8% [2.4%, 11.1%]); (p <0.001 and p=0.036, respectively).

At week 24, the proportion of patients achieving an ACR20 response was statistically significantly higher in the filgotinib 200mg (69.4% [61.6%, 77.2%]) and filgotinib 100mg (54.9% [46.7%, 63.1%]) groups compared with placebo (34.5% [26.5%, 42.5%]); (p <0.001 for both). Similarly, the proportion of patients who achieved an ACR50 response was statistically significantly higher in the filgotinib 200mg (45.6% [37.2%, 54.0%]) and filgotinib 100mg (35.3% [27.4%, 43.2%]) compared with placebo (18.9% [12.3%, 25.6%] of responders); (p <0.001 and p=0.002, respectively). Finally, the proportion of patients who achieved ACR 70 response was also statistically significantly higher in the filgotinib 200mg (32.0% [24.1%, 39.9%]) and filgotinib 100mg (20.3% [13.6%, 27.0%]) groups compared with placebo (8.1% [3.4%, 12.8%]); (p <0.001 and p=0.004, respectively).

An overview of the ACR20/50/70 response rates over time is presented in Figure 10, Figure 11 and Figure 12, demonstrating rapid onset of activity for filgotinib 200mg and 100mg doses.

Figure 7. ACR20 Response Rates by study visit week (NRI; Full Analysis Set)

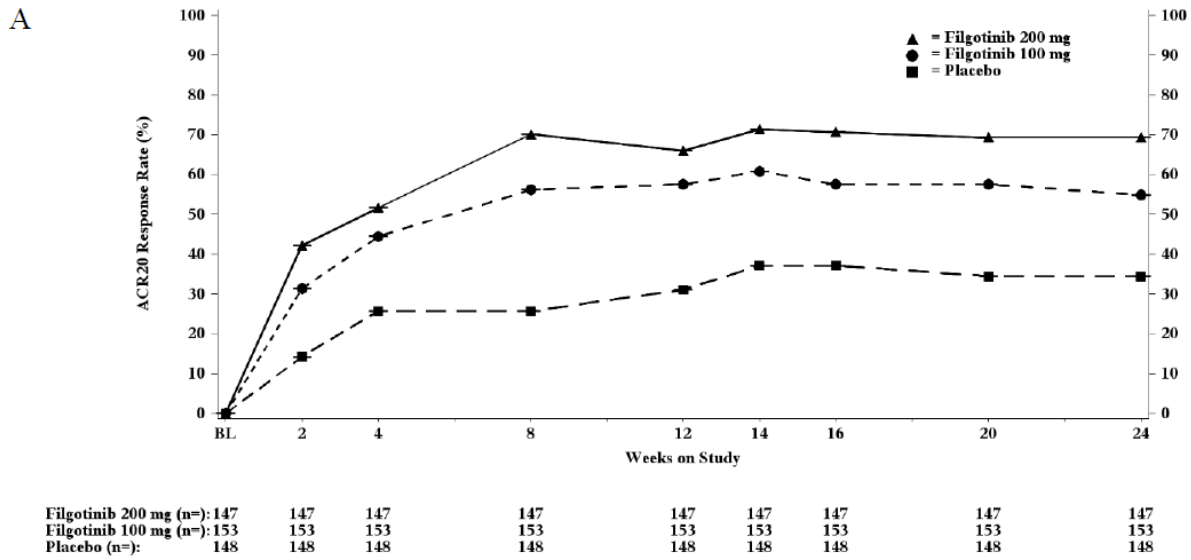


Figure 8. ACR50 Response Rates by study visit week (NRI; Full Analysis Set)

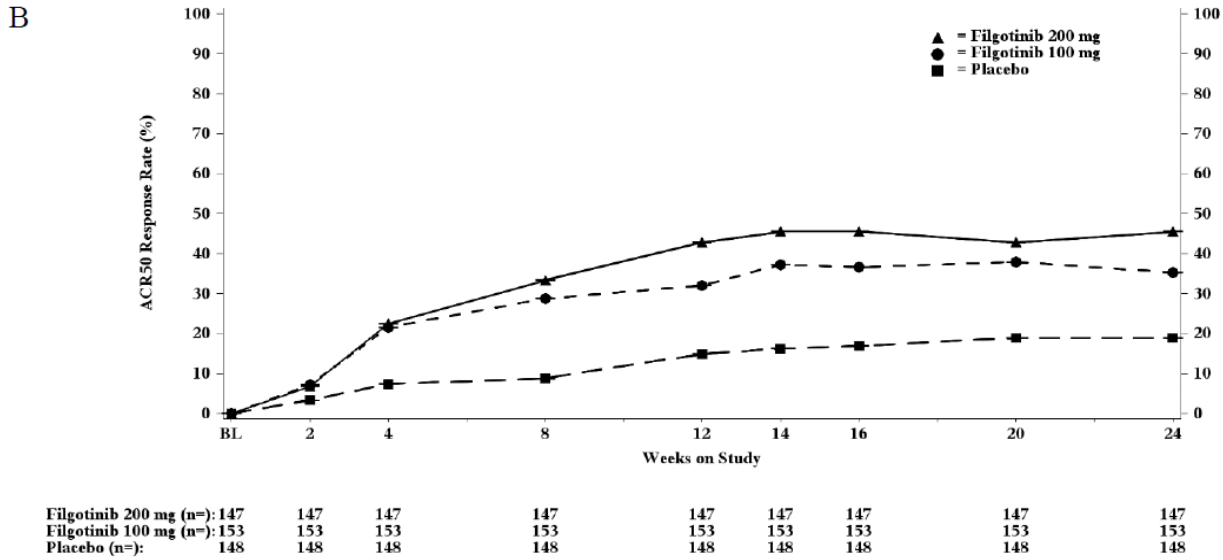
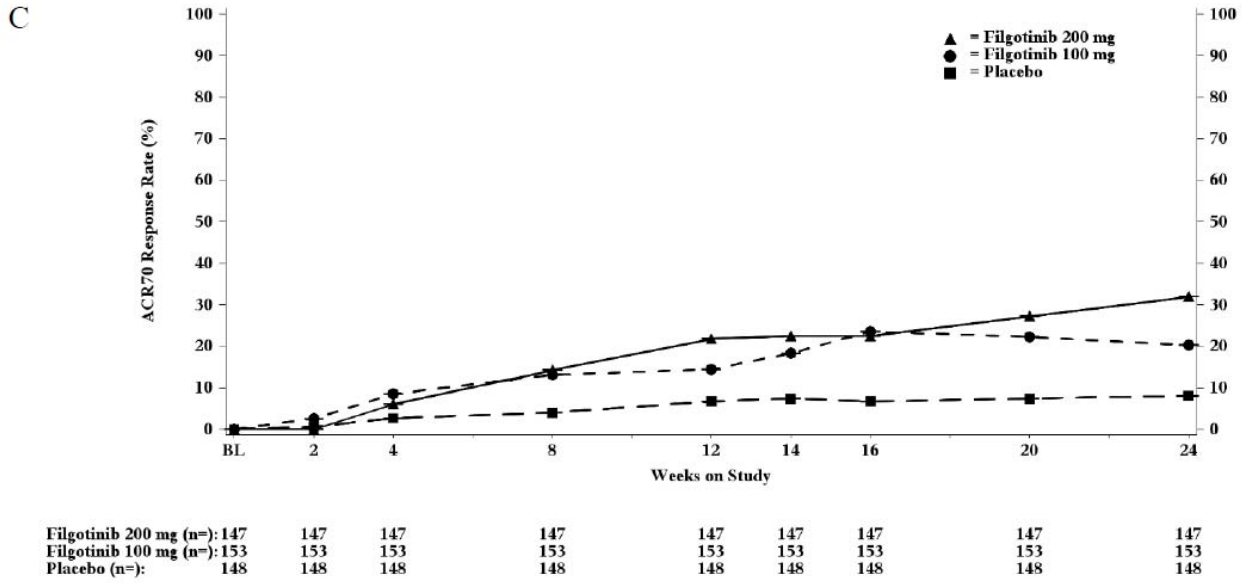


Figure 9. ACR70 Response Rates by study visit week (NRI; Full Analysis Set)



Proportion of subjects who achieved DAS28-CRP <2.6 (remission)

At week 12, the proportion of patients achieving DAS28-CRP <2.6 was statistically significantly higher in the filgotinib 200mg (24.8% [16.7%, 31.8%]) and filgotinib 100mg (28.5% [20.5%, 36.4%]) groups compared with placebo (9.4% [3.9%, 14.8%]) (p=0.001 and p <0.001, respectively).

Similarly, at week 24, the proportion of patients achieving DAS28-CRP <2.6 was statistically significantly higher in the filgotinib 200mg (30.6% [22.8%, 38.4%]) and filgotinib 100mg (26.1% [18.9%, 33.4%]) groups compared with placebo (12.2% [6.6%, 17.8%]) (p<0.001 and p=0.003, respectively).

Proportion of subjects who achieved DAS28-CRP ≤3.2 (LDA)

At week 12, the proportion of patients achieving DAS28-CRP ≤3.2 was statistically significantly higher in the filgotinib 200mg (40.8% [32.5%, 49.1%]) and filgotinib 100mg (37.3% [29.3%, 45.2%]) groups compared with placebo (15.5% [9.4%, 21.7%]) (p <0.001 for both).

Similarly, at week 24, the proportion of patients achieving DAS28-CRP ≤3.2 was statistically significantly higher in the filgotinib 200mg (48.3% [39.9%, 56.7%]) and

filgotinib 100mg (37.9% [29.9%, 45.9%]) groups compared with placebo (20.9% [14.1%, 27.8%]) (p <0.001 and p=0.001 respectively).

EULAR response

At week 12, filgotinib 200mg (42.6%) and filgotinib 100mg (40.9%) demonstrated a higher percentage of patients achieving a good EULAR response compared with placebo (18.0%).

At week 24, filgotinib 200mg (57.9%) and filgotinib 100mg (52.3%) demonstrated a higher percentage of patients achieving a good EULAR response compared with placebo (35.2%).

Change from baseline in HAQ-DI (physical function)

At week 12, a statistically significantly greater mean change from baseline in HAQ-DI was shown in the filgotinib 200mg (−0.55 [-0.61, -0.40]) and filgotinib 100mg (−0.48 [-0.56, -0.35]) groups compared with placebo (−0.23 [-0.30, -0.08]) (p <0.001 for both).

Key secondary endpoints in FINCH 2 are summarised in Table 11.

Table 11. Summary of secondary efficacy outcomes, FINCH 2

Efficacy assessment	Time point	Filgotinib QD dose groups		Placebo + cDMARDs (n=148)
		200 mg + cDMARD(s) (n=147)	100 mg + cDMARD(s) (n=153)	
Change from baseline in the HAQ-DI score (mean change, SD) (95%CI)	week 12	-0.55 (0.590) *** [-0.61, -0.40]	-0.48 (0.602) *** [-0.56, -0.35]	-0.23 (0.547) [-0.30, -0.08]
EULAR response %	week 12	42.6	40.9	18.0
	week 24	57.9	52.3	35.2
Proportion of patients who achieved DAS28-CRP ≤3.2 (%)	week 12	40.8*** [32.5%, 49.1%]	37.3*** [29.3%, 45.2%]	15.5 [9.4%, 21.7%]
	week 24	48.3*** [39.9%, 56.7%]	37.9*** [29.9%, 45.9%]	20.9 [14.1%, 27.8%]
Change from baseline in SF-36 PCS score mean change, [95%CI] (SD)	week 12	[redacted]	[redacted]	[redacted]
	week 12	24.3*** [16.7%, 31.8%]	28.5*** [20.5%, 36.4%]	9.4 [3.9%, 14.8%]

Proportion of patients who achieved DAS28-CRP <2.6 (%) [95%CI]	week 24	30.6*** [22.8%, 38.4%]	26.1** [18.9%, 33.4%]	12.2 [6.6%, 17.8%]
Change from baseline in FACIT-fatigue score (mean change, [95%CI] (SD)	week 12	[redacted]	[redacted]	[redacted]
Change from Baseline in Subject's pain assessment mean [95%CI] (SD)	week 12	[redacted]	[redacted]	[redacted]

*P<0.05; **P<0.01; ***P<0.001; versus placebo.
cDMARD=conventional synthetic disease-modifying antirheumatic drug; DAS28-CRP=Disease Activity Score based on 28 joints and C reactive protein value; FACIT=Functional Assessment of Chronic Illness Therapy; HAQ-DI=Health Assessment Questionnaire-Disability Index; placebo=placebo; QD=once per day; SD=standard deviation; SF-36 PCS=36-item Short Form Health Survey Physical Component Summary. SOURCE: Gilead Data on File. FINCH 2 CSR. 2019 (68)

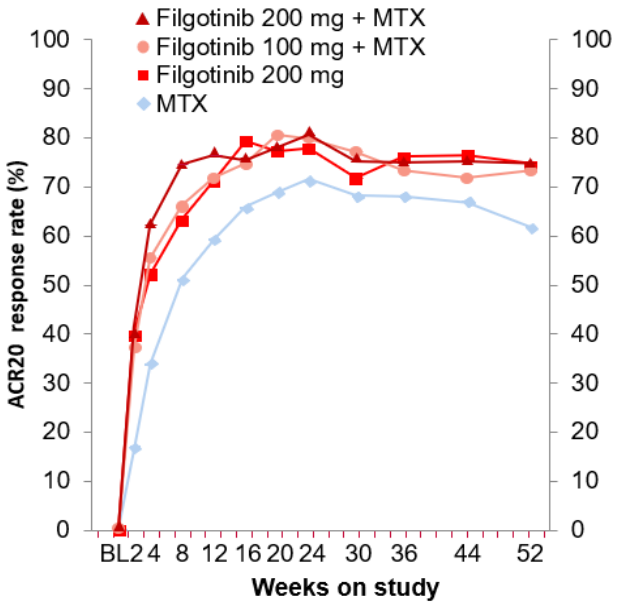
2.6.3 FINCH 3

FINCH 3 (69) met its primary endpoint, with study results demonstrating the superiority of filgotinib 200mg + MTX over MTX monotherapy in ACR20 response at week 24 (81.0% [77.1%, 84.9%] and 71.4% [66.9%, 75.9%] respectively) (p<0.001). ACR20 response rate at week 24 was numerically higher for filgotinib 200mg monotherapy (78.1% [72.3%, 83.9%]) as compared to MTX monotherapy (p=0.058). Filgotinib 200mg monotherapy demonstrated statistically significant improvements over MTX monotherapy for ACR50 and ACR70 responses at week 24, as well as for the proportions of patients who achieved remission measured by DAS28-CRP <2.6 (54.1% [49.2%, 59.0%] versus 29.1% [24.6%, 33.6%] for MTX monotherapy [p<0.001]), change from baseline in radiographic progression mTSS (0.21 versus 0.51 (mean−0.29 [−0.61, 0.02]) for MTX monotherapy [p=0.068]) and for the change in physical function HAQ-DI score (-0.94 [-1.06, -0.93] versus -0.79 [-1.06, -0.93] for MTX monotherapy[p<0.001]).

Figure 10,

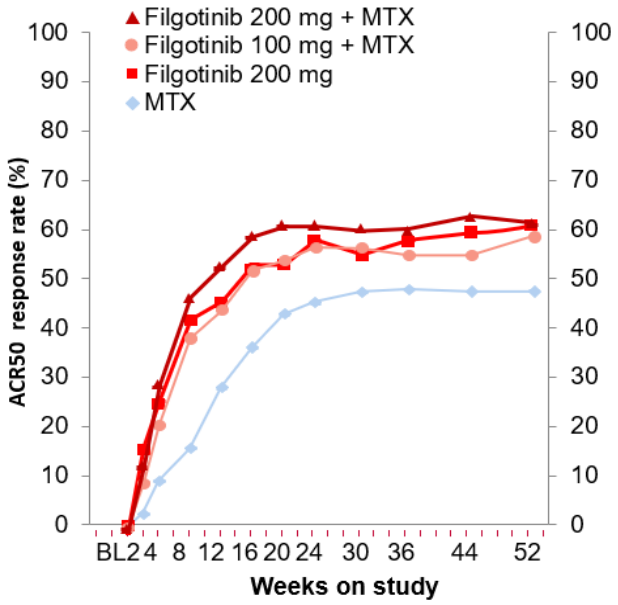
Figure 11 and Figure 12 show ACR20, ACR50 and ACR70 over time. These demonstrate filgotinib's rapid onset of action, as well as the maintenance response across the 52-week study period.

Figure 10. ACR20 response rates by visit through week 52, Full analysis set



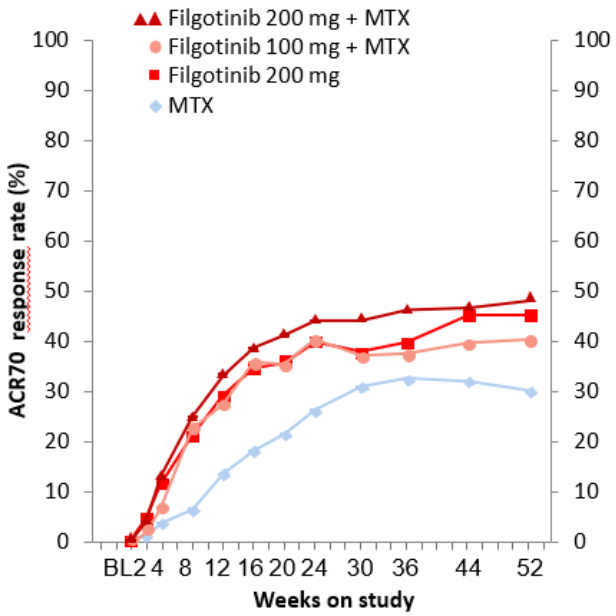
ACR, American College of Rheumatology, MTX, methotrexate

Figure 11. ACR50 response rates by visit through week 52, Full analysis set



ACR, American College of Rheumatology, MTX, methotrexate

Figure 12. ACR70 response rates by visit through week 52, Full analysis set



ACR, American College of Rheumatology, MTX, methotrexate

ACR 20/50/70 response rates for filgotinib monotherapy compared to MTX monotherapy

ACR20 response rates were higher in the filgotinib 200mg monotherapy group compared with the MTX monotherapy group at all study visits starting at week 2 through week 52, with statistically significantly higher response rates at these visits, except at weeks 24 and 30. For ACR50 response, filgotinib 200mg monotherapy (58.1% [51.2%, 65.0%]) also demonstrated superiority compared with MTX monotherapy (45.7% [40.8%, 50.6%]), (p=0.003). The superiority of filgotinib 200mg monotherapy (40.0% [33.1%, 46.9%]) compared with MTX monotherapy (26.0% [21.6%, 30.3%]); was demonstrated again for ACR70 (p<0.001).

ACR 20/50/70 response rates for filgotinib monotherapy and filgotinib combination therapy

The study was not powered to compare statistical differences across the filgotinib combination and monotherapy arms. However, a similar proportion of patients on filgotinib 200mg monotherapy (78.1% [72.3%, 83.9%]) and filgotinib 200g combination therapy (81.0% [77.1%, 84.9%]) achieved ACR20 at week 24. For ACR50, filgotinib

200mg monotherapy (58.1% [51.2%, 65.0%]) also showed a numerically comparable response to filgotinib 200mg combination therapy (61.5% [56.7%, 66.3%]). Finally, for ACR70 at week 24, filgotinib 200mg monotherapy (40.0% [33.1%, 46.9%]) also demonstrated a numerically comparable response to filgotinib 200mg combination therapy (43.8% [38.9%, 48.6%]).

Key secondary endpoints in FINCH 3 are summarised in Table 12.

Table 12. Summary of secondary efficacy outcomes, FINCH 3

Efficacy assessment	Time point	Filgotinib 200 mg + MTX (n=416)	Filgotinib 100 mg + MTX (n=207)	Filgotinib 200 mg monotherapy (n= 210)	MTX monotherapy (n=416)
Change from baseline in HAQ-DI, mean (SD)	week 24	−0.94 *** [-1.06, -0.93] (0.722)	−0.90 (0.675) –[1.01, -0.84] **	−0.89 (0.631) *# [-0.99, -0.82]	−0.79 (0.634) [-0.86, -0.74]
EULAR response	week 24	75.7	66.8	68.9	50.5
DAS28-CRP <2.6, %	week 24	54.1*** [49.2%, 59.0%]	42.5*** [**35.5%, 49.5%]**	42.4***# [35.5%, 49.3%]	29.1 [24.6%, 33.6%]
Change from baseline in mTSS, mean (SD)	week 24	0.21 (1.682) **– [**0.14, 0.40]	0.22 (1.530) –[0.21, 0.48]	−0.04 (1.710) **# [-0.47, 0.24]	0.51 (2.892) [0.17, 0.71]
Change from baseline in SF-36, mean (SD)	week 24	12.3 ***# [11.8, 13.6] (8.89)	11.1 *# [10.2, 12.6] (9.00)	10.4 [9.5, 11.8] (9.09)	9.7 [8.9, 10.7] (8.62)
Change from baseline in FACIT-Fatigue score, mean (SD)	week 24	10.6 10.2, 12.4] (11.50)	11.4 [9.9, 12.8] (11.26)	10.2 [8.9, 11.8] (11.37)	10.1 [8.9, 11.1] (11.19)
Change from Baseline in Subject's pain assessment mean (SD	week 24	-41 *** [-45, -39] (28.0)	-37 [-41, -34] (27.8)	-39 [-42, -35] (26.1)	-34 [-37, -31] (27.6)

*P<0.05; **P<0.01; ***P<0.001; versus MTX monotherapy. #P value is nominal.
DAS28-CRP=Disease Activity Score based on 28 joints and C reactive protein value; FACIT=Functional Assessment of Chronic Illness Therapy; HAQ-DI=Health Assessment Questionnaire-Disability Index; mTSS=modified total Sharp score; MTX=methotrexate; SD=standard deviation; SF-36 PCS=36-item Short Form Health Survey Physical Component Summary.
SOURCE: Gilead Data on File. FINCH 3 CSR. 2019 (69)

B.2.7 Subgroup analysis

A post-hoc subgroup analysis of FINCH 1 was conducted for patients with moderate disease activity at baseline (as defined by DAS28 score 3.2 to 5.1 inclusive at baseline). Filgotinib was compared with the corresponding subgroup of patients receiving comparator treatments (i.e. adalimumab and placebo). This analysis was

conducted only in FINCH 1 to allow separate analysis of patients with moderate disease activity with inadequate response to cDMARD and are naïve to bDMARD and JAK inhibitors in the economic model. In total, [redacted] patients [redacted] in FINCH 1 had moderate disease activity at baseline.

B.2.7.1 Baseline characteristics

Baseline characteristics for all treatment arms in the moderately active RA subgroup are presented in Table 13. Overall, the baseline characteristics of the patients in the moderate subgroup analysis are similar to the overall population, mostly female [redacted] with an average age of [redacted] years, and an average duration of RA of [redacted] years.

Table 13. Baseline characteristics for the moderate RA subgroup in the FINCH 1 trial (SAS)

Parameter	Filgotinib 200mg + MTX (n=104)	Filgotinib 100mg + MTX (n=121)	Adalimumab + MTX (n=72)	Placebo + MTX (n=128)	Total (n=425)
Age (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of RA (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
hsCRP (mg/L), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RF-positive, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 cDMARD, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥2 cDMARDs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
bDMARD-naïve, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DAS28 (CRP), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SJC66, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TJC68, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SGA (mm), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGA (mm), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain (mm), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

bDMARD, biologic disease-modifying antirheumatic drug; cDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28 (CRP), Disease Activity Score for 28 joints with C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; hsCRP, high sensitivity C-reactive protein; placebo, placebo; PGA, Physician's Global Assessment of Disease Activity; RA, rheumatoid arthritis; RF, rheumatoid factor; SAS, safety analysis set; SD, standard deviation; SGA, Subject's Global Assessment of Disease Activity; SJC66, swollen joint count based on 66 joints; TJC66, tender joint count based on 68 joints.

B.2.7.2 Moderate subpopulation – Efficacy results

The results of the analyses for the moderate subpopulation are presented in the sections below. For a range of endpoints, the subgroup analyses demonstrated that results for the overall moderately to severely active population, and the moderate sub-population were comparable.

ACR20/50/70 at week 12

At week 12, results showed that for filgotinib 200mg, a statistically significantly higher proportion of patients achieved ACR20 response compared with patients receiving placebo in the moderate subgroup ([redacted]) and a numerically higher proportion of patients than for adalimumab ([redacted]). Additionally, for filgotinib 100mg, a statistically significantly higher proportion of patients achieved ACR20 response compared with placebo ([redacted]) and a numerically higher proportion of patients than for adalimumab ([redacted] versus [redacted]). Full results, including ACR50 and ACR70 at week 24 are shown in Figure 14 below.

At week 12, results showed that for both filgotinib 200mg and filgotinib 100mg, a statistically significantly higher proportion of patients achieved ACR50 response compared with patients receiving placebo in the moderate subgroup ([redacted] for both). In the comparison with adalimumab, a numerically comparable proportion of patients achieved ACR50 response, for both filgotinib 200mg ([redacted]), and filgotinib 100mg ([redacted]).

At week 12, results showed that for both filgotinib 200mg and filgotinib 100mg, a statistically significantly higher proportion of patients achieved ACR70 response compared with patients receiving placebo in the moderate subgroup ([redacted]). In the comparison with adalimumab, a numerically

comparable proportion of patients achieved ACR70 response, for both filgotinib 200mg and filgotinib 100mg ([redacted]).

When compared with the overall moderately to severely active population in FINCH 1, at week 12, filgotinib 200mg showed comparable ACR20, 50 and 70 response rates in the moderate subgroup ([redacted] respectively), indicating that filgotinib is similarly effective in both populations.

Figure 13 ACR20, ACR50 and ACR70 responses at week 12 – Moderate disease activity subgroup

ACR20/50/70 at week 24

At week 24, results showed that for filgotinib 200mg, a statistically significantly higher proportion of patients achieved ACR20 response compared with patients receiving placebo in the moderate subgroup ([redacted]) and a numerically

higher proportion of patients than for adalimumab ([redacted]). Additionally, for filgotinib 100mg, a statistically significantly higher proportion of patients achieved ACR20 response compared with placebo ([redacted]) and a numerically higher proportion of patients than for adalimumab ([redacted] versus [redacted]). Full results, including ACR50 and ACR70 at week 24 are shown in Figure 14 below.

At week 24, results showed that for both filgotinib 200mg and filgotinib 100mg, a statistically significantly higher proportion of patients achieved ACR50 response compared with patients receiving placebo in the moderate subgroup ([redacted]). In the comparison with adalimumab, a numerically comparable proportion of patients achieved ACR50 response, for both filgotinib 200mg ([redacted]), and filgotinib 100mg ([redacted]).

At week 24, results showed that for both filgotinib 200mg and filgotinib 100mg, a statistically significantly higher proportion of patients achieved ACR70 response compared with patients receiving placebo in the moderate subgroup ([redacted]). In the comparison with adalimumab, a numerically comparable proportion of patients achieved ACR70 response, for both filgotinib 200mg and filgotinib 100mg ([redacted]).

When compared with the overall moderately to severely active population in FINCH 1, at week 24, filgotinib 200mg showed comparable ACR20, 50 and 70 response rates in the moderate subgroup ([redacted]

[redacted]

[redacted] respectively), indicating that filgotinib is similarly effective in both populations.

Figure 14. ACR20, ACR50 and ACR70 at week 24 – Moderate disease activity subgroup

ACR20/50/70 at week 52

At week 52, results showed that for both filgotinib 200mg and filgotinib 100mg, a numerically comparable proportion of patients achieved ACR20 response compared with patients receiving adalimumab in the moderate subgroup ([redacted]). For filgotinib 200mg and filgotinib 100mg, a numerically comparable proportion of patients also achieved ACR50 compared with adalimumab ([redacted]), and ACR70 compared with adalimumab ([redacted]).

When compared with the overall moderately to severely active RA population in FINCH1, at week 52, filgotinib 200mg showed comparable ACR20, 50 and 70

response rates in the moderate subgroup ([redacted]), indicating that filgotinib is similarly effective in both populations.

DAS28 (CRP) <2.6 (remission) at week 12 and 24

The results of the moderate subgroup analysis for clinical remission (defined by a DAS28-CRP <2.6) at week 24 showed that for filgotinib 200mg, a [redacted] of patients achieved remission versus placebo ([redacted]) and a numerically higher proportion of patients achieved remission versus adalimumab ([redacted]). The results for patients achieving a DAS28-CRP <2.6 at both 12 and 24 weeks are presented in Figure 15 below.

When compared with the overall moderately to severely active RA population, a [redacted] of moderate filgotinib 200mg subgroup patients achieved DAS28 (CRP) <2.6 response at week 24 than in the total population ([redacted] See section 2.6.1 for full details.

Figure 15. DAS28 (CRP) <2.6 at weeks 12 & 24 – Moderate disease activity subgroup

[redacted]

DAS28 (CRP) ≤3.2 (LDA) at week 12 and 24

For the secondary outcome, low disease activity (LDA), as defined by DAS28-CRP ≤3.2, for filgotinib 200mg, a [redacted] in the moderate subgroup ([redacted]) and [redacted] of patients achieved LDA versus adalimumab ([redacted]) at 24 weeks.

Detailed results for both filgotinib 200mg and 100mg at week 12 and 24 are shown in Figure 16 below.

Figure 16. DAS28 (CRP) ≤3.2 at weeks 12 & 24 – moderate disease activity subgroup

[redacted]

EULAR at week 24

For the secondary outcome, EULAR response at week 24, filgotinib 200mg demonstrated a [redacted] in the moderate subgroup ([redacted]) and when compared with adalimumab [redacted] at week 24.

When compared with the overall moderately to severely active RA population included in FINCH 1, a [redacted] of moderate filgotinib 200mg subgroup patients

achieved a good EULAR response than in the overall population ([redacted]) at week 24. Detailed EULAR response results at 24 weeks are shown in Table 14 below.

Table 14. EULAR responses at week 24 – moderate disease activity subgroup

Parameter	Filgotinib 200mg (n=104)	Filgotinib 100mg (n=121)	Adalimumab (n=72)	Placebo (n=128)
Week 24, n	[redacted]	[redacted]	[redacted]	[redacted]
Good response	[redacted]	[redacted]	[redacted]	[redacted]
Moderate response	[redacted]	[redacted]	[redacted]	[redacted]
No response	[redacted]	[redacted]	[redacted]	[redacted]

Overall, the efficacy results for the moderate subgroup are comparable to the results of the overall FINCH 1 population presented in B2.6. Sub-population results for patients in FINCH 1 with severely active RA are presented in Appendix E.

B.2.8 Meta-analysis

In order to compare the efficacy of filgotinib to the comparators specified in the NICE scope, a network meta-analysis (NMA) was conducted. Whilst a meta-analysis of RCT's was theoretically feasible, performing a comprehensive NMA allows for a more precise estimation of relative treatment effects, therefore no meta-analysis was performed. Please see section B.2.9 below for details on the NMA.

B.2.9 Indirect and mixed treatment comparisons

A network-meta analysis (NMA) was performed to inform the economic model for the assessment of the cost-effectiveness of filgotinib relative to the other treatments in RA. Studies for this were identified from a systematic literature review using criteria in line with previous NICE appraisals in RA (TA466 (33), TA485 (31) and MTA375 (35), with the final set of studies included in the NMA selected in line with previous NICE appraisals (see Appendix D for full details). In line with the NICE scope, separate NMAs were conducted in the cDMARD-IR and bDMARD-IR populations, with ACR at week 12 and 24, and EULAR at 24 weeks the primary outcomes considered. As the FINCH 1 (cDMARD-IR) and FINCH 2 (bDMARD-IR) trials did not include filgotinib monotherapy arms, an NMA for monotherapy was not feasible. Additionally, studies in RA do not frequently stratify results by moderate and severe disease, rather reporting

results across moderate to severe RA. Therefore, separate NMAs for moderate and severe RA were also not feasible.

B.2.9.1 Search strategy

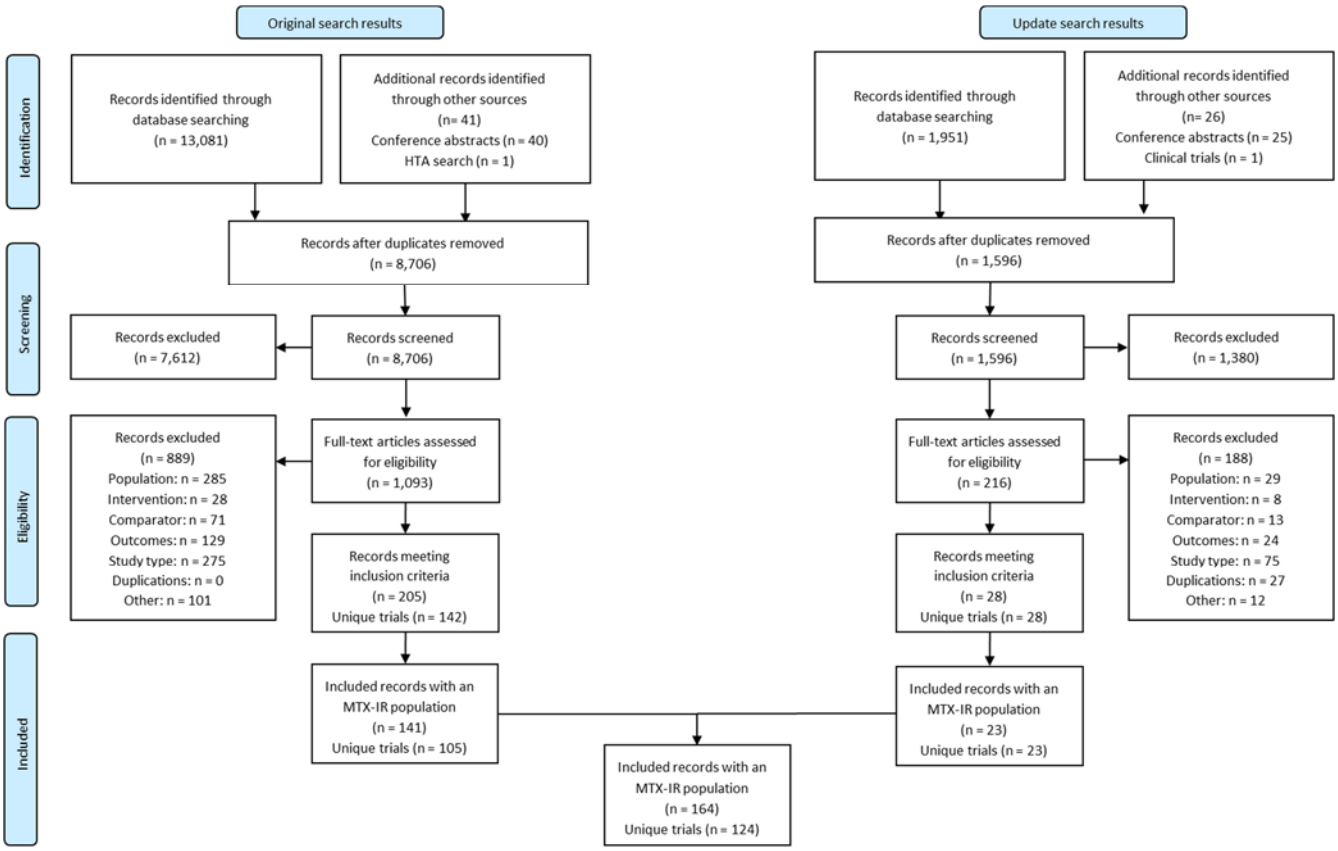
Two systematic literature reviews (SLRs) were conducted, one in the cDMARD-IR population and one in the bDMARD-IR population, across the following databases; MEDLINE, Embase and the Cochrane library (please see Appendix D). The objectives of the SLRs were to identify relevant clinical data from the published literature regarding the clinical effectiveness of filgotinib and other treatments for RA based on the clinical outcomes outlined by the NICE scope. The original review was conducted in August of 2018 with a subsequent update in September 2019. Note that while the SLR considered safety outcomes, safety outcomes frequently focused on the most commonly reported AEs and data for specific AEs tend not be reported consistently across studies, therefore an NMA for safety was not performed.

Studies identified in the SLR were independently assessed by one reviewer in order to ascertain whether they met the pre-defined inclusion and exclusion criteria for the review based on the population, intervention, comparator, outcomes and study design (PICOS). The PICOS criteria was designed to align with the following NICE appraisals: TA466 (33), TA485 (31) and MTA375 (35), and is detailed in Appendix D.

B2.9.2 Trials included in the SLR: cDMARD-IR

Overall, a total of 124 unique studies were eligible for inclusion across the original review and subsequent update (conducted on the 18th September 2019) for cDMARD-IR patients. A PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) diagram (Figure 17) shows the overall flow of studies across the original review and update.

Figure 17. PRISMA flow diagram for the clinical SLR for the cDMARD-IR population

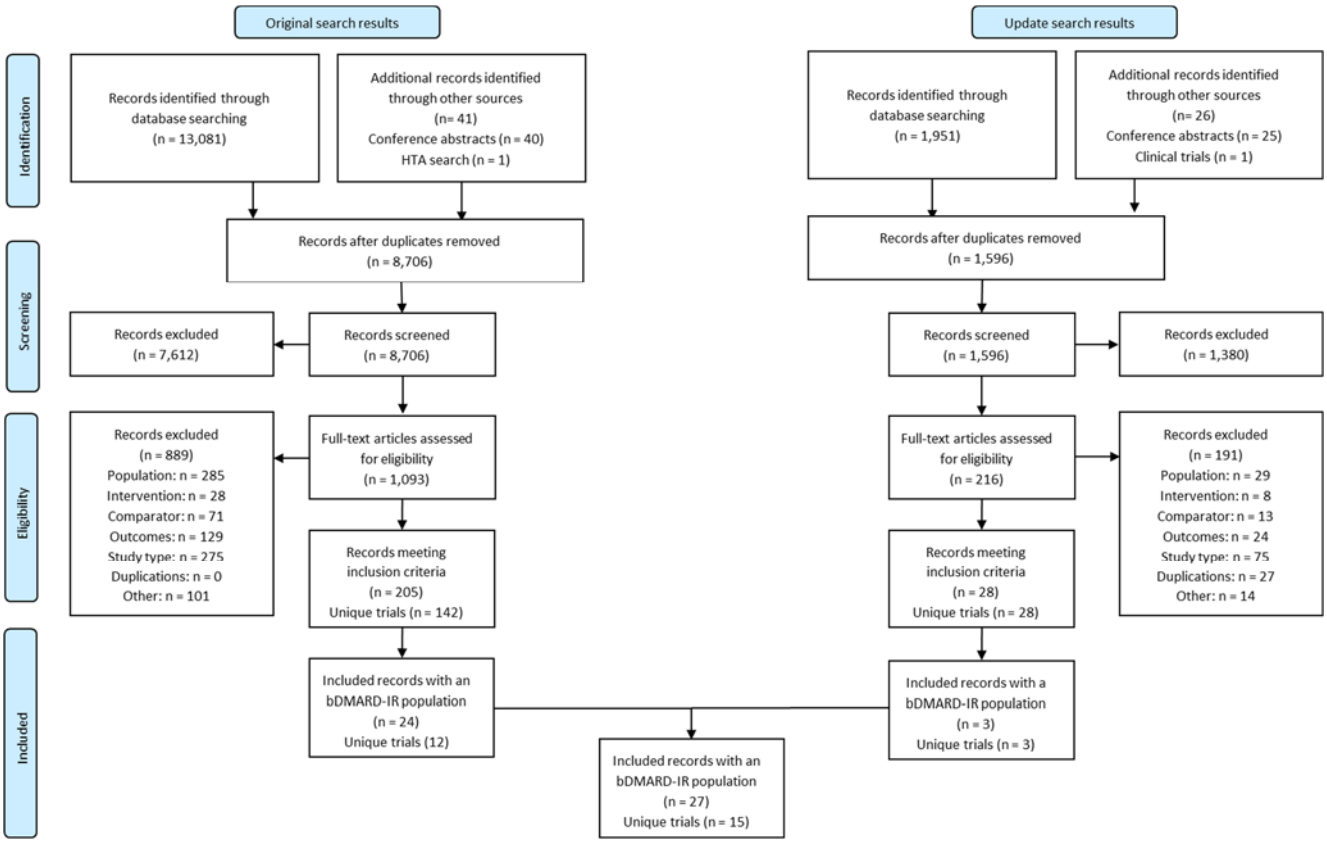


B2.9.3 Trials included in the SLR: bDMARD-IR

In total, 27 publications representing 15 unique trials were identified by the SLR, as presented in the PRISMA diagram in

Figure 18.

Figure 18. PRISMA flow diagram for the clinical SLR for the bDMARD-IR population



B2.9.4 Studies selected for the NMA

To further refine the results of the SLR to more closely meet the requirements of the decision problem and produce relevant networks, several studies from each SLR were excluded in the NMA. The list of studies excluded from each NMA along with associated reasons are available in Appendix D.

The final number of studies included in each NMA are shown below:

- **cDMARD-IR population:** A total of 50 unique trials from the 124 unique trials identified in the SLR were included, with 73 studies excluded.
- **bDMARD-IR population:** A total of 10 unique trials in the final networks from the 15 identified in the SLR were included, with 5 studies excluded.

A summary of the studies included in the evidence networks for each outcome in the cDMARD-IR population is presented in Table 15 and for the bDMARD-IR population

in Table 16 below. The list of studies excluded from the NMA along with the reasons for exclusions can be found in Appendix D.

Table 15: Summary of studies included for each NMA outcome - cDMARD-IR

Trial	Treatment	ACR 12-week inclusion	ACR 24-week inclusion	EULAR 24-week inclusion
Abe et al. (72)	IFX (3mg/kg) +cDMARDs	✓	×	×
	cDMARDs	✓	×	×
AIM (73)	ABT (10mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
ATTEST, (NCT00095147) (74)	ABT	×	✓	×
	IFX (3mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
Baek et al. (75)	TCZ (8mg/kg)	×	✓	✓
	cDMARDs	×	✓	✓
Beals et al. (76)	IFX (3mg/kg) +cDMARDs	✓	×	×
	cDMARDs	✓	×	×
Chen et al. (77)	ADA (40mg/kg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
Cohen et al. (78)	ANK (100mg) +cDMARDs	×	✓	×
	cDMARDs	×	✓	×
DANCER (79) (80)	RTX (1000mg)	×	✓	✓
	cDMARDs	×	✓	✓
DARWIN 1 (81)	FIL (100mg) + cDMARDs	✓	×	×
	FIL (200mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
Etanercept 309 (82)	ETN + intensive cDMARDs	×	✓	×
	cDMARDs	×	✓	×
EXXELERATE (83)	CZP + cDMARDs	✓	×	×
	ADA (40mg/kg) + cDMARDs	✓	×	×
	FIL (100mg)/ (200mg) +	✓	✓	✓

Trial	Treatment	ACR 12-week inclusion	ACR 24-week inclusion	EULAR 24-week inclusion
FINCH 1	cDMARDs			
	ADA + cDMARDs	✓	✓	✓
	cDMARDs	✓	✓	✓
GOFURTHER (84-86)	GLM (2mg/kg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
J-RAPID (NCT00791999) (87)	CZP (400mg) + cDMARDs	✓	×	✓
	CZP (200mg) + cDMARDs	✓	×	✓
	cDMARDs	✓	×	✓
KAKEHASI (88, 89)	SARI (200mg) +cDMARDs	✓	✓	×
	SARI (150mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×
Keystone et al. (90)	ADA (40mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
Kim et al. (91)	ADA (40mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
Kremer et al. (92)	Intensive cDMARDs	×	✓	×
	cDMARDs	×	✓	×
Lim et al. (93)	TCZ (8mg/kg)	×	✓	✓
	cDMARDs	×	✓	✓
MOBILITY (94-96)	SARI (150mg) + cDMARDs	×	✓	×
	SARI (200mg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
NCT00345748 (97)	ABT (10mg/kg) + cDMARDs	×	✓	×
	ABT (2mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
NCT00405275 (98)	ETN (50mg) + HCQ (400mg)	×	✓	×
	SSZ (1-2mg) + HCQ (400mg)	×	✓	×

Trial	Treatment	ACR 12-week inclusion	ACR 24-week inclusion	EULAR 24-week inclusion
NCT00413660	TOF (5mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
NCT00544154 (99)	CZP (400mg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
NCT00603512 (100)	TOF (5mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
NCT00993317 (101)	CZP (200mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×
I4V-MC-JADA (NCT01185353) (102)	BARI (4mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
NCT01313208 (103)	ETN (50mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
NCT01554696 (104)	PFT (25, 50, 100, 150mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
NCT01710358 (105, 106)	BARI (4mg) + cDMARDs	✓	✓	×
	ADA (40mg/kg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×
NCT01758198 (107)	ABT (10mg/kg) +cDMARDs	×	✓	×
	cDMARDs	×	✓	×
NCT02557100	ADA (40mg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
OPTION (108)	TCZ (8mg/kg) + cDMARDs	×	✓	✓
	TCZ (4mg/kg) + cDMARDs	×	✓	✓
	cDMARDs	×	✓	✓
RA-BUILD (109)	BARI (4mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×

Trial	Treatment	ACR 12-week inclusion	ACR 24-week inclusion	EULAR 24-week inclusion
RA0025 (110)	CZP + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
RA-BALANCE (111)	BARI (4mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
RAJ3 (112)	PFT (50mg) + cDMARDs	✓	×	×
	PFT (100mg) + cDMARDs	✓	×	×
	PFT (150mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
RAJ4 (112)	PFT (100mg) + cDMARDs	✓	×	×
	PFT (150mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
RAPID 1 (113)	CZP (400mg) + cDMARDs	×	✓	×
	CZP + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
RAPID 2, (NCT00175877) (114)	CZP (400mg) + cDMARDs	×	✓	×
	CZP + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
RA-SCORE(115)	RTX (1000mg) + cDMARDs	×	✓	✓
	cDMARDs	×	✓	✓
SARIL-RA-MOBILITY (116)	SARI (150mg) q2w / qw + cDMARDs	✓	×	×
	SARI (200mg) qw + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
SELECT-COMPARE (117)	UPA (15mg) + cDMARDs	✓	✓	×
	ADA (40mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×
SELECT-NEXT(118, 119)	UPA (15mg) +cDMARDs	✓	×	×

Trial	Treatment	ACR 12-week inclusion	ACR 24-week inclusion	EULAR 24-week inclusion
	cDMARDs	✓	×	×
SELECT-SUNRISE	UPA (15mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
SERENE (120)	RTX (1000mg) + cDMARDs	×	✓	✓
	cDMARDs	×	✓	✓
Smolen et al.	UPA (15mg) +cDMARDs	✓	×	×
	UPA (30mg) +cDMARDs	✓	×	×
	cDMARDs	✓	×	
Tanaka et al.(121)	BARI (4mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
TOWARD (122)	TCZ (8mg/kg)	×	✓	✓
	cDMARDs	×	✓	✓
Weinblatt et al. (123)	ETN (25mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×

ABT, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; ANK, anakinra; BARI, baricitinib; CRP, C-reactive protein; cDMARDs, conventional synthetic disease modifying anti-rheumatic drug, CZP, certolizumab pegol; DAS28, disease activity score; ETN, etanercept; EULAR, European League Against Rheumatism; FIL, filgotinib; GLM, golimumab; IFX, infliximab; PFT, peficitinib; qw, weekly; q2w, biweekly; RTX, rituximab; SAR, sarilumab; TCZ, tocilizumab; TOF, tofacitinib; tsDMARD, targeted synthetic disease modifying anti-rheumatic drug; UPA, upadacitinib.

Table 16: Summary of studies included for each NMA outcome – bDMARD-IR

Trial	Treatment	ACR 12-week inclusion	ACR 24-week inclusion	EULAR 24-week inclusion
ATTAIN (124)	ABT (10mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
BREVACTA (125)	TCZ (162mg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
FINCH 2 (126)	FIL (100mg) + cDMARDs	✓	✓	✓
	FIL (200mg) + cDMARDs	✓	✓	✓
	cDMARDs	✓	✓	✓

NCT01147341 (127)	CZP (400mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
ORAL-STEP	TOF (5mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
RA-BEACON (128, 129) (130)	BARI (4mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×
RADIATE (131)	TCZ (8mg/kg) + cDMARDs	×	✓	✓
	TCZ (4mg/kg) + cDMARDs	×	✓	✓
	cDMARDs	×	✓	✓
REFLEX (132, 133)	RTX (1000mg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
SELECT-BEYOND (134)	UPA (15mg) + cDMARDs	✓	×	×
	UPA (30mg) + cDMARDs	×	×	×
	cDMARDs	✓	×	×
TARGET (135)	SARI (150mg) + cDMARDs	✓	✓	×
	SARI (200mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×

ADA, adalimumab; BARI, baricitinib; cDMARD, conventional synthetic disease modifying anti-rheumatic drug; CZP, certolizumab pegol; ETN, etanercept; FIL, filgotinib; GLM, golimumab; IFX, infliximab; RTX, rituximab; SARI, sarilumab; TOF, tofacitinib; UPA, upadacitinib

B2.9.5 Evidence networks

Evidence networks for each outcome for the cDMARD-IR and bDMARD-IR populations are presented in the section below.

Both bDMARDs and cDMARDs may be administered as monotherapy or in combination with cDMARDs. As the only evidence available for filgotinib in the FINCH 1 and FINCH 2 studies was in combination with cDMARDs, only combination therapies were included in the NMA.

cDMARD-IR

The evidence network for ACR at weeks 12 and 24 are presented in Figure 19 and Figure 20 below. The analysis network for ACR at week 12 comprised 23 treatments across 27 studies, which were connected via the common comparator of cDMARDs.

Figure 19. ACR at week 12 network geometry for the cDMARD-IR population

ADA, adalimumab; BARI, baricitinib; bid, twice daily; biw, twice weekly; cDMARD, conventional disease modifying anti-rheumatic drug; CZP, certolizumab pegol; ETN, etanercept; FIL, filgotinib; GLM, golimumab; IFX, infliximab; PFT, peficitinib; qd, every day; qw, once weekly; q2w, once every two weeks; SARI, sarilumab; UPA, upadacitinib;

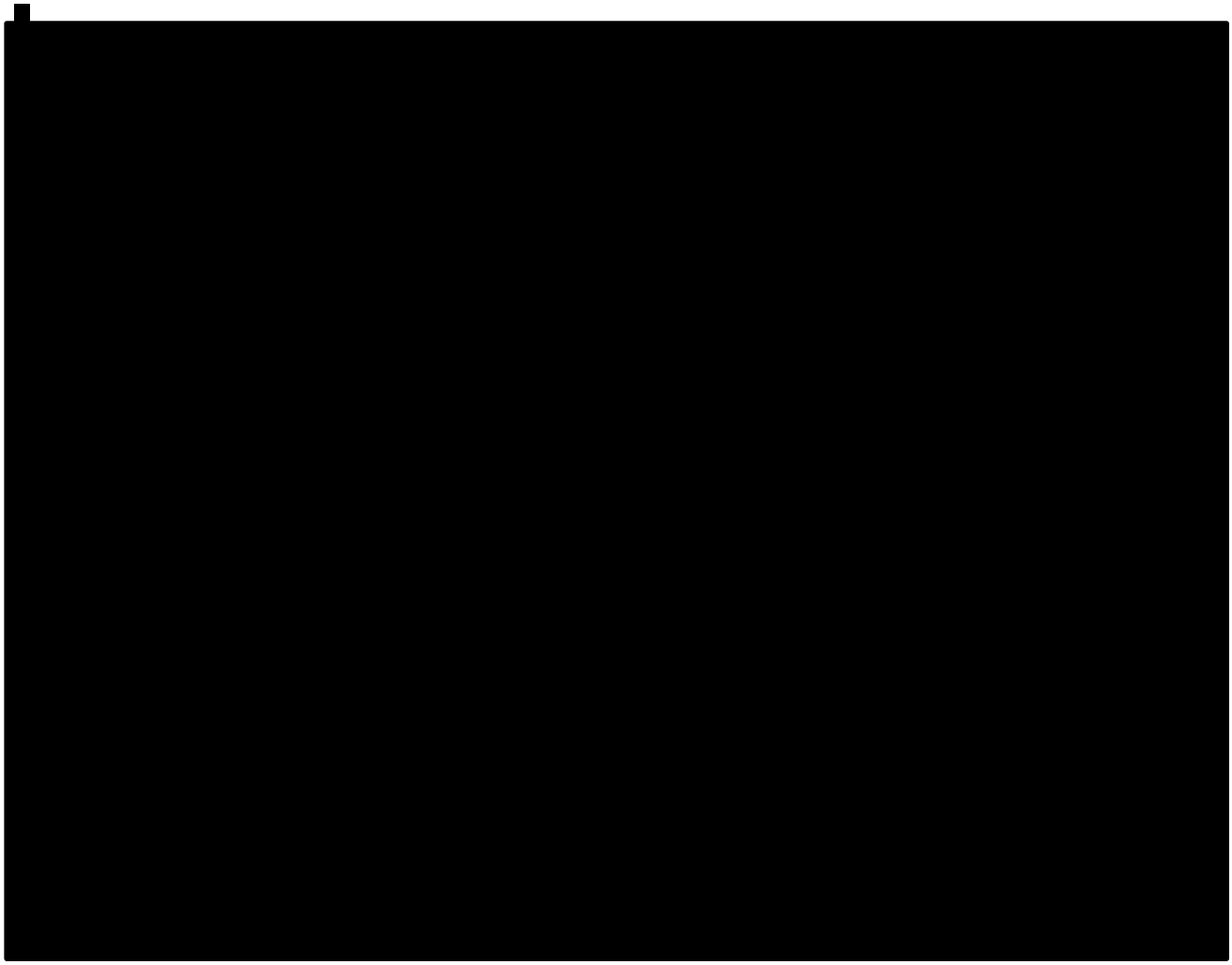
The analysis network for the ACR at week 24 endpoint consisted of 22 treatments across 30 studies, which were connected via the common comparator of cDMARDs.

Figure 20. ACR at week 24 network geometry for the cDMARD-IR population

ABT, abatacept; ADA, adalimumab; ANK, anakinra; BARI, baricitinib; biw, twice weekly; cDMARDs, conventional disease modifying anti-rheumatic drug ; CZP, certolizumab pegol; ETN, etanercept; FIL, filgotinib; IFX, infliximab; qw, once weekly; q2w, every two weeks; q4w, every 4 weeks; RTX, rituximab; SARI, sarilumab; TCZ, tocilizumab; UPA, upadacitinib;

The analysis network for EULAR at 24 weeks consisted of nine treatments across nine studies, which were connected via the common comparator of cDMARDs (as shown in Figure 21 below).

Figure 21. EULAR at week 24 Network geometry for the cDMARD-IR population



ADA, adalimumab; cDMARD, conventional disease modifying anti-rheumatic drug; CZP, certolizumab pegol; FIL, filgotinib; q2w, every two weeks; q4w, every 4 weeks; RTX, rituximab; TCZ, tocilizumab

bDMARD-IR

The analysis network for ACR at week 12 consisted of nine treatment groups across six studies, which were connected via the common comparator of cDMARDs. The network geometry is shown in Figure 22.

However, treatment with CZP in combination with cDMARDs appeared to be an outlier in the analysis, exhibiting extreme values for the relative effectiveness versus alternative therapies. One study in the network included CZP, and as this study was small (there were only 10 patients in the cDMARDs arm, and 27 patients in the CZP arm). It was therefore excluded from the analysis.

Figure 22. ACR at week 12 network geometry for the bDMARD-IR population

BARI, baricitinib; bid, twice daily; cDMARD, conventional disease modifying anti-rheumatic drug; qd, every day; q2w, every two weeks; SARI, sarilumab; TOF, tofacitinib; UPA, upadacitinib;

The analysis network for ACR at week 24 consisted of 11 treatment groups across seven studies, which were connected via the common comparator of cDMARDs. The geometry of the network is displayed in Figure 23.

Figure 23. ACR at week 24 network geometry for the bDMARD-IR population

ABT, abatacept; BARI, baricitinib; cDMARD, conventional disease modifying anti-rheumatic drug; q2w, every two weeks; q4w, every 4 weeks; RTX, rituximab; SARI, sarilumab; TCZ, tocilizumab

The analysis network for EULAR at week 24 consisted of six treatment groups across three studies, which were connected via the common comparator of cDMARDs. The geometry of the network is displayed in Figure 24.

Figure 24. EULAR at week 24 bDMARD-IR – network geometry

cDMARD, conventional disease modifying anti-rheumatic drug; FIL, filgotinib; q4w, every 4 weeks; RTX, rituximab; TCZ, tocilizumab

B2.9.6 Studies excluded from the analysis

Trials identified in the clinical SLR that were not included in the NMA are listed in Appendix D, with the reasons for exclusion.

B2.9.7 Methods and outcomes of included studies

Rationale for choice of outcome measure and scale

<u>Primary outcomes</u>

The outcomes included in the indirect comparison, ACR and EULAR response, are among those which are most commonly reported in clinical trials in RA, including the FINCH Phase 3 programme, are directly relevant to patients and were set out in the

NICE scope. In addition, these endpoints have been used in previous HTA submissions in RA, including MTA375 (136).

- ACR scores (137) are the primary endpoints in the FINCH Phase 3 programme and many other clinical trials in RA. ACR requires both an improvement in tender or swollen joint counts, and in at least three of the following: patients global assessment, physician global assessment, pain-visual analogue scale (VAS), disability/functional questionnaire (the HAQ) and erythrocyte sedimentation rate (ESR) or C-reactive protein. ACR is classified as (138):
    - No response (<20% improvement in ACR criteria)
    - 20% or greater improvement in ACR criteria (ACR20)
    - 50% or greater improvement in ACR criteria (ACR50)
    - 70% or greater improvement in ACR criteria (ACR70)
- EULAR response, classifies patients depending on depending on both the change in value from baseline of the disease activity score in 28 joints (DAS28) following treatment and the actual DAS28 score achieved after treatment (139). It consists of the following categorisations:
    - No response
    - Moderate response
    - Good response

For EULAR response, some studies reported the categories of good and moderate response combined. These outcomes were utilised where moderate and good response were not reported separately.

The majority of studies identified in the clinical SLR reported ACR, whilst EULAR was less commonly reported. However, the cost-effectiveness analysis is based on EULAR response, which is more appropriate for use in Europe and aligns with European treatment guidelines as well as previous TA's. Therefore, EULAR was considered as the endpoint for analysis in order to inform cost-effectiveness modelling, either using direct EULAR comparative effectiveness estimates or ACR estimates converted to

EULAR. ACR responses can be mapped to EULAR responses using the established algorithm used in MTA375 derived from US Veterans Affairs Rheumatoid Arthritis Registry (VARA) data.

Comparative ACR response was assessed at 12 weeks and 24 weeks following study drug initiation in line with the primary efficacy endpoints across the FINCH studies and treatment guidelines. Comparative EULAR response was assessed at 24 weeks in line with EULAR 2019 recommendations (21).

B2.9.8 Populations included

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

B2.9.9 Assessment of heterogeneity in trials included in the NMA

There are several published NMAs in RA, including those carried out to inform previous HTA in this area (e.g. TA247, TA485 and TA466), illustrating the feasibility of forming appropriate networks for comparisons in this indication. Therefore, for the purpose of this NMA, a formal feasibility assessment was not conducted, and the homogeneity of the trials was deemed sufficient to conduct the analysis.

B2.9.10 Risk of bias

A quality assessment of each trial in the cDMARD-IR and bDMARD-IR NMA was completed using the Cochrane Collaborations tool for assessing risk of bias (140) and is provided in Appendix D.

B2.9.11 Methods of analysis

Methodology and primary endpoint

NMA was undertaken to evaluate the comparative effectiveness of filgotinib versus alternative treatments for RA in accordance with published NICE Decision Support Unit (DSU) guidance (141, 142). A Bayesian approach to estimation was adopted whereby posterior distributions for treatment effects were estimated using a

generalised linear model framework to synthesise data from trials identified by the clinical SLR and outcomes reported from the FINCH clinical trials.

The primary endpoints considered in this report are ordinal categorical variables (ACR and EULAR response). Each endpoint is made up of ordered values based on response thresholds, as outlined in section B2.9.7. Endpoints of this type may be analysed either by dichotomising the outcomes into binary variables (henceforth referred to as the 'dichotomised approach'; for example, considering ACR20 in a separate analysis to ACR50 and ACR70) or by conducting an analysis of ACR as a single endpoint (henceforth referred to as the 'single model approach'; i.e. including ACR20, ACR50 and ACR70 in one model). The single model approach utilises a conditional binomial likelihood with probit link (allowing for analysis of an ordered categorical variable), where the dichotomised approach utilises a binomial likelihood with a logit link (focussing on an analysis of each component separately).

Figure 25. Top-line comparison of the advantages of the two modelling approaches to the EULAR and ACR outcomes

Advantages of single model approach	Advantages of the dichotomised approach
Considers ACR / EULAR as a single endpoint: Rather than multiple analyses which consider the separate cut-offs within each endpoint, all cut-offs are considered in a single analysis.	**More intuitive interpretation of treatment effects:** In the single model approach, the effect of treatment with bDMARD 2 versus bDMARD 1 (d_{21}) is to change the probit score by d_{21} standard deviations. In the dichotomised approach, standard odds ratios (ORs) are reported.
Takes account of the ordinal nature of the variable: Both ACR and EULAR are based upon categorisation of variables which are on a continuous scale. The dichotomised approach would not account for the natural ordering and correlations between the categories within the outcome measure.	**Proportional odds assumption:** The single model approach assumes that the treatment effect is the same regardless of cut-off. For example; it is assumed that the treatment effect of a bDMARD on achieving ACR20 to be the same as the treatment effect of achieving ACR50. No such assumption is required as per the dichotomised approach.

ACR, American College of Rheumatology; bDMARD, biologic disease modifying anti-rheumatic drug; EULAR, European League Against Rheumatism.

NICE DSU guidelines have included examples using both single model (141)and dichotomised approaches (142). Specifically, they analyse ACR50 as a binary endpoint (142). However, in previous NICE HTA submissions, the ERG has analysed ACR and EULAR using the single model approach, as the dichotomous approach ignores the natural ordering and correlations between the categories within the outcome measure.

Therefore, analyses considered the single endpoint approach (i.e. all thresholds of ACR and EULAR were included in a single model). Whilst the treatment effect estimates produced by the model are less interpretable than that of a traditional odds ratio, the credible interval for the treatment effects can be interpreted in a similar manner to a log-odds ratio: a credible interval crossing 0 is non-significant. Furthermore, additional model outputs were produced to facilitate interpretation of the results, including calculation of absolute probabilities of achieving the thresholds within the endpoints and relative risks.

Data manipulation was undertaken in R Version 3.4.2 or higher, with WinBUGS version 1.4.3 was utilised for all NMA.

Each analysis consisted of multiple Markov chain Monte Carlo (MCMC) chains, with each chain simulated from different sets of starting values. Vague prior distributions were assumed for all model parameters, in line with NICE DSU guidelines (141). Inferences were made from the posterior distributions of the treatment effects between treatments for outcomes of interest, derived over at least 25,000 iterations following burn in (the iterations to be discarded whilst the chains converge). The number of iterations for burn-in was 25,000 unless additional iterations were required to ensure convergence.

WinBUGS code

WinBUGS version 1.4.3 was used for the NMA with the precise code supplied in Appendix D.

B2.9.12 Choice of model

Both fixed effects and random effects models were considered for each analysis included in the NMA. Absolute model fit was considered through examination of the

total residual deviance, in keeping with NICE DSU guidelines (141). The deviance information criterion (DIC) was used to compare the fit of the different models with the same likelihood (e.g. fixed and random effects models, models with and without covariates), with a difference of <5 considered negligible. The DIC considers the absolute fit of the model, whilst adding a penalty for model complexity (i.e. the effective number of parameters). Lower values of the DIC suggest a more parsimonious model, which informed which models should be given most weight when interpreting the results. The goodness of fit diagnostics for the random and fixed effects models for the base-case network in cDMARD-IR and bDMARD-IR populations is shown in the tables below.

cDMARD-IR population

ACR at 12 and 24 weeks

For ACR at 12 weeks, the random effects model was chosen as the model with which to weight the interpretation of results, as the DIC was smaller in this model (388.353 and 330.142 for the fixed and random effects models, respectively) as shown in Table 17.

The random effects model appeared to fit the data better than the fixed effects model, with the total residual deviance, 261.7, relatively close to the number of data points, 190, included in the analysis

Table 17. Fixed and random-effect model fit statistics in cDMARD-IR for ACR at 12 weeks

Analysis	Data points	Total residual deviance Mean	DIC
Fixed effects	190	337.3	388.353
Random effects	**190**	**261.7**	**330.142**

ACR, American College of Rheumatology; cDMARD-IR, conventional disease modifying anti-rheumatic drug insufficient response; DIC, deviance information criterion

Additionally, for ACR at 24 weeks, the random effects model was chosen as the model with which to weight the interpretation of results, as the DIC was smaller in this model (461.316 and 416.795 for the fixed and random effects models, respectively), as

shown in Table 18. The random effects model also has a lower total residual deviance, which is closer to the number of data points than the fixed effects model.

Table 18. Fixed and random effect model fit statistics in cDMARD-IR for ACR at 24 weeks

Analysis	Data points	Total residual deviance Mean	DIC
Fixed effects	215	408.3	461.316
Random effects	**215**	**348.8**	**416.795**

ACR, American College of Rheumatology; cDMARD-IR, conventional disease modifying anti-rheumatic drug insufficient response; DIC, deviance information criterion

EULAR at 24 weeks

For EULAR at 24 weeks, the fixed effects model was chosen, as the DIC was similar in both models (93.809 and 92.352 for the fixed and random effects models, respectively), as shown in Table 19. Therefore, as the fixed effects model is simpler, this approach informed the base case analysis.

Additionally, the fixed effects model had lower total residual deviance, which is closer to the number of data points than the random effects model.

Table 19. Fixed and random effect model fit statistics in the cDMARD-IR population for EULAR at 24 weeks

Analysis	Data points	Total residual deviance Mean	DIC
Fixed effects	**39**	**71.08**	**92.352**
Random effects	39	75.72	93.809

cDMARD-IR, conventional disease modifying anti-rheumatic drug insufficient response; DIC, deviance information criterion; EULAR, European League Against Rheumatism

bDMARD-IR population

ACR at 12 and 24 weeks

In the bDMARD-IR population, for ACR at 12 weeks, the fixed effects model was chosen as it is the simpler model and as the DIC was similar in both models (59.473 and 59.854 for the fixed and random effects models, respectively), with differences of < 5 considered negligible (Table 20). For ACR at 24 weeks, the fixed model was also

chosen for simplicity in light of similar DIC in both model (85.112 and 85.296 for the fixed and random effects models, respectively) as shown in Table 21. The mean residual deviance is similar for both random and fixed effects models.

Table 20. Fixed and random effect model fit statistics in the bDMARD-IR population for ACR at 12 weeks

Analysis	Data points	Total residual deviance Mean	DIC
Fixed effects	**36**	**45.57**	**59.473**
Random effects	36	45.76	59.854

ACR, American College of Rheumatology; bDMARD-IR, biological disease modifying anti-rheumatic drug insufficient response; DIC, deviance information criterion

Table 21. Fixed and random effect model fit statistics in the bDMARD-IR population for ACR at 24 weeks

Analysis	Data points	Total residual deviance Mean	DIC
Fixed effects	**47**	**66.21**	**85.112**
Random effects	47	66.3	85.296

ACR, American College of Rheumatology; bDMARD-IR, biological disease modifying anti-rheumatic drug insufficient response; DIC, deviance information criterion

EULAR at 24 weeks

For EULAR at 24 weeks, the DIC suggested that there was little difference between the fixed and random effects model in terms of model fit when accounting for model complexity (20.183 for the fixed effects model versus 19.798 for the random effects models). Therefore, the interpretation of point estimates is based upon the simpler, fixed effects model (shown in Table 22). The mean residual deviance is similar for both models.

Table 22. Fixed and random effect model fit statistics in the bDMARD-IR population for EULAR at 24 weeks

Analysis	Data points	Total residual deviance Mean	DIC
Fixed effects	**13**	**11.09**	**20.183**
Random effects	13	10.9	19.798

B2.9.13 Results

Statistics for the posterior distribution of relative effects on the probit scale are reported, including mean, standard deviation (SD), median and 95% credible interval (CrI) for the models (Appendix D), with forest plots for relative effects (chosen model) shown in the sections below.

Similarly, the modelled probabilities of response are reported, as well as relative risks for each level or response, based upon the modelled probabilities (please see Appendix D). The modelled probabilities of response are based on an assumed probability of achieving the first level of response (e.g. ACR20) in the reference treatment group. The assumed probability was based upon conducting a meta-analysis (MA) of responses within the reference treatment arms of included studies, as outlined within NICE DSU guidelines (143).

cDMARD-IR: ACR at 12 weeks

Filgotinib (100mg) showed [redacted] to any treatments other than cDMARDs, were filgotinib 100mg was [redacted]. However, filgotinib 100mg [redacted]

Filgotinib (200mg) also showed [redacted]. Filgotinib (200mg) was [redacted]

For the random effects model, a forest plot of the relative effects to filgotinib (100mg) and filgotinib (200mg) are displayed in Figure 26 and

Figure 27. Modelled probabilities of ACR response for all treatments is reported in

Table 23.

Figure 26. ACR at week 12 for the cDMARD-IR population - forest plot for relative effects to filgotinib (100mg) on the probit scale

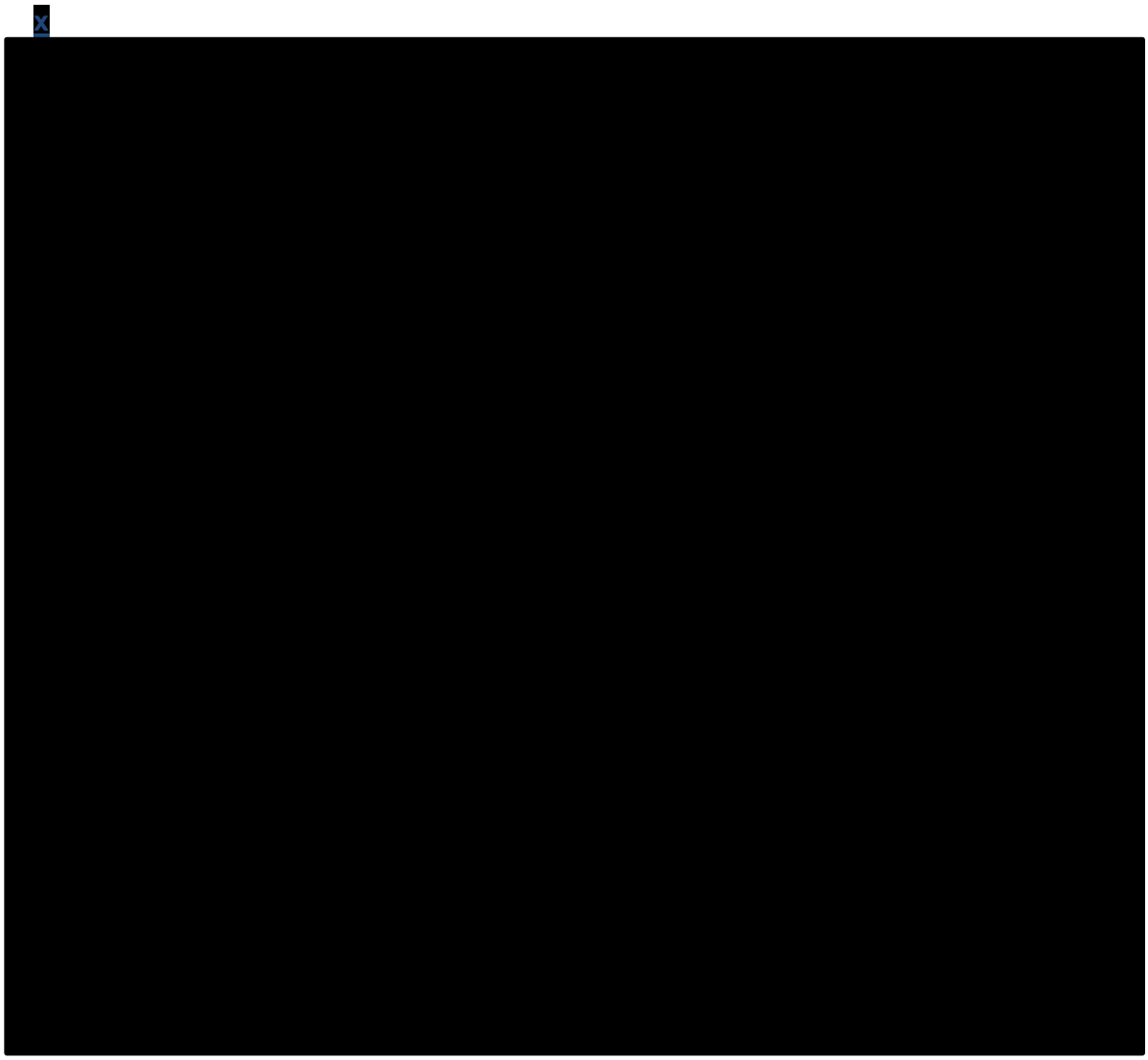


Figure 27. ACR at week 12 for the cDMARD-IR population - forest plot for relative effects to filgotinib (200mg) on the probit scale

Table 23: ACR at week 12 for the cDMARD-IR population - modelled probability of ACR response

Treatment	Modelled probability of response – posterior median (95% CrI)		
	ACR20	ACR50	ACR70
cDMARDs	[redacted]	[redacted]	[redacted]
FIL (100mg) + cDMARDs	[redacted]	[redacted]	[redacted]
FIL (200mg) + cDMARDs	[redacted]	[redacted]	[redacted]
ADA (40mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
BARI (4mg) + cDMARDs	[redacted]	[redacted]	[redacted]
CZP (200mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
CZP (200mg) + cDMARDs	[redacted]	[redacted]	[redacted]
CZP (400mg) + cDMARDs	[redacted]	[redacted]	[redacted]
ETN (50mg qw) + cDMARDs	[redacted]	[redacted]	[redacted]
ETN (25mg biw) + intensive cDMARDs	[redacted]	[redacted]	[redacted]
GLM (2mg/kg) + cDMARDs	[redacted]	[redacted]	[redacted]
IFX (3mg/kg) + cDMARDs	[redacted]	[redacted]	[redacted]
PFT (100mg qd) + cDMARDs	[redacted]	[redacted]	[redacted]
PFT (150mg qd) + cDMARDs	[redacted]	[redacted]	[redacted]
PFT (25mg qd) + cDMARDs	[redacted]	[redacted]	[redacted]
PFT (50mg qd) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (100mg qw) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (150mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (150mg qw) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (200mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
TOF (5mg bid) + cDMARDs	[redacted]	[redacted]	[redacted]

UPA (15mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
UPA (15mg qd) + cDMARDs	[redacted]	[redacted]	[redacted]

ACR: American College of Rheumatology; ADA: adalimumab; BARI: baricitinib; bid: twice per day; biw: twice per week; CrI: credible interval; cDMARDs: conventional synthetic disease modifying anti-rheumatic drug; CZP; certolizumab pegol; ETN: etanercept; FIL: filgotinib; GLM: golimumab; IFX: infliximab; PFT: peficitinib; qd: daily; bid: twice per day; q2w: once every two weeks; qw: once every week; SARI: sarilumab; TOF: tofacitinib; UPA: upadacitinib.

Probability of achieving ACR20 in reference treatment (cDMARDs) based on baseline natural history model as detailed in NICE DSU guidelines TSD5 (143)

cDMARD-IR: ACR at 24 weeks

Filgotinib (100mg) showed [redacted]. Filgotinib was also [redacted] to certolizumab pegol (200mg). Filgotinib (100mg) was [redacted] to all other treatments (Figure 28). Modelled probabilities of ACR response for all treatments is reported in

Table 24.

Filgotinib (200mg) [redacted] However, [redacted] (Figure 28). However, the modelled probabilities of ACR response were very similar for combination therapy of

[redacted] compared with filgotinib (200mg). Full details are shown in

Table 24.

Figure 28. ACR at week 24 for the cDMARD-IR population - forest plot for

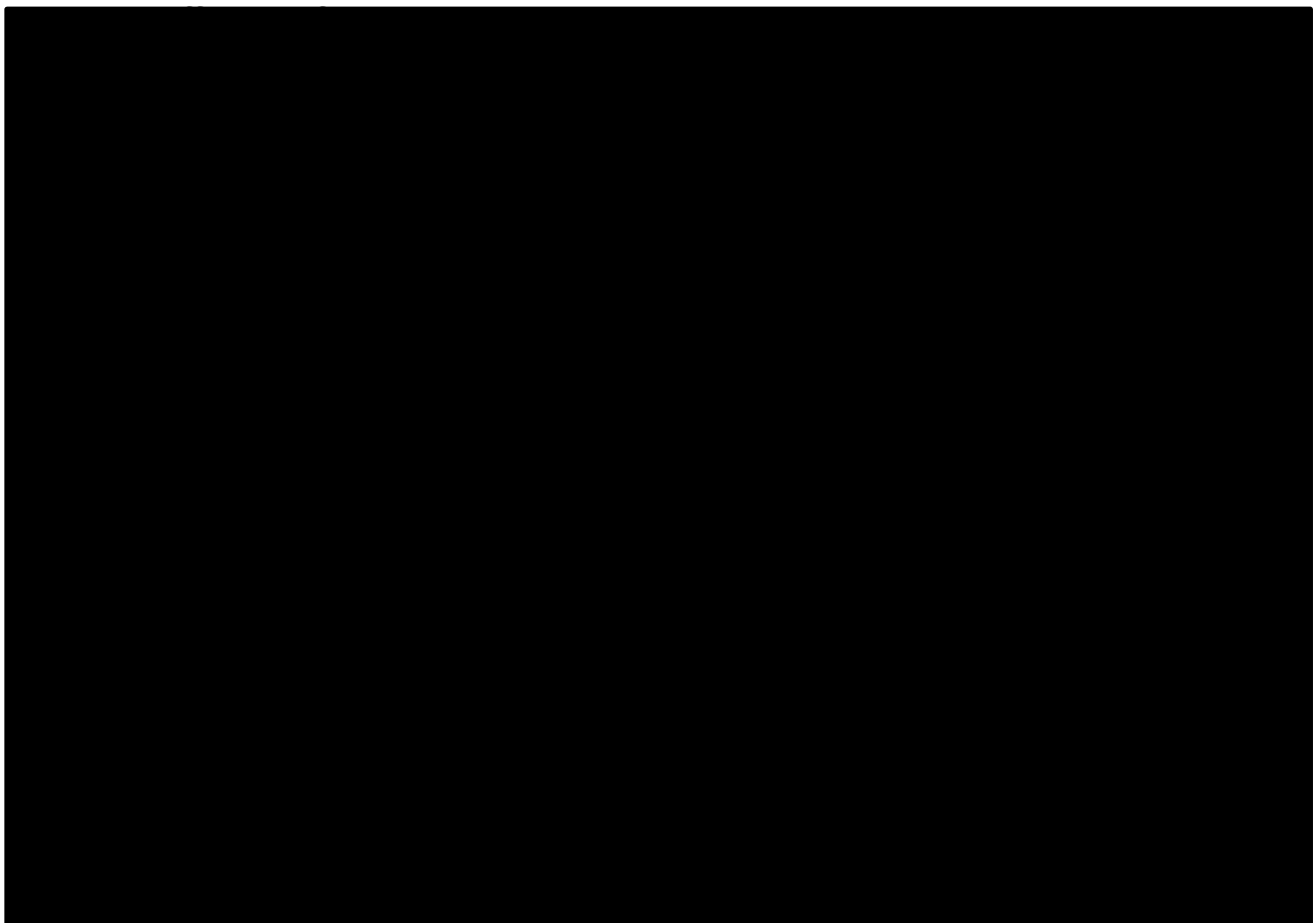


Figure 29. ACR at week 24 cDMARD-IR - forest plot for relative effects to filgotinib (200mg) on the probit scale

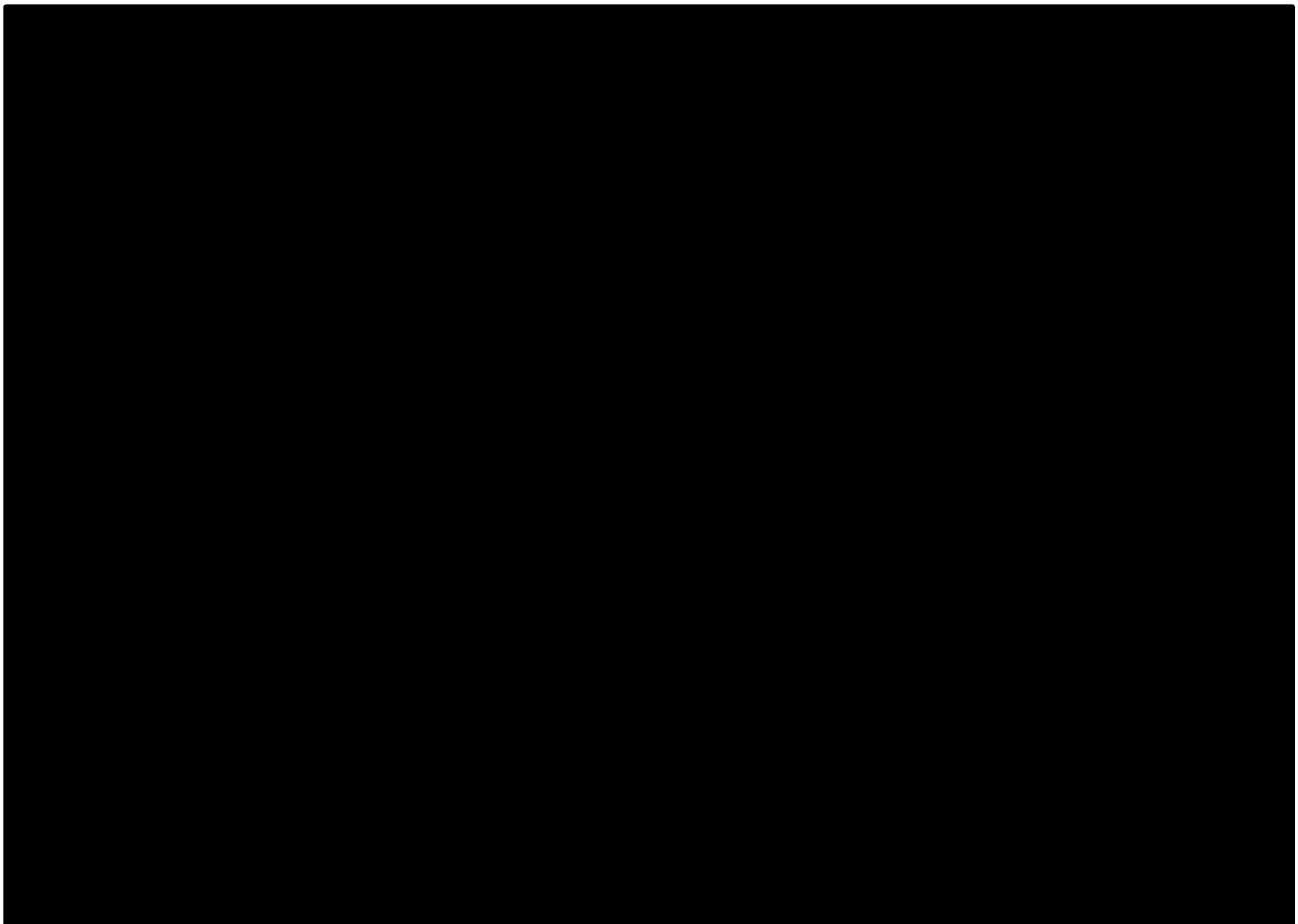


Table 24: ACR at week 24 cDMARD-IR – modelled probability of ACR response

Treatment	Modelled probability of response – posterior median (95% CrI)		
	ACR20	ACR50	ACR70
cDMARDs	[redacted]	[redacted]	[redacted]
FIL (100mg) + cDMARDs	[redacted]	[redacted]	[redacted]
FIL (200mg) + cDMARDs	[redacted]	[redacted]	[redacted]
ABT (10mg/kg) + cDMARDs	[redacted]	[redacted]	[redacted]
ABT (125mg qw) + cDMARDs	[redacted]	[redacted]	[redacted]
ABT (2mg/kg) + cDMARDs	[redacted]	[redacted]	[redacted]
ADA (40mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
ANK (100mg) + cDMARDs	[redacted]	[redacted]	[redacted]
BARI (4mg) + cDMARDs	[redacted]	[redacted]	[redacted]
CZP (200mg q2w) +	[redacted]	[redacted]	[redacted]

cDMARDs	[redacted]	[redacted]	[redacted]
CZP (200mg) + cDMARDs	[redacted]	[redacted]	[redacted]
CZP (400mg) + cDMARDs	[redacted]	[redacted]	[redacted]
ETN (50mg qw) + cDMARDs	[redacted]	[redacted]	[redacted]
ETN (25mg biw) + Intensive cDMARDs	[redacted]	[redacted]	[redacted]
IFX (3mg/kg) + cDMARDs	[redacted]	[redacted]	[redacted]
Intensive cDMARDs	[redacted]	[redacted]	[redacted]
RTX (1000mg) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (150mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (200mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
TCZ (4mg/kg q4w) + cDMARDs	[redacted]	[redacted]	[redacted]
TCZ (8mg/kg q4w) + cDMARDs	[redacted]	[redacted]	[redacted]
UPA (15mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]

ABT: abatacept; ACR: American College of Rheumatology; ADA: adalimumab; ANK: anakinra; BARI: baricitinib; CrI: credible interval; cDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; CZP; certolizumab pegol; ETN: etanercept; FIL: filgotinib; IFX: infliximab; RTX: rituximab; qw: weekly; q2w: once every two weeks; q4w: once every four weeks; SARI: sarilumab; TCZ: tocilizumab; UPA: upadacitinib.

Probability of achieving ACR20 in reference treatment (cDMARDs) based on baseline natural history model as detailed in NICE DSU guidelines TSD5 (143)

cDMARD-IR: EULAR at 24 weeks

Filgotinib (100mg) was [redacted], other than cDMARDs (Figure 30).

Filgotinib (200mg) was [redacted] to adalimumab (40mg q2w) and cDMARDs [redacted] inferior to certolizumab pegol (200mg), certolizumab pegol (400mg) and tocilizumab (8mg/kg) as shown in Figure 30. Filgotinib (200mg) was [redacted] to other combination therapies, [redacted] for rituximab 1000mg and tocilizumab 4mg/kg as shown by the modelled probabilities of response in xTable 25.

Patients in the FINCH 1 study exhibited extremely high levels of response when treated with cDMARDs. Therefore, these results should be interpreted with caution, bearing in mind the large differences in included studies in terms of EULAR response in the control arms.

Figure 30. EULAR at week 24 for cDMARD-IR - forest plot for relative effects to filgotinib (100mg and 200mg) based therapies on the probit scale

[redacted]Table 25: EULAR at week 24 cDMARD-IR - modelled probability of EULAR response

Treatment	Modelled probability of response – posterior median (95% CrI)	
	Moderate response	Good response
cDMARDs	[redacted]	[redacted]
FIL + cDMARDs (100mg)	[redacted]	[redacted]
FIL + cDMARDs (200mg)	[redacted]	[redacted]
ADA + cDMARDs (40mg q2w)	[redacted]	[redacted]
CZP + cDMARDs (200mg)	[redacted]	[redacted]
CZP + cDMARDs (400mg)	[redacted]	[redacted]
RTX + cDMARDs (1000mg)	[redacted]	[redacted]
TCZ + cDMARDs (4mg/kg q4w)	[redacted]	[redacted]
TCZ + cDMARDs (8mg/kg q4w)	[redacted]	[redacted]

ADA, adalimumab; cDMARDs, conventional synthetic disease modifying anti-rheumatic drug; CrI, credible interval; EULAR, European League Against Rheumatism; FIL, filgotinib; RTX, rituximab; q2w, once every two weeks; q4w, once every four weeks; TCZ, tocilizumab.

*Probability of achieving at least specified response.

bDMARD-IR: ACR at 12 weeks

Filgotinib (100mg) showed [redacted] (Figure 31). Filgotinib 100mg was [redacted] to sarilumab 150mg and tofacitinib 5mg, but differences were small, as demonstrated in the modelled probabilities of response in xTable 26. Filgotinib 100mg was [redacted] to upadacitinib 15mg, baricitinib 4mg, and sarilumab 200mg.

Filgotinib (200mg) was shown to have similar efficacy to other treatment in the network. Filgotinib (200mg) [redacted] to sarilumab (150mg) and cDMARDs and was [redacted] to all other therapies in the network, however, these results were [redacted] (Figure 31). The modelled probabilities of response for ACR are shown in xTable 26.

Figure 31. ACR at week 12 bDMARD-IR - forest plot for relative effects to filgotinib (100mg and 200mg) based therapies on the probit scale

[redacted]Table 26: ACR at week 12 bDMARD-IR - modelled probability of ACR response

Treatment	Modelled probability of response – posterior median (95% CrI)		
	ACR20	ACR50	ACR70
cDMARDs	[redacted]	[redacted]	[redacted]
FIL (100mg) + cDMARDs	[redacted]	[redacted]	[redacted]
FIL (200mg) + cDMARDs	[redacted]	[redacted]	[redacted]
BARI (4mg) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (150mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (200mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
TOF (5mg bid) + cDMARDs	[redacted]	[redacted]	[redacted]
UPA (15mg qd) + cDMARDs	[redacted]	[redacted]	[redacted]

ACR, American College of Rheumatology; BARI, baricitinib; bid, twice daily; CrI, credible interval; cDMARDs, conventional synthetic disease modifying anti-rheumatic drugs; FIL, filgotinib; qd, daily; q2w; every 2 weeks; SARI, sarilumab; TOF, tofacitinib; UPA, upadacitinib.

Probability of achieving ACR20 in reference treatment (cDMARDs) based off of baseline natural history model as detailed in NICE DSU guidelines TSD5. (143)

bDMARD-IR: ACR at 24 weeks

Filgotinib (100mg) was [redacted] to rituximab (1000mg) and tocilizumab (8mg/kg q4w) (Error! Reference source not found.). There were [redacted] between filgotinib (100mg) and other therapies ([redacted] Filgotinib (100mg) was [redacted] although [redacted] for baricitinib (4mg) and sarilumab (150mg) as demonstrated in the modelled probabilities of response (xTable 27).

Filgotinib (200mg) showed similar efficacy to other treatment in the network and [redacted] to cDMARDs. Filgotinib (200mg) was [redacted] to abatacept (10mg/kg), baricitinib (4mg), sarilumab (150mg q2w), sarilumab (200mg q2w), tocilizumab (162mg q2w), and tocilizumab (4mg/kg), [redacted] (Error! Reference source not found.). Filgotinib 200mg was [redacted] to tocilizumab (4mg/kg) and rituximab (1000mg), [redacted]

The modelled probabilities of ACR response are shown in xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxTable 27.

[redacted] **Table 27: ACR at week 24 bDMARD-IR – modelled probability of ACR response**

Treatment	Modelled probability of response – posterior median (95% CrI)		
	ACR20	ACR50	ACR70
cDMARDs	[redacted]	[redacted]	[redacted]
FIL (100mg) + cDMARDs	[redacted]	[redacted]	[redacted]
FIL (200mg) + cDMARDs	[redacted]	[redacted]	[redacted]
ABT (10mg/kg) + cDMARDs	[redacted]	[redacted]	[redacted]
BARI (4mg) + cDMARDs	[redacted]	[redacted]	[redacted]
RTX (1000mg) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (150mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (200mg q2w) +	[redacted]	[redacted]	[redacted]

cDMARDs	[redacted]	[redacted]	[redacted]
TCZ (162mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
TCZ (4mg/kg q4w) + cDMARDs	[redacted]	[redacted]	[redacted]
TCZ (8mg/kg q4w) + cDMARDs	[redacted]	[redacted]	[redacted]

ABT, abatacept; ACR, American College of Rheumatology; BARI, baricitinib; CrI, credible interval; cDMARDs, conventional synthetic disease modifying anti-rheumatic drugs; FIL, filgotinib; q2w, every 2 weeks, q4w, every 4 weeks; RTX, rituximab; SARI, sarilumab; TCZ, tocilizumab.

Probability of achieving ACR20 in reference treatment (cDMARDs) based off of baseline natural history model as detailed in NICE DSU guidelines TSD5. (143)

Figure 32. ACR at week 24 bDMARD-IR - forest plot for relative effects to filgotinib (100mg and 200mg) based therapies on the probit scale

[redacted]

bDMARD-IR: EULAR at 24 weeks

The studies included in this network showed a large degree of variability in the control arm (cDMARD) response, for example 86.4% of patients achieved at least a moderate response in the cDMARDs arm in FINCH 2, compared with only 16.5% in the RADIATE and 22% in REFLEX studies. As such, estimates of the modelled probabilities of response were highly uncertain.

The point estimates suggest (xTable 28) that rituximab and tocilizumab (both doses) were favourable to filgotinib; but due to the much higher control arm level of response in the FINCH 2 study, results should be interpreted with caution.

Figure 33. EULAR at week 24 bDMARD-IR - forest plot for relative effects to filgotinib based therapies on the probit scale

B.2.10 Adverse reactions

Filgotinib has a manageable and consistent safety and tolerability profile, a summary of adverse events by trial is provided in the sections below.

B.2.10.1 Summary of safety data from FINCH 1

In FINCH 1, at week 24 (placebo-controlled period) a similar proportion of patients experienced serious treatment-emergent adverse events (TEAEs) in each treatment group (4.4% in the filgotinib 200mg arm, 5.0% in the filgotinib 100mg arm, 4.3% in the adalimumab arm and 4.2% in the placebo arm). By week 52 (overall period), these figures were [redacted] in the filgotinib 200mg arm, [redacted] in the filgotinib 100mg arm, and [redacted] in the adalimumab arm.

By week 24, there were two-treatment related deaths in the filgotinib 200mg group (septic shock; septic shock secondary to pneumonia), one treatment-related death in the filgotinib 100mg group in a patient with multiple risk factors (myocardial infarction on day 13), no deaths in the adalimumab group and two deaths in the placebo group (toxic reaction not related to study drug, septic shock non-treatment emergent SAE).

A summary of rates of TEAEs in FINCH 1 up to week 24 and [redacted] is shown in Table 29.

Table 29. TEAEs from baseline to week 24 (placebo-controlled period) and for the overall period up to week 52 (overall period) in FINCH 1 (SAS)

Safety assessment	Week	Filgotinib 200mg + MTX (n=475)	Filgotinib 100mg + MTX (n=480)	Adalimumab + MTX (n=325)	Placebo + MTX (n=475)
TEAE, n (%)	*24*	287 (60.4%)	287 (59.8%)	186 (57.2%)	253 (53.3%)
	52	[redacted]	[redacted]	[redacted]	[redacted]
TEAE related to study drug, n (%)	*24*	103 (21.7%)	104 (21.7%)	70 (21.5%)	87 (18.3%)
	52	[redacted]	[redacted]	[redacted]	[redacted]
TEAE with Grade 3 or higher (%)	*24*	34 (7.2%)	35 (7.3%)	20 (6.2%)	33(6.9%)
	52	[redacted]	[redacted]	[redacted]	[redacted]

Safety assessment	Week	Filgotinib 200mg + MTX (n=475)	Filgotinib 100mg + MTX (n=480)	Adalimumab + MTX (n=325)	Placebo + MTX (n=475)
TEAE leading to premature discontinuation of study drug, n (%)	*24*	15 (3.2%)	9 (1.9%)	13 (4.0%)	15 (3.2%)
	52	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE, n (%)	*24*	21 (4.4%)	24 (5.0%)	14 (4.3%)	20 (4.2%)
	52	[redacted]	[redacted]	[redacted]	[redacted]
Death, n (%)	*24*	2 (0.4%)	1 (0.2%)	0	2 (0.4%)
	52	[redacted]	[redacted]	[redacted]	[redacted]

AE, adverse event; MTX, methotrexate; placebo, placebo; SAS, safety analysis set; TEAE, treatment-emergent adverse event.

*At week 24, all patients assigned to placebo were reassigned 1:1 to either filgotinib 100mg + MTX or filgotinib 200mg + MTX in a blinded fashion and continued in the study per protocol up to week 52. Source: Gilead Data on File. FINCH 1 CSR. 2019. (67)

By week 24, in the filgotinib 200mg arm, the most frequently reported AEs (≥5% of patients), across all grades of severity, were nasopharyngitis (6.5%) and upper respiratory tract infection (5.3%). Nasopharyngitis and upper respiratory tract infection were also reported most frequently across all other study arms with 6.0% and 6.9% in the filgotinib 100mg arm, 4.6% and 5.2% in the adalimumab arm and 5.3% and 2.9% in the placebo arm, respectively. Table 30 presents the most common adverse events, across all grades, as well as the most commonly reported AEs classified as Grade 3 or higher at week 52.

Table 30. FINCH 1 most common TEAEs and most common Grade 3 or higher AEs at week 52, SAS

Safety assessment	Filgotinib 200mg + MTX (n=475)	Filgotinib 100mg +
Most common AEs (≥5% of patients) (%)	• [redacted]	• [redacted]
Most common Grade 3 or higher (≥1% of	[redacted]	• [redacted]

patients) (%)		

AE, adverse event; MTX, methotrexate; placebo, placebo; SAS, safety analysis set; TEAE, treatment-emergent adverse event. Source: Gilead Data on File. FINCH 1 CSR. 2020. (67)

B.2.10.2 Summary of safety data from FINCH 2

In FINCH 2, at week 24, a similar proportion of patients experienced serious TEAEs in each treatment group (4.1% in the filgotinib 200mg arm, 5.2% in the filgotinib 100mg arm, and 3.4% in the placebo arm). No deaths occurred due to any cause by week 24 (68).

A summary of the main TEAEs in FINCH 2 at week 24 is shown in Table 31.

Table 31. TEAEs from baseline to week 24 in FINCH 2 (SAS)

Safety assessment	Filgotinib QD dose groups		Placebo + cDMARD(s) (n=148)
	200mg + cDMARD(s) (n=147)	100mg + cDMARD(s) (n=153)	
TEAE, n (%)	102 (69.4%)	97 (63.4%)	100 (67.6%)
TEAE related to study drug, n (%)	32 (21.8%)	29 (19.0%)	23 (15.5%)
TEAE leading to premature discontinuation of study drug, n (%)	5 (3.4%)	6 (3.9%)	3 (2.0%)
TEAE with Grade 3 or Higher	8 (5.4%)	13 (8.5%)	9 (6.1%)
Serious TEAE, n (%)	6 (4.1%)	8 (5.2%)	5 (3.4%)
Death, n (%)	0	0	0

AE, adverse event; MTX, methotrexate; placebo, placebo; QD, once per day; SAS, safety analysis set; TEAE, treatment-emergent adverse event. Source: Gilead Data on File. FINCH 2 CSR. 2019. Genovese et al. 2018. (68) (126)

The most frequently reported AEs, across all grades, in the filgotinib 200mg arm were nasopharyngitis (10.2%), upper respiratory tract infection (5.4%), bronchitis (5.4%) and headache (5.4%). Incidence of adverse events was similar in the filgotinib 100mg arm with nasopharyngitis (5.9%), upper respiratory tract infection (5.9%), headache (5.9%) and nausea (5.2%) being the most frequently reported. In the placebo arm, the most commonly reported AEs were rheumatoid arthritis (6.1%), bronchitis (5.4%),

nasopharyngitis (4.7%), upper respiratory tract infection (4.1%) and nausea (4.1%) (68).

Grade 3 or above AEs reported for in >1% of patients in any treatment group comprised RA (placebo: three patients, 2.0%) and neutropenia (filgotinib 200mg: two patients, 1.4%) (68).

B.2.10.3 Summary of safety data from FINCH 3

In FINCH 3, at week 24, a similar proportion of patients experienced serious TEAEs in each treatment group (4.1% of patients in the filgotinib 200mg + MTX arm, 2.4% in the filgotinib 100mg + MTX arm, 4.8% in the filgotinib 200mg monotherapy arm and 3.1% of patients in the MTX monotherapy arm).

By week 24, one treatment-related death was reported in the filgotinib 200mg + MTX arm (lupus cardiomyopathy on day 7). A summary of the main TEAEs at week 24 and week 52 in FINCH 3 is shown in Table 32 (69).

Table 32. TEAEs from baseline to week 24 and for the overall period to week 52 in FINCH 3, SAS

Safety assessment	Week	Filgotinib 200mg + MTX (n=416)	Filgotinib 100mg + MTX (n=207)	Filgotinib 200mg monotherapy (n=210)	MTX monotherapy (n=416)
TEAE, n (%)	*24*	275 (66.1%)	144 (69.6%)	117 (55.7%)	263 (63.2)
	52	[redacted]	[redacted]	[redacted]	[redacted]
TEAE related to study drug, n (%)	*24*	158 (38.0%)	91 (44.0%)	49 (23.0%)	141 (33.9%)
	52	[redacted]	[redacted]	[redacted]	[redacted]
TEAE with Grade 3 or Higher	*24*	33 (7.9%)	17 (8.2%)	10 (4.8%)	22 (5.3%)
	52	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to premature discontinuation of study drug, n (%)	*24*	20 (4.8%)	7 (3.4%)	4 (1.9%)	4 (1.9%)
	52	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE, n (%)	*24*	17 (4.1%)	5 (2.4%)	10 (4.8%)	13 (3.10%)
	52	[redacted]	[redacted]	[redacted]	[redacted]
Death, n (%)	*24*	1 (0.2%)	0	0	0
	52	[redacted]	[redacted]	[redacted]	[redacted]

AE, adverse event; MTX, methotrexate; QD, once per day; SAS, safety analysis set; TEAE, treatment-emergent adverse event. Source: Gilead Data on File. FINCH 3 CSR. 2019. (69)

By week 24, the three most commonly reported AEs, across all grades of severity, in the filgotinib 200mg + MTX arm were nausea (10.3%), upper respiratory tract infection (5.0%), and headache (4.3%). In the filgotinib 100mg + MTX arm these were nausea (15.5%), nasopharyngitis and alopecia (16.3% for both), and diarrhoea (4.8%). In the filgotinib 200mg monotherapy arm nausea (6.2%), nasopharyngitis (15.7%), and upper respiratory tract infection (4.3%) were most frequently reported. Finally, in the MTX monotherapy, nausea (10.8%), diarrhoea (4.8%), and headache (4.6%) were most common. Table 33 presents the most common adverse events, across all grades of severity, as well as the most commonly reported AEs classified as Grade 3 or higher at week 52.

Table 33. FINCH 3 Most common TEAEs and most common Grade 3 or higher AEs at week 52, SAS

Safety assessment	Filgotinib 200mg + MTX (n=416)	Filgotinib 100mg + M

Most common AEs (≥5% of patients) (%)	• [redacted]	• [redacted]
Most common Grade 3 or higher (≥1% of patients) (%)	[redacted]	• [redacted]

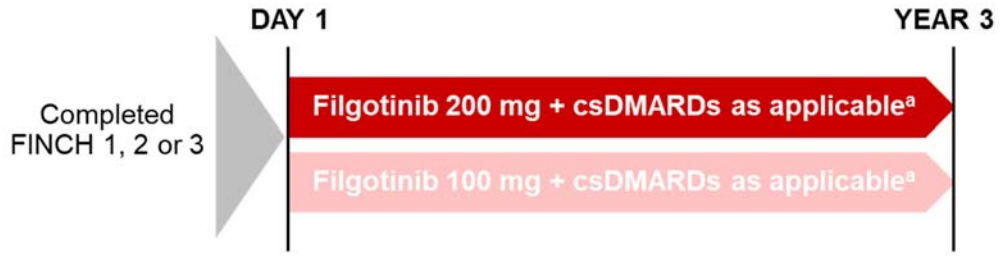
AE, adverse event; MTX, methotrexate; QD, once per day; SAS, safety analysis set; TEAE, treatment-emergent adverse event. Source: Gilead Data on File. FINCH 3 CSR. 2019 (69).

Further details of adverse events can be found in Appendix F.

B.2.11 Ongoing studies

FINCH 4 (144) is an ongoing long-term extension study, to assess the long-term safety and efficacy of filgotinib in patients who have completed one of the other Phase 3 filgotinib studies (FINCH 1, 2 or 3). FINCH 4 is a randomised, double-blind, parallel assignment trial. The two treatment arms comprise of filgotinib 200mg + cDMARDs, and filgotinib 100mg + cDMARDs, see Figure 34. In this study, patients continue their filgotinib dose, and any concomitant treatments, from the parent study (i.e. filgotinib + MTX if the parent study was FINCH 1; filgotinib ± MTX if the parent study was FINCH 3, or filgotinib + cDMARD(s) if the parent study was FINCH 2).

Figure 34. FINCH 4 trial design



Double-blind continued filgotinib dose from parent study. If not receiving filgotinib in parent study, randomised to 200mg or 100mg of filgotinib. cDMARD=conventional synthetic disease-modifying antirheumatic drug.

Source: Gilead Data on File. FINCH 4 CSR. 2018 (144)

The primary endpoints are the proportion of patients experiencing an AE and the proportion of patients experiencing clinically significant laboratory abnormalities during a follow-up period of up to 3 years. The secondary endpoint is the proportion who achieve ACR-N response. (144)

Exploratory endpoints that will be analysed are:

- Achievement of ACR20/50/70
- EULAR responses (ACR/EULAR remission)
- Evolution of CDAI, SDAI and DAS28-CRP over time
- Evolution of PROs over time

B.2.12 Innovation

Filgotinib is a next generation, potent reversible JAK inhibitor with a selectivity for JAK1. Cytokines associated with JAK1 are involved in the inflammatory signalling pathway that drives RA progression. Targeted inhibition of JAK1 could reduce dominant inflammatory cytokine signalling involved in RA, whilst limiting impact on normal physiological function.

Its oral method of administration, similarly to other JAK inhibitors, means there are no additional costs associated with training for administering the treatment, unlike treatments given by intravenous infusion (IV), or subcutaneously (SC). It also provides more convenient storage for patients compared with regular IV or SC injections that require refrigeration.

In addition to the above, neither filgotinib nor its active metabolite induce or inhibit cytochrome P450 enzymes or inhibit critical drug transporter enzymes, including P-glycoprotein. Therefore, the potential for drug-drug interactions is low, which means filgotinib can be administered with commonly used RA drugs without the need for dose adjustments (2).

B.2.13 Interpretation of clinical effectiveness and safety evidence

Filgotinib is a convenient, once daily, oral, selective and reversible JAK1 inhibitor, with low drug-drug interaction potential (see section B.1.2).

Within the current treatment pathway in England, patients with moderately-to-severely active RA are treated with cDMARDs and are switched to bDMARDs or JAK inhibitors (apart from patients with moderate disease activity, who are currently only treated with cDMARDs in England) if they show inadequate response. Where these patients fail to respond, or are intolerant to, their first advanced treatment, they may be switched to another. JAK inhibitors also represent an important therapeutic option for these non-responder or intolerant patients. The response rates of patients treated with filgotinib underscores its place, and clinical value, in the treatment of patients with moderately -to-severely active RA who have had an inadequate response to, or who are intolerant to, one or more DMARDs.

The efficacy and safety of filgotinib has been investigated in three pivotal Phase 3 trials across the treatment pathway. FINCH 1 (detailed in section B.2.1) compared filgotinib with adalimumab and placebo, all in combination with methotrexate, in patients who had previously experienced an inadequate response to methotrexate monotherapy. FINCH 2 (detailed in section B.2.6.2) compared filgotinib with placebo (both in combination with cDMARDs), in patients with a previous inadequate response or intolerance to at least one bDMARD. Finally, FINCH 3 (detailed in section B.2.6.3) compared filgotinib (with methotrexate or as monotherapy), with methotrexate monotherapy in patients naïve to methotrexate. Within these three studies, the demographics and other baseline characteristics were well-balanced across the different treatment arms and can be considered to be broadly generalisable to those of patients seen in NHS clinical practise in England.

The primary endpoint of all three trials was ACR20 response (at week 12 or 24), with filgotinib meeting this endpoint in all three trials, demonstrating significantly higher response rates when compared with placebo (FINCH 1 and FINCH 2), or methotrexate monotherapy (FINCH 3). For ACR20/50 and 70, filgotinib demonstrated a rapid onset of action, and demonstrated the maintenance of response with efficacy being generally maintained over the full study period up to 52 weeks. Additionally, clinically relevant results for ACR50 and ACR70 (at 12 and 24 weeks) demonstrated significantly higher response rates across all three studies. Physical function (as measured by HAQ-DI score) and proportion of patients achieving remission (DAS28-CRP <2.6), key secondary efficacy endpoints, demonstrated significant improvement in the change

from baseline at week 12 and week 24 across all three trials in filgotinib arms. Filgotinib also showed superiority over placebo for EULAR good response at week 24 across all three trials. Finally, filgotinib 200mg also showed numerical superiority over adalimumab in the secondary endpoint of clinical remission (DAS28-CRP <2.6), as well as ACR50/70 and EULAR efficacy endpoints. Detailed outcomes from the trials are presented in section B.2.6.

Post-hoc subgroup analysis (detailed in section B.2.7) of patients with moderately active RA in FINCH 1 was conducted which compared filgotinib with comparator treatments (i.e. adalimumab and placebo) within the subgroup.

Results of the subgroup analysis for the moderate sub-population demonstrated that for ACR20, [redacted] Additionally, clinically relevant results for ACR50 and ACR70 (at week 24) demonstrated that filgotinib 200mg [redacted] and [redacted] with adalimumab. For the key secondary endpoints, proportion of patients achieving remission (DAS28-CRP <2.6) and LDA, (DAS28-CRP ≤3.2), filgotinib 200mg [redacted] compared with placebo and a [redacted] versus adalimumab.

When compared with the results of the overall moderately to severely active RA population, filgotinib 200mg [redacted] ACR20, ACR50 and ACR70 response rate at week 24 and a [redacted] of patients achieving clinical remission (defined by a DAS28-CRP <2.6) in the moderate sub-population.

Filgotinib monotherapy showed numerical improvement in primary endpoint, ACR20, compared with MTX monotherapy, and superior improvements to MTX monotherapy in several key secondary endpoints in MTX-naïve populations in FINCH 3, providing supportive evidence for filgotinib as monotherapy. Filgotinib monotherapy also demonstrated numerically comparable response to filgotinib combination therapy for different endpoints such as ACR20, ACR50 and ACR70. Despite the paucity of clinical efficacy data in the filgotinib Phase 3 clinical trial programme for patients receiving

monotherapy in DMARD-IR populations, the Phase 2 study DARWIN 2 provides further supportive evidence for filgotinib monotherapy in the MTX-IR population, achieving its primary endpoint of ACR20 response at week 12 for both filgotinib 100mg and filgotinib 200mg, in addition to significant improvements in key secondary endpoints.

It should be also noted that in MTA375, the Committee agreed that the minority of (cDMARD-IR) patients with severe active rheumatoid arthritis who could not tolerate methotrexate should not be treated differently from those with severe disease, as far as possible. The Committee concluded that biologic DMARDs should be recommended as a cost-effective use of NHS resources when used as monotherapy for severely active disease previously treated with DMARDs, where the Marketing Authorisation of the bDMARD allows for this recommendation to be made. It is anticipated that the filgotinib label indication will include use as both monotherapy and combination therapy.

Filgotinib was reported to be generally well tolerated and to have a consistent AE profile; most AEs were mild to moderate and rates were similar across subgroups by geographic region. There are no additional adverse events identified for filgotinib over and above DMARDs used in current clinical practice. In addition, filgotinib is anticipated to have slightly reduced monitoring requirements to currently available JAK inhibitors. Evidence for adverse events is detailed in section B.2.10.

Finally, in addition to direct clinical evidence, a network meta-analysis, with standard RA treatments not included in the clinical trial programme, was also undertaken to support the efficacy results of filgotinib.

The results of the NMA in the cDMARD-IR population for ACR at 24 weeks indicated that filgotinib 200mg combination therapy [redacted] compared with adalimumab (40mg q2w), rituximab (1000mg), and tocilizumab (4mg/kg q4w) combination therapies. Although filgotinib 200mg was not [redacted] compared with other advanced combination therapies, the differences in modelled probabilities of ACR response were very similar compared with baricitinib (4mg), infliximab (3mg/kg) and intensive cDMARDs. For EULAR at 24 weeks, filgotinib 200mg was [redacted] to

adalimumab (40mg q2w) and showed [redacted] to rituximab (1000mg) and tocilizumab (4mg/kg q4w), [redacted]. Filgotinib (200mg) was [redacted] to certolizumab pegol (200mg and 400mg) and tocilizumab (8mg/kg).

In the bDMARD-IR population, ACR at 24 weeks results showed that filgotinib 200mg combination therapy was [redacted] abatacept (10mg/kg), baricitinib (4mg), sarilumab (150mg q2w), sarilumab (200mg q2w), tocilizumab (162mg q2w), and tocilizumab (4mg/kg), [redacted] to rituximab (1000mg). For EULAR at 24 weeks, estimates indicated that filgotinib 200mg was [redacted] tocilizumab (4mg/kg q4w) and [redacted] compared with rituximab (1000mg) and tocilizumab (8mg/kg q4w). However, it should be noted that due to the high degree of variability in the control arm (cDMARDs), response in this network the results should be interpreted with caution. In summary, filgotinib can be considered to be broadly similar to other treatments across both populations. For full details of the NMA, please see section B.2.9.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

B3.1.1 Identification of studies

A systematic literature review was conducted to identify published economic evaluations in moderate to severe RA, which could be used to address the decision problem and inform the economic model structure. Full details of the search are provided in Appendix G, as well as detailed inclusion/exclusion criteria for the review.

B.3.2 Economic analysis

The systematic literature review search of cost-effectiveness studies (detailed in Appendix G) identified 103 unique economic evaluations in RA. No relevant economic evaluations able to provide estimates for the cost-effectiveness of filgotinib in RA were identified. Therefore, a model in line with that presented in MTA375 was developed using Microsoft® Excel® (Office 365, version 1902) with Visual Basic for Applications (VBA) functionality.

As in previous TAs in RA, the economic evaluation conducted by the assessment group (AG) in MTA375 was deemed the most relevant for decision-making in moderate to severe RA in England and Wales (145). Therefore, to the extent feasible, the economic evaluation detailed in this submission was developed to be consistent with that of MTA375, in addition to those presented in subsequent TAs e.g. TA480 and TA466. The comparability between the modelling approaches in MTA375 and this submission is discussed in the proceeding sections, with full details of the model structure discussed in section B3.2.2.

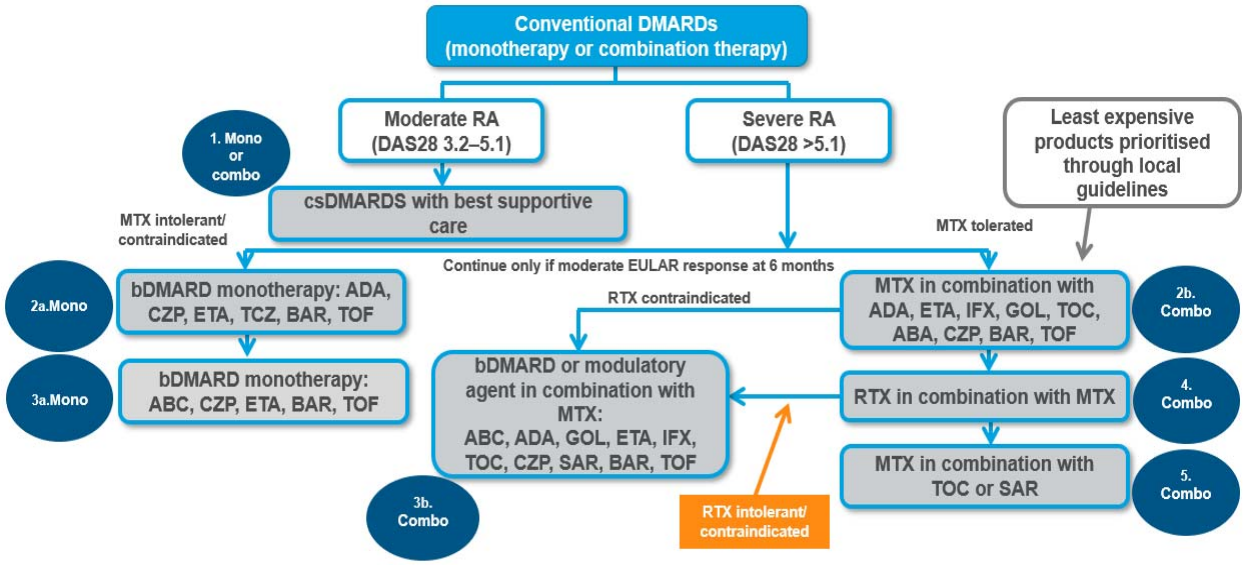
B3.2.1 Patient population

The cost-effectiveness analysis models patients with moderately to severely active RA. Patients are categorised into subpopulations depending on their disease severity, line of treatment and tolerance to guideline-recommended treatments. Broadly, patients encompass three main groups:

1. Adults with moderate RA (DAS28 of 3.2-5.1) who have had inadequate response to or are intolerant to csDMARDs (moderate cDMARD-IR)
2. Adults with severe RA (DAS28 >5.1) who have an inadequate response to csDMARDs only (severe cDMARD-IR)
3. Adults with severe RA (DAS28 >5.1) who have an inadequate response to bDMARDs (severe bDMARD-IR)

In line with NICE treatment guidelines (shown in Figure 35), patients are further sub-categorised providing a total of eight individually analysed populations. Therefore, this cost-effectiveness analysis reflects the use of filgotinib within its anticipated Marketing Authorisation, the populations outlined in the NICE scope, and clinical practice in the UK.

Figure 35. Current NICE treatment guidance on treatment of moderately to severely active RA



ADA=adalimumab; ABC=abatacept; BAR=baricitinib; Combo = combination therapy with methotrexate; CZP=certolizumab pegol; DAS=Disease Activity Score; DMARD=Synthetic disease modifying antirheumatic drugs; ETA=etanercept; GOL=golimumab; IFX=infliximab; Mono = monotherapy; MTX=Methotrexate; RA=Rheumatoid arthritis; RTX=Rituximab; TCZ=tocilizumab; TOF=tofacitinib;

Source: NICE 2009 clinical guideline: 2020 update [NG100] (146)

Two patient populations are modelled for the use of filgotinib in moderate RA:

1a. As monotherapy after two or more cDMARD failures in patients who are MTX ineligible

1b. As combination therapy after two or more cDMARD failures in patients who are MTX eligible

Four patient populations are modelled for the use of filgotinib in combination with MTX in severe RA, for patients who are MTX eligible:

2b. As first line advanced therapy after failure of 2+ csDMARDs

3b. After first line advanced therapy failure in patients who are RTX ineligible

4. After first line advanced therapy failure in patients who are RTX eligible

5. After failure of RTX in combination with MTX

Two patient populations are modelled for the use of filgotinib monotherapy in severe RA, for patients who are MTX ineligible:

2a. As first line advanced therapy after failure of 2+ csDMARDs

3a. After first line advanced therapy failure

B3.2.2 Model perspective

The perspective for this analysis is that of the NHS and Personal and Social services (PSS) in England and Wales (in line with current NICE guidance). This cost-effectiveness analysis therefore excluded patients' out of pocket expenses, carers' costs, and lost productivity costs. All costs are report in pounds sterling (2019/20).

B3.2.3 Model Structure

Model structure and flow

The cost-effectiveness analysis is conducted using a discrete event simulation (DES) model, consistent with MTA375 (145), as well as subsequent submissions in RA. As such, the model generates a cohort of patients, these patients are tracked over time, during which time key events are captured. Each patient's flow through the model is described as follows:

1. Patients are sampled at random from the provided patient population (based on the patient baseline characteristics in the FINCH clinical trial programme)

2. Each patient is simulated through the following process:

    I. Patient time to death is calculated

        i. Upon model initiation a patient's time of death is determined dependent on their age, sex and HAQ-DI.

        ii. If a patient dies within the first six months, this is modelled as an immediate death incurring no costs or QALYs and a new patient is subsequently sampled.

    II. Patients alive at six months progress to the initial treatment phase where they either continue treatment, or discontinue treatment if they do not achieve a good or moderate EULAR response

        i. If a patient remains alive at six months (after the initial treatment phase), then they progress to the six-month initial treatment phase. Thus, all patients who do not die during the initial six months are assumed to complete the initial phase of treatment.

        ii. If a patient experiences an AE during this phase of the model, they complete the initial treatment phase gaining no treatment benefit but incur costs and QALYs based on their baseline HAQ-DI and the respective AE. The patient then re-enters the six-month initial treatment phase on the next treatment line.

        iii. For patients not experiencing an AE by the end of the six-month initial treatment phase, a EULAR treatment response is sampled, based on the efficacy of the specific treatment. If no EULAR response is achieved, then the patient discontinues the current treatment accruing costs and QALYs based on their baseline HAQ-DI and re-enter the model at the six-month initial treatment phase on the next treatment in the sequence.

    III. Patients enter the maintenance treatment phase upon achieving a good or moderate EULAR response

i. Once a patient enters the maintenance treatment phase, time to treatment discontinuation is sampled and compared with time to death. The trajectory of a patient's HAQ-DI score from treatment initiation to the either death or discontinuation (whichever occurs first) is then estimated and relevant utilities, costs, LYs and QALYs are accrued and calculated accordingly.

ii. Note that utility is accrued linearly over each six-month period. For example, if a patient has utility of 0.5 at the start of the period and 1 at the end of the period, the QALYs accrued in the model will be 0.75/2 = 0.375 per six-monthly cycle. This is equivalent to assuming utility increases linearly over, for example, the initial treatment period, or decreases linearly over the last treatment period before discontinuation.

iii. In the event of discontinuation, the patient's HAQ-DI score rebounds to their baseline score, i.e. it is reduced by the same amount as the initial treatment effect, and the patient moves onto the next treatment in the treatment sequence.

iv. If death occurs before treatment discontinuation, the patient's lifetime costs, QALYs and LYs are accrued and the model restarts with the next simulated patient.

v. The model assumes that the final treatment in every treatment sequence is BSC. Therefore, once a patient starts BSC, no discontinuation time is sampled, and the patient remains on this line of treatment until death.

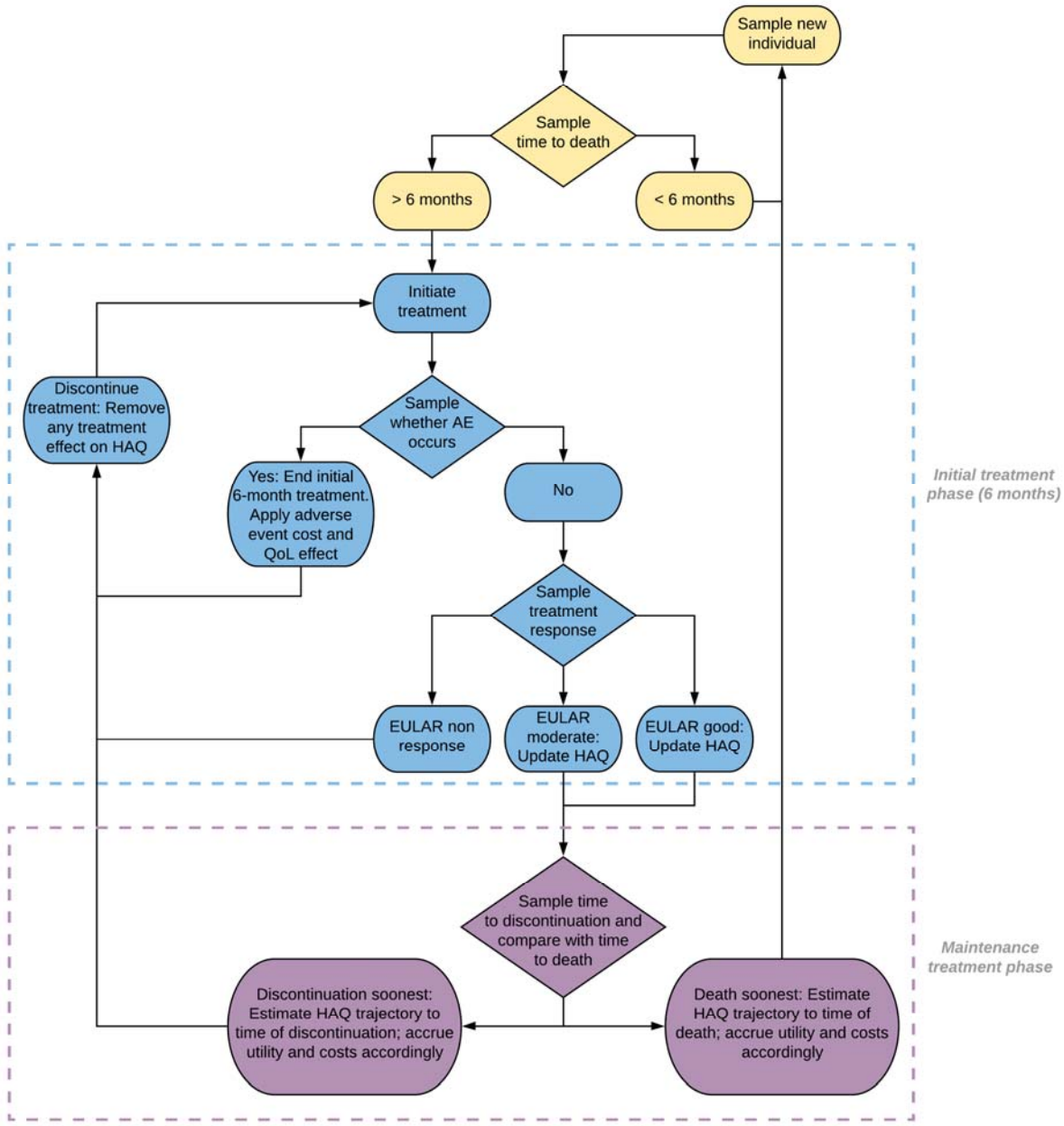
3. Following the death of a simulated patient a new patient is sampled at random with replacement from the provided patient population.

This process is repeated until the sampled population size reaches that specified by the model user, and the base case analysis were conducted using 10,000 patients. Once the full population has been modelled the process is repeated for any additional

treatment arms (strategies) as specified by the user. A set of random numbers is used for sampling events, which is the same for each arm. Therefore, the population in each arm is identical, and the randomly sampled events will occur in the same way, with the only difference being the introduction of different treatments in comparator arms.

A schematic depicting the model pathway is outlined in Figure 36.

Figure 36.Cost-effectiveness model schematic



AE, adverse event; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; QoL, quality of life

The main features of the economic analysis, and other recent NICE submissions in RA, are presented in Table 34.

Table 34. Features of the economic analysis

Factor	Previous appraisals								Current appraisal	
	TA375 (2016) (145)	**TA485 (2017) (31)**	**TA480 (2017) (147)**	**TA466 (2017) (148)**	**TA415 (2016) (149)**	**TA247 (2011) (150)**	**TA225 (2010) (151)**	**TA195 (2010) (152)**	**Chosen values**	**Justification**
Model type	Patient-level CEA model using DES structure				Markov model	Patient-level CEA model using DES structure	Markov model	Patient-level CEA model using DES structure	Patient-level CEA model using DES structure	Consistent with previous models, and MTA375
Were health effect measured in QALYs; if not, what was used?	Yes								Yes	Recommended in the NICE methods guide
Perspective	UK NHS and PSS								UK NHS and PSS	Recommended in the NICE methods guide
Time horizon	Lifetime								Lifetime	Long enough to reflect all important differences in costs or outcomes between the technologies being compared
Discount for utilities and costs	3.5%								3.5%	Recommended in the NICE methods guide
Source of utilities	HAQ-DI values are mapped to EQ-5D utility using algorithm designed by Hernandez-Alva et al. 2013	EQ-5D utility was estimated from patient HAQ-DI using the algorithm developed by Malottki et al. 2011 (153)	HAQ-DI values are mapped to EQ-5D utility using algorithm designed by Hernandez-Alva et al. 2013 (154)	HAQ-DI values are mapped to EQ-5D utility using algorithm designed by Hernandez-Alva et al. 2012	Initial response on first-line treatment was estimated using data from the PREDICT study. HAQ-DI scores were	The base case analysis uses a quadratic equation to map HAQ-DI to utility, as reported in TA198 (updated and	EQ-5D values were estimated from HAQ-DI using a regression function from Chen et al. 2006 (155)	The Assessment Group used a non-linear equation to convert HAQ-DI scores to EQ-5D scores	HAQ-DI values are mapped to EQ-5D utility using algorithm designed by Hernandez-Alva et al. 2013	Established approach in RA economical evaluations, and in line with MTA375

					mapped to EQ-5D utilities for the following treatments by using the mapping algorithm from Brennan et al.	replaced by TA247)				
Source of costs	TA247 NHS reference costs 2011-2012 Malottki et al. 2011	TA375 PSSRU 2016 NHS Reference Costs 2015–16	British National Formulary 2016 NHS Reference Costs 2015–16 and 2010-11 PSSRU 2016 Malottki et al 2011	British National Formulary 2016 TA375 MIMS 2016	British National Formulary 2016 NHS reference costs 2014/15 PSSRU 2015 TA247	British National Formulary 2011 NOAR database	NHS Reference Costs 2008 PSSRU 2009	Chen et al. 2006 (155) PSSRU 2008 British National Formulary 58	TA375 (145) MIMS 2019	Use of latest drug pricing data, as well as inflated costs from the most relevant model, MTA375

Abbreviations: CEA, cost-effectiveness analysis; DES, discrete event simulation; EQ-5D, EuroQol 5 dimension; HAQ-DI, Health Assessment Questionnaire – Disability Index; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NOAR, Norfolk Arthritis Register; PSSRU, Personal Social Services Research Unit; PSS, Personal Social Services; QALY, quality adjusted life year; RA, rheumatoid arthritis; TA, technology appraisal; UK, United Kingdom.

Molecules assessed in TAs: TA485, sarilumab; TA480, tofacitinib; TA466, baricitinib; TA415, certolizumab pegol; TA247, tocilizumab; TA225, golimumab; TA195, adalimumab, etanercept, infliximab, rituximab and abatacept.

B3.2.4 Intervention technology and comparators

The model assessed the first-line comparators and subsequent treatments in sequence, with up to eight treatments considered in a treatment sequence. The efficacy of filgotinib and its comparators were informed by a network meta-analysis (NMA), which informed EULAR response rates in the model.

Intervention

The intervention considered in the model is filgotinib 200mg, administrated once daily orally in combination with methotrexate or as monotherapy. Filgotinib is indicated for the treatment of moderately to severely active RA in adult patients who have responded inadequately to or are intolerant to one or more csDMARDs.

Comparator

Comparators included in the model are consistent with NICE recommendations in the RA treatment pathway and are in line with the final NICE scope for filgotinib, which includes csDMARDs, bDMARDs as well as BSC. BSC was assumed to comprise of 'post-biologic' cDMARD therapies (Leflunomide, gold, cyclophosphamide), in line with MTA375.

Specific molecules were selected based on market share data (Therapy Watch (156)) and clinical validation regarding the most likely sequences utilised in clinical practise. The full treatment sequences modelled are detailed in section B3.2.5.

B3.2.5 Treatment sequences in the model

The model considered treatment sequences of up to eight treatment lines. The specific treatment sequences in each target population are described in Table 35 through Table 43. The treatment sequences used in this submission are in keeping with treatments suggested by NICE guidelines and have been validated using both market share data and clinical expert validation.

Population 1: Moderate RA

Clinical opinion indicated that most patients with moderate disease activity would receive 2 csDMARDs. Failing this, BSC is the only option which includes low dose csDMARDs (which may have been previously trialled) and corticosteroids.

1a. Moderate RA patients after 2 cDMARD failures (MTX ineligible)

Table 35: Treatment sequences considered in moderately active cDMARD-IR patients after two cDMARD failures

Sequence	First-line treatment	Second-line treatment
1	***FIL***	***BSC***
2	PBO/BSC	BSC
Abbreviations: BSC, best supportive care; FIL, filgotinib; MTX, methotrexate; PBO, placebo		

1b. Moderate RA patients after 2 cDMARD failures (MTX eligible)

Table 36: Treatment sequences considered in moderately active cDMARD-IR patients after two cDMARD failures

Sequence	First-line treatment	Second-line treatment
1	***FIL + MTX***	***BSC***
2	PBO/BSC	BSC
Abbreviations: BSC, best supportive care; FIL, filgotinib; MTX, methotrexate; PBO, placebo		

Population 2: cDMARD-IR

2a. Severe RA patients in first line advanced therapy treatment of (MTX ineligible)

Market share data indicates 69% of 1L advanced therapy (not mono- and combination-therapy specific) in the UK comprises of an anti-TNF agent, of which 29.3% and 29.8% is attributable to ADA and ETN (including biosimilars), respectively. BAR is the most commonly used JAK in 1L advanced therapy, contributing 6.1% in the UK compared 2.3% for TOF. Finally, TCZ accounts for 11.2% of all 1L therapies and clinical expert opinion indicated its use in 1L would be mostly in monotherapy. Given 1L and 2L monotherapy options are largely the same, it was agreed that ABT would be the most

likely 2L option and that anti-TNF cycling is not a clinically preferred approach. Throughout analyses, subcutaneous formulations were selected based on clinical preference.

This appropriateness of this selection was validated by clinical experts.

Table 37: Treatment sequences considered in first line advanced therapy treatment of severe RA (MTX ineligible)

Sequence	First-line treatment	Second-line treatment	Third-line treatment
1	***FIL***	***ABC SC***	***BSC***
2	ADA	ABC SC	BSC
3	ETN	ABC SC	BSC
4	BAR	ABC SC	BSC
5	TCZ SC	ABC SC	BSC

Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; MTX, methotrexate; TCZ, tocilizumab

2b. Severe RA patients in first line advanced therapy treatment (MTX eligible)

For patients who are MTX eligible and RTX is tolerated the rationale for the choice of 1L comparators is as per population 2a, with the omission of TCZ based on clinical opinion as described above. At 3L clinical expert opinion indicated that TCZ would be

the most utilised option and that SAR should only be modelled if there are significant differences in costs as its usage is expected to be low.

Table 38: Treatment sequences considered in first line advanced therapy treatment of severe RA (MTX eligible, RTX tolerated)

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment
1	***FIL + MTX***	***RTX + MTX***	***TCZ SC + MTX***	***BSC***
2	ADA + MTX	RTX + MTX	TCZ SC + MTX	BSC
3	ETN + MTX	RTX + MTX	TCZ SC + MTX	BSC
4	BAR + MTX	RTX + MTX	TCZ SC + MTX	BSC
Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; MTX, methotrexate; RTX, rituximab; SAR, sarilumab; TCZ, tocilizumab				

For patients who are MTX eligible but RTX is contraindicated (or not tolerated) the rationale for 1L treatments is as per Table 38. At 2L, anti-TNF cycling is not considered appropriate (see above) although clinical expert opinion indicated that 2L options could

include IL-6 or CD-80 agents. TCZ was preferred to SAR as the 2L option based on clinical opinion and 2L market share data (11.2% vs. 0.5%, respectively).

Table 39: Treatment sequences considered in first line advanced therapy treatment of severe RA (MTX eligible, RTX contraindicated)

Second line IL-6			
Sequence	**First-line treatment**	**Second-line treatment**	**Third-line treatment**
1	***FIL + MTX***	***TCZ SC + MTX***	***BSC***
2	ADA + MTX	TCZ SC + MTX	BSC
3	ETN + MTX	TCZ SC + MTX	BSC
4	BAR + MTX	TCZ SC + MTX	BSC
Second line CD80			
Sequence	**First-line treatment**	**Second-line treatment**	**Third-line treatment**
5	***FIL + MTX***	***ABC SC + MTX***	***BSC***
6	ADA + MTX	ABC SC + MTX	BSC
7	ETN + MTX	ABC SC + MTX	BSC
8	BAR + MTX	ABC SC + MTX	BSC
Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; MTX, methotrexate; RTX, rituximab; SAR, sarilumab; TCZ, tocilizumab			

Population 3: bDMARD-IR

3a. Severe RA patients after failure of first line advanced therapy treatment (MTX ineligible, RTX ineligible)

Comparators were selected in line with the NICE treatment pathway. A limited number of molecules are recommended as 2L advanced treatments. Anti-TNF agents were not included based on clinical expert feedback that anti-TNF cycling is not an optimal treatment approach. All other recommended drug classes are included.

Table 40: Treatment sequences considered after failure of first line advanced therapy treatment of severe RA (MTX ineligible, RTX ineligible)

Sequence	First-line treatment	Second-line treatment
1	***FIL***	***BSC***
2	ABC SC	BSC
3	BAR	BSC
4	TOF	BSC
Abbreviations: ABC, abatacept; BAR, baricitinib; BSC, best supportive care; FIL, filgotinib; MTX, methotrexate; RTX, rituximab; TOF, tofacitinib		

3b. Severe RA patients after failure of first line advanced therapy treatment (MTX eligible, RTX ineligible)

As per clinical advice, the most commonly used agent in each class (at 2L) was selected. Anti-TNFs were excluded as described above.

Table 41: Treatment sequences considered after failure of first line advanced therapy treatment of severe RA (MTX eligible, RTX ineligible)

Sequence	First-line treatment	Second-line treatment
1	***FIL + MTX***	***BSC***
2	ABC SC + MTX	BSC
3	TCZ SC + MTX	BSC
4	SAR + MTX	BSC
5	BAR + MTX	BSC
Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; FIL, filgotinib; MTX, methotrexate; RTX, rituximab; SAR, sarilumab; TCZ, tocilizumab		

Severe RA patients after failure of first line advanced therapy (MTX eligible, RTX eligible)

The only guideline recommended option is RTX. TCZ was preferred to SAR as the appropriate final active therapy based on clinical advice and market share.

Table 42: Treatment sequences considered after failure of first line advanced therapy in MTX eligible patients (RTX eligible)

Sequence	First-line treatment	Second-line treatment	Third-line treatment
1	***FIL + MTX***	***TCZ SC + MTX***	***BSC***
2	RTX + MTX	TCZ SC + MTX	BSC
Abbreviations: BSC, best supportive care; ETN, etanercept; FIL, filgotinib; MTX, methotrexate; RTX, rituximab; SAR, sarilumab; TCZ, tocilizumab			

Severe RA patients after failure of rituximab in combination with methotrexate

After failure of RTX, TCZ and SAR are the only guideline recommend options.

Table 43: Treatment sequences considered in severely active RA, RTX-IR population

Sequence	First-line treatment	Second-line treatment
1	***FIL + MTX***	***BSC***
2	TCZ SC + MTX	BSC
3	SAR + MTX	BSC
Abbreviations: BSC, best supportive care; FIL, filgotinib; MTX, methotrexate; RTX, rituximab; SAR, sarilumab; TCZ, tocilizumab		

B.3.3 Clinical parameters and variables

B3.3.1 Patient population

A patient cohort was generated by random sampling, using characteristics derived from the Phase 3 filgotinib FINCH trials. Where characteristics required for the model were not available from the clinical trials, values have been taken from the Early Rheumatoid Arthritis Study (ERAS) dataset as described by Norton et al (157).

The baseline population characteristics used in the cost-effectiveness model (CEM) are outlined in Table 44. These inputs are taken directly from the FINCH 1 and FINCH 2 trials (67, 68), using data stratified according to disease severity. Using these summary statistics, a cohort of 1,000 patients was sampled randomly, using appropriate probability distributions.

Table 44: Patient baseline characteristics used in the CEM

Characteristics	Moderate cDMARD-IR		Severe cDMARD-IR		Severe bDMARD-IR	
	Mean (SD)	Source	Mean (SD)	Source	Mean (SD)	Source
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion female	[redacted]		[redacted]		[redacted]	
Duration of disease (years)	[redacted]		[redacted]		[redacted]	
Number of prior DMARDs	[redacted]		[redacted]		[redacted]	
Baseline HAQ-DI	[redacted]		[redacted]		[redacted]	
Baseline Pain (VAS)	[redacted]		[redacted]		[redacted]	
Weight (kg)	[redacted]		[redacted]		[redacted]	
DAS28	[redacted]		[redacted]		[redacted]	
RF (positive)	[redacted]		[redacted]		[redacted]	
IMD quartile	2.37	Norton et al. (157)	2.37	Norton et al. (157)	2.37	Norton et al. (157)
ACR (positive)	0.71		0.71		0.71	

Abbreviations: ACR, American College of Rheumatology; bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug; DMARD, disease-modifying anti-rheumatic drug; DAS28, disease activity score 28 joints; HAQ-DI, Health Assessment Questionnaire – Disability index; IMD, index of multiple deprivation; IR, insufficient response; RF, rheumatoid factor; SD, standard deviation; VAS, visual analogue scale

Values were sampled from the following distributions:

- Normal distribution for weight and age
- Variables expected to be positively skewed were sampled using gamma distribution for duration: duration of disease, disease activity score (DAS28), health assessment questionnaire disability index (HAQ-DI) and number of prior DMARDs
- As the pain variable has a limited range (from 0 to 100), a beta distribution was used for sampling baseline pain

Sampled values were bounded by minimum and maximum values, where appropriate. DAS28 was restricted to values ranging from 2 to 10, and patients were assumed to be adults between 18 and 100 years of age.

Additionally, HAQ-DI scores were restricted to values ranging from 0 to 3 by an increment of 0.125, as was done in MTA375. Initially, HAQ-DI scores were assigned to each patient at baseline, by sampling from a gamma distribution. HAQ-DI scores were then rounded up or down to the nearest valid score, using a random variable.

B3.3.2 Efficacy

Clinical response in the model is based on the EULAR response criteria. The probability of achieving a EULAR response (none, moderate or good) at six months (24 weeks) for filgotinib and comparators in the model were estimated from the NMAs evaluating treatment response for RA treatments in both the cDMARD-IR and bDMARD-IR populations. Full details of the NMA are detailed in section 2.9.

Although the ACR response metric is widely used in RA clinical trials, the EULAR response criteria is the preferred measurement of treatment response in UK clinical practice, and is recommended for use in the NICE guidance (146) for RA. The EULAR response is thus the treatment measure used for the economic modelling. ACR responses can be converted to EULAR response based on an approach developed by Stevenson et al., using US Veterans' Affairs Rheumatoid Arthritis Registry (VARA) data where both measures were reported (145). The mapping algorithm as described and used in MTA375, has been applied in this analysis, where applicable.

Efficacy estimates are shown as a proportion of the population achieving response in each outcome: EULAR response (none, moderate or good) in Table 45 and ACR response converted to EULAR response in Table 46.

Table 45: Probability of achieving a given response based on 24-week EULAR data.

Treatment	cDMARD-IR population			bDMARD-IR population		
	No response	Moderate response	Good response	No response	Moderate response	Good response
FIL (200mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA (40mg q2w) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX (1000mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
csDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Abbreviations: ADA, adalimumab; bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional synthetic disease-modifying anti-rheumatic drug; EULAR, European League Against Rheumatism; IR, insufficient response; MTX, methotrexate; q2w, once every two weeks; q4w, once every four weeks; RTX, rituximab; TCZ, tocilizumab

*A comparison was not possible in the NMA.

Table 46: Probability of achieving a given response based on 24-week ACR data converted to EULAR.

Treatment	cDMARD-IR population			bDMARD-IR population		
	No response	Moderate response	Good response	No response	Moderate response	Good response
FIL (200mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABC (10mg/kg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABC (125 mg qw) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA (40mg q2w) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BAR (4mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN (50mg qw) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX (1000mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAR (200mg q2w) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ (162mg q2w) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
csDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABC, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; BAR, baricitinib; bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug ; ETN, etanercept; IR, insufficient response; MTX, methotrexate; qw, once a week; q2w, once every two weeks; q4w, once every four weeks; RTX, rituximab; SAR, sarilumab; TCZ, tocilizumab;

* A comparison was not possible in the NMA.

For treatments where the efficacy could not be informed by the NMA, a number of assumptions were made (see Table 47).

BSC is assumed to have no treatment effect (i.e. EULAR non-response), in line with the assumption made in MTA375. Additionally, recent submissions in RA have made the same assumption (TA485, TA480 and TA466 (31, 147, 148)).

Efficacy data for filgotinib as monotherapy in the cDMARD-IR and bDMARD-IR populations are not available from the filgotinib clinical trial programme. Therefore, monotherapies were not included in the NMA as no comparison to filgotinib monotherapy can be made for these populations. For the purpose of this economic evaluation, it is assumed that monotherapy will have the same relative effect across all treatments as combination therapy. Data from FINCH 3 demonstrated that the addition of MTX to filgotinib 200mg produced no marked improvement over filgotinib

200mg monotherapy in an MTX-naïve population (percentage of ACR20 responders were 78.1% and 81.0% in the monotherapy and combination therapy arm, respectively at week 24) supporting the assumption of equivalent efficacy for monotherapy versus combination therapy, see B2.6. Furthermore, this approach is in line with that employed in TA466 and is further supported by the committee guidance in MTA375. The guidance indicated that the minority of (cDMARD-IR) patients with severe active rheumatoid arthritis who could not tolerate methotrexate should not be treated differently from other people with severe disease, as far as possible.

Individual studies included in both the cDMARD-IR and bDMARD-IR NMAs mainly reported data for the moderately to severely active RA population, i.e. results stratified by disease severity (for the moderate and severe population separately) are rarely reported. Therefore, due to the lack of available data, NMAs were not conducted separately by disease severity. Therefore, for this economic analysis, it was assumed that the efficacy results from the NMA in the cDMARD-IR population were applicable for both patients in the moderate and severe populations. Similarly, trials included in the bDMARD-IR NMA included patients with moderately to severely active RA but the efficacy results were considered applicable for patients with severely active RA. This is consistent with the approach taken by the Assessment Group in MTA375.

Comparisons of the moderate and severe subgroups efficacy results in the FINCH 1 trial to the whole cohort suggest that the efficacy was similar across the populations considered (see section B2.7). Thus, the use of the same efficacy data is additionally supported by the trial data.

For three treatments, (TCZ SC and ABC SC combination therapies, TOF monotherapy) used in the severe cDMARD-IR and bDMARD-IR populations, additional efficacy assumptions were needed.

A summary of the assumptions relating to treatment efficacy are detailed in Table 47 below.

Table 47: Summary of efficacy assumptions included in the CEM

Patient population	Treatments to which assumption applies	Assumptions	Justification
All populations	All interventions	Due to a paucity of studies reporting results stratified by severity, no NMA was performed separately for the moderate and severe populations. Therefore, efficacy for the moderate and severe subgroups was assumed equivalent to treatment effect in the overall moderately to severely active RA NMAs.	Efficacy results were similar across moderate and severe subpopulations in the FINCH 1 trial
Severe cDMARD-IR	• TCZ SC + MTX	No data available from the cDMARD-IR NMA. Efficacy assumed equivalent to TCZ SC + MTX (in bDMARD-IR NMA)	Relative efficacy not expected to differ significantly through treatment lines
Severe bDMARD-IR	• ABC SC + MTX	No data available from the bDMARD-IR NMA. Efficacy assumed equivalent to ABC IC + MTX (in cDMARD-IR NMA)	Relative efficacy not expected to differ significantly through treatment lines
	• TOF monotherapy	No data available from the bDMARD-IR NMA. Efficacy assumed equivalent to BAR + MTX (in bDMARD-IR NMA)	This approach has previously been applied in TA10389
All populations	• All monotherapy interventions	No NMA for monotherapies was performed, as efficacy data was not available for cDMARD-IR and bDMARD-IR populations for filgotinib as monotherapy. Therefore, all monotherapies are assumed to have the same relative effect as the corresponding combination therapies.	Efficacy results were similar across monotherapy and combination therapy in the FINCH 3 trial

Abbreviations: ABC, abatacept; BAR, baricitinib; bDMARD biologic disease-modifying anti-rheumatic drug; cDMARD conventional disease-modifying anti-rheumatic drug; FIL, filgotinib; IR, insufficient response; IV, intravenous; JAK, Janus kinase; MTX, methotrexate; NMA, network meta-analysis; SC, subcutaneous; TCZ, tocilizumab; TOF, tofacitinib

B3.3.3 HAQ-DI progression

Initial reduction

At the end of the six-month initial treatment phase a patient's HAQ-DI score is assumed to reduce dependent upon the initial treatment effect (i.e. whether achieving a moderate or good EULAR response). Patients with no response do not experience a reduction in HAQ-DI, i.e. their HAQ-DI trajectory is assumed to be constant. The reduction applied was derived by the Assessment Group in MTA375 using data from the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA). Due to limited data availability, this initial HAQ-DI value reduction is independent of treatments received, an approach consistent with that taken in MTA375, and other recent submissions (TA485 (31), TA480 (147), TA466 (148)). The initial reductions in HAQ-DI applied in the model are summarised in Table 48.

Table 48: Initial reduction in HAQ-DI based on the BSRBR-RA database (158)

EULAR response	Mean change in HAQ	SE
Good	-0.672	0.112
Moderate	-0.317	0.048

Abbreviations: BSRBR-RA, British Society of Rheumatology Biologics Register for Rheumatoid Arthritis; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire Disability Index; SE, standard error

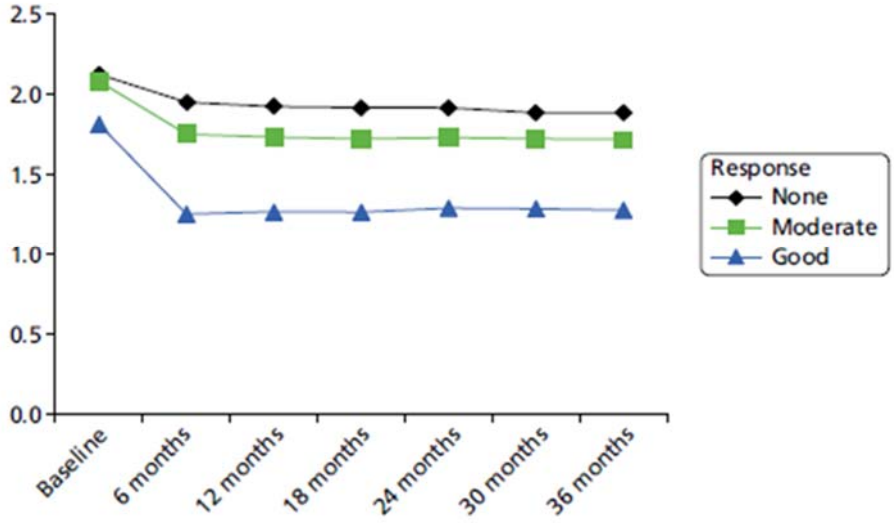
Long-time progression

After the initial six-month treatment phase, as a patient progresses further through the model, the change in HAQ-DI score is dependent on the treatment received. Patients achieving a good or moderate EULAR response at six months continue receiving their current treatment, and experience a treatment-dependent HAQ-DI progression as described below:

- Treatment with a bDMARD results in a HAQ-DI trajectory based on those reported in the 36-month BSRBR dataset analysed by the AG in MTA375 (145). This trajectory is dependent on the initial response of the patient (moderate or good response) and their baseline characteristics including disease duration at initiation. The first 36 months of the trajectory are estimated using the

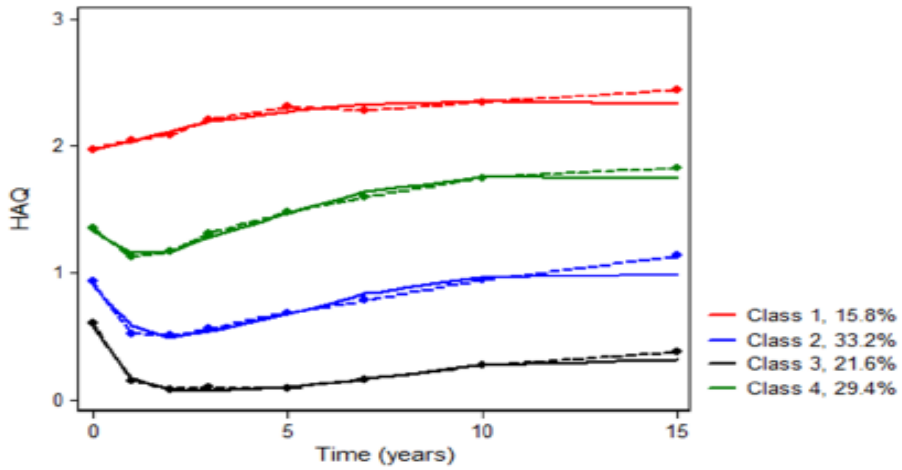
autoregressive latent trajectory model in MTA375, after which HAQ-DI is assumed to remain stable. This method is in line with that applied in MTA375. The data used to model the progression is depicted in Figure 37.

Figure 37. Mean HAQ-DI by EULAR response category for those receiving bDMARDs. Figure sourced from MTA375.



- Those patients receiving csDMARDs experience a trajectory in HAQ-DI score based on the 15-year ERAS cohort data described by Norton et al (157). Estimates reported by Norton et al. combined with patient baseline characteristics from the FINCH trials defined the long-term HAQ-DI trajectory for individual patients for 15 years following treatment with a cDMARD, after which HAQ-DI is assumed to remain stable. This assumption is consistent with the approach taken in MTA375. The findings of Norton et al are shown visually in Figure 38; note that the concern of the cost-effectiveness model is to estimate the expected change in HAQ over time, not with the latent classes per se. The latent class analysis provides a more flexible and appropriate method of modelling HAQ change over time

Figure 38. HAQ-DI trajectory for csDMARDs (four latent class) based on Norton et al. (157)



- The patients receiving BSC are assumed to experience the same HAQ-DI trajectory as patients receiving csDMARDs.
- HAQ-DI is assumed to change immediately at the end of each six-month period.

In a scenario analysis, the sensitivity of the model to the chosen HAQ-DI trajectory approach was explored, by assuming patients receiving csDMARDs and BSC experienced a linear HAQ-DI progression based on Malottki et al. (153) (detailed in Table 49) rather than the base case approach by Norton et al.

Table 49: Annual increase in HAQ-DI score for patients on csDMARDs and BSC sourced from Malottki et al.

Treatment	Mean change in HAQ-DI
csDMARDs	0.045
BSC	0.060
Abbreviations: BSC, best supportive care; cDMARD, conventional synthetic disease-modifying anti-rheumatic drug; Health Assessment Questionnaire Disability Index	

B3.3.4 Treatment discontinuation

Treatment discontinuation over time is dependent on a patient's EULAR response (moderate or good response) to treatment and is based on the BSRBR dataset analysis by the AG in MTA375. Patients who achieve a EULAR response (good or moderate) following the first six-month phase continue their current treatment. Time to

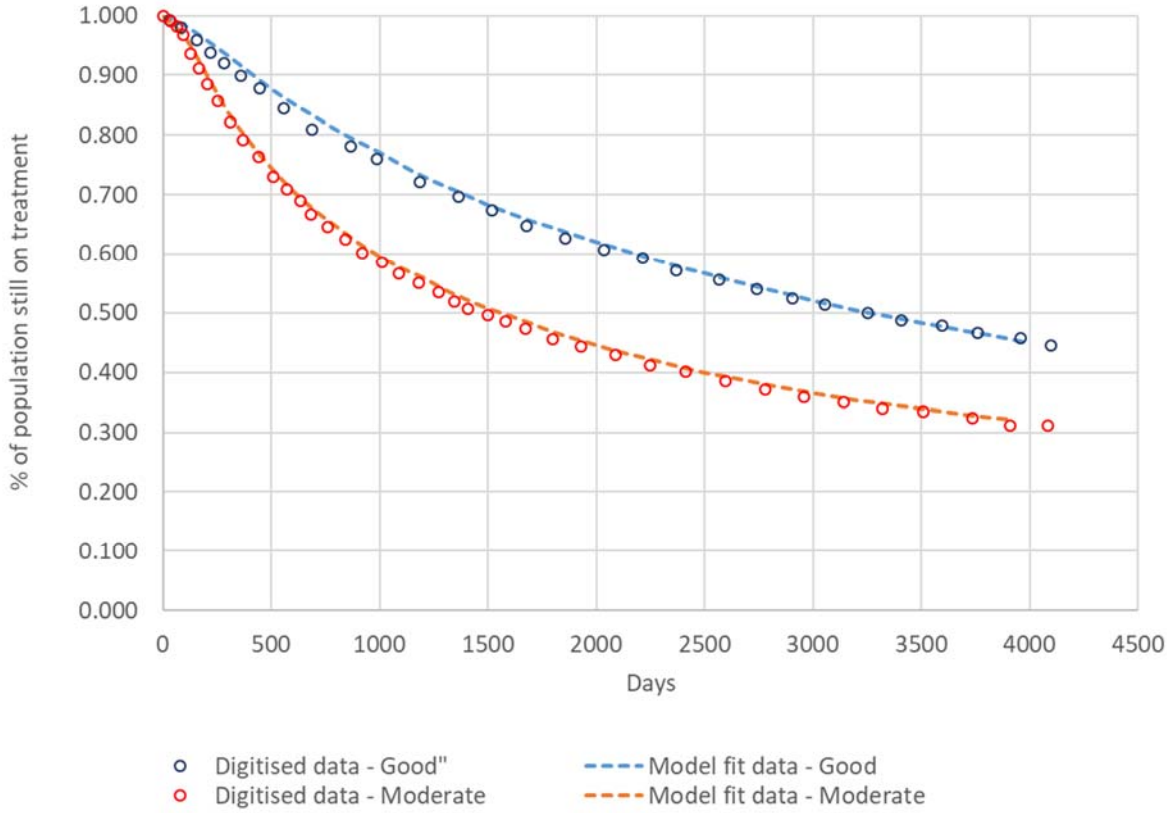
treatment discontinuation is sampled for each patient once they enter the maintenance treatment phase.

Model parameters were not published as part of the analysis. Therefore, the published curve was digitised and used to generate individual patient data. This was then used to fit a survival curve (generalised Gamma, in line with the parametric model described in MTA375), the parameters of which have been applied in the model to obtain sampled time to discontinuation for each patient (Table 50). Model fit to digitised data can be seen in Figure 39.

Table 50: Parameters for time to discontinuation for moderate and good EULAR response

Parameters	Moderate EULAR response	Good EULAR response
mu	6.897	8.135
Sigma	1.701	1.612
Q	-0.745	0.067
Abbreviations: EULAR, European League Against Rheumatism		

Figure 39. Parametric survival models estimating time to discontinuation of treatment for patients with moderate and good EULAR response



B3.3.5 Mortality

Age- and sex-specific all-cause survival was derived from UK life-tables 2015-2017(159) . Consistent with the methodology applied in MTA375, Gompertz curves were fitted to the raw data and adjusted within the model dependent on the starting age of the individual patient. Survival was adjusted by relative risk as a function of baseline HAQ-DI. It was assumed that only the baseline HAQ-DI score was important for predicting mortality, in line with the approach taken in MTA375. The hazard ratios (HRs), sourced from MTA375, for survival stratified by HAQ-DI score are outlined in Table 51. As the model considers HAQ-DI score in 0.125 increments, the scores are stratified accordingly. For the reference case, patients with HAQ-DI score of 0, only the all-cause mortality is considered. Other patients experience disease-related mortality calculated using the appropriate HR.

Table 51: Hazard ratio for mortality associated with HAQ-DI category

HAQ-DI score	HR (95% CI)
0.000	1.00 (reference)
0.125 – 0.375	1.40 (1.10, 1.80)
0.500 – 0.875	1.50 (1.20, 1.90)
1.000 – 1.375	1.80 (1.40, 2.20)
1.500 – 1.875	2.70 (2.20, 3.50)
2.000 – 2.375	4.00 (3.10, 5.20)
2.500 – 3.000	5.50 (3.90, 7.70)
Abbreviations: CI, confidence interval; HAQ-DI, health assessment questionnaire disability index; HR, hazard ratio.	

B.3.4 Measurement and valuation of health effects

B3.4.1 Health-related quality-of-life data from clinical trials

The EQ-5D questionnaire was used to collect utility data in the filgotinib Phase 3 trials. EQ-5D scores were collected until the end of each trial, week 52 (FINCH 1) and week 24 (FINCH 2). However, to align the modelling of health related quality of life (HRQoL) with previous submissions (MTA375 and all other submissions identified in Table 34), HRQoL was assumed to be dependent on patient HAQ-DI score progression. This relationship can be used to obtain long-term patient utility based on treatment effects, as opposed to using short-term trial data.

This was done by mapping patients' long-term HAQ-DI score trajectory (detailed in section B3.3.3) to EQ-5D, based on a published mapping algorithm detailed by Hernandez-Alva et al (see section B3.4.2) (154). This approach to RA economic modelling is well established and was applied by the AG in MTA375.

B3.4.2 Mapping

In line with MTA375, and other recent NICE submissions in RA (39, 147), the four latent class model produced by Hernandez-Alva et al (154). is used in the base case to determine utility from current modelled HAQ-DI and pain VAS scores over the entire model horizon. This approach fits with the DES model framework in which HAQ-DI progression is simulated over time and in which there are no defined "health states" to

which specific EQ-5D utility values can be directly attributed. Therefore, this cost-effectiveness analysis utilises the standard approach to mapping EQ-5D to HAQ-DI.

The algorithm presented by Hernandez-Alva et al. (154) uses patients' current age, sex, HAQ-DI and VAS pain scores to determine a utility value at any point in the model.

The mapping algorithm is applied using the following steps:

1. Patients' VAS pain score was estimated using their current HAQ-DI as the input for the mapping algorithm. The polynomial curve, which represents VAS scores as a function of HAQ-DI, published in MTA375, was digitised and fitted with a ninth order polynomial curve in the R software package. The digitised and fitted points are illustrated in Figure 40. The polynomial coefficients obtained are reported in Table 52.

Figure 40. Digitised points and fitted points of the polynomial used to estimate patient pain score in MTA375, and this submission

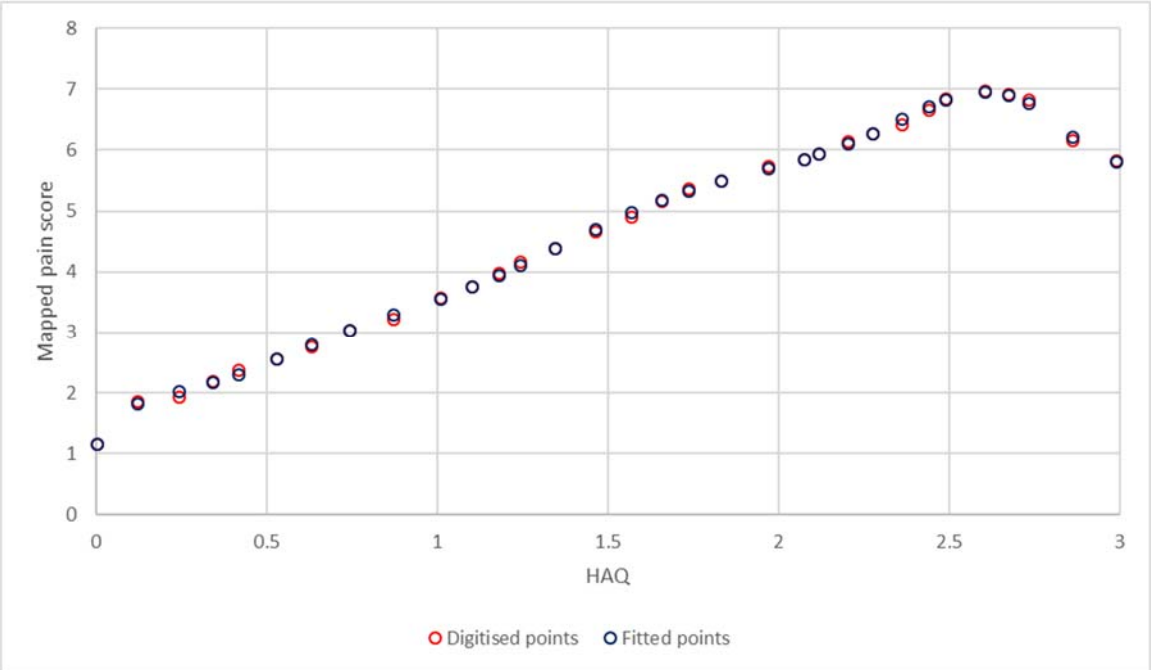


Table 52: Parameters for estimating pain from HAQ-DI

Polynomial term	Coefficient
Intercept	1.13
X	10.15
X^2	-53.78
X^3	163.22
X^4	-268.48
X^5	258.01
X^6	-148.40
X^7	50.15
X^8	-9.16
X^9	0.70

2. The probability of belonging to each of the four latent classes was estimated based each patient's simulated HAQ-DI score and VAS pain score using coefficients reported in Hernandez et al. (154)

3. Utility was estimated based on each patient's HAQ-DI score, pain, age and sex, using coefficients reported in Hernandez et al. (154)

To test the sensitivity of model estimates to this HAQ-DI utility mapping algorithm, an alternative approach was applied in a scenario analysis. A method outlined by Malottki et al. (153) was tested which estimated utility using each patient's current modelled HAQ-DI score using the following equation:

$$Utility = 0.804 - 0.203 \times HAQ - 0.045 \times HAQ^2$$

B3.4.3 Health-related quality-of-life studies

A systematic literature review was conducted to identify published literature reporting health state utility values in RA, the details of which are discussed in Appendix H. The identified studies were not used to inform the CEM, as none of the studies were found to present a robust alternative to assessing long-term EQ-5D in RA. As described in Section B.3.4.2, the utility values in the model were found by using the mapping applied by the AG in MTA375, estimating EQ-5D derived from HAQ-DI scores.

B3.4.4 Adverse events

The only AE considered in the base case analysis was serious infection, which is assumed to occur only during the first six months of any active treatment, an approach which is consistent with MTA375 (145). Rates of AEs (serious infections) were based on those identified as part of the Singh et al. (160) Cochrane review, and were dependent on class of therapy, rather than being treatment-specific. Although the approach represents a simplification of the disease and safety profile of RA therapies, this is considered a conservative approach, as filgotinib is considered to have a favourable safety and tolerability profile in patients with moderately to severely active RA.

The incidence of AEs from Singh et al (160) are reported in Table 53. AEs were assumed not to occur in patients receiving BSC.

Table 53: SAE incidence rate in the CEM

Drug class	Rate of SAE per six-month period
cDMARDs	2.5%
bDMARDs (Inc. JAKs)	3.6%
Abbreviations: bDMARDs, biologic disease-modifying anti-rheumatic drugs; cDMARD, conventional disease-modifying anti-rheumatic drugs	

Additionally, SAE incidence rates reported from the FINCH 1 trial at 24 weeks were applied in a scenario analysis, using data from the filgotinib arm (applied for JAKs), adalimumab arm (applied for other bDMARDs), and the placebo arm (applied for csDMARDs).

Table 54: SAE incidence rate from FINCH 1 applied in scenario analyses

Drug class	Rate of SAE per six-month period
cDMARDs	0.8%
bDMARDs (Excl. JAKs)	2.5%
JAKs	1.7%
Abbreviations: bDMARDs, biologic disease-modifying anti-rheumatic drugs; cDMARD, conventional disease-modifying anti-rheumatic drugs	

For each AE occurrence, a decrement of 0.156 (161) is applied to the patient's overall utility, in line with MTA375. This disutility is applied by assuming that each patient experiences an AE for a total of 28 days of the six-month period.

B3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

HRQoL were unique to each patient and were mapped to the EQ-5D scale from HAQ-DI scores over the model time horizon. Full details of the mapping are presented in section B3.4.2.

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

B3.5.1 Identification of studies

A systematic literature review was conducted to identify cost and resource use data associated with patients with RA from the published literature. Full details of the search are provided in Appendix I. The identified studies were not used to inform the CEM, as no studies identified were found to present a robust alternative to the costing applied by MTA375.Additionally, maintaining consistency with MTA375, to the extent possible, aids the comparability of the outcomes of this analysis with that of MTA375.

B3.5.2 Intervention and comparators' costs and resource use

The model includes separate costs for drug acquisition and administration. Costs are applied six-monthly and are separated for initial treatment (including any loading doses) and maintenance treatment.

Treatment costs provided in the model are based on UK costs and dosing regimens from MIMS 2020 (162). Confidential patient access schemes (PAS) were excluded for Orencia® (abatacept), Olumiant® (baricitinib), Xeljanz® (tofacitinib), Kevzara® (sarilumab), RoActemra® (tocilizumab), and Rixathon® (rituximab). No treatment considered in this analysis has a non-confidential PAS price. Biosimilars, where available, are costed in the same way. The model only considers the lowest priced biosimilars as comparators. Biosimilars for adalimumab and etanercept are included in the model.

For strategies were treatments are used in combination with MTX, the six-monthly cost of MTX was added to the six-monthly cost of the treatments.

The cost of BSC was estimated from MTA375. The costs of BSC are reflective of healthcare costs for patients who are managed without targeted therapy. The costs comprise post-biologic csDMARD therapy (e.g., leflunomide, gold, cyclosporine), and were £360 per 6 months (£60 per month).

For drugs with weight-based dosing (e.g., tocilizumab), doses for patients were computed based on the simulated baseline weight of each patient.

Similarly, the cost of csDMARDs was assumed to equal the cost of MTX, which is considered a more conservative approach than including more expensive csDMARDs, such as sulfasalazine or hydroxychloroquine.

A summary of the pack costs, sizes and dosing regimens for treatments included in the model with the resultant six-monthly medication costs is shown in Table 55 below.

Table 55: Summary of pack cost, sizes and dosing regimens for each treatment

Treatment		Pack cost	Pack size	Dosing regimen (maintenance)	Total monotherapy cost		Total combination therapy cost	
					Initial 6 months	Subsequent 6-monthly	Initial 6 months	Subsequent 6-monthly
ETN	Erelzi™ (biosimilar)	£643.50	50mg x 4	50mg q1w	£4,182.75	£4,182.75	£4,196.27	£4,196.27
ADA	Hulio™ (biosimilar)	£616.25	40mg x 2	40mg q2w	£4,005.63	£4,005.63	£4,019.15	£4,019.15
TCZ	RoActemra® (brand)	£913.12	162mg x 4	162mg q1w	£5,935.28	£5,935.28	£5,948.80	£5,948.80
ABC	Orencia® (brand)	£1,209.60	125mg x 4	125mg q1w	£7,862.40	£7,862.40	£7,875.92	£7,875.92
RTX	Rixathon® (biosimilar)	£1,571.67	500mg x 2	1000mg twice every 6 months	£3,143.34	£3,143.34	£3,156.86	£3,156.86
BAR	Olumiant® (brand)	£2,416.68	4mg x 84	4mg qd	£5,236.14	£5,236.14	£5,249.66	£5,249.66
TOF	Xeljanz® (brand)	£690.03	5mg x 56	5mg bid	£4,485.20	£4,485.20	£4,498.71	£4,498.71
FIL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAR	Kevzara® (brand)	£912.25	200mg x 2	200mg q2w	£5,929.63	£5,929.63	£5,943.15	£5,943.15
MTX (generic)		£52.01	10mg x 100	10mg q1w	£13.52	£13.52	NA	NA

Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; bid, twice a day; ETN, etanercept; IV, intravenous; MTX, methotrexate; PAS, patient access scheme; qd, once daily q1w ,once a week; q2w, once every two weeks; q4w, once every four weeks; qw, once a week; RTX, rituximab; SAR, sarilumab; SC, subcutaneous; TCZ, tocilizumab; TOF, tofacitinib

*model uses cost per kg to calculate cost for each individual patient

Treatment administration costs applied in the model are reflective of route of administration, dosing guidance in MIMS 2020 and the administration costs outlined in MTA375 (145). These administration costs were inflated to 2018/2019 prices using the HCHS and NHSCII indices (163). This amounts to £2.93 per subcutaneous (SC) injection and £173.01 per intravenous (IV) infusion (as shown in Table 56).

Table 56: Drug administration costs

Route of administration	Cost (2019 £)	Source
IV	173.01	MTA375 (145) inflated to 2018/2019 prices using the HCHS and NHSCII indices
SC	2.93	
Oral	0.00	
Abbreviations: IV, intravenous; SC, subcutaneous		

Table 57:Summary of administration costs applied in the model per treatment

Treatments		Mode of Administration	Number of doses		Administration cost (2019 £)	
			Initial 6 months	Subsequent 6-monthly	Initial 6 months	Subsequent 6-monthly
ETN	Erelzi™	SC	26	26	£76.18	£76.18
ADA	Hulio™	SC	13.5	13.5	£38.09	£38.09
		SC	13.5	13.5	£38.09	£38.09
TCZ	RoActemra®	SC	26	26	£76.18	£76.18
ABC	Orencia®	SC	26	26	£76.18	£76.18
RTX	Rixathon®	IV	2	2	£346.02	£346.02
BAR	Olumiant®	Oral	182	182	N/A	N/A
FIL	N/A	Oral	182	182	N/A	N/A
TOF	Xeljanz®	Oral	364	364	N/A	N/A
SAR	Kevzara®	SC	13.5	13.5	£38.09	£38.09
MTX		Oral	26	26	N/A	N/A
Abbreviations: ABC: abatacept; ADA: adalimumab; BAR: baricitinib; ETN: etanercept; Fil, filgotinib, MTX: methotrexate; RTX: rituximab; SAR: sarilumab; TCZ, tocilizumab; TOF, tofacitinib						

B3.5.3 Health-state unit costs and resource use

As discrete event simulation (DES) models do not explicitly have health states, monitoring costs and cost related to hospitalisations are presented in the sections below.

Monitoring costs

Monitoring costs are modelled separately for initial treatment phase and maintenance phase, to allow for more intense monitoring during initiation. Current monitoring costs are sourced from MTA375 (145) and inflated to 2018/2019 prices using the HCHS and NHSCII indices (163). A summary of the six-monthly monitoring costs is shown in Table 58.

Table 58: Monitoring costs

Monitoring cost	Six-monthly cost (2019 £)
Initial treatment phase	£1,870.54
Maintenance phase	£884.66

Hospitalisation costs per HAQ-DI

In line with the approach taken in MTA375, hospital costs are broken down into six categories, according to HAQ-DI level, to reflect the increasing cost burden associated with worsening RA. Current UK costs are taken from MTA375 (145). No resource level breakdown was provided for these costs, as such the overall hospital costs have been inflated to 2018/2019 prices using the HCHS and NHSCII indices (163). A summary of the six-monthly costs applied in the model are shown in Table 59.

Table 59: Hospital costs based on HAQ-DI score

HAQ-DI score	Six-month cost (2019 £)
<0.60	£94.04
0.60-1.10	£57.60
1.10-1.60	£204.85
1.60-2.10	£295.28
2.10-2.60	£700.04
≥2.60	£1,509.87
Abbreviations: HAQ-DI; Health assessment questionnaire disability index	

B3.5.4 Adverse reaction unit costs and resource use

The cost-effectiveness analysis included costs of AEs in the form of serious infections, which were considered the most important treatment related AE (see section B3.4.4 Adverse events The current UK cost of an AE in the model is taken from MTA375 and inflated to 2018/2019 prices using the HCHS and NHSCII indices (163) . The cost per event, as shown in Table 60, is applied to all AEs irrespective of which treatment the patient is receiving.

AEs were assigned a utility decrement of 0.156 (136) per event, which is applied assuming that the event occurs for a duration of 28 days out of the six-month period in which the AE is experienced. The probability of experiencing an AE differed between csDMARDs and bDMARDs, the details of which are described in section B3.4.4.

Table 60: Adverse events costs

Treatment	Cost per event (2019 £)	Source
csDMARDs, bDMARDs & JAK inhibitors	£1,661.55	TA375, HCHS and NHSCII indices (163)
Abbreviation: bDMARD= biologic disease-modifying anti-rheumatic drug; csDMARD= conventional synthetic disease modifying anti-rheumatic drug(s); HCHS= hospital & community health services; JAK= Janus kinase		

B3.5.5 Miscellaneous unit costs and resource use

No additional costs or resource use items were included in the model which are not already included in the preceding sections.

B.3.6 Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

A summary of the base case inputs used in the model is presented in Table 61.

Table 61. Summary of variables applied in the economic model

Variable	Value		Measurement of uncertainty and distribution	Reference to section in submission
Model settings				
Time horizon	Lifetime		NA	Section 3.2
Discounting - costs	3.5%		Low: 0%, high: 6%	Section 3.2
Discounting - utilities	3.5%			Section 3.2
Clinical inputs				
Patient baseline characteristics	Baseline characteristics from the FINCH-I trial (csDMARD-IR population), and FINCH- II trial (bDMARD-IR population)		NA	Section 3.2
Treatment efficacy (EULAR response)	Based on the NMA, Week 24 ACR efficacy data converted to EULAR, Table 46		95% CI from the NMA	Section 3.3
HAQ-DI trajectory	As previously reported by MTA375 based on analysis of BSRBR dataset (bDMARDs), and ERAS cohort data described by Norton et al. (157)		NA	Section 3.3
Discontinuation	As previously reported by MTA375 based on BSRBR dataset analysis (generalised gamma distribution applied)		NA	Section 3.3
Pain (VAS score)	Estimated from patients' HAQ-DI score, as previously reported by MTA375 based on NDB data		NA	Section 3.4
AE's (serious infections)	Rates were based on Singh et al,2011 (160)		Varied by +/- 100%	Section 3.4
Treatment costs				
Treatment	Initial 6 months	Subsequent 6 months	NA	Section 3.5
[redacted]	[redacted]	[redacted]		
ABC SC	£7,862.40	£7,862.40		
ADA	£8,011.25	£8,011.25		
BAR	£5,236.14	£5,236.14		
ETN	£4,182.75	£4,182.75		
TCZ SC	£5,948.80	£5,948.80		
TOF	£4,485.20	£4,485.20		
[redacted]	[redacted]	[redacted]		
ABC SC + MTX	£7,875.92	£7,875.92		
ADA + MTX	£4,019.15	£4,019.15		
BAR + MTX	£5,249.66	£5,249.66		
ETN + MTX	£4,196.27	£4,196.27		
RTX + MTX	£3,156.86	£3,156.86		
SAR + MTX	£5,943.15	£5,943.15		
TCZ SC + MTX	£5,948.80	£5,948.80		
MTX	£13.52	£13.52		

Variable	Value		Measurement of uncertainty and distribution	Reference to section in submission
BSC	£360	£360		
Monitoring costs (6-monthly)				
Initial period	£1,870.54		Varied by +/- 20%	Section 3.5
Maintenance period	£884.66			Section 3.5
Administration costs (6-monthly)				
Treatment	Initial 6 months	Subsequent 6 months	Varied by +/- 20%	Section 3.5
ETN (SC)	£76.18	£76.18		
ADA (SC)	£38.09	£38.09		
TCZ (SC)	£76.18	£76.18		
ABC (SC)	£76.18	£76.18		
RTX (IV)	£346.02	£346.02		
SAR (SC)	£38.09	£38.09		
Hospital costs (6-monthly)				
HAQ-DI <0.6	£94.04		Varied by +/- 20%	Section 3.5
HAQ-DI 0.6-<1.1	£57.60			Section 3.5
HAQ-DI 1.1-<1.6	£204.85			Section 3.5
HAQ-DI 1.6-<2.1	£295.28			Section 3.5
HAQ-DI 2.1-<2.6	£700.04			Section 3.5
HAQ-DI ≥2.6	£1,509.87			Section 3.5
Adverse events				
Adverse Event Costs (per event)	£1,661.55		Varied by +/- 20%	Section 3.5
Utility inputs				
HAQ-DI utility mapping	Based on the algorithm reported by Hernandez et al (154)		NA	Section 3.4
AE utility decrement	0.156		Varied by +/- 100%	Section 3.4
Mortality				
Sex-specific background mortality	Gompertz curves fitted on UK 2015-2017 life tables, in line with NICE MTA375		NA	Section 3.4
Mortality stratified by HAQ-DI group				
HAQ-DI 0.000	1.00 (reference)		NA	Section 3.4
HAQ-DI 0.125–0.375	1.40		95% CI: 1.10 - 1.80	Section 3.4
HAQ-DI 0.500–0.875	1.50		95% CI: 1.20 - 1.90	Section 3.4
HAQ-DI 1.000–1.375	1.80		95% CI: 1.40 - 2.20	Section 3.4
HAQ-DI 1.500–1.875	2.70		95% CI: 2.20 - 3.50	Section 3.4
HAQ-DI 2.000–2.375	4.00		95% CI: 3.10 - 5.20	Section 3.4
HAQ-DI 2.500–3.000	5.50		95% CI: 3.90 - 7.70	Section 3.4

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Distributions applied for PSA			
Parameter	Distribution		
Proportion of good/moderate responders by treatment	Dirichlet	N/A	Section 3.8
Initial HAQ-DI reduction	Normal		
Survival hazard ratios	Lognormal		
Hospitalisation costs	Gamma		

Abbreviations: ACR, American College of Rheumatology; AE, adverse event; CI, confidence interval; EULAR, European League Against Rheumatism; FIL, filgotinib; HAQ-DI, Health Assessment Questionnaire – Disability Index; IR, insufficient response; NA, not applicable; NDB, National Databank for Rheumatic Diseases, NMA, network meta-analysis; VAS, visual analogue scale: SC, Subcutaneous injection; IV, intravenous injection.

B3.6.2 Assumptions

A list of assumptions applied in the economic analysis, with the associated rationale, is provided in Table 62.

Table 62. Assumptions applied in the economic model

Base case modelling approach/assumption	Assumption detailed	Aligned with MTA375 model?
Death during initial 6-months	If a patient experiences death during the first six-months of treatment, death is assumed to occur instantly and no QALYs or costs will be accrued.	Yes
Discontinuation due to adverse events	If a patient experiences an AE, they complete the initial treatment phase with no treatment effect, automatically discontinue treatment and re-enter the initial phase on the subsequent treatment line.	Yes
Discontinuation due to loss of effect	Discontinuation due to loss of effect can only occur following at least six months of treatment in either phase. After discontinuation, patients re-enter the model at the initial treatment phase, and move to the next treatment in the sequence.	Yes
Treatment with BSC	Once a patient starts on BSC, the patient remains on this line of treatment until death.	Yes
Treatment effect of BSC	Patients on BSC do not experience a EULAR response	Yes
Efficacy of monotherapy	Relative efficacy between treatments assumed to be the same in monotherapy as estimated for combination therapies with MTX. This approach is consistent with recommendations in MTA375 and previous submissions.	Yes
Efficacy of ABC SC and TCZ SC	ABC SC efficacy for csDMARD-IR patients was assumed equivalent to bDMARD-IR patient efficacy, and TCZ SC efficacy for bDMARD-IR patients was assumed equivalent to csDMARD-IR patient efficacy.	NA
Efficacy in moderate disease activity	Assumed that relative efficacy in moderate disease activity the same as for the moderate to severe population. Sub-group analysis of FINCH 3 confirmed this assumption.	NA
Utility change in the initial treatment phase	During the six-month initial treatment phase, utility is assumed to remain the same. Utility may only change following a successful response after which treatment-related QALYs will begin to accrue.	Yes
AE occurrence	AEs may only occur in the first six months of treatment and are accrued at the end of that six-month period.	Yes
AE occurrence for patients on BSC	AEs do not occur for patients on BSC at any time	Yes
AEs do not affect treatment sequences	The incident of an AE does not change the order of treatments.	Yes

Base case modelling approach/assumption	Assumption detailed	Aligned with MTA375 model?
Cost of AEs	The cost of AEs and associated QALYs are assumed consistent across all treatments i.e. these are not treatment-specific.	Yes
Initial change in HAQ-DI	Patients with no EULAR response at 6 months do not experience a reduction in HAQ-DI. Mean initial change is found for each patient using the average initial effect for other response groups (moderate and good response). This is detailed in section B.3.3.3.	Yes
HAQ-DI trajectory continuation	The HAQ-DI trajectory continues for three years during bDMARD treatment and 15 years for csDMARD treatment. Following this HAQ-DI is assumed to remain constant at its last modelled value until death.	Yes
HAQ-DI trajectory for patients on BSC	The HAQ-DI trajectory of patients receiving BSC is assumed to be the same as those receiving csDMARDs.	Yes
Abbreviations: AE, adverse event; bDMARD, biologic disease-modifying anti-rheumatic drugs ; BSC, best supportive care; csDMARD, conventional disease-modifying anti-rheumatic drugs; HAQ-DI, Health Assessment Questionnaire – Disability Index; QALY, quality adjusted life years;		

B.3.7 Base case results

The deterministic base case cost-effectiveness results for the populations outlined in section B3.2.1 are presented below. All base case analyses were conducted by simulating 10,000 patients, using an annual price of [redacted] for filgotinib.

1a. Moderate RA patients after 2 csDMARD failures (MTX ineligible)

The results of the base case analysis for the moderate, MTX ineligible patient population after at least two csDMARD failures are presented in Table 63. Compared to BSC, filgotinib 200mg monotherapy was associated with QALY gains (0.607), and increased costs [redacted]), generating an incremental cost-effectiveness ratio (ICER) of £21,721 per QALY. The model currently applies the conservative assumption that patients with moderately active RA to not progress to a severe state. The incorporation of disease progression in a recent submission indicated that this results in an important reduction in the ICER.

Table 63: Two csDMARD failure, MTX ineligible, moderate RA – versus FIL 200mg monotherapy (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	15.810	[redacted]	-	-	-	21,721.27	-
FIL	[redacted]	15.810	[redacted]	13,182.52	0.000	0.607	-	21,721.27
Abbreviations: BSC, best supportive care; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year								

1b. Moderate RA patients after 2 csDMARD failures (MTX eligible)

The results of the base case analysis for the moderate, MTX eligible patient population after at least two csDMARD failures are presented in Table 64. Compared to BSC, filgotinib 200mg combination therapy was associated with QALY gains (0.607), and increased costs (£13,305), generating an ICER of £21,924 per QALY. The model currently applies the conservative assumption that patients with moderately active RA to not progress to a severe state.

Table 64: Two csDMARD failure, MTX eligible, moderate RA – versus FIL 200mg in combination with MTX (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	15.810	[redacted]	-	-	-	21,923.81	-
FIL + MTX	[redacted]	15.810	[redacted]	13,305.44	0.000	0.607	-	21,923.81
Abbreviations: BSC, best supportive care; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year								

2a. Severe RA patients in first line advanced therapy treatment (MTX ineligible)

The results of the base case analysis for the severe, csDMARD-IR, MTX ineligible patient population are presented in. Filgotinib 200mg monotherapy was associated with lower costs than all comparators and similar QALYs.

Table 65: csDMARD-IR, MTX ineligible, severe RA – versus FIL 200mg monotherapy (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL	[redacted]	14.639	[redacted]	-	-	-	-	-
ADA	[redacted]	14.639	[redacted]	18,513.58	0.000	-0.013	Dominated	Dominated
ETN	[redacted]	14.639	[redacted]	3,250.59	0.000	0.076	342,678.87 SW	42,542.73
BAR	[redacted]	14.639	[redacted]	8,015.03	0.000	-0.039	1,231,213.04 SW	Dominated
TCZ SC	[redacted]	14.639	[redacted]	5,000.95	0.000	-0.048	Dominated	Dominated

Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; TCZ, tocilizumab

2b. Severe RA patients in first line advanced therapy treatment (MTX eligible)

The results of the base case analysis for the severe, csDMARD-IR, MTX eligible, RTX eligible patient population are presented in Table 66. Filgotinib 200mg combination therapy was associated with lower costs than all comparators and similar QALYs.

Table 66: csDMARD-IR, MTX eligible, RTX eligible, severe RA – versus FIL 200mg in combination with MTX (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.639	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.639	[redacted]	18,263.14	0.000	-0.011	Dominated	Dominated
ETN + MTX	[redacted]	14.639	[redacted]	4,100.90	0.000	0.064	418,614.42 SW	63,661.88
BAR + MTX	[redacted]	14.639	[redacted]	7,638.94	0.000	-0.033	1,466,495.03 SW	Dominated

Abbreviations: ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

The results of the base case analysis for the severe, csDMARD-IR, MTX eligible, RTX contraindicated patient population (using second line IL-6) are presented in Table 67. Filgotinib 200mg combination therapy was associated with lower costs than all comparators and similar QALYs.

Table 67: csDMARD-IR, MTX eligible, RTX ineligible, severe RA (using second line IL-6) – versus FIL 200mg in combination with MTX (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.639	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.639	[redacted]	18,275.44	0.000	-0.014	Dominated	Dominated
ETN + MTX	[redacted]	14.639	[redacted]	4,522.59	0.000	0.086	317,815.33 SW	52,874.08
BAR + MTX	[redacted]	14.639	[redacted]	7,348.72	0.000	-0.045	1,110,108.52 SW	Dominated

Abbreviations: ADA, adalimumab; BAR, baricitinib; ETN, etanercept; FIL, filgotinib; IL-6, interleukin 6; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

The results of the base case analysis for the severe, csDMARD-IR, MTX eligible, RTX eligible patient population (using second line CD80) are presented in Table 68. Filgotinib 200mg combination therapy was associated with lower costs than all comparators and similar QALYs.

Table 68: csDMARD-IR, MTX eligible, RTX ineligible severe RA (using second line CD80) – versus FIL 200mg in combination with MTX (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.639	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.639	[redacted]	18,511.67	0.000	-0.013	Dominated	Dominated
ETN + MTX	[redacted]	14.639	[redacted]	3,261.87	0.000	0.076	342,826.47 SW	42,690.46
BAR + MTX	[redacted]	14.639	[redacted]	8,008.97	0.000	-0.039	1,231,350.00 SW	Dominated

Abbreviations: ADA, adalimumab; BAR, baricitinib; CD80, cluster of differentiation 80; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

3a. Severe RA patients after failure of first line advanced therapy treatment (MTX ineligible, RTX ineligible)

The results of the base case analysis for the severe, bDMARD-IR, MTX eligible patient population are presented in Table 69. Filgotinib 200mg monotherapy was associated with lower costs than all comparators and similar QALYs.

Table 69: bDMARD-IR, MTX ineligible, RTX ineligible, severe RA – versus FIL 200mg monotherapy (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL	[redacted]	13.638	[redacted]	-	-	-	-	-
TOF	[redacted]	13.638	[redacted]	18,837.66	0.000	-0.105	Dominated	Dominated
BAR	[redacted]	13.638	[redacted]	5,915.81	0.000	0.000	Dominated	Dominated
ABC	[redacted]	13.638	[redacted]	38,824.93	0.000	0.204	644,289.94 SW	190,639.45
Abbreviations: ABC, abatacept; BAR, baricitinib; FIL, filgotinib; LYG, life year gained; QALY, quality adjusted life year; TOF, tofacitinib								

3b. Severe RA patients after failure of first line advanced therapy treatment (MTX eligible, RTX ineligible)

The results of the base case analysis for the severe, bDMARD-IR, MTX eligible patient population are presented in Table 70. Filgotinib 200mg combination therapy was associated with lower costs than all comparators and similar QALYs.

Table 70: bDMARD-IR, MTX eligible, RTX ineligible, severe RA – versus FIL 200mg in combination with MTX (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.638	[redacted]	-	-	-	-	-
BAR + MTX	[redacted]	13.638	[redacted]	24,736.31	0.000	-0.105	Dominated	Dominated
TCZ + MTX	[redacted]	13.638	[redacted]	6,551.69	0.000	0.008	Dominated	864,430.99
SAR + MTX	[redacted]	13.638	[redacted]	431.84	0.000	0.014	Dominated	30,919.04
ABC + MTX	[redacted]	13.638	[redacted]	31,874.15	0.000	0.182	644,447.82 SW	175,026.45

Abbreviations: ABC, abatacept; BAR, baricitinib; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; SAR, sarilumab; TCZ, tocilizumab

4. Severe RA patients after failure of first line advanced therapy (MTX eligible, RTX eligible)

The results of the base case analysis for the severe, bDMARD-IR, MTX eligible patient population are presented in Table 71. Filgotinib 200mg combination therapy was associated with lower costs than all comparators and similar QALYs.

Table 71: bDMARD-IR, MTX eligible, RTX eligible, severe RA – versus FIL 200mg in combination with MTX (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.638	[redacted]	-	-	-	-	-
RTX + MTX	[redacted]	13.638	[redacted]	14,735.41	0.000	0.009	1,582,703.38 SW	1,582,703.38
Abbreviations: FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; RTX, rituximab;								

5. Severe RA patients after failure of rituximab in combination with methotrexate

The results of the base case analysis for the severe, bDMARD-IR, MTX eligible patient population are presented in Table 72. Filgotinib 200mg combination therapy was associated with lower costs than all comparators and similar QALYs.

Table 72: bDMARD-IR, MTX eligible, RTX IR, severe RA – versus FIL 200mg in combination with MTX (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.638	[redacted]	-	-	-	-	-
TCZ + MTX	[redacted]	13.638	[redacted]	31,288.00	0.000	-0.097	Dominated	Dominated
SAR + MTX	[redacted]	13.638	[redacted]	431.84	0.000	0.014	Dominated	30,919.04
Abbreviations: FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; SAR, sarilumab; TCZ, tocilizumab								

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to simultaneously vary multiple parameters, sampled from their assigned distributions, and re-estimate model outputs. In order to reduce computational time, the PSA was conducted using 500 patients. Results are based on 1,000 model runs. Probabilistic sensitivity analyses were conducted for all populations included in the base case analysis.

Table 73: Summary of inputs used for probabilistic sensitivity analyses

Parameter	Section	Distribution	Description
Efficacy			
Proportion of good/moderate responders by treatment	B3.3.2	Dirichlet	Treatment effects in terms of EULAR response (no response, moderate response, good response) were varied by sampling from a multivariate Dirichlet distribution.
Initial HAQ-DI reduction	B3.3.2	Normal	Mean HAQ-DI and standard error reported in MTA375 were used to vary response. Standard error was sampled from a normal distribution.
Hazard ratios			
Survival hazard ratios	*B3.3.5*	Lognormal	HRs were sourced from Michaud et al. (164) with a 95% CI. CIs were used to sample HRs using a lognormal distribution.
Costs			
Hospitalisation costs	*B3.5.3*	Gamma distribution	Hospital costs were taken from MTA375. However, no measure of uncertainty nor breakdown of costs was reported. Therefore, a standard error of 1/10th costs was assumed for each category and costs were sampled from a gamma distribution.

Abbreviations: CI, confidence interval; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire – Disability Index; HR, hazard ratio

Results

1a. Moderate RA patients after 2 csDMARD failures (MTX ineligible)

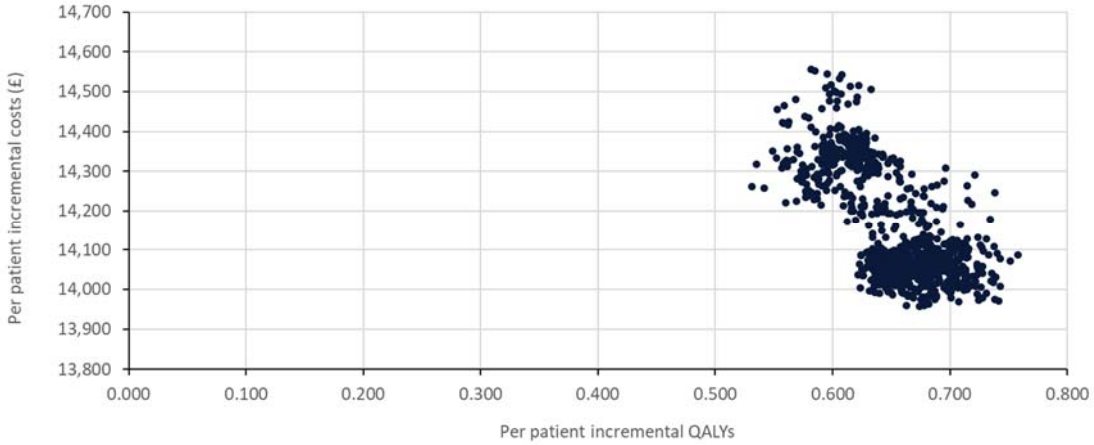
The results of the PSA are presented in Table 74, with a cost-effectiveness acceptability curve in Figure 41 and a cost-effectiveness plane in Figure 42. Results in PSA are in line with those from the base case results, with an average ICER of £21,745 compared to the base case ICER of £21,721. At a WTP threshold of £20,000, filgotinib had a 9.8% probability of being the optimal treatment. At a WTP of £30,000, this increased to 100%.

Table 74: Two csDMARD failures, MTX ineligible, moderate RA – versus FIL 200mg monotherapy (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	16.081	[redacted]	-	-	-	21,745.28	-
FIL	[redacted]	16.081	[redacted]	14,153.16	0.000	0.651	-	21,745.28
Abbreviations: BSC, best supportive care; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year								

Figure 41. Two csDMARD failures, MTX ineligible, moderate RA – CEAC for PSA

Figure 42. Two csDMARD failures, MTX ineligible, moderate RA – CE plane for PSA: filgotinib vs BSC



1b. Moderate RA patients after 2 csDMARD failures (MTX eligible)

The results of the PSA are presented in Table 75, with a cost-effectiveness acceptability curve in Figure 43 and a cost-effectiveness plane in Figure 44. Results in PSA are in line with those from the base case results, with an average ICER of £21,990 compared to the base case ICER of £21,924. At a WTP threshold of £20,000, filgotinib had a 6.8% probability of being the optimal treatment. At a WTP of £30,000, this increased to 100%.

Table 75: Two csDMARD failures, MTX eligible, moderate RA – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	16.081	[redacted]	-	-	-	21,989.61	-
FIL + MTX	[redacted]	16.081	[redacted]	14,286.15	0.000	0.651	-	21,989.61
Abbreviations: BSC, best supportive care; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year								

Figure 43. Two csDMARD failures, MTX eligible, moderate RA – CEAC for PSA

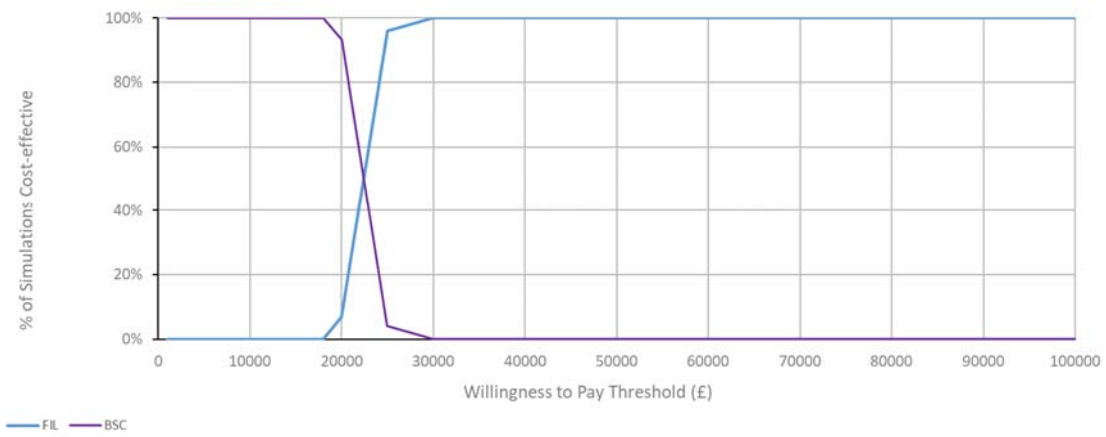
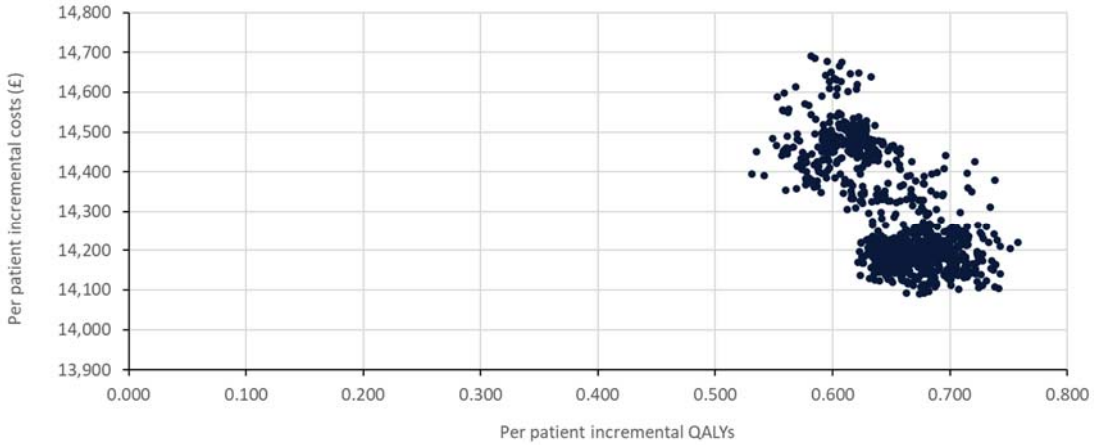


Figure 44. Two csDMARD failures, MTX eligible, moderate RA – CE plane for PSA: filgotinib vs BSC



2a. Severe RA patients in first line advanced therapy treatment of (MTX ineligible)

The results of the PSA are presented in Table 76, with a cost-effectiveness acceptability curve in Figure 45 and a cost-effectiveness plane in

Figure 46. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 76: csDMARD-IR, MTX ineligible, severe RA – versus FIL 200mg monotherapy (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL	[redacted]	14.656	[redacted]	-	-	-	-	-
ADA	[redacted]	14.656	[redacted]	21,450.89	0.000	-0.022	Dominated	Dominated
ETN	[redacted]	14.656	[redacted]	5,307.94	0.000	0.117	244,123.42 SW	37,053.13
BAR	[redacted]	14.656	[redacted]	6,890.12	0.000	-0.058	855,066.54 SW	Dominated
TCZ	[redacted]	14.656	[redacted]	16,014.94	0.000	-0.069	Dominated	Dominated

Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; TCZ, tocilizumab

Figure 45. csDMARD-IR, MTX ineligible, severe RA – CEAC for PSA

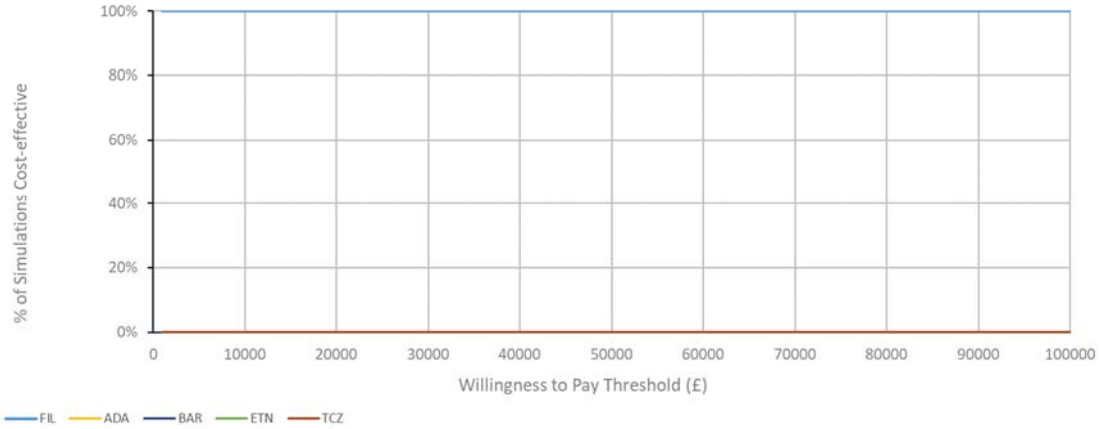
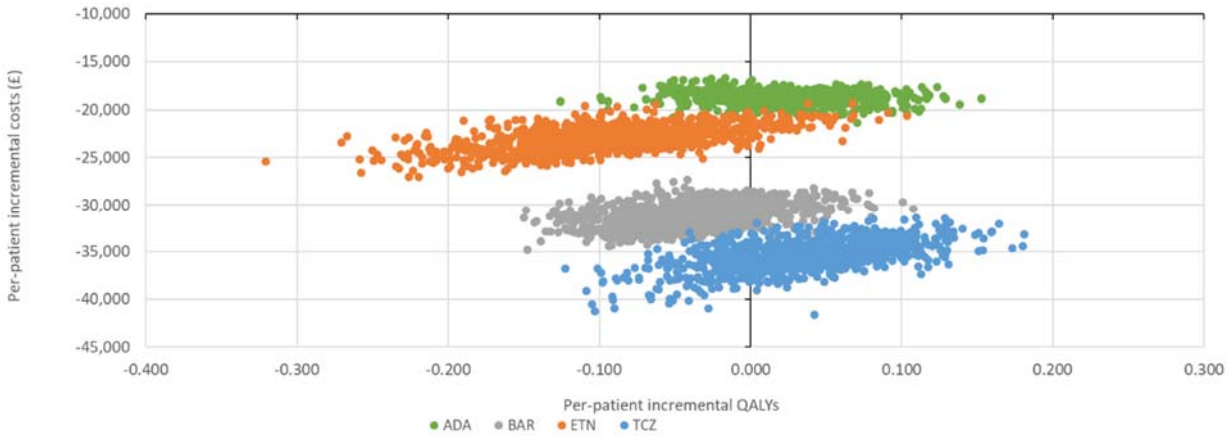


Figure 46. csDMARD-IR, MTX ineligible, severe RA – CE plane for PSA: filgotinib vs comparators



2b. Severe RA patients in first line advanced therapy treatment (MTX eligible)

The results of the PSA for the RTX eligible population are presented in Table 77, with a cost-effectiveness acceptability curve in

Figure 47 and a cost-effectiveness plane in Figure 48. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 77: csDMARD-IR, MTX eligible, RTX eligible, severe RA – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.656	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.656	[redacted]	18,841.28	0.000	-0.013	Dominated	Dominated
ETN + MTX	[redacted]	14.656	[redacted]	4,666.57	0.000	0.080	352,554.74 SW	58,514.09
BAR + MTX	[redacted]	14.656	[redacted]	7,458.41	0.000	-0.045	1,405,757.21 SW	Dominated

Abbreviations: ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Figure 47. csDMARD-IR, MTX eligible, RTX eligible, severe RA – CEAC for PSA

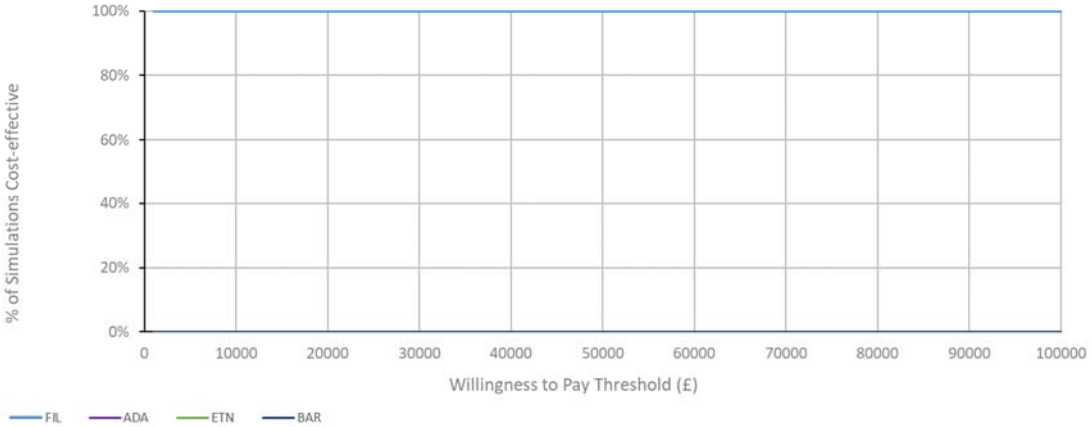
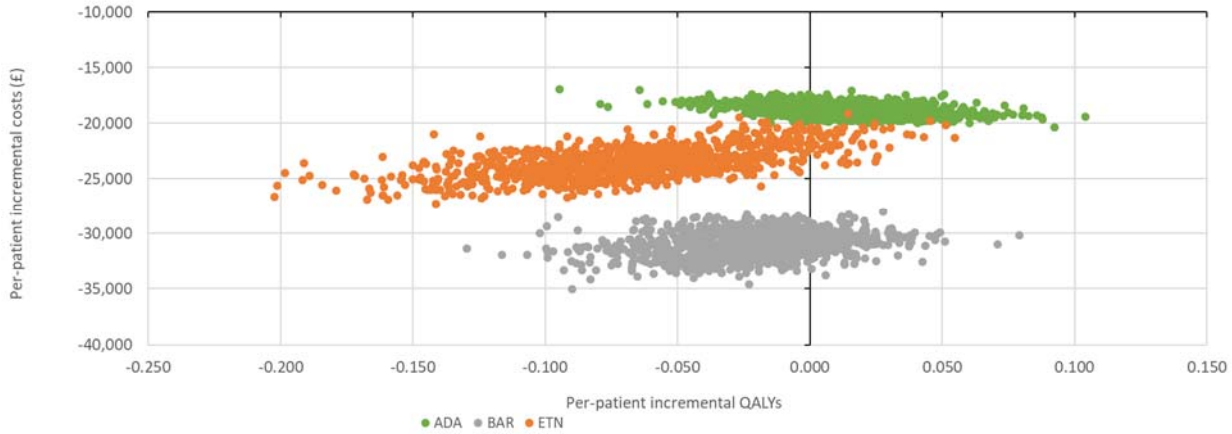


Figure 48. csDMARD-IR, MTX eligible, RTX eligible, severe RA – CE plane for PSA: filgotinib vs comparators



The results of the PSA for the RTX contraindicated population (using second line IL-6) are presented in Table 78, with a cost-effectiveness acceptability curve in Table 78 and Figure 51, and a cost-effectiveness plane in Figure 50. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 78: csDMARD-IR, MTX eligible, RTX contraindicated, severe RA (using second line IL-6) – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.656	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.656	[redacted]	18,451.45	0.000	-0.024	Dominated	Dominated
ETN + MTX	[redacted]	14.656	[redacted]	6,125.72	0.000	0.131	229,792.85 SW	46,830.69
BAR + MTX	[redacted]	14.656	[redacted]	6,902.16	0.000	-0.070	842,696.71SW	Dominated

Abbreviations: ADA, adalimumab; BAR, baricitinib; ETN, etanercept; FIL, filgotinib; IL-6, interleukin 6; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Figure 49. csDMARD-IR, MTX eligible, RTX contraindicated, severe RA, second line IL-6 – CEAC for PSA

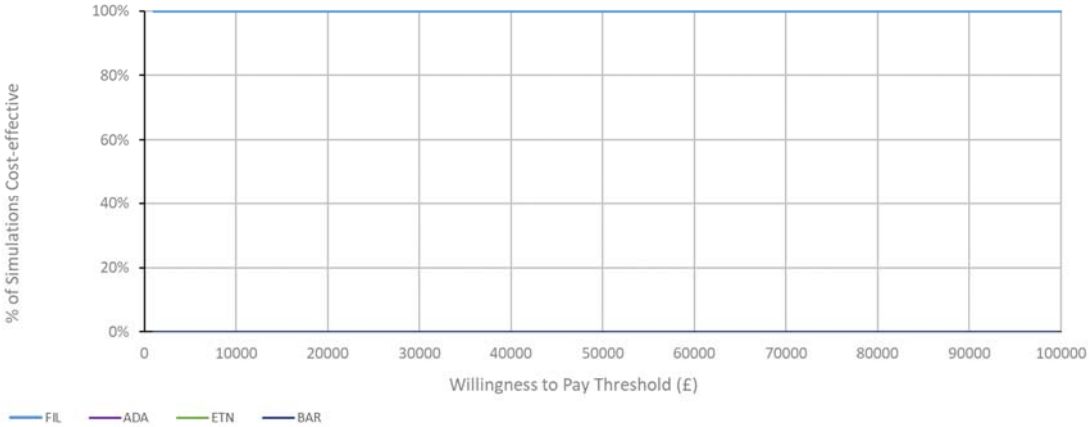
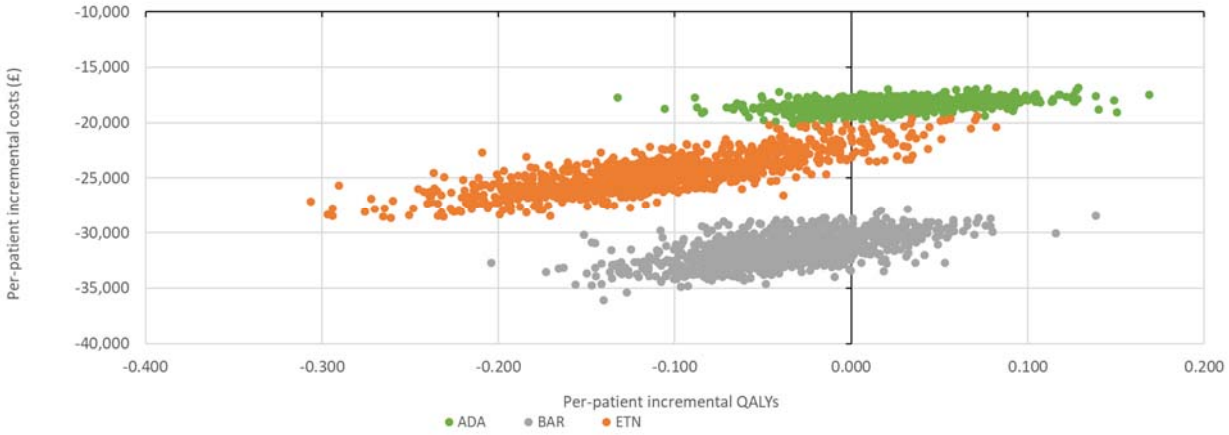


Figure 50. csDMARD-IR, MTX eligible, RTX contraindicated, severe RA, second line IL-6 – CE plane for PSA: filgotinib vs comparators



The results of the PSA for the RTX contraindicated population (using second line CD80) are presented in Table 79, with cost-effectiveness acceptability curve in Figure 51, and cost-effectiveness planes in Figure 52. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 79: csDMARD-IR, MTX eligible, RTX contraindicated, severe RA (using second line CD80) – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.656	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.656	[redacted]	18,699.05	0.000	-0.023	Dominated	Dominated
ETN + MTX	[redacted]	14.656	[redacted]	4,485.31	0.000	0.124	230,139.63 SW	36,160.93
BAR + MTX	[redacted]	14.656	[redacted]	7,940.20	0.000	-0.065	872,987.15 SW	Dominated

Abbreviations: ADA, adalimumab; BAR, baricitinib; CD80, cluster of differentiation 80; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Figure 51. csDMARD-IR, MTX eligible, RTX contraindicated, severe RA, second line CD80 – CEAC for PSA

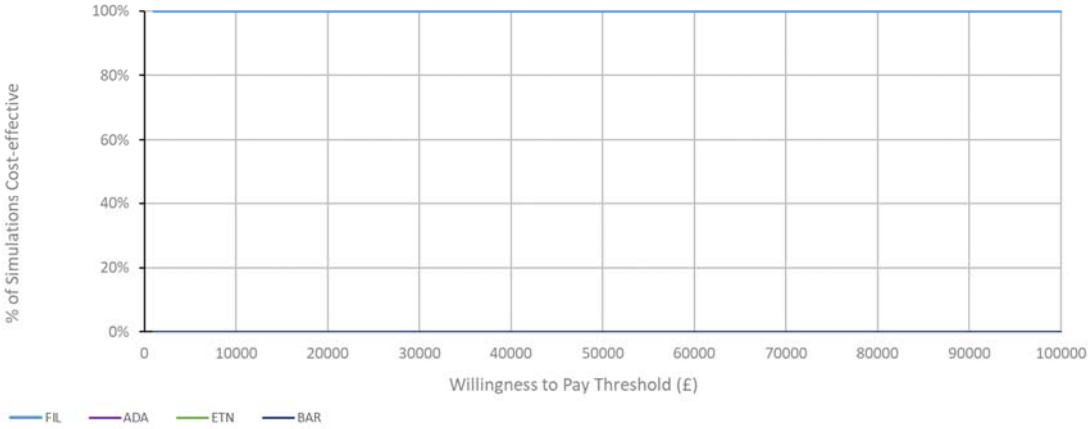
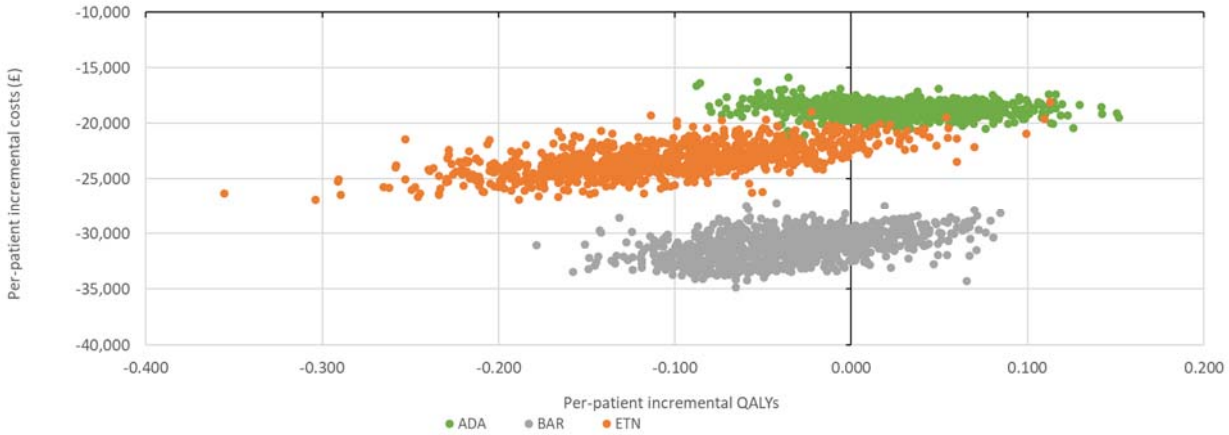


Figure 52. csDMARD-IR, MTX eligible, RTX contraindicated, severe RA, second line CD80 – CE plane for PSA: filgotinib vs comparators



3a. Severe RA patients after failure of first line advanced therapy treatment (MTX ineligible, RTX ineligible)

The results of the PSA are presented in Table 80, with a cost-effectiveness acceptability curve in Figure 53 and a cost-effectiveness plane in Figure 54. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 80: bDMARD-IR, MTX ineligible, RTX ineligible, severe RA – versus FIL 200mg monotherapy (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL	[redacted]	13.675	[redacted]	-	-	-	-	-
TOF	[redacted]	13.675	[redacted]	18,805.00	0.000	-0.150	Dominated	Dominated
BAR	[redacted]	13.675	[redacted]	6,104.92	0.000	0.001	Dominated	4,867,538.53
ABC	[redacted]	13.675	[redacted]	44,099.65	0.000	0.261	615,197.79 SW	169,046.99

Abbreviations: ABC, abatacept; BAR, baricitinib; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; TOF, tofacitinib

Figure 53. bDMARD-IR, MTX ineligible, RTX ineligible, severe RA – CEAC for PSA

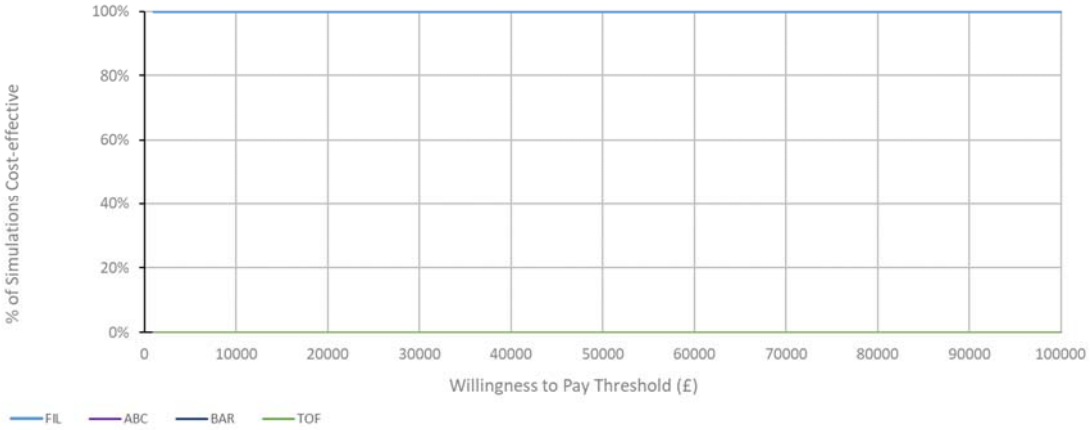
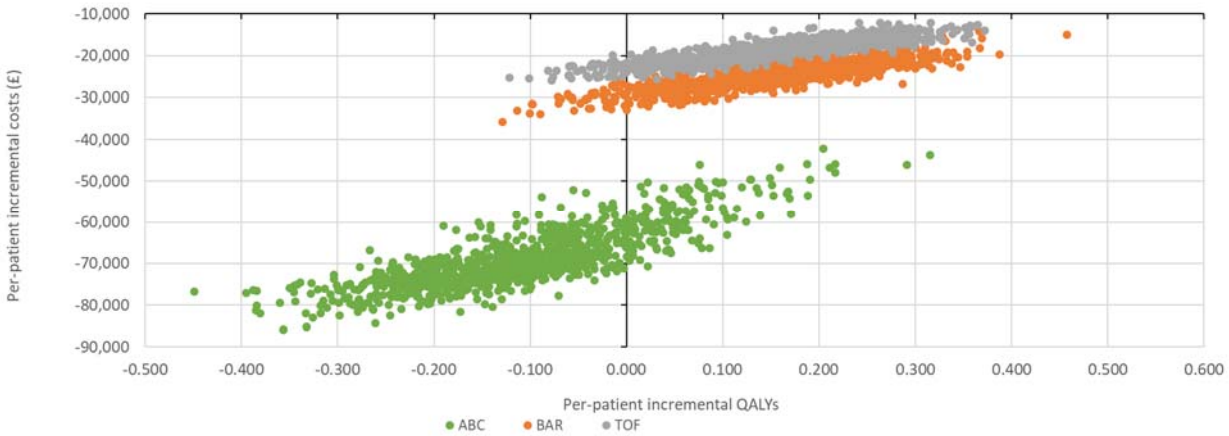


Figure 54. bDMARD-IR, MTX ineligible, RTX ineligible, severe RA – CE plane for PSA: filgotinib vs comparators



3b. Severe RA patients after failure of first line advanced therapy treatment (MTX eligible, RTX ineligible)

The results of the PSA are presented in Table 81, with a cost-effectiveness acceptability curve in Figure 55 and a cost-effectiveness plane in Figure 56. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 81: bDMARD-IR, MTX eligible, RTX ineligible, severe RA – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.675	[redacted]	-	-	-	-	-
BAR + MTX	[redacted]	13.675	[redacted]	24,916.53	0.000	-0.145	Dominated	Dominated
TCZ + MTX	[redacted]	13.675	[redacted]	6,863.21	0.000	0.008	Dominated	869,497.06
SAR + MTX	[redacted]	13.675	[redacted]	568.07	0.000	0.017	Dominated	32,883.63
ABC + MTX	[redacted]	13.675	[redacted]	36,383.58	0.000	0.232	615,737.45 SW	157,038.65

Abbreviations: ABC, abatacept; BAR, baricitinib; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life-year; SAR, sarilumab; TCZ, tocilizumab

Figure 55. bDMARD-IR, MTX eligible, RTX ineligible, severe RA – CEAC for PSA

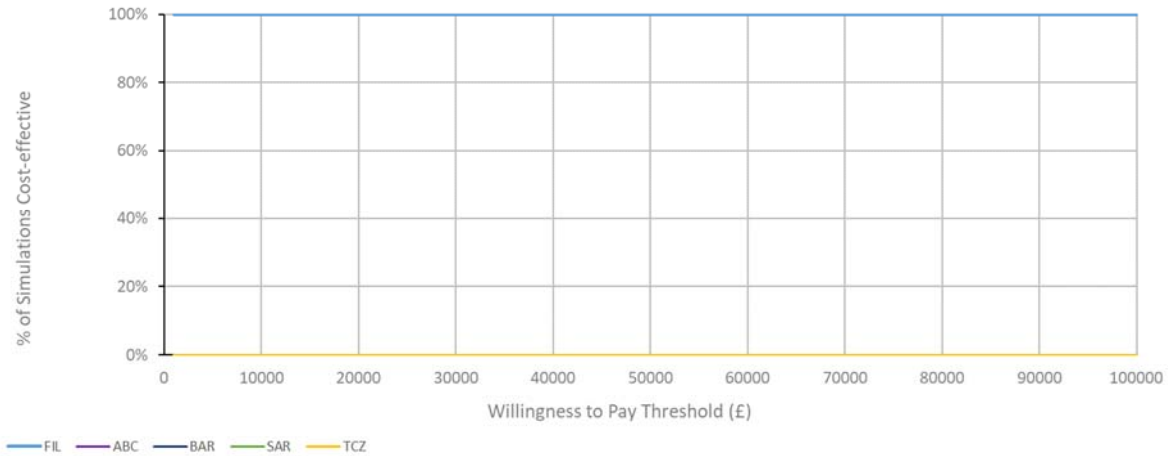
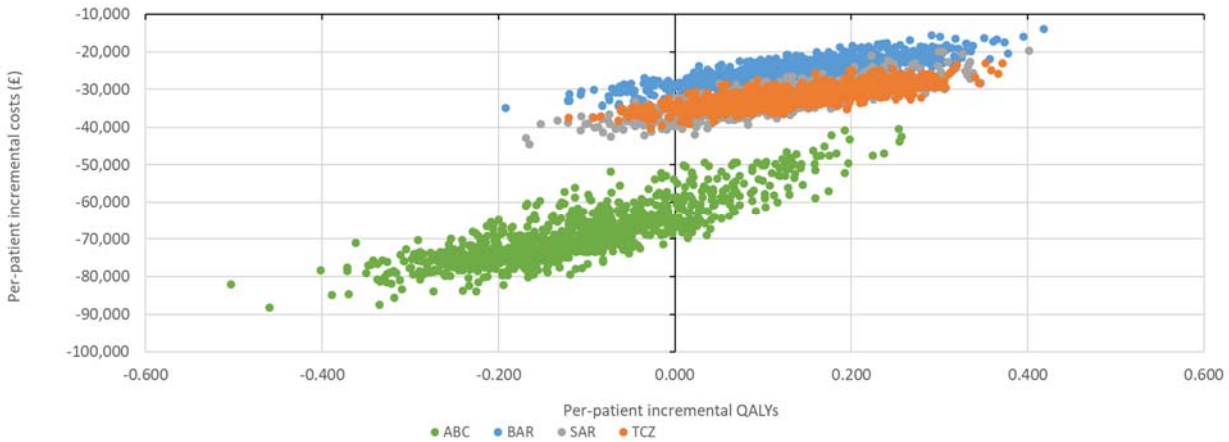


Figure 56. bDMARD-IR, MTX eligible, RTX ineligible, severe RA – CE plane for PSA: filgotinib vs comparators



4. Severe RA patients after failure of first line advanced therapy (MTX eligible, RTX eligible)

The results of the PSA are presented in Table 82, with a cost-effectiveness acceptability curve in Figure 57 and a cost-effectiveness plane in Figure 58. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 82: bDMARD-IR, MTX eligible, RTX eligible, severe RA – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.675	[redacted]	-	-	-	-	-
RTX + MTX	[redacted]	13.675	[redacted]	15,927.37	0.000	0.014	1,108,459 SW	1,108,459
Abbreviations: FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; RTX, rituximab;								

Figure 57. bDMARD-IR, MTX eligible, RTX eligible, severe RA – CEAC for PSA

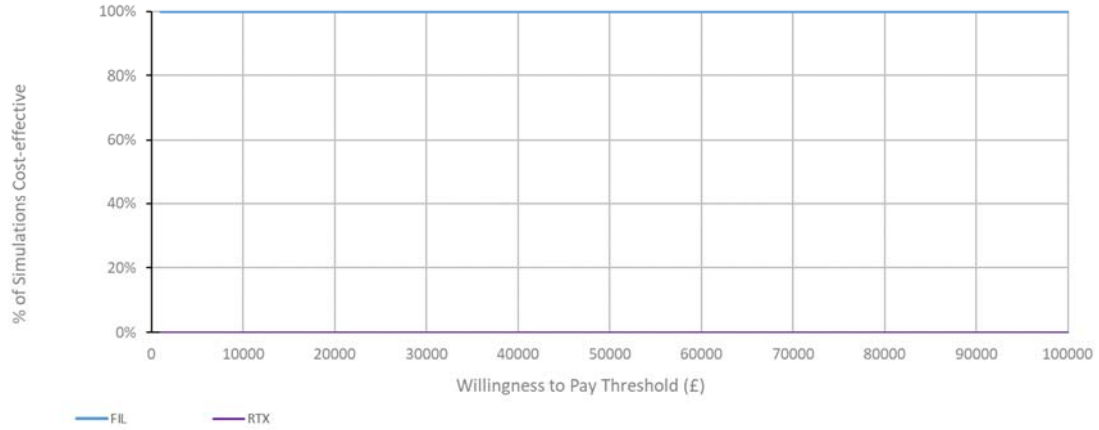


Figure 58. bDMARD-IR, MTX eligible, RTX eligible, severe RA – CE plane for PSA: filgotinib vs RTX

5. Severe RA patients after failure of rituximab in combination with methotrexate

The results of the PSA are presented in Table 83, with a cost-effectiveness acceptability curve in Figure 59 and a cost-effectiveness plane in Figure 60. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 83: bDMARD-IR, MTX eligible, RTX IR, severe RA – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.675	[redacted]	-	-	-	-	-
TCZ + MTX	[redacted]	13.675	[redacted]	31,912.18	0.000	-0.135	Dominated	Dominated
SAR + MTX	[redacted]	13.675	[redacted]	558.90	0.000	0.017	Dominated	Dominated

Abbreviations: FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; SAR, sarilumab; TCZ, tocilizumab

Figure 59. bDMARD-IR, MTX eligible, RTX IR, severe RA – CEAC for PSA

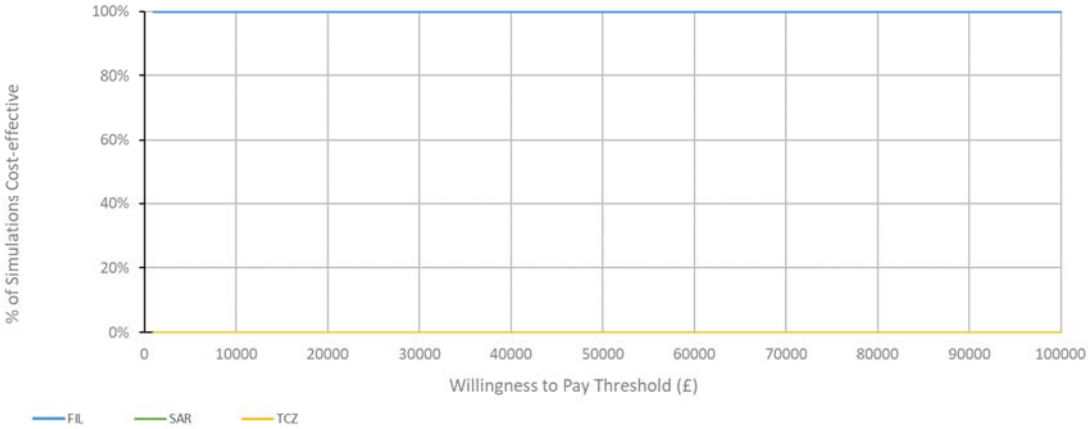
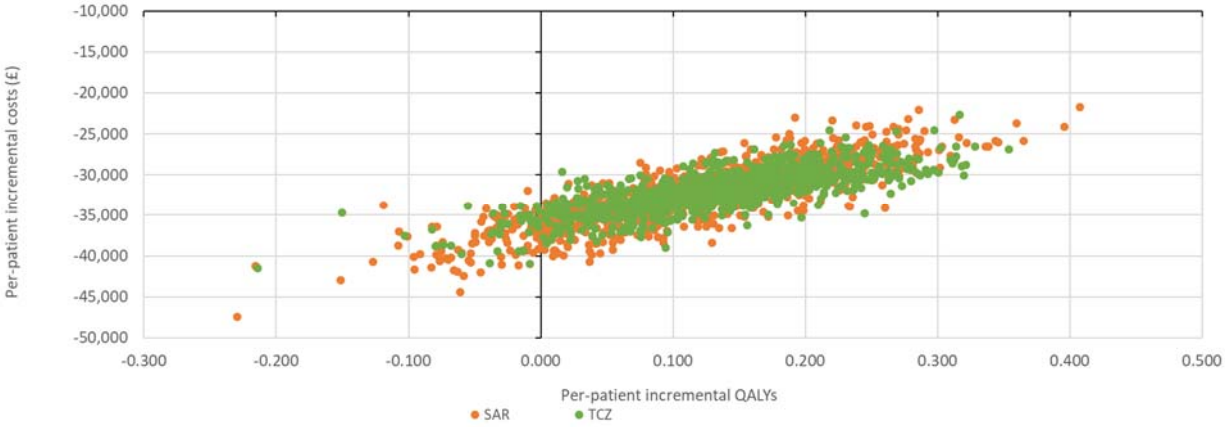


Figure 60. bDMARD-IR, MTX eligible, RTX IR, severe RA – CE plane for PSA: filgotinib vs comparators



B.3.8.2 Deterministic sensitivity analysis

The robustness of the model was tested by a set of deterministic sensitivity analyses (DSAs) and scenario analyses. One parameter or model assumption was varied at a time while the other parameters were kept at base case values. Results are presented in tornado diagrams (Figure 61, Figure 62, and Figure 63). Table 84 summarises the list of parameters and assumptions tested in DSA and scenario analyses. As the ICERs were in many cases in the south-west quadrant, the tornado diagrams are based on net monetary benefit, using a WTP threshold of £20,000.

Three tornado diagrams are presented in this section, for one population from each of the moderate csDMARD-IR, severe csDMARD-IR, and bDMARD-IR populations. Results for other populations are presented in Appendix J.

The tornado diagrams show the results of varying the parameters, as well as the results of the scenario analyses.

Table 84: Parameters and scenarios tested in deterministic sensitivity analysis

Parameters	Base case	DSA input
Discount rate for costs and QALYs	3.5%	0% and 6%
Treatment EULAR response	Median point estimates from the NMA (Section B2.9)	95% CI from the NMA

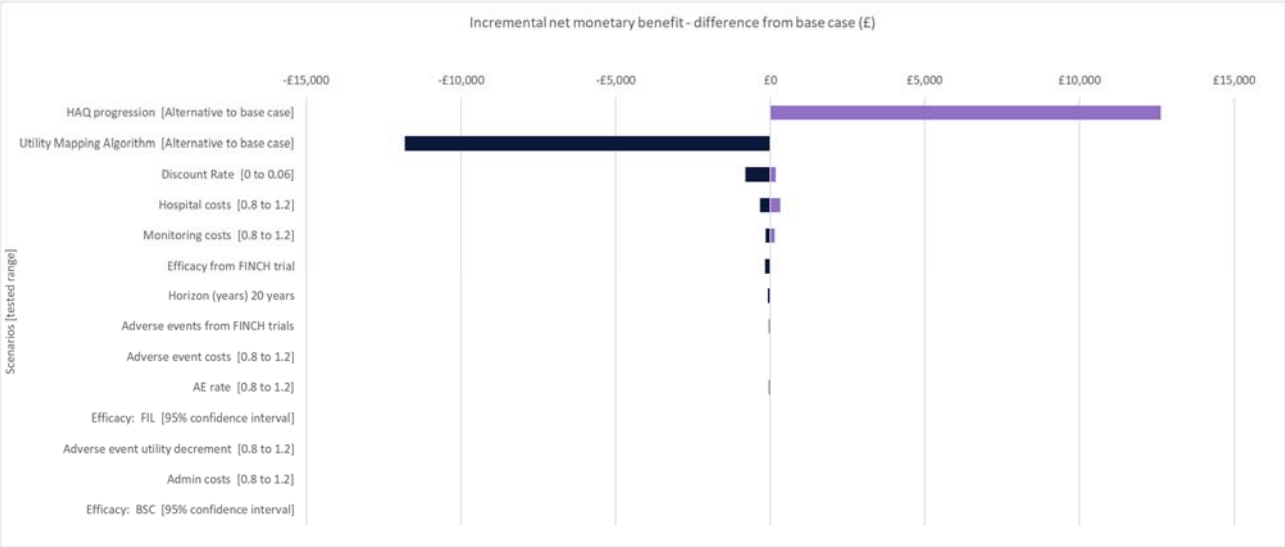
Parameters	Base case	DSA input
AE rate	Sourced from Singh et al. Cochrane review (Section B3.4.4 Adverse events)	Varied by ±20%
Administration costs	Sourced from MTA375 (Section B3.5.2 Intervention and comparators' costs and resource use)	Varied by ±20%
Monitoring costs	Sourced from MTA375 (Section B3.5.2 Intervention and comparators' costs and resource use)	Varied by ±20%
Hospital costs	Sourced from MTA375 (Section B3.5.2 Intervention and comparators' costs and resource use)	Varied by ±20%
AE costs	Sourced from MTA375 (145) (Section B3.5.2)	Varied by ±20%
AE utility decrement	Sourced from Oppong et al. (Section B3.4.4 Adverse events (161))	Varied by ±20%
Scenario	**Base case**	**DSA input**
Time horizon	Lifetime (patient maximum age 100 years)	20-year time horizon
Using filgotinib EULAR response from the FINCH 1 trial (moderate population only)	Median point estimates from the NMA (Section B2.9)	Subgroup data from FINCH 1
Using AE rates from FINCH 1	Sourced from Singh et al. Cochrane review (Section B3.4.4 Adverse events)	JAKs: 1.7% (rate for filgotinib) bDMARDs: 2.5% (rate for adalimumab) csDMARDs: 0.8% (rate for methotrexate)
Using an alternative HAQ-DI to EQ-5D mapping	Mapping sourced from Hernandez-Alva et al (Section 3.4.2) (154)	Utility mapping algorithm sourced from Malottki et al. (153)
Assuming patients receiving csDMARDs and BSC experienced a linear HAQ-DI progression	HAQ-DI trajectory based on data described by Norton et al. (157)	Linear HAQ-DI progression based on Malottki et al. (153)
Abbreviations: AE, adverse event; bDMARD, biologic disease-modifying anti-rheumatic drug; CI, confidence interval; csDMARDs, conventional disease-modifying anti-rheumatic drugs; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire – Disability Index; JAK, Janus kinase; NMA, network meta-analysis; QALY, quality adjusted life year;		

Moderate population, two csDMARD failures, MTX eligible

The results of the deterministic sensitivity analysis for the moderate, MTX eligible patient population for filgotinib combination therapy versus BSC is presented in Figure

61. The key model drivers are the HAQ progression, HAQ to EQ-5D mapping algorithm, and discount rate.

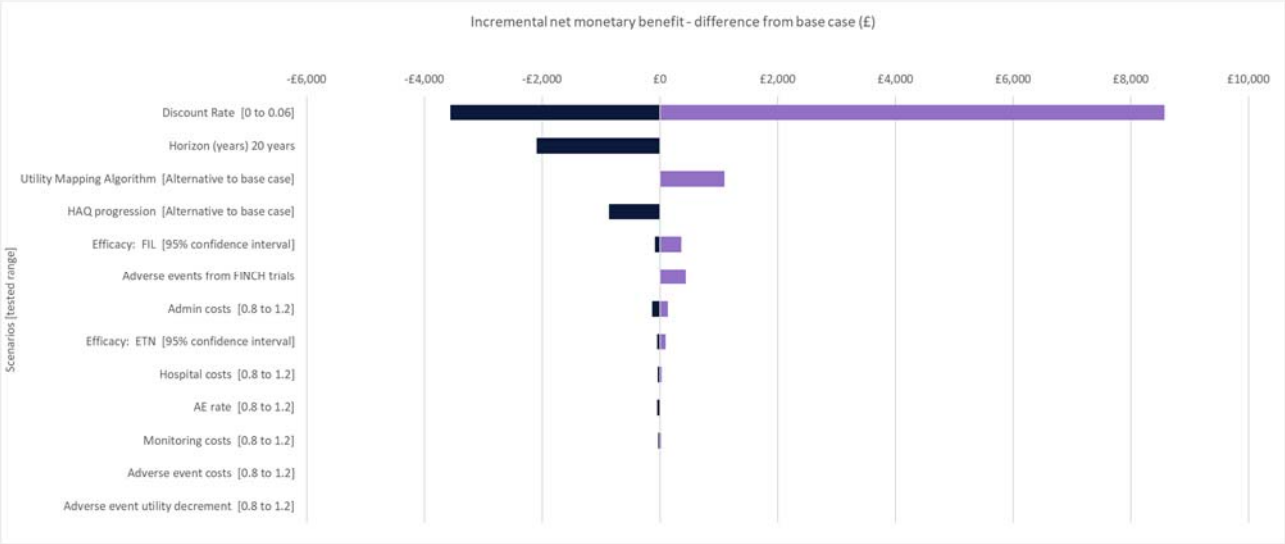
Figure 61. Tornado diagram in csDMARD-IR, MTX eligible, RTX eligible, severe RA (filgotinib combination therapy vs. BSC)



Severe csDMARD-IR, MTX eligible, RTX eligible

The results of the deterministic sensitivity analysis for the severe, csDMARD-IR, MTX eligible, RTX eligible patient population for filgotinib combination therapy presented in Figure 62. The most cost-effective comparator (i.e. with the lowest ICER in the south-west quadrant) was chosen for the analysis, which in this case is etanercept in combination with methotrexate. The key model drivers are the discount rate, annual price of filgotinib, and time horizon.

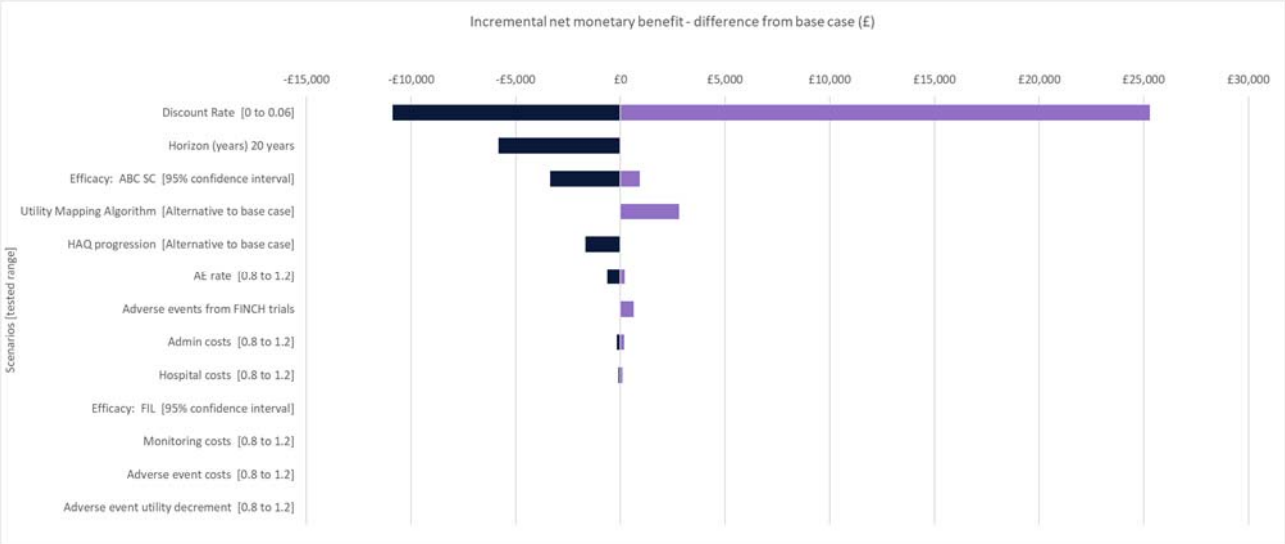
Figure 62. Tornado diagram in csDMARD-IR, MTX eligible, RTX eligible, severe RA (filgotinib combination therapy vs. ETN combination therapy)



Severe bDMARD-IR, MTX eligible, RTX ineligible

The results of the deterministic sensitivity analysis for the severe, bDMARD-IR, MTX eligible, RTX ineligible patient population for filgotinib combination therapy presented in Figure 63. The most cost-effective comparator was chosen for the analysis, which in this case is abatacept in combination with methotrexate. The key model drivers are the discount rate, time horizon, and efficacy of abatacept.

Figure 63. Tornado diagram in bDMARD-IR, MTX eligible, RTX ineligible, severe RA (filgotinib combination therapy vs. ABC combination therapy)



B.3.9 Subgroup analyses

The base case analysis includes separate analyses by disease severity and line of therapy, therefore, no further subgroups analyses are presented here.

B.3.10 Validation

Evaluations were carried out to assess the accuracy of the decision problem, model structure, evidence, treatment sequences, and assumptions in replicating the clinical pathway of interest. These evaluations were performed frequently throughout model development.

Internal validation

Internal quality assurance measures were undertaken. Model outputs were individually validated against their input equations for both survival and treatment discontinuation. Furthermore, a review was carried out to ensure the model operates as expected over the full range of inputs. To ensure consistency, parameter estimations within the model were checked against estimates generated by spreadsheet-based duplicated models. Model programming, calculations and inputs have also been reviewed.

External validation

The model approach has been validated by an independent third-party clinician. The third-party clinician did not identify any shortcomings with the model, and the guidance provided on treatment sequences was incorporated into the model.

Comparison of model output to MTA375 costs and QALYs

The sequences presented in Table 85 were used to validate the cost and QALY outputs of the economic model in this submission with that of the MTA375 model, using the costs and efficacy inputs outlined in sections 3.3 and Table 85, as well as the severe population baseline characteristics from FINCH 1. These sequences are sourced from the ERG report in TA10389 (39).

Table 85: Sequences used to validate the filgotinib model outputs using MTA375 model outputs

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment
1	Int. csDMARDs	IFX + MTX	BSC	-
2	Int. csDMARDs	ADA + MTX	IFX + MTX	BSC
3	ADA + MTX	IFX + MTX	Int. csDMARDs	BSC
4	ADA + MTX	IFX + MTX	BSC	-

Abbreviations: ADA, adalimumab; BSC, best supportive care; csDMARDs, conventional disease modifying anti-rheumatic drug; IFX, infliximab; MTX, methotrexate;

Results compared to the filgotinib model are presented in Table 86. MTA375 model outputs were sourced from a validation conducted by the ERG in TA10389 (39), and were obtained using the inputs presented in TA10389 for upadacitinib, including inputs from the NMA and cost inputs. In all cases, the filgotinib model produces higher costs and QALYs than the MTA375 model, however this variation remained within [redacted]. It should be noted however, that as the results for the two models were found using two different sources of efficacy inputs, these results should be interpreted with caution. This validation exercise suggests that the filgotinib CEM is consistent with the model described in MTA375, as well as other preceding NICE submissions in RA.

Table 86: Results from the filgotinib model compared to the MTA375 model

Sequence	Total discounted costs			Total discounted QALYs		
	FIL model	TA375 model	Ratio	FIL model	TA375 model	Ratio
1	[redacted]	£64,926	[redacted]	[redacted]	7.16	[redacted]
2	[redacted]	£78,306	[redacted]	[redacted]	7.70	[redacted]
3	[redacted]	£92,003	[redacted]	[redacted]	7.77	[redacted]
4	[redacted]	£94,925	[redacted]	[redacted]	7.28	[redacted]

Abbreviations: FIL, filgotinib; QALY, quality adjusted life year

B.3.11 Interpretation and conclusions of economic evidence

B3.11.1 Overall conclusions

The cost-effectiveness of filgotinib has been evaluated across each point in the treatment pathway, in line with the final scope and deemed relevant to all groups likely to benefit from treatment. The results of this analysis demonstrate that filgotinib represents a cost-effective option in moderate and severe disease as both a combination and monotherapy.

Filgotinib has been priced to be cost-effective in both moderate and severe populations. In moderate disease, filgotinib sequences generated a cost-effective incremental cost-effectiveness ratio (ICER) as both combination therapy with MTX (£21,924/QALY) and as monotherapy (£21,721/QALY) compared with BSC. These are likely to be conservative estimates given the model assumption that last-line patients remain on BSC and disease does not progress. This addition to the model could be expected to lower the ICER by approximately £9,000/QALY (29).

A post-hoc subgroup analysis of patients with moderate disease severity in FINCH 1 confirmed the efficacy of filgotinib in this population showing statistically significant efficacy benefit compared with placebo across a range of outcomes including ACR20, ACR50, ACR70 and DAS28 (CRP and LDA) at week 24. Absolute results were also similar to the whole population confirming efficacy across the spectrum of disease activity. Further, similar response to adalimumab was observed across endpoints including ACR at week 52.

In patients with severely active RA, filgotinib sequences were associated with similar QALYs but significantly lower costs than all comparators across all points in the treatment pathway. Although the relative efficacy of monotherapy could not be estimated within the NMA, comparison of the combination and monotherapy arms in FINCH 3 confirmed comparable efficacy across a range of clinically meaningful outcomes including ACR20, ACR50, ACR70 and HAQ-DI.

The robustness of base case results was assessed through deterministic, scenario and probabilistic analyses with results demonstrating the stability of base case results as well as a high level of certainty. This strengthens the conclusions drawn

from the base case analyses. The economic model was found to be most sensitive to scenarios where alternative inputs inform HAQ-DI progression, the algorithm used to map HAQ-DI to EQ-5D, discount factor and time horizon.

The inputs and methodologies employed in developing the economic model are well established in RA modelling and consistent with methods described for the economic model developed by ScHARR in MTA375, as well as subsequent NICE submissions (TA466, TA480 and TA485 (31, 147, 148)). Validation work confirmed similar outputs between the manufacturers model and MTA375 allowing for comparability of model outputs (Table 86). Modelled treatment sequences for each population follow NICE guidelines and were validated through clinical expert advice to ensure applicability to clinical practice in England and Wales.

Filgotinib has been shown to be a cost-effective treatment option in moderate and severe disease activity across all points in the treatment pathway. The results have been shown to be both robust and generalisable to a UK population.

B3.11.2 Strengths, limitations and further analysis

Strengths

The model structure, inputs and methodology follow that of MTA375 and other recent NICE submissions to the extent possible and are in line with clinical practise in the UK. In the base case the model applies conservative assumptions, for example, biosimilar costs have been used where available and csDMARDs are costed as per MTX, which is the least costly option. Base case assumptions have been extensively tested by varying model parameters as well as including a range of scenario analyses, for example using trial specific data. Cost-effectiveness conclusions remain largely unchanged across scenario and sensitivity analyses.

Limitations and further analysis

The efficacy of filgotinib monotherapy is assumed to be equivalent to combination therapy. While trial data is not available in the specific populations of interest, this assumption is supported by the similarity of efficacy between filgotinib monotherapy

and combination therapy arms in FINCH 3 (MTX-naïve population). This assumption was also validated through clinical opinion.

A study of UK patients in the Early RA Network (ERAN), a cohort of newly diagnosed RA patients receiving csDMARDs, showed the rate of patients progressing from moderately to severely active disease was 19% over a two-year period (16). The current model does not include the possibility for patients with moderately active RA to progress to severe disease. However, this is likely to be a conservative approach as has been demonstrated in a recent submission where disease progression was incorporated, resulting in significantly improved cost-effectiveness.

The recent TA evaluating upadacitinib in RA included analyses that demonstrated allowing patients to progress from moderate to severe disease resulted in significantly lower ICERs (approximately £9,000/QALY lower) compared with not allowing for disease progression. In addition, the proportion of patients progressing to a severe state was concluded to be an underestimation by the technical team. Including this functionality has been considered appropriate by the ERG and technical team in previous TAs in RA (TA10389, TA485). To better reflect clinical experience, future modelling could include this progression.

The base case analysis estimated ICERs below £22,000/QALY in moderate disease when filgotinib is used as monotherapy or in combination with MTX. Given moderate to severe disease progression was not incorporated in the model, including this progression would be expected to lower the ICER to below the willingness-to-pay threshold of £20,000/QALY.

B.4 References

1. Gilead. Filgotinib Draft Summary of Product Characteristics. 2020.
2. Namour F, Desrivot J, Van der Aa A, Harrison P, Tasset C, van't Klooster G. Clinical Confirmation that the Selective JAK1 Inhibitor Filgotinib (GLPG0634) has a Low Liability for Drug-drug Interactions. Drug Metab Lett. 2016;10(1):38-48.
3. McInnes IB, Schett G. The Pathogenesis of Rheumatoid Arthritis. New England Journal of Medicine. 2011;365(23):2205-19.
4. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis & Rheumatism. 2010;62(9):2569-81.
5. Gibofsky A. Epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis: A Synopsis. Am J Manag Care. 2014;20(7 Suppl):S128-35.
6. Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch MH, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). Annals of the Rheumatic Diseases. 2014;73(1):62-8.
7. van Steenbergen HW, Aletaha D, Beaart-van de Voorde LJJ, Brouwer E, Codreanu C, Combe B, et al. EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis. Annals of the Rheumatic Diseases. 2017;76(3):491-6.
8. Fransen J. Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. Rheumatology. 2004;43(10):1252-5.
9. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part I. Arthritis & Rheumatism. 2008;58(1):15-25.
10. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, et al. The global burden of rheumatoid arthritis: estimates from the Global Burden of Disease 2010 study. Annals of the Rheumatic Diseases. 2014;73(7):1316-22.
11. Symmons D. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. Rheumatology. 2002;41(7):793-800.
12. Office for National Statistics. Population estimates for the UK, England and Wales, Scotland and Northern Ireland.
13. Gilead data on file. Rheumatoid Arthritis Epidemiology. Decision Resources Group Report. 2017.
14. Humphreys JH, Verstappen SMM, Hyrich KL, Chipping JR, Marshall T, Symmons DPM. The incidence of rheumatoid arthritis in the UK: comparisons using the 2010 ACR/EULAR classification criteria and the 1987 ACR classification criteria. Results from the Norfolk Arthritis Register. Annals of the Rheumatic Diseases. 2013;72(8):1315-20.
15. Gilead data on file. Adelphi Market Research. 2020.
16. Kiely P, Walsh D, Williams R, Young A, for the Early Rheumatoid Arthritis N. Outcome in rheumatoid arthritis patients with continued conventional therapy for moderate disease activity--the early RA network (ERAN). Rheumatology. 2011;50(5):926-31.

17. Diffin JG, Lunt M, Marshall T, Chipping JR, Symmons DP, Verstappen SM. Has the severity of rheumatoid arthritis at presentation diminished over time? J Rheumatol. 2014;41(8):1590-9.
18. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. Nature Reviews Disease Primers. 2018;4(1):1-23.
19. Tymms K, Zochling J, Scott J, Bird P, Burnet S, de Jager J, et al. Barriers to Optimal Disease Control for Rheumatoid Arthritis Patients With Moderate and High Disease Activity: Optimal Disease Control Barriers in RA. Arthritis Care & Research. 2014;66(2):190-6.
20. Cole Z, Blanthorn-Hazel S, Mohammed D, Parker B. E044 Healthcare resource utilisation associated with management of patients with moderate rheumatoid arthritis in the UK: initial data from a multi-centre, retrospective, non-interventional study. Rheumatology. 2019;58(Supplement_3):kez110.043.
21. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Annals of the Rheumatic Diseases. 2020:annrheumdis-2019-216655.
22. Scott IC, Mount J, Barry J, Kirkham B. 213 Factors associated with disability in rheumatoid arthritis patients with persistent moderate disease activity. Rheumatology. 2018;57(suppl_3).
23. El Miedany Y. Co-morbidity index in rheumatoid arthritis: time to think. Clin Rheumatol. 2015;34(12):1995-2000.
24. Michaud K, Berglind N, Franzén S, Frisell T, Garwood C, Greenberg JD, et al. Can rheumatoid arthritis (RA) registries provide contextual safety data for modern RA clinical trials? The case for mortality and cardiovascular disease. Annals of the Rheumatic Diseases. 2016;75(10):1797-805.
25. Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther. 2015;17(1).
26. Matcham F, Scott IC, Rayner L, Hotopf M, Kingsley GH, Norton S, et al. The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: A systematic review and meta-analysis. Seminars in Arthritis and Rheumatism. 2014;44(2):123-30.
27. Safiri S, Kolahi AA, Hoy D, Smith E, Bettampadi D, Mansournia MA, et al. Global, regional and national burden of rheumatoid arthritis 1990–2017: a systematic analysis of the Global Burden of Disease study 2017. Annals of the Rheumatic Diseases. 2019;78(11):1463-71.
28. Lundkvist J, Kastäng F, Kobelt G. The burden of rheumatoid arthritis and access to treatment: health burden and costs. Eur J Health Econ. 2008;8(2):49-60.
29. XE Currency Table:s EUR - Euro 2007 [Available from: https://www.xe.com/currencytables/?from=EUR&date=2007-01-01.
30. National Institute for Health and Care Excellence. Rheumatoid arthritis in adults: management. NICE guideline [NG100]. 2018.
31. National Institute for Health and Care Excellence. Overview | Sarilumab for moderate to severe rheumatoid arthritis | Guidance | NICE.
32. Overview | Tofacitinib for moderate to severe rheumatoid arthritis | Guidance | NICE.

33. Overview | Baricitinib for moderate to severe rheumatoid arthritis | Guidance | NICE.
34. Overview | Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor | Guidance | NICE.
35. Overview | Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed | Guidance | NICE.
36. Overview | Tocilizumab for the treatment of rheumatoid arthritis | Guidance | NICE.
37. Overview | Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs | Guidance | NICE.
38. Overview | Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor | Guidance | NICE.
39. National Institute for Health and Care Excellence. Single Technology Appraisal: Upadacitinib for previously treated moderate to severe active rheumatoid arthritis [ID1400]. Committee Papers. 2019.
40. National Institute for Health and Care Excellence. Project information | Sirukumab for previously treated moderate to severe active rheumatoid arthritis (ID1002) | Guidance | NICE [Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10180.
41. National Institute for Health and Care Excellence. Project information | Rheumatoid arthritis (after the failure of conventional DMARDs) -rituximab [ID333] | Guidance | NICE [Available from: https://www.nice.org.uk/guidance/indevelopment/gid-tag418.
42. Kearsley-Fleet L, Davies R, De Cock D, Watson KD, Lunt M, Buch MH, et al. Biologic refractory disease in rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Annals of the Rheumatic Diseases. 2018:annrheumdis-2018-213378.
43. Atzeni F, Masala IF, di Franco M, Sarzi-Puttini P. Infections in rheumatoid arthritis. Current Opinion in Rheumatology. 2017;29(4):323-30.
44. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: A population-based study. Arthritis & Rheumatism. 2002;46(9):2287-93.
45. Winthrop KL, Yamanaka H, Valdez H, Mortensen E, Chew R, Krishnaswami S, et al. Herpes Zoster and Tofacitinib Therapy in Patients With Rheumatoid Arthritis. Arthritis & Rheumatology. 2014;66(10):2675-84.
46. Singh JA, Cameron C, Noorbaloochi S, Cullis T, Tucker M, Christensen R, et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet (London, England). 2015;386(9990):258-65.
47. Woodrick RS, Ruderman EM. Safety of biologic therapy in rheumatoid arthritis. Nature reviews Rheumatology. 2011;7(11):639-52.
48. Vyas D, O'Dell KM, Bandy JL, Boyce EG. Tofacitinib: the first Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis. The Annals of pharmacotherapy. 2013;47(11):1524-31.
49. Genovese MC, Kremer JM, van Vollenhoven RF, Alten R, Scali JJ, Kelman A, et al. Transaminase levels and hepatic events during tocilizumab treatment: pooled

analysis of long-term clinical trial safety data in rheumatoid arthritis. Arthritis Rheumatol. 2017;69(9):1751-61.
50. European Medicines Agency. Tofacitinib (Xeljanz) SPC. Available at: www.ema.europa.eu/documents/product-information/xeljanz-epar-product-information_en.pdf. Accessed February 2019.
51. European Medicines Agency. Baricitinib (Olumiant) SPC. Available at: www.ema.europa.eu/documents/product-information/olumiant-epar-product-information_en.pdf. Accessed February 2019.
52. European Medicines Agency. Methotrexate (Nordimet) SPC. Available at: www.ema.europa.eu/documents/product-information/nordimet-epar-product-information_en.pdf. Accessed January 2019.
53. Dhawan SS, Quyyumi AA. Rheumatoid arthritis and cardiovascular disease. Current atherosclerosis reports. 2008;10(2):128-33.
54. Zhang J, Chen L, Delzell E, Muntner P, Hillegass WB, Safford MM, et al. The association between inflammatory markers, serum lipids and the risk of cardiovascular events in patients with rheumatoid arthritis. Ann Rheum Dis. 2014;73(7):1301-8.
55. Gonzalez-Gay MA, Gonzalez-Juanatey C. Inflammation and lipid profile in rheumatoid arthritis: bridging an apparent paradox. Ann Rheum Dis. 2014;73(7):1281-3.
56. Pfizer Limited. Pfizer Statement on Ongoing Tofacitinib FDA PostMarketing Requirement Study In Patients With Rheumatoid Arthritis 2019 [Available from: https://investors.pfizer.com/investor-news/press-release-details/2019/Pfizer-Announces-Modification-to-Ongoing-Tofacitnib-FDA-Post-Marketing-Requirement-Study-in-Patients-with-Rheumatoid-Arthritis/default.aspx.
57. Li N, Betts KA, Messali AJ, Skup M, Garg V. Real-world Effectiveness of Biologic Disease-modifying Antirheumatic Drugs for the Treatment of Rheumatoid Arthritis After Etanercept Discontinuation in the United Kingdom, France, and Germany. Clinical Therapeutics. 2017;39(8):1618-27.
58. Wei W, Knapp K, Wang L, Chen C-I, Craig GL, Ferguson K, et al. Treatment Persistence and Clinical Outcomes of Tumor Necrosis Factor Inhibitor Cycling or Switching to a New Mechanism of Action Therapy: Real-world Observational Study of Rheumatoid Arthritis Patients in the United States with Prior Tumor Necrosis Factor Inhibitor Therapy. Adv Ther. 2017;34(8):1936-52.
59. Barclay N, Tarallo M, Hendrikx T, Marett S. Patient Preference for Oral Versus Injectable and Intravenous Methods of Treatment for Rheumatoid Arthritis. Value in Health. 2013;16(7):A568.
60. Louder AM, Singh A, Saverno K, Cappelleri JC, Aten AJ, Koenig AS, et al. Patient Preferences Regarding Rheumatoid Arthritis Therapies: A Conjoint Analysis. Am Health Drug Benefits. 2016;9(2):84-93.
61. Bolge SC, Goren A, Tandon N. Reasons for discontinuation of subcutaneous biologic therapy in the treatment of rheumatoid arthritis: a patient perspective. Patient Prefer Adherence. 2015;9:121-31.
62. Svensson B, Andersson ML, Bala SV, Forslind K, Hafstrom I, group Bs. Long-term sustained remission in a cohort study of patients with rheumatoid arthritis: choice of remission criteria. BMJ Open. 2013;3(9):e003554.
63. Nagy G, van Vollenhoven RF. Sustained biologic-free and drug-free remission in rheumatoid arthritis, where are we now? Arthritis Res Ther. 2015;17:181.

64. Conaghan PG, D'Agostino MA, Le Bars M, Baron G, Schmidely N, Wakefield R, et al. Clinical and ultrasonographic predictors of joint replacement for knee osteoarthritis: results from a large, 3-year, prospective EULAR study. Annals of the Rheumatic Diseases. 2010;69(4):644-7.
65. Gwinnutt JM, Symmons DPM, MacGregor AJ, Chipping JR, Marshall T, Lunt M, et al. Twenty-Year Outcome and Association Between Early Treatment and Mortality and Disability in an Inception Cohort of Patients With Rheumatoid Arthritis. Arthritis & Rheumatology. 2017;69(8).
66. Fautrel B, den Broeder AA. De-intensifying treatment in established rheumatoid arthritis (RA): Why, how, when and in whom can DMARDs be tapered? Best Practice & Research Clinical Rheumatology. 2015;29(4):550-65.
67. Gilead. A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 weeks in Combination with Methotrexate to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate (FINCH 1) Clinical Study Report. 2020.
68. Gilead. Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 24 Weeks in Combination with Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug(s) (csDMARDs) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Biologic DMARD(s) Treatment (FINCH 2). Clinical Study Report. 2020.
69. Gilead. A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 Weeks Alone and in Combination with Methotrexate (MTX) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are Naive to MTX Therapy (FINCH 3). Clinical Study Report. 2020.
70. Gilead. Long Term Extension Study to Assess the Safety and Efficacy of Filgotinib in Adults With Rheumatoid Arthritis (FINCH 4). 2018.
71. al Le. Establishing Non-Inferiority of a New Treatment in a Three-Arm Trial: Apply a Step-Down Hierarchical Model in a Papulopustular Acne Study and an Oral Prophylactic Antibiotics Study. International Journal of Statistics in Medical Research. 2014(3):11-20.
72. Abe T. A Multicenter, Double-Blind, Randomized, Placebo Controlled Trial of Infliximab Combined with Low Dose Methotrexate In Japanese Patients With Rheumatoid Arthritis. The Journal of Rheumatology. 2006;33(1).
73. Genant HK, Peterfy CG, Westhovens R, Becker JC, Aranda R, Vratsanos G, et al. Abatacept inhibits progression of structural damage in rheumatoid arthritis: results from the long-term extension of the AIM trial. Ann Rheum Dis. 2008;67(8):1084-9.
74. Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis. 2008;67(8):1096-103.
75. Baek HJ, Lim MJ, Park W, Park SH, Shim SC, Yoo DH, et al. Efficacy and safety of tocilizumab in Korean patients with active rheumatoid arthritis. Korean J Intern Med. 2019;34(4):917-31.

76. Beals C, Baumgartner R, Peterfy C, Balanescu A, Mirea G, Harabagiu A, et al. Magnetic resonance imaging of the hand and wrist in a randomized, double-blind, multicenter, placebo-controlled trial of infliximab for rheumatoid arthritis: Comparison of dynamic contrast enhanced assessments with semi-quantitative scoring. PLoS One. 2017;12(12):e0187397.
77. Chen D-Y. Randomized, Double-blind, Placebo-controlled, Comparative Study of Human Anti-TNF Antibody Adalimumab in Combination with Methotrexate and Methotrexate Alone in Taiwanese Patients with Active Rheumatoid Arthritis. J Formos Med Assoc. 2009;108(4).
78. Cohen S. Interleukin 1 receptor antagonist anakinra improves functional status in patients with rheumatoid arthritis. J Rheumatol. 2003;30(2).
79. Emery P. Treatment of Rheumatoid Arthritis Patients with Abatacept and Methotrexate Significantly Improved Health-Related Quality of Life. The Journal of Rheumatology. 2006.
80. Mease P. Improved health-related quality of life for patients with active rheumatoid arthritis receiving rituximab: Results of the Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) Trial. The Journal of Rheumatology. 2008;35(1).
81. Westhovens R, Taylor PC, Alten R, Pavlova D, Enriquez-Sosa F, Mazur M, et al. Filgotinib (GLPG0634/GS-6034), an oral JAK1 selective inhibitor, is effective in combination with methotrexate (MTX) in patients with active rheumatoid arthritis and insufficient response to MTX: results from a randomised, dose-finding study (DARWIN 1). Ann Rheum Dis. 2017;76(6):998-1008.
82. Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis. 2006;65(10):1357-62.
83. Smolen JS, Burmester G-R, Combe B, Curtis JR, Hall S, Haraoui B, et al. Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. The Lancet. 2016;388(10061):2763-74.
84. Weinblatt M. Intravenous Golimumab Inhibits Radiographic Progression and Maintains Clinical Efficacy and Safety in Patients with Active Rheumatoid Arthritis Despite Methotrexate Therapy: 1-Year Results of a Phase 3 Trial. 2012.
85. Weinblatt ME, Schiff M, Valente R, van der Heijde D, Citera G, Zhao C, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. Arthritis Rheum. 2013;65(1):28-38.
86. Weinblatt ME, Westhovens R, Mendelsohn AM, Kim L, Lo KH, Sheng S, et al. Radiographic benefit and maintenance of clinical benefit with intravenous golimumab therapy in patients with active rheumatoid arthritis despite methotrexate therapy: results up to 1 year of the phase 3, randomised, multicentre, double blind, placebo controlled GO-FURTHER trial. Ann Rheum Dis. 2014;73(12):2152-9.
87. Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. Mod Rheumatol. 2014;24(5):715-24.

88. Tanaka Y. Efficacy and safety of sarilumab plus methotrexate in a phase 3 trial in Japanese patients with active rheumatoid arthritis (KAKEHASI). International journal of rheumatic diseases. 2018.
89. Tanaka Y, Wada K, Takahashi Y, Hagino O, van Hoogstraten H, Graham NMH, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a randomized, placebo-controlled phase III trial in Japan. Arthritis Res Ther. 2019;21(1):79.
90. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004;50(5):1400-11.
91. Ho-Youn K. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR Journal of Rheumatology. 2007(10).
92. Kremer J. Concomitant Leflunomide Therapy in Patients with Active Rheumatoid Arthritis despite Stable Doses of Methotrexate. Annals of Internal Medicine. 2002.
93. Lim MJ. A double-blind, placebo-controlled, multicenter trial of tocilizumab in moderate to severe active RA patients with inadequate response to methotrexate in korean population. 2013.
94. Genovese MC, Fleischmann R, Kivitz AJ, Rell-Bakalarska M, Martincova R, Fiore S, et al. Sarilumab Plus Methotrexate in Patients With Active Rheumatoid Arthritis and Inadequate Response to Methotrexate: Results of a Phase III Study. Arthritis Rheumatol. 2015;67(6):1424-37.
95. Genovese MC, van Adelsberg J, Fan C, Graham NMH, van Hoogstraten H, Parrino J, et al. Two years of sarilumab in patients with rheumatoid arthritis and an inadequate response to MTX: safety, efficacy and radiographic outcomes. Rheumatology (Oxford). 2018;57(8):1423-31.
96. Strand V, Kosinski M, Chen CI, Joseph G, Rendas-Baum R, Graham NM, et al. Sarilumab plus methotrexate improves patient-reported outcomes in patients with active rheumatoid arthritis and inadequate responses to methotrexate: results of a phase III trial. Arthritis Res Ther. 2016;18:198.
97. Takeuchi T, Miyasaka N, Zang C, Alvarez D, Fletcher T, Wajdula J, et al. A phase 3 randomized, double-blind, multicenter comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity, and safety in Japanese subjects with active rheumatoid arthritis. Mod Rheumatol. 2013;23(4):623-33.
98. O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 2013;369(4):307-18.
99. Choy E, McKenna F, Vencovsky J, Valente R, Goel N, Vanlunen B, et al. Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. Rheumatology (Oxford). 2012;51(7):1226-34.
100. Tanaka Y, Suzuki M, Nakamura H, Toyoizumi S, Zwillich SH, Tofacitinib Study I. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in

patients with rheumatoid arthritis and an inadequate response to methotrexate. Arthritis Care Res (Hoboken). 2011;63(8):1150-8.
101. Kang YM, Park YE, Park W, Choe JY, Cho CS, Shim SC, et al. Rapid onset of efficacy predicts response to therapy with certolizumab plus methotrexate in patients with active rheumatoid arthritis. Korean J Intern Med. 2018;33(6):1224-33.
102. Keystone EC, Taylor PC, Drescher E, Schlichting DE, Beattie SD, Berclaz PY, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Ann Rheum Dis. 2015;74(2):333-40.
103. Hobbs K, Deodhar A, Wang B, Bitman B, Nussbaum J, Chung J, et al. Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of etanercept in patients with moderately active rheumatoid arthritis despite DMARD therapy. Springerplus. 2015;4:113.
104. Kivitz A. Peficitinib, a JAK Inhibitor, in the Treatment of Moderate-to-Severe Rheumatoid Arthritis in Patients With an Inadequate Response to Methotrexate. Arthritis & Rheumatology. 2017;69(4):709–19.
105. Taylor PC. Baricitinib Versus Placebo or Adalimumab in Patients with Active Rheumatoid Arthritis (RA) and an Inadequate Response to Background Methotrexate Therapy: Results of a Phase 3 Study. 2015 ACR/ARHP Annual Meeting2015.
106. Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J, et al. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. N Engl J Med. 2017;376(7):652-62.
107. Matsubara T, Inoue H, Nakajima T, Tanimura K, Sagawa A, Sato Y, et al. Abatacept in combination with methotrexate in Japanese biologic-naive patients with active rheumatoid arthritis: a randomised placebo-controlled phase IV study. RMD Open. 2018;4(2):e000813.
108. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. The Lancet. 2008;371(9617):987-97.
109. Dougados M, van der Heijde D, Chen YC, Greenwald M, Drescher E, Liu J, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. Ann Rheum Dis. 2017;76(1):88-95.
110. Kang YM. Efficacy and Safety Of Certolizumab Pegol (Czp) With Concomitant Methotrexate (Mtx) In Korean Rheumatoid Arthritis (Ra) Patients (Pts) With An Inadequate Response To Mtx. Ann Rheum Dis. 2013.
111. Li Z, Hu J, Bao C, Li X, Li X, Xu J, et al. SAT0218 Efficacy and safety of baricitinib in mtx-ir patients with rheumatoid arthritis: 52 week results from a phase 3 study (RA-BALANCE). Saturday, 16 JUNE 20182018. p. 969.2-70.
112. Takeuchi T, Tanaka Y, Tanaka S, Kawakami A, Iwasaki M, Katayama K, et al. Efficacy and safety of peficitinib (ASP015K) in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III randomised, double-blind, placebo-controlled trial (RAJ4) in Japan. Ann Rheum Dis. 2019;78(10):1305-19.
113. Keystone E, Heijde D, Mason D, Jr., Landewe R, Vollenhoven RV, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than

placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 2008;58(11):3319-29.
114. Smolen J, Landewe RB, Mease P, Brzezicki J, Mason D, Luijtens K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009;68(6):797-804.
115. Peterfy C, Emery P, Tak PP, Ostergaard M, DiCarlo J, Otsa K, et al. MRI assessment of suppression of structural damage in patients with rheumatoid arthritis receiving rituximab: results from the randomised, placebo-controlled, double-blind RA-SCORE study. Ann Rheum Dis. 2016;75(1):170-7.
116. Huizinga TW, Fleischmann RM, Jasson M, Radin AR, van Adelsberg J, Fiore S, et al. Sarilumab, a fully human monoclonal antibody against IL-6Ralpha in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. Ann Rheum Dis. 2014;73(9):1626-34.
117. Fleischmann R. Upadacitinib Versus Placebo or Adalimumab in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Results of a Phase III, Double- Blind, Randomized Controlled Trial. Arthritis & Rheumatology. 2019;71(11):788–1800.
118. Burmester GR. A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study of Upadacitinib (ABT-494), a Selective JAK-1 Inhibitor, in Patients with Active Rheumatoid Arthritis with Inadequate Response to Conventional Synthetic Dmards. 2017 ACR/ARHP Annual Meeting2018.
119. Burmester GR, Kremer JM, Van den Bosch F, Kivitz A, Bessette L, Li Y, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. The Lancet. 2018;391(10139):2503-12.
120. Emery P, Deodhar A, Rigby WF, Isaacs JD, Combe B, Racewicz AJ, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). Ann Rheum Dis. 2010;69(9):1629-35.
121. Tanaka Y. 12-week Results of a Phase 2b Dose-Ranging Study of Baricitinib, An Oral JAK1/JAK2 Inhibitor in Japanese Patients with Rheumatoid Arthritis on Background Methotrexate Therapy. 2013.
122. Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. 2008;58(10):2968-80.
123. Weinblatt M. A Trial Of Etanercept, A Recombinant Tumor Necrosis Factor Receptor:Fc Fusion Protein, In Patients With Rheumatoid Arthritis Receiving Methotrexate. The New England Journal of Medicine. 1999;340(4).
124. Genovese M. Abatacept for Rheumatoid Arthritis Refractory to Tumor Necrosis Factor a Inhibition. N Engl J Med. 2005(353).

125. Kivitz A, Olech E, Borofsky MA, Zazueta B, Navarro-Sarabia F, Radominski SC, et al. Two-year Efficacy and Safety of Subcutaneous Tocilizumab in Combination with Disease-modifying Antirheumatic Drugs Including Escalation to Weekly Dosing in Rheumatoid Arthritis. J Rheumatol. 2018;45(4):456-64.
126. Genovese MC, Kalunian K, Gottenberg JE, Mozaffarian N, Bartok B, Matzkies F, et al. Effect of Filgotinib vs Placebo on Clinical Response in Patients With Moderate to Severe Rheumatoid Arthritis Refractory to Disease-Modifying Antirheumatic Drug Therapy: The FINCH 2 Randomized Clinical Trial. JAMA. 2019;322(4):315-25.
127. Schiff MH, von Kempis J, Goldblum R, Tesser JR, Mueller RB. Rheumatoid arthritis secondary non-responders to TNF can attain an efficacious and safe response by switching to certolizumab pegol: a phase IV, randomised, multicentre, double-blind, 12-week study, followed by a 12-week open-label phase. Ann Rheum Dis. 2014;73(12):2174-7.
128. Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, et al. Baricitinib in Patients with Refractory Rheumatoid Arthritis. N Engl J Med. 2016;374(13):1243-52.
129. Smolen JS, Kremer JM, Gaich CL, DeLozier AM, Schlichting DE, Xie L, et al. Patient-reported outcomes from a randomised phase III study of baricitinib in patients with rheumatoid arthritis and an inadequate response to biological agents (RA-BEACON). Annals of the rheumatic diseases (no pagination), 2016. 2016;Date of Publication: October 31.
130. Zamani O. Efficacy and Safety of Baricitinib In Patients With Active Rheumatoid Arthritis And Inadequate Response To Tumour Necrosis Factor Inhibitors: Summary Results From The 24-Week Phase III RA-Beacon Study. 2016.
131. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008;67(11):1516-23.
132. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54(9):2793-806.
133. Keystone E, Burmester GR, Furie R, Loveless JE, Emery P, Kremer J, et al. Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum. 2008;59(6):785-93.
134. Genovese M. Upadacitinib (ABT-494) in Patients with Active Rheumatoid Arthritis and Inadequate Response or Intolerance to Biological Dmards: A Phase 3 Randomized, PlaceboControlled, Double-Blind Study of a Selective JAK-1 Inhibitor. 2017 ACR/ARHP Annual Meeting2017.
135. Fleischmann R. Efficacy and Safety of Sarilumab in Combination with csDMARDs in Patients with Active Rheumatoid Arthritis Who Were Inadequate Responders or Intolerant of Anti-TNF-I Therapy: Results from a Phase 3 Study. 2015 ACR/ARHP Annual Meeting2015.

136. National Institute for Health and Care Excellence. Overview | Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed | Guidance | NICE.
137. Felson. American College of Rheumatology Preliminary Definition of Improvement In Rheumatoid Arthritis. Arthritis & Rheumatism. 1995;Volume 38(Number 6,):727-35.
138. Felson. American College of Rheumatology 20/50/70 criteria (ACR20/50/70) 1999.
139. DAS28. EULAR response criteria 2019
140. Higgins. Cochrane handbook for systematic reviews of interventions. 2008.
141. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making. 2013;33(5):607-17.
142. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. Med Decis Making. 2013;33(5):618-40.
143. Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence Synthesis for Decision Making 5. Medical Decision Making. 2013;33(5):657-70.
144. Gilead. A Multicenter, Double-blind, Long Term Extension Study to Assess the Safety and Efficacy of Filgotinib in Subjects with Rheumatoid Arthritis (FINCH 4). Clinical Study Protocol. 2020.
145. Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J, et al. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. Health Technol Assess. 2016;20(35):1-610.
146. National Institute for Health and Care Excellence. NICE Pathway: Rheumatoid arthritis overview 2020.
147. National Institute for Health and Care Excellence. Overview | Tofacitinib for moderate to severe rheumatoid arthritis | Guidance | NICE.
148. National Institute for Health and Care Excellence. Overview | Baricitinib for moderate to severe rheumatoid arthritis | Guidance | NICE.
149. National Institute for Health and Care Excellence. Overview | Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor | Guidance | NICE.
150. National Institute for Health and Care Excellence. Overview | Tocilizumab for the treatment of rheumatoid arthritis | Guidance | NICE.
151. National Institute for Health and Care Excellence. Overview | Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs | Guidance | NICE.
152. National Institute for Health and Care Excellence. Overview | Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor | Guidance | NICE.
153. Malottki K, Barton P, Tsourapas A, Uthman AO, Liu Z, Routh K, et al. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of

rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. Health Technol Assess. 2011;15(14):1-278.
154. Hernandez Alava M, Wailoo A, Wolfe F, Michaud K. The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis. Rheumatology (Oxford). 2013;52(5):944-50.
155. Chen Y-F. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technology Assessment 2006;10(42).
156. Therapy Watch. 2019.
157. Norton S, Fu B, Scott DL, Deighton C, Symmons DP, Wailoo AJ, et al. Health Assessment Questionnaire disability progression in early rheumatoid arthritis: systematic review and analysis of two inception cohorts. Semin Arthritis Rheum. 2014;44(2):131-44.
158. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford). 2011;50(1):124-31.
159. Office for National Statistics. Statistics OfN. National life tables, UK: 2015 to 2017.
160. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev. 2011(2):CD008794.
161. Oppong R, Kaambwa B, Nuttall J, Hood K, Smith RD, Coast J. The impact of using different tariffs to value EQ-5D health state descriptions: an example from a study of acute cough/lower respiratory tract infections in seven countries. Eur J Health Econ. 2013;14(2):197-209.
162. Monthly Index of Medical Specialities (MIMS) 2020 [Available from: http://www.mims.co.uk/.
163. Curtis LB, Amanda. Unit Costs of Health and Social Care 2018. Project report. University of Kent. 2018.
164. Michaud K, Vera-Llonch M, Oster G. Mortality risk by functional status and health-related quality of life in patients with rheumatoid arthritis. J Rheumatol. 2012;39(1):54-9.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Filgotinib for treating moderate to severe rheumatoid arthritis [ID1632]

Clarification questions

May 2020

File name	Version	Contains confidential information	Date
ID1632 Filgotinib clarification letter 070520_Responses_v4_redacted	**5.0**	**Yes**	**06th of October, 2020**

Section A: Clarification on effectiveness data

Search Strategy

A1. Clinical & cost effectiveness searches:

a) Please clarify how the HEED database was searched on 8.8.18 and which host was used to access the resource. Please provide a URL for the HEED access point.

b) Please confirm whether HEED was searched on 8.8.18 and for the update on 18.9.19.

c) Please describe how relevant, recent reviews published in the last two years were identified as part of the systematic review search process (reported on page 9 of Appendix D, and page 4 of Appendix I).

d) In the Embase and PubMed strategies in Appendix D (page 3 and 5), please explain why the Emtree term “Rheumatoid arthritis/” was exploded to include “Juvenile rheumatoid arthritis” in #1, which was then removed in #3 using the NOT operator.

e) The same question applies to the Embase and PubMed searches in Appendix I (page 3 and 5), and lines #1 and #3 respectively.

f) Please provide URLs, search terms used and the number of results for each of the conference proceedings searches reported in Appendix D (page 9) and Appendix I (page 8).

g) Please explain the rationale for limiting the Embase and PubMed searches to English language only. Please describe what steps were taken to mitigate for potential language bias.

A1. Answer:

a) At the time of running the reviews, it was assumed that HEED was included within the Cochrane Library. Since only NHS-EED but not HEED was part of the Cochrane Library, the latter was not searched for this review. We do not

routinely search for economic SLR submissions to NICE. The systematic review searches for economic data

b) See response to a)

c) Recent systematic reviews were identified via desk research, which included a free text internet searching and a search of Medline via PubMed using a combination of medical subject headings (Mesh) terms for rheumatoid arthritis and the NIHs filter PubMed Subject Filters for Systematic Reviews https://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html

d) Exploding terms is a standard way of searching a given disease. For Rheumatoid arthritis, the emtree terms include: adult onset still disease, felty syndrome, juvenile rheumatoid arthritis and rheumatoid nodule. Juvenile rheumatoid arthritis was not relevant to the review and therefore this term was excluded by using the 'NOT' search string

e) See response to A1. d).

f) Embase includes conference abstracts and these were not excluded from the search strategy (i.e. the total number of records identified in Embase include conference abstracts). Websites and abstract books of specified conferences were hand searched in order to identify any proceedings that might be missing from the database search. Therefore, specific search terms and exact number of records identified cannot be provided. URLs to the conferences are provided below:

- American Congress of Rheumatology (ACR) - https://www.rheumatology.org/Learning-Center/Publications-Communications/Abstract-Archives
- European League Against Rheumatism (EULAR) - https://www.eular.org/public_affairs_brussels_conference.cfm
- Asia Pacific League of Associations for Rheumatology (APLAR) - https://www.aplar.org/events_page/conferences-and-meetings/

- British Society for Rheumatology (BSR) - https://www.rheumatology.org.uk/events-learning/conferences
- Australian Rheumatology Association (ARA) - https://rheumatology.org.au/

g) A language restriction was applied due to the high volume of identified studies and due to limitations in assessing information in languages other than English. This is common practice in many systematic reviews conducted to support NICE submissions (e.g. TA466 has also used an English language restriction). Previous work has shown that there is limited evidence of a systematic use of language restrictions in systematic reviews in medicine (1). In addition, the effects of language bias may potentially have diminished in the recent years as there is a shift towards publication of studies in English language (2).

A2. Clinical effectiveness searches:

a) Please explain why Emtree and MeSH indexing terms were not included for any of the comparators in the Drugs facet. This question refers to lines #4-#31 of the Embase search (page 3) and lines #4-#31 of the PubMed search (page 5).

b) Please clarify which controlled trials study design filter was used, and if possible, provide a reference to that filter.

c) Reporting of the update search date limits in Table 1 (Appendix D, Section D1.4) is unclear. Please clarify whether the Embase search was limited to 1999-2018 (line #53), as well as 2018-2019 (line #56).

d) Please report which host was used to access the Cochrane Library for the search reported in Appendix D.

e) Please list exactly which sections of the Cochrane Library were searched for the update search on 18.9.19.

f) Please provide a rationale for including a clinical studies methodological filter in the Cochrane Library search strategy.

g) Please explain why editorials, letters, case studies, reviews, comments, guidelines and case reports were 'NOT'-d out of the Cochrane Library search.

h) Please explain the rationale for limiting the Cochrane Library search to 'Trials' only (#57) after a clinical studies filter had already been applied (lines #37 to #45).

i) Please explain why line #3 was not included in the final results combination of the update search of the DARE, NHS EED and HTA databases via the CRD website.

j) Please describe how relevant, recent reviews published in the last two years were identified as part of the systematic review search process (reported on page 9 of Appendix D).

A2. Answer:

a) The search strategy used free text terms for all interventions/comparators of interest including drug generic names, trade names and any other name they are known as. Those names are expected to be found in the title and/or abstract of any eligible studies.

b) A combination of index terms and keywords were used to search for controlled trials that were adapted from NICE guidance documents and were further developed for the systematic review search. No specific filter, such as SIGN, was used.

c) Yes, both date filters were applied to the Embase search update by mistake. The result is that 2019 Embase records were not retrieved. We are investigating the impact of this and will follow-up 27/05. Note we have screened 2019 results from PubMed and expect that no key trials for the 2019 NMA were missed.

d) The Cochrane library was searched via their website: https://www.cochranelibrary.com/advanced-search

e) The search was limited to the Cochrane Central Register of Controlled Trials by limiting to the *Trials* tab

f) There is no requirement to use a study filter here since there is a tab for CENTRAL that reports all trials. However, further filtering has focused on RCTs.

g) Editorials, letters, case studies, reviews and case reports were not considered to be relevant study designs.

h) The Limit to 'Trials' indicates the tab in the Cochrane Library where studies were reported. The trials tab relates to Cochrane Central Register of Controlled Trials (CENTRAL).

i) There was an error in reporting of the search strategy. Line #3 was part of a scoping exercise during the development of the search strategy. Line #3 records are all included within line #4 so line #3 is redundant and should be deleted from the search strategy reported in Appendix D.

j) See Response to A1. c).

A3. Cost and healthcare resource identification, measurement and valuation searches:

a) Please report which host was used to access Embase for the search reported in Appendix I.

b) Please provide a rationale for including an economics study design filter in the Cochrane Library search strategy.

c) Please explain why editorials, letters, case studies, reviews and case reports were ‘NOT’-d out of the Cochrane Library search.

d) Please report which host was used to access EconLit for the search reported in Appendix I.

A3. Answer:

a) Embase was accessed via their website (www.embase.com).

b) The use of an economic filter may be justified in order to limit to those trials and reviews that potentially include a cost-effectiveness analysis.

c) Editorials, letters, case studies, reviews and case reports were not considered to be relevant study designs.

d) EconLit was accessed via EBSCO (www.ebsco.com).

Decision Problem

A4. Priority question: Table 1 of the CS presents an overview of the Final Scope issued by NICE and how this was addressed in the CS. According to Table 1, several comparators mentioned in the scope were not included in the CS (e.g. infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept or sarilumab for severely active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs). However, infliximab, certolizumab pegol, golimumab, and sarilumab were included in the NMA (CS, Figure 25, page 107).

a) Please clarify which comparators mentioned in the scope were included in the NMA for each of the two populations, cDMARD-IR and bDMARD-IR.

b) According to Table 1, best supportive care (BSC) was included in the CS and the CS states that: “BSC is assumed to have no treatment effect (i.e. EULAR non-response” (page150). Please clarify that BSC was therefore not included in the NMA and provide a justification for this.

c) Please justify for each comparator mentioned in the scope why it was not included in the NMA.

A4. Answers:

a)

Population	bDMARD-IR population	cDMARD-IR population
Comparators mentioned in the scope of the submission and included in the NMA	- Baricitinib (oral) + csDMARDs - Tofacitinib (oral)+ csDMARDs - Sarilumab (SC)+ csDMARDs - Abatacept (IV)+ csDMARDs - Tocilizumab (IV,SC)+ csDMARDs - Rituximab (IV) + csDMARDs - Certolizumab (SC) + csDMARDs - Upadacitinib (oral) + csDMARDs	- Baricitinib (oral) + csDMARDs - Etanercept (SC) + csDMARDs - Adalimumab (SC) + csDMARDs - Infliximab (IV) + csDMARDs - Abatacept (IV,SC) + csDMARDs - Tocilizumab (IV) + csDMARDs - Tofacitinib (oral) + csDMARDs - Certolizumab pegol (SC)+ csDMARDs - Upadacitinib (oral) + csDMARDs - Sarilumab (SC) + csDMARDs - Golimumab (IV) + csDMARDs

csDMARDs= cDMARDs, conventional DMARDS; IV= intravenous; SC=subcutaneous

b) BSC was defined as last line therapy of cDMARDs that patients have already failed on, administered at lower doses, and was not included in the NMA as no comparison could be made to this treatment from the trials identified. The FINCH 1 and FINCH 2 trials included patients on a therapeutic dose of 7.5mg to 20mg of methotrexate per week in both active and placebo arms. Additionally, no study identified for the NMA included a background therapy of cDMARDs that was recorded at a lower dose. This is in line with recent technical appraisals in RA that have not considered BSC in the network (TA485, TA480, TA466)(3-5).

c) We have provided a list of the RCTs which were available to include in NMA in the NICE appendices. Comparators were included where evidence was identified in an RCT to include them which was appropriate for the population, timepoint and endpoint of interest. Where trials were excluded from the NMA we have listed these and included the reason for exclusion. No comparators were excluded for any other reasons.

A5. The company refers to “failure” of treatment in the company submission (e.g. CS, page 13). Please clarify whether this is synonymous with lack of response or intolerance as specified in the scope.

A5. Answer: The company can confirm that “failure” of treatment refers to both lack of response or intolerance.

A6. The populations considered in the decision problem include: Filgotinib for moderately active RA:

a) As monotherapy after two or more cDMARD failures in patients who are MTX ineligible

b) As combination therapy with MTX after two or more cDMARD failures in patients who are MTX eligible

Please clarify how eligibility for MTX is determined and whether this includes prior MTX failure. If it does, is this counted as one of the ‘two or more cDMARD failures’?

A6. Answer: Eligibility for MTX would be determined by the prescribing clinician. This may include patients who previously have failed MTX i.e. had an insufficient response to MTX therapy alone or in combination with another cDMARD, or patients who may tolerate only a low dose of MTX, therefore, this is counted as ‘one of the two cDMARD failures’

A7. We note from Table 2 (CS, Section B.1.2.2) that the proposed dose of filgotinib is 200mg per day given orally for most patients and that a lower dose of 100mg per day is recommended only for those with severe renal impairment (defined as creatinine clearance of 15 to 30 mL/min). We also see that both doses are included in the three FINCH trials, in combination with either MTX (FINCH 1, FINCH 3) or cDMARD (FINCH 2) (CS, Table 6 in Section B.2.3). The assessment of people with severe renal impairment is not mentioned in the participant inclusion criteria for the three trials and therefore it would appear that those without this condition would be randomised to receive the 100mg dose. We are not clear why this lower dose is being used in non-renal impaired patients in the trial populations and would be grateful if the rationale for this could be clarified. Please also clarify why the 100mg dose is included in the NMA.

A7. Answer: The Phase 3 filgotinib studies, GS-US-417-0301 (FINCH1), GS-US-417-0302 (FINCH2), and GS-US-417-0303 (FINCH3), were designed to characterise the efficacy and safety of filgotinib in key rheumatoid arthritis patient populations, and evaluated 2 doses of filgotinib, 200 mg and 100mg, administered once daily alone or in combination with methotrexate or other csDMARDs. These studies were designed taking into consideration advice on the development of filgotinib from the Committee for Medicinal Products for Human Use (CHMP) in the EU and the United States Food and Drug Administration (US FDA). The lower 100 mg dose was included in these studies on the basis of these regulatory interactions

In the Phase 3 filgotinib studies, exposure-efficacy relationships using a composite exposure (AUC_{eff} and C_{eff}) of filgotinib and its primary and active metabolite, GS-829845, across various endpoints were examined. All analyses consistently revealed high response rates (approximately 65%-80% for ACR20 at Week 12) across the exposure range for both the filgotinib 200-mg and 100-mg doses. A trend of increasing response with increasing exposure was observed over the exposure range for other secondary efficacy endpoints including ACR50 and ACR70 with a plateau in response corresponding to 200 mg exposures. Exposure-safety relationships established that filgotinib and GS-829845 exposures (AUC_{0-24} and maximum observed concentration of drug [C_{max}]) were similar regardless of the presence or absence of the most frequent adverse events (AEs) and Grade 3/4 laboratory abnormalities indicating no exposure-safety relationship. Taken together,

the exposure-response analyses indicate both the 200 mg and 100 mg doses are efficacious in subjects with moderately to severely active RA with similar safety profiles. The trend towards greater efficacy with higher exposures for some secondary endpoints (ACR50 and ACR70) and a lack of exposure-safety relationship indicates an advantage to the 200-mg filgotinib dose relative to the 100-mg filgotinib dose.

The impact of comorbidities on filgotinib PK was determined in a single-centre Phase I study. Subjects with mild (estimated glomerular filtration rate [eGFR]: 60–89 mL/min/1.73 m²; n=6), moderate (eGFR: 30–59 mL/min/1.73 m²; n=6) and severe (eGFR: 15–29 mL/min/1.73 m²; n=3) renal impairment and one group with normal renal function (eGFR: ≥90 mL/min/1.73 m²; n=9) received filgotinib 100 mg QD and the effect of renal impairment on filgotinib PK was evaluated. Renal clearance of filgotinib and its main active metabolite decreased with the degree of renal impairment, leading to a 1.5-fold decrease in exposure to filgotinib and a 2.7-fold increase in exposure to its main active metabolite in subjects with severe renal impairment (6).

For completeness both approved doses of filgotinib, available from the Phase 3 clinical trials (100mg and 200mg) were included in the NMA. As described above, exposure-response analyses indicate both the 200 mg and 100 mg doses are efficacious in subjects with moderately to severely active RA with similar safety profiles.

Filgotinib Trials

A8. Please provide evidence that the FINCH 1 and 2 trials are generalisable to a UK setting.

Age and gender are two key prognostic factors associated with rheumatoid arthritis. The majority of patients in FINCH 1 (MTX-IR) were female (81.8%) with a mean trial population age of 53 years. Baseline characteristics from a UK population reported in the Norfolk Arthritis Register by Humphreys *et al* were comparable such that the majority of patients were also female (69%) and the mean age of the population was 54 years. (7)

The baseline characteristics of patients in FINCH 2 (bDMARD-IR patients), as well as the severe subgroup in FINCH 1 who may be considered a more progressed subgroup, are similar to those of patients in the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR), a UK RA registry considering patients starting a first-line TNFi between 2001 and 2014 (Table 1). The registry therefore represents adult patients in the UK with severe RA as patients are only eligible for treatment with advanced therapy once they have severe RA. This was compared to a subgroup of baseline characteristics of FINCH 2 patients and of severe subgroup patients of FINCH 1. (8, 9)

In both populations, women account for a similar proportion (76% in the BSRBR and 81.6% in FINCH 2). The two populations also have a similar mean age (57 years in the BSRBR population and 56 years in FINCH 2). The duration of disease in FINCH 2 (12.4 years) is aligned to what would be expected in the United Kingdom (10 years in the BSRBR population). In FINCH 2, patients had a mean baseline DAS28 of 5.9 (0.96). This is comparable to mean baseline DAS28 levels (6.5 [5.8 to 7.2]) reported for the population of the BSRBR. The conclusion that FINCH 2 patients are generalisable to UK patients with severe RA who are eligible for treatment with advanced therapies is aligned to clinical expert opinion at an advisory board conducted in Sep 2019. Table 1 contains a detailed comparison of FINCH 2, the severe subgroup of FINCH 1 and BSRBR patients.

Table 1 Baseline characteristics of the eligible for bDMARDs patient cohort in the BSRBR registry compared to the population of the FINCH 2 trial

	FINCH 1				**FINCH 2**			**BSRBR registry**
	Filgotinib 200mg + MTX (n=369)	**Filgotinib 100mg + MTX (n=358)**	**Adalimumab + MTX (n=251)**	**placebo + MTX (n=347)**	**Filgotinib 200mg n=148**	**Filgotnib 100mg n=153**	**Placebo n=148**	**Eligible for bDMARDs n=11 798**
Age, mean (S.D.),	[redacted]	[redacted]	[redacted]	[redacted]	56 (12.5)	55 (12.0)	56 (12.1)	56 (12)

years								
Gender, female (%)	[redacted]	[redacted]	[redacted]	[redacted]	120 (81.6)	119 (77.8%)	121 (81.8)	8777 (76)
DAS-28, mean (S.D.)	[redacted]	[redacted]	[redacted]	[redacted]	5.9 (1.03)	5.9 (0.98)	5.9 (0.86)	6.5 (1.0)
HAQ score, mean (S.D.)	[redacted]	[redacted]	[redacted]	[redacted]	1.70 (0.656)	1.64 (0.683)	1.65 (0.633)	2.0 (0.6)

A9. How many patients are from the UK in FINCH 2?

Trial region	**Country**	**Number of patients**
Region 1	United States	255
	Spain	16
	Germany	15
	Belgium	13
	United Kingdom	**9**
	France	9
	South Korea	5
	Australia	4
	Israel	3
	Switzerland	2
Region 2	Hungary	16

	Poland	19
Region 3	Mexico	30
	Argentina	12
Region 4	Japan	40

Countries within the same regions are considered to have broadly similar health care systems.

A10. Please supply supporting statements for the quality assessment of the FINCH trials in Table 9 of the CS.

A10. Answer:

Was randomisation carried out appropriately?

In all studies subject eligibility was established at the conclusion of the screening evaluations. The screening number and subject identification number (ID) were assigned for each subject by an interactive web response system (IWRS) [FINCH 1] or interactive voice/web response system (IXRS) [FINCH 2 and FINCH 3]. It was the responsibility of the investigator to ensure that each subject was eligible for the study prior to enrolment. Subjects were assigned a screening number at the time of consent.

In all studies subjects were randomly allocated to a dosing group according to a prespecified randomization scheme. Upon qualification for each study, subjects were randomized using a computerized IWRS [FINCH 1] or IXRS [FINCH 2 and FINCH 3]. Randomisation was stratified in each study by pre-defined variables:

- FINCH 1 - Randomization was stratified by geographic region, prior exposure to bDMARD (Yes or No), and presence of RF or anti-CCP antibodies (Yes or No) at screening (for RF, “No” if RF < 15 IU/mL and for anti-CCP antibodies, “No” if anti-CCP antibody quantity < 17 U/mL).

- FINCH 2 - Randomization was stratified by geographic region, prior exposure to number of bDMARDs (< 3 or ≥ 3 bDMARDs), and presence of RF or anti-CCP Ab at screening.

- FINCH 3 - Randomization was stratified by geographic region, and presence of RF or anti-CCP antibodies (Yes or No) at screening (for RF, “No” if RF < 15 IU/mL and for anti-CCP antibodies, “No” if anti-CCP antibody quantity < 17 U/mL).

In all studies an IWRS [FINCH 1] or IXRS [FINCH 2 and FINCH 3] provided the appropriate kit number to be dispensed to the subject at each dispensing visit. The kit contained the relevant study drugs for the period until the next dispensation visit.

Was the concealment of treatment allocation adequate?

In all studies a computerized IWRS [FINCH 1] or IXRS system [FINCH 2 and FINCH 3] was employed to manage subject randomization and treatment assignments.

Were the groups similar at the outset of the study in terms of prognostic factors?

Patient baselines characteristics for all trials are presented in CS section B2.3 Table 7, across all studies patient demographics and disease characteristics were balanced across the treatment groups. No notable differences were identified.

Were the care providers, participants and outcome assessors blind to treatment allocation?

All those involved in the FINCH studies (including care providers, participants and outcomes assessors were blinded to treatment allocation. In all studies a computerized IWRS [FINCH 1] or IXRS system [FINCH 2 and FINCH 3] was employed to manage subject randomization and treatment assignments. It was the responsibility of the investigator to ensure that the subject was eligible for the study prior to enrolment. Subjects were assigned a screening number at the time of consent.

In the event of a medical emergency where breaking the blind was required to provide medical care to the subject, the investigator may have obtained the individual subject treatment assignment directly from the IWRS [FINCH 1] or IXRS system [FINCH 2 and FINCH 3]. Gilead recommended, but does not require, that the

investigator contact the Gilead medical monitor before breaking the blind. Treatment assignments should have remained blinded unless that knowledge was necessary to determine emergency medical care for the subject. The rationale for unblinding must have been clearly explained in source documentation and on the eCRF, along with the date on which the treatment assignment was unblinded. The investigator was requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment was critical to the integrity of the FINCH trials and therefore, if a subject's treatment assignment was disclosed to the investigator, the subject had study drug discontinued.

Gilead Pharmacovigilance and Epidemiology (PVE) may have independently unblinded cases for expedited reporting of suspected unexpected serious adverse reactions to Regulatory Authorities.

Were there any unexpected imbalances in drop-outs between groups?

In all FINCH trials, a similar proportion of patients for all groups discontinued the study drug. Higher discontinuation rates were noted for placebo and MTX monotherapy groups, however these were not unexpected given lower anticipated treatment efficacy.

In FINCH 1, overall, 1417 subjects (80.7%) in the Safety Analysis Set had completed treatment with study drug and 338 subjects (19.3%) prematurely discontinued study drug: filgotinib 200 mg, 77 subjects (16.2%); filgotinib 100 mg, 82 subjects (17.1%); adalimumab 40 mg, 59 subjects (18.2%); placebo to filgotinib 200 mg, 16 subjects (8.4%); placebo to filgotinib 100 mg; 10 subjects (5.2%).

In FINCH 2, overall, 340 subjects (75.9%) in the Safety Analysis Set had completed treatment with study drug and 108 subjects (24.1%) prematurely discontinued study drug: filgotinib 200 mg, 21 subjects (14.3%); filgotinib 100 mg, 35 subjects (22.9%); placebo, 52 subjects (35.1%).

In FINCH 3, overall, 975 subjects (78.1%) in the Safety Analysis Set completed treatment with study drug and 274 subjects (21.9%) prematurely discontinued

treatment with study drug: filgotinib 200 mg + MTX, 83 subjects (20.0%); filgotinib 100 mg + MTX, 35 subjects (16.9%); filgotinib 200 mg monotherapy, 40 subjects (19.0%); MTX monotherapy, 116 subjects (27.9%).

Is there any evidence to suggest that the authors measured more outcomes than they reported?

All pre-planned outcomes and analyses are reported within the FINCH 1, FINCH 2 and FINCH 3 CSRs (provided with the company submission). Outcomes measured are consistent with other Phase 3 clinical trials in RA.

Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

Across all trials analyses were conducted using the Full Analysis Set (FAS), comprising all patients who were randomised and received at least 1 dose of study drug. Following randomisation, a minimal number of patients did not receive study drug and were therefore excluded from the FAS. In FINCH 1 of the 1,759 subjects randomised to treatment 4 did not receive study drug; in FINCH 2 of the 449 patients randomised to treatment 1 did not receive study drug; in FINCH 3 of the 1,252 randomised to treatment 3 did not receive study drug.

In general, missing data were not imputed unless methods for handling missing data were specified. Only observed values were used for analysis. No missing data imputation was performed. Where non-responder's imputation was used, missing data were imputed as non-response e.g. ACR20, ACR50 and ACR70.

A11. How was an inadequate response to MTX defined in the FINCH trials?

A11 response: Patients who had an inadequate response to MTX are defined as patients who have received at least 12 weeks of oral MTX on a continuous basis at a stably prescribed dose of 7.5 to 25mg/week prior to day1, and met the clinical trial inclusion criteria showing signs & symptoms at study entry of moderately to severely active RA.

A12. Results for FINCH 1 and 2 are presented as percentages with p values. All results need to be presented in full with numerical data and confidence intervals. We

can obtain these from the clinical study reports but the CSRs may be marked as ACiC. Please clarify whether data from the CSRs is ACiC. Please provide full numerical data and confidence intervals for all outcomes reported in the CS in your response so that it can be reported without ACIC marking.

A12 response: Please see Appendix 1. Document B has been updated to include this information.

A13. Priority question: The CS reports efficacy analyses for the moderate subgroup of FINCH 1. Also, separate data for the severe subgroup of FINCH 1 are reported in Appendix E. Please present full numerical data with confidence intervals for these outcomes for both subgroups (moderate and severe) from FINCH 1 and please provide the same data for FINCH 2.

A13. Answer: Please see Appendix 1 and Appendix 2. Document B and Appendix E have been updated to include this information for the moderate and severe subgroups, respectively. FINCH 2 has been deprioritised as agreed with the ERG.

A14. Priority question: The week 12 results for ACR20, 50 and 70 do not appear in the submission for the moderate and severe subgroup analyses of FINCH 1. Please supply these (full numerical data with confidence intervals) for both FINCH 1 and FINCH 2.

A14. Answer: Please see Appendix 1 and Appendix 2. Document B and Appendix E have been updated to include this information for the moderate and severe subgroups, respectively. FINCH 2 has been deprioritised as agreed with the ERG.

A15. When will results be available for the FINCH 4 long-term extension study? Are any interim analyses planned? Are there any other relevant ongoing studies?

A15 response: Study GS-US-417-0304 (FINCH 4) is an ongoing long-term extension study that enrolled eligible subjects from the three parent Phase 3 studies (GS-US-417-0301 [FINCH 1], GS-US-417-0302 [FINCH 2], and GS-US-417-0303 [FINCH 3]) and will provide long-term safety and efficacy data. Subjects enrolled in the study were randomized and received filgotinib 200 mg or 100 mg once daily for up to 6 years. An interim clinical study report including safety data has been submitted to regulatory agencies as part of the globally submitted marketing application. An interim clinical study report including both long-term safety and

efficacy data will be completed and submitted by 4Q 2020. Subsequent interim analyses including both safety and efficacy data may be performed every two years and the final study report will be submitted by Q4 2025

A16. Priority question: Appendix D mentions the DARWIN studies of filgotinib. However, these are not fully described in the clinical effectiveness section of the CS. Please provide details of the studies and their results in the same format as the FINCH trials (full numerical data with confidence intervals). Please also provide the CSRs of the DARWIN studies.

A16. Answer: Details of the DARWIN studies of filgotinib, in the same format as the FINCH trials, are provided below. Confidence intervals were not available for all outcomes in the CSRs; more time will be required to provide this information. (10, 11)

Trial methodologies

A summary of the trial methodologies used in DARWIN 1 and DARWIN 2 is provided in Table 2. (10, 11)

Table 2. Comparative summary of trial methodology for DARWIN1 and DARWIN2

Trial no. (acronym)	GLPG0634CL203 (DARWIN1)	GLPG0634-CL-204 (DARWIN2) (12)(12)(12)(12)(12)(12)
Trial design	This was a double-blind, placebo-controlled, methotrexate (MTX) add-on study in subjects with moderately to severely active RA who had an inadequate response to MTX (oral or parenteral). A total of 595 subjects were planned to be randomized to 1 of 6 filgotinib doses/dose regimens (3 different dose levels, each administered either once or twice daily [q.d. or b.i.d.]) or placebo on top of each subject's stable dose of MTX. At Week 12, subjects on placebo who had not achieved a 20% improvement in swollen joint count based on 66 joints (SJC66) and tender joint count based on 68 joints (TJC68) were to be re-randomized (automatically via interactive voice/web response system [IXRS]) to receive treatment with filgotinib 100 mg q.d. or 50 mg b.i.d. doses in a blinded fashion; subjects on filgotinib 50 mg q.d.	This was a double-blind, placebo-controlled, monotherapy study in subjects with moderately to severely active RA who had an inadequate response to methotrexate (MTX) alone. A total of 280 subjects were planned to be randomized to 1 of 3 once daily (q.d.) dose regimens of GLPG0634 (50 mg q.d., 100 mg q.d., 200 mg q.d.) or to placebo. At Week 12, all subjects on placebo and the subjects on the 50 mg dose who had not achieved a 20% improvement in swollen joint count 66 (SJC66) and tender joint count 68 (TJC68) were to be assigned (automatically via interactive voice/web response system [IXRS]) to 100 mg q.d. in a blinded fashion and were to continue the study until Week 24. Subjects in the other groups were to

Trial no. (acronym)	GLPG0634CL203 (DARWIN1)	GLPG0634-CL-204 (DARWIN2) (12)(12)(12)(12)(12)(12)
	who had not achieved a 20% improvement in SJC66 and TJC68 were to be assigned to filgotinib 100 mg q.d., and subjects on filgotinib 25 mg b.i.d. who had not achieved a 20% improvement in SJC66 and TJC68 were to be assigned to filgotinib 50 mg b.i.d. All rerandomized and re-assigned subjects continued their new dose until Week 24. Subjects in the other groups were to maintain their randomized treatment until Week 24. The planned treatment duration was 24 weeks. Analysis Populations: • ITT: all subjects randomized, exposed at least once, and with post-Baseline data for at least one efficacy parameter. • PP: subpopulation of ITT, excluding all critical (=major) protocol deviations. This is decided during the blind review meeting before final database lock. • Safety: all subjects randomized and exposed at least once.	maintain their randomized treatment until Week 24. The planned treatment duration was 24 weeks.
Eligibility criteria for participants	Main inclusion criteria: • male or female subjects who were ≥18 years of age, on the day of signing informed consent • had a diagnosis of RA since ≥6 months prior to Screening and met the 2010 ACR/EULAR criteria of RA and ACR functional class I-III • had ≥6 swollen joints (from a 66 joint count) and ≥8 tender joints (from a 68-joint count) at Screening and at Baseline • Screening serum CRP ≥0.70 x upper limit of laboratory normal range (ULN) Note that this inclusion criterion related to the serum CRP was not included in the original clinical study protocol, which was more strict (CRP of ≥14 mg/L); this numeric value was changed to 1.5xULN in Protocol Amendment 1 and later decreased to 1.2xULN (Protocol Amendment 3), and again to 0.7xULN (Protocol Amendment 5). • had received MTX for ≥6 months	Main inclusion criteria: • male or female subjects who were ≥18 years of age, on the day of signing informed consent • had a diagnosis of RA since ≥6 months prior to Screening and met the 2010 ACR/EULAR criteria of RA and ACR functional class I-III • had ≥6 swollen joints (from a 66 joint count) and ≥8 tender joints (from a 68-joint count) at Screening and at Baseline • Screening serum CRP ≥0.70 x upper limit of laboratory normal range (ULN) Note that this inclusion criterion related to the serum CRP was not included in the original clinical study protocol, which was more strict (CRP of ≥14 mg/L); this numeric value was changed to 1.5xULN in Protocol Amendment 1 and later decreased to 1.2xULN (Protocol Amendment 3), and again to 0.7xULN (Protocol

Trial no. (acronym)	GLPG0634CL203 (DARWIN1)	GLPG0634-CL-204 (DARWIN2) (12)(12)(12)(12)(12)(12)
	and had been on a stable dose (15 to 25 mg/week) of MTX for at least 4 weeks prior to Screening and willing to continue on their current regimen for the duration of the study. Stable doses of MTX as low as 10 mg/week were allowed when there was documented evidence of intolerance or safety issues at higher doses Main exclusion criteria: • current therapy with any disease modifying anti rheumatic drugs (DMARD) other than MTX, including oral or injectable gold, sulfasalazine, antimalarials, azathioprine, or D-penicillamine within 4 weeks prior to Baseline, cyclosporine within 8 weeks prior to Baseline, and leflunomide within 3 months prior to Baseline or a minimum 4 weeks prior to Baseline if after 11 days of standard cholestyramine therapy, • current or previous RA treatment with a biologic DMARD, with the exception of biologic DMARDs administered in a single clinical study setting more than 6 months prior to Screening (12 months for rituximab or other B cell depleting agents), where the biologic DMARD was effective, and if discontinued, this should not be due to lack of efficacy • previous treatment at any time with a cytotoxic agent, other than MTX, before Screening • history of active or latent tuberculosis	Amendment 5). • had received MTX for ≥6 months and had been on a stable dose (15 to 25 mg/week) of MTX for at least 4 weeks prior to Screening and willing to continue on their current regimen for the duration of the study. Stable doses of MTX as low as 10 mg/week were allowed when there was documented evidence of intolerance or safety issues at higher doses Main exclusion criteria: • current therapy with any disease modifying anti rheumatic drugs (DMARD) other than MTX, including oral or injectable gold, sulfasalazine, antimalarials, azathioprine, or D-penicillamine within 4 weeks prior to Baseline, cyclosporine within 8 weeks prior to Baseline, and leflunomide within 3 months prior to Baseline or a minimum 4 weeks prior to Baseline if after 11 days of standard cholestyramine therapy, • current or previous RA treatment with a biologic DMARD, with the exception of biologic DMARDs administered in a single clinical study setting more than 6 months prior to Screening (12 months for rituximab or other B cell depleting agents), where the biologic DMARD was effective, and if discontinued, this should not be due to lack of efficacy • previous treatment at any time with a cytotoxic agent, other than MTX, before Screening • history of active or latent tuberculosis
Settings and locations where the data were	This was a multicentre study. Subjects were included from 106 sites across 21 countries (Argentina, Australia, Belgium, Bulgaria, Chile, Columbia, Czech Republic, France, Germany,	This was a multicentre study. Subjects were included from 59 sites across 18 countries (Argentina, Austria, Bulgaria, Chile, Columbia, Germany, Guatemala, Hungary, Latvia, Mexico,

Trial no. (acronym)	GLPG0634CL203 (DARWIN1)	GLPG0634-CL-204 (DARWIN2) (12)(12)(12)(12)(12)(12)
collected	Guatemala, Hungary, Israel, Latvia, Mexico, New Zealand, Poland, Republic of Moldova, Russian Federation, Spain, Ukraine, and the United States).	New Zealand, Poland, Romania, Republic of Moldova, Russian Federation, Spain, Ukraine, and the United States).
Trial drugs	**Interventions:** • Filgotinib q.d dosing groups o 50mg (n=86) o 100mg (n=85) o 200mg (n=86) • Filgotinib b.i.d dosing groups o 25mg (n=86) o 50mg (n=85) o 100g (n=84) **Comparators:** • Placebo (n=72) For the subjects in the placebo and low dose groups who switched to 100 mg/day during the second study period: they were handled as if they discontinued at Week 12 and were imputed from Week 12 onwards in the second study period.	**Interventions:** • Filgotinib q.d dosing groups o 50mg (n= 72) ▪ Responders remain on 50 mg q.d ▪ Non-responders assigned to 100 mg q.d. o 100mg (n=70) o 200mg (n=69) **Comparators:** • Placebo (n=72) For the subjects in the placebo and low dose groups who switched to 100 mg/day during the second study period: they were handled as if they discontinued at Week 12 and were imputed from Week 12 onwards in the second study period.
Permitted and disallowed concomitant medications	Concomitant therapies taken for the long-term treatment of pre-existing conditions could continue during the study provided they were in accordance with the inclusion and exclusion criteria. It was preferred that these medications were stabilized and continued without variation of dose or regimen during the study. In case new therapies needed to be administered during the study, the risk/benefit to the subject should have been carefully assessed and consideration should have been given to the timing of any necessary introduction of new medications. Permitted concomitant medications at Screening and during the study included: • NSAIDs, provided that the dose was stable for ≥2 weeks prior to Baseline and, if possible, was kept constant during the study. • Oral steroids, provided that the dose was stable, was ≤10 mg/day prednisone or equivalent for ≥ 4 weeks prior to baseline and was kept stable for the study duration. • Analgesics, other than NSAIDs, up to the maximum recommended doses may have been used for pain as required.	Concomitant therapies taken for the long-term treatment of pre-existing conditions could continue during the study provided they were in accordance with the inclusion and exclusion criteria. It was preferred that these medications were stabilized and continued without variation of dose or regimen during the study. In case new therapies needed to be administered during the study, the risk/benefit to the subject should have been carefully assessed and consideration given to the timing of any necessary introduction of new medications. Permitted concomitant medications at Screening and during the study included: • antimalarials, which had to be at a stable dose for at least 12 weeks prior to Baseline • NSAIDs, provided that the dose was stable for ≥2 weeks prior to Baseline and, if possible, was to be kept constant during the study • oral steroids, provided that the dose was stable, was ≤ 10

Trial no. (acronym)	GLPG0634CL203 (DARWIN1)	GLPG0634-CL-204 (DARWIN2) (12)(12)(12)(12)(12)(12)
	However, subjects could not take analgesics within 24 hours before a visit where clinical efficacy assessments were performed and recorded. All local standard-of-care practices for the administration of MTX, including laboratory testing, follow-up care, and contraindications should have been performed according to local standards of care throughout the study. If subjects were taking folic acid at Screening as a preventive measure for MTX toxicity, this should have been continued at a stable dose for the duration of the study. Female subjects of childbearing potential were to use highly effective birth-control methods as outlined in the inclusion criteria and agree to continue their use during the study and for ≥ 12 weeks after the last dose of study medication. The use of hormonal contraceptives was recorded in the Concomitant Therapy section of the eCRF. Applicable procedures and treatment guidance based on package inserts were to be respected. Hormone replacement therapy was to be allowed in post-menopausal women if it was ongoing at the time of Screening. The use of hormone replacement therapy was to be recorded in the Concomitant Therapy section of the eCRF. Applicable procedures and treatment guidance based on package inserts were to be respected. Prohibited medications during the study included any DMARDs, other than background MTX, including oral or injectable gold, sulfasalazine, antimalarials, azathioprine, or D-penicillamine within 4 weeks prior to Baseline, cyclosporine within 8 weeks prior to Baseline, and leflunomide within 3 months prior to Baseline or ≥4 weeks prior to Baseline if after 11 days of standard cholestyramine therapy. Current or previous RA treatment with a biologic DMARD was prohibited, with the exception of biologic DMARDs administered in a single clinical study setting > 6 months prior to Screening (12 months for rituximab or other B cell	mg/day prednisone or equivalent for ≥ 4 weeks prior to Baseline, and was kept stable for the study duration • analgesics, other than NSAIDs, up to the maximum recommended doses could be used for pain as required. However, subjects could not take analgesics within 24 hours before a visit where clinical efficacy assessments were performed and recorded Female subjects of childbearing potential were to use highly effective birth-control methods as outlined in the inclusion criteria and agree to continue their use during the study and for ≥12 weeks after the last dose of study medication. The use of hormonal contraceptives was to be recorded in the Concomitant Therapy section of the eCRF. Applicable procedures and treatment guidance based on package inserts were respected. Hormone replacement therapy was to be allowed in post-menopausal women if it was ongoing at the time of Screening. The use of hormone replacement therapy was to be recorded in the Concomitant Therapy section of the eCRF. Applicable procedures and treatment guidance based on package inserts were respected. Prohibited medications during the study included any biological DMARDs. Current or previous RA treatment with a biologic DMARD was prohibited, with the exception of biologic DMARDs administered in a single clinical study setting >6 months prior to Screening (12 months for rituximab or other B cell depleting agents), where the biologic DMARD was effective, and if discontinued, this could not be due to lack of efficacy. Previous treatment at any time with a cytotoxic agent, other than MTX, before Screening was prohibited. These agents included, but were not limited to chlorambucil, cyclophosphamide, nitrogen mustard, and other alkylating agents.

Trial no. (acronym)	GLPG0634CL203 (DARWIN1)	GLPG0634-CL-204 (DARWIN2) (12)(12)(12)(12)(12)(12)
	depleting agents), where the biologic DMARD was effective, and if discontinued, this could not be due to lack of efficacy.	Previous use of JAK inhibitors was prohibited. Receipt of an intra-articular or parenteral corticosteroid injection within 4 weeks prior to Screening was prohibited.
Primary outcomes	The primary efficacy endpoint was the proportion of subjects who achieved an ACR20 response at week 12.	The primary efficacy endpoint was the proportion of subjects who achieved an ACR20 response at week 24.
Key secondary outcomes (including scoring methods and timings of assessments)	The percentage of subjects achieving: • ACR20, • ACR50, • ACR70, • ACR-N, • Disease Activity Score based on 28 joints and CRP (DAS28[CRP]), • European League Against Rheumatism (EULAR) response, • ACR/EULAR remission, • Clinical Disease Activity Index (CDAI), • Simplified Disease Activity Index (SDAI)	The percentage of subjects achieving: • ACR20, • ACR50, • ACR70, • ACR-N, • Disease Activity Score based on 28 joints and CRP (DAS28[CRP]), • European League Against Rheumatism (EULAR) response, • ACR/EULAR remission, • Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI)
Other secondary outcomes	• Absolute value and change from baseline in SF-36, • Absolute value and change from baseline in FACIT-Fatigue score	• Absolute value and change from baseline in SF-36, • Absolute value and change from baseline in FACIT-Fatigue score

ACR, American College of Rheumatology;; CDAI, clinical disease activity index; CRP, C-reactive protein; DAS, disease activity score; DMARDs, disease modifying anti-rheumatic drugs; bDMARDs, biologic DMARDs, cDMARDs, conventional DMARDS; EQ-5D, EuroQol five dimension; EULAR, European League Against Rheumatism; FACIT-F, functional assessment of chronic illness therapy-fatigue; FAS, full analysis set; HAQ-DI, health assessment questionnaire disability index, low disease activity;; MTX, methotrexate; NA, not applicable; PCS, Physical Component Summary; PTM, placebo-to-match; RA, rheumatoid arthritis; RF, Rheumatoid factor; SDAI, simplified disease activity index; SF-36, 36-item short form survey; SJC, Swollen joint count; TJC, Tender joint count, ULN, upper limit of laboratory normal range

DARWIN 1

Patients baseline characteristics are summarised in Table 3.(11)

Table 3. Baseline characteristics of patients in DARWIN 1

	Placebo (n=86)	Filgotinib q.d Dose Groups			Filgotinib b.i.d Dose Groups		
		50g (n=82)	100 mg (n=85)	200mg (n=86)	25mg (n=86)	50mg (n=85)	100mg (n=84)
Age, mean (SD)	52.0 (1.36)	52.8 (1.47)	52.3 (1.42)	54.8 (1.28)	52.4 (1.37)	55.4 (1.25)	53.9 (1.27)

Sex at birth, n (%)							
Male	16 (18.6)	13 (15.9)	20 (23.5)	12 (14.0)	18 (20.9)	20 (23.5)	14 (16.7)
Female	70 (81.4)	69 (84.1)	65 (76.5)	74 (86.0)	68 (79.1)	65 (76.5)	70 (83.3)
Race, n (%)							
Asian	0	0	1 (1.2)	0	0	1 (1.2)	0
Black or African American	1 (1.2)	0	0	1 (1.2)	0	0	1 (1.2)
White	59 (68.6)	61 (74.4)	62 (72.9)	67 (77.9)	63 (73.3)	65 (76.5)	66 (78.6)
Other	26 (30.2)	21 (25.6)	22 (25.9)	18 (20.9)	23 (26.7)	19 (22.4)	17 (20.2)
BMI, mean kg/m² (SD)	28.21 (0.657)	27.86 (0.719)	28.05 (0.565)	27.51 (0.564)	28.31 (0.536)	29.16 (0.581)	28.54 (0.657)
Mean duration of RA from diagnosis, years (SD)	8.21 (0.772)	7.21 (0.576)	7.67 (0.731)	8.51 (0.853)	8.88 (0.789)	7.79 (0.731)	9.74 (1.005)
RF positive, n (%)	65 (76.5)	64 (78.0)	57 (67.1)	65 (75.6)	66 (76.7)	64 (75.3)	65 (77.4)
Anti-CCP positive, n (%)	72 (83.7)	64 (78.0)	60 (70.6)	69 (80.2)	70 (82.4)	70 (82.4)	68 (81.0)
RF positive + anti-CCP positive, n (%)	64 (74.4)	60 (73.2)	54 (63.5)	64 (74.4)	65 (75.6)	61 (71.8)	63 (75.0)

BMI=body mass index (weight [kg]/height² [cm²]);CCP=cyclic citrullinated peptide, eCRF=electronic case report form; N=number of subjects per treatment group; n=number of subjects per category; q.d.=*quaque die*, once daily; RA=rheumatoid arthritis; RF=rheumatoid factor, SE=standard error

Table 4 is a summary of the primary and secondary efficacy outcomes for DARWIN1. (11)

Table 4. DARWIN 1 - Summary of primary and secondary outcomes at weeks 12 and 24 (NRI [ITT Population])

	Week	Filgotinib q.d Dose Groups			Filgotinib b.i.d Dose Groups			Placebo (n=86)
		50g (n=82)	100 mg (n=85)	200mg (n=86)	25mg (n=86)	50mg (n=85)	100mg (n=84)	
ACR20 responders (%)	12	46 (56.1)	54 (63.5) *	59 (68.6) **	49 (57.0)	51 (60.0)	66 (78.6) ***	38 (44.2)
	24	45 (54.9)	52 (61.2) *	63 (73.3) ***	48 (55.8)	51 (60.0) *	67 (79.8) ***	36 (41.9)
ACR50 responders (%)	12	27 (32.9) *	32 (37.6) **	37 (43.0) ***	24 (27.9) *	29 (34.1) *	46 (54.8) ***	13 (15.1)
	24	29 (35.4) **	40 (47.1) ***	43 (50.0) ***	30 (34.9) **	30 (35.3) **	46 (54.8) ***	14 (16.3)
ACR70 responders (%)	12	13 (15.9)	18 (21.2)	21 (24.4) *	12 (14.0)	16 (18.8)	26 (31.0) **	7 (8.1)
	24	18 (22.0) *	28 (32.9) **	25 (29.1) **	18 (20.9) *	20 (23.5) *	33 (39.3) ***	8 (9.3)

ACR/EULAR remission	12	3 (3.7)	3 (3.5)	5 (5.8)	4 (4.7)	4 (4.7)	8 (9.5)	3 (3.5)
	24	9 (11.0)	7 (8.2)	10 (11.6)	5 (5.8)	3 (3.5)	16 (19.0) *	1 (1.2)
Number of patients who achieved DAS28-CRP <2.6, %	12	10 (12.2)	17 (20.0)	19 (22.1) *	12 (14.0)	15 (17.6)	30 (35.7) ***	6 (7.0)
	24	17 (20.7) *	24 (28.2)	21 (24.4) *	18 (20.9) *	19 (22.4) *	34 (40.5) ***	8 (9.3)
Number of patients who achieved DAS28-CRP ≤3.2, %	12	20 (24.4)	27 (31.8) *	32 (37.2) **	23 (26.7)	24 (28.2)	42 (50.0) ***	12 (14.0)
	24	25 (30.5)	36 (42.4) **	41 (47.7) ***	31 (36.0) *	30 (35.3) *	50 (59.5) ***	16 (18.6)
Patients (n) who achieved SDAI remission (%)	12	6 (7.3)	6 (7.1)	10 (11.6)	7 (8.1)	8 (9.4)	14 (16.7)	4 (4.7)
	24	13 (15.9) *	13 (15.3) *	12 (14.0) *	10 (11.6) *	12 (14.1) *	16 (19.0) *	1 (1.2)
Patients (n) who achieved CDAI remission (%)	12	6 (7.3)	7 (8.2)	9 (10.5)	9 (10.5)	7 (8.2)	15 (17.9)	2 (2.3)
	24	15 (18.3) *	18 (21.2) **	13 (15.1) *	11 (12.8) *	13 (15.3) *	16 (19.0) **	2 (2.3)
Change from baseline in HAQ-DI, mean (95%CI)	12	-0.577 (-0.733; -0.421)	-0.653 (0.796;-0.510)*	-0.753 (0.880;0.626) ***	-0.590 (0.719;0461)	-0.584 (-0.717;-0.451)	-0.840 (-0.982; -0.698) ***	-0.383 (-0.518; -0.248)
	24	-0.633 (-0.789; -0.477) **	-0.783 (-0.932; -0.634) ***	-0.818 (-0.950;-0.686) ***	-0.618 (-0.747;-0.489) **	-0.659 (-0.797;-0.521) **	-0.903 (-1.062; -0.744) ***	-0.365 (-0.497;-0.233)

Note 1: p-values were based on a pairwise comparisons of each group vs. the placebo group using a logistic regression model with factors treatment group, geographical region, and prior use of biologics; Hummel-corrected p-value. Note 2: The denominator for the percentage calculations = the total number of subjects per group with a response (yes or no) at that time point;
Note 3: Subjects who switched treatment at Week 12 were handled as if they discontinued at Week 12.
* p< 0.05; ** p< 0.01; *** p < 0.001
Note 4 Mean Change in ACR-N and Change from baseline in HAQ-DI are (LOCF [ITT population]) ACR=American College of Rheumatology; b.i.d.=*bis in die*, twice daily; CDAI= Clinical Disease Activity Index DAS28= Disease Activity Score based on 28 joints and C-reactive protein. CI= Confidence interval; EULAR= European League Against Rheumatism HAQ-DI= Health Assessment Questionnaire – Disability Index ITT=Intent-to-Treat; N=number of subjects per group; n=number of subjects with an ACR response; NRI=non-responder imputation; q.d.=*quaque die*, once daily; SDAI= Simplified Disease Activity Index, w= week

A summary of rates of TEAEs in DARWIN 1 up to week 12 and up to week 24 is shown in Table 5 and Table 6 respectively. (11)

Table 5. summary of rates of Treatment-emergent Adverse Events at week 12 (Safety Population)

	Filgotinib q.d Dose Groups			**Filgotinib b.i.d Dose Groups**			**Placebo (n=86)**
	50g (n=82)	**100 mg (n=85)**	**200mg (n=86)**	**25mg (n=86)**	**50mg (n=85)**	**100mg (n=84)**	
≥1 TEAE	34 (41.5)	27 (31.8)	41 (47.7)	34 (39.5)	37 (43.5)	38 (45.2)	34 (39.5)
≥1 serious TEAE	0	3 (3.5)	0	2 (2.3)	0	2 (2.4)	2 (2.3)

≥1 TE death	0	0	0	0	0	0	0
≥1 treatment-related TEAE	15 (18.3)	7 (8.2)	14 (16.3)	14 (16.3)	13 (15.3)	15 (17.9)	7 (8.1)
≥1 treatment-related serious TEAE	0	1 (1.2)	0	0	0	0	0
≥1 TEAE leading to temporary discontinuation of study medication	5 (6.1)	5 (5.9)	5 (5.8)	2 (2.3)	5 (5.9)	5 (6.0)	5 (5.8)
≥1 TEAE leading to permanent discontinuation of study medication	2 (2.4)	4 (4.7) a	1 (1.2)	4 (4.7)	1 (1.2)	1 (1.2)	0

b.i.d. = *bis in die*, twice daily; N = Number of subjects per group; n = number of subjects with event; q.d. = *quaque die*, once daily; TE = treatment-emergent; TEAE = treatment-emergent
adverse event.
Note 1: The denominator for percentage calculations is the total number of subjects per treatment group in the Safety Population.
Note 2: Treatment-emergent was defined as “started on or after the first intake of study medication”.
Note 3: Treatment-related was defined as “at least possibly related to the study medication according to the investigator”.
Note 4: TEAE for stopping rule was a TEAE which was a protocol-defined stopping criterion, which is included in the TEAEs leading to permanent study medication
discontinuation.
Note 5: “Continued Groups” were defined as “treatment groups in which subjects used the same study medication (either placebo or GLPG0634) and the same dose of study medication
(GLPG0634) from the start of the treatment period up to Week 24”.
a. One subject had a pre-treatment AE (decreased lymphocyte count) which was ongoing throughout the study, for which the study medication was permanently discontinued. This AE was not

Table 6. Treatment-emergent Adverse Events up to Week 24 in “Continued Groups” (Safety Population)

	Filgotinib q.d Dose Groups			**Filgotinib b.i.d Dose Groups**			**Continued Placebo (Week 12 Responder) (n=56)**
	50 mg q.d. (Week 12 Responder) (n=63)	**100 mg (n=85)**	**200mg (n=86)**	**25 mg b.i.d. (Week 12 Responder) (n=69)**	**50mg (n=85)**	**100mg (n=84)**	
≥1 TEAE (%)	33 (52.4)	37 (43.5)	50 (58.1)	37 (53.6)	46 (54.1)	45 (53.6)	32 (57.1)
≥1 serious TEAE (%)	0	4 (4.7)	2 (2.3)	1 (1.4)	0	3 (3.6)	4 (7.1)
≥1 TE death (%)	0	0	0	0	0	1 (1.2)	0
≥1 treatment-related TEAE (%)	13 (20.6)	11 (12.9)	21 (24.4)	14 (20.3)	19 (22.4)	21 (25.0)	6 (10.7)
≥1 treatment-related serious TEAE (%)	0	2 (2.4)	1 (1.2)	0	0	1 (1.2)	0

≥1 TEAE leading to temporary discontinuation of study medication (%)	4 (6.3)	5 (5.9)	7 (8.1)	4 (5.8)	6 (7.1)	8 (9.5)	8 (14.3)
≥1 TEAE leading to permanent discontinuation of study medication (%)	2 (3.2)	5 (5.9) aa	3 (3.5)	5 (7.2)	2 (2.4)	3 (3.6)	2 (3.6)

b.i.d. = *bis in die*, twice daily; N = Number of subjects per group; n = number of subjects with event; q.d. = *quaque die*, once daily; TE = treatment-emergent; TEAE = treatment-emergent adverse event.
Note 1: The denominator for percentage calculations is the total number of subjects per treatment group in the Safety Population.
Note 2: Treatment-emergent was defined as "started on or after the first intake of study medication".
Note 3: Treatment-related was defined as "at least possibly related to the study medication according to the investigator".
Note 4: TEAE for stopping rule was a TEAE which was a protocol-defined stopping criterion which is included in the TEAEs leading to permanent study medication discontinuation.
Note 5: "Continued Groups" were defined as "treatment groups in which subjects used the same study medication (either placebo or GLPG0634) and the same dose of study medication (GLPG0634) from the start of the treatment period up to Week 24"

DARWIN 2

Patients baseline characteristics are summarised in Table 7.(10)

Table 7. Baseline characteristics of patients in DARWIN 2 (Safety population)

Baseline characteristic	**Placebo (n=72)**	**Filgotinib q.d Dose Groups**		
		50g (n=72)	**100 mg (n=70)**	**200mg (n=69)**
Age, mean (SD)	51.5 (1.44)	52.1 (1.59)	52.8 (1.36)	51.8 (1.42)
Sex at birth, n (%)				
Male	16 (22.2)	10 (13.9)	17 (24.3)	9 (13.0)
Female	56 (77.8)	62 (86.1)	53 (75.7)	60 (87.0)
Race, n (%)				
Asian	0	1 (1.4)	0	0
Black or African American	1 (1.4)	1 (1.4)	1 (1.4)	0
Native Hawaiian or Pacific Islander	1 (1.4)	0	0	0
White	53 (73.6)	53 (73.6)	53 (75.7)	54 (78.3)

Other	17 (23.6))	17 (23.6)	16 (22.9)	15 (21.7)
BMI, mean kg/m^2 (SD)	27.24 (0.692)	27.73 (0.664)	27.55 (0.628)	27.72 (0.662)
Mean duration of RA from diagnosis, years (SD)	9.46 (0.837)	8.63 (0.774)	8.57 (0.829)	8.68 (0.987)
RF positive, n (%)	57 (79.2)	53 (73.6)	51 (72.9)	50 (72.5)
Anti-CCP positive, n (%)	58 (80.6)	56 (77.8)	54 (77.1)	57 (82.6)
RF positive + anti-CCP positive, n (%)	55 (76.4)	50 (69.4)	47 (67.1)	47 (68.1)

BMI=body mass index (weight [kg]/height² [cm²]); CCP=cyclic citrullinated peptide, eCRF=electronic case report form; N=number of subjects per treatment group; n=number of subjects per category; q.d.=*quaque die*, once daily; RA=rheumatoid arthritis; RF=rheumatoid factor, SE=standard error

Table 8 is a summary of the primary and secondary efficacy outcomes for DARWIN 2. (11)

Table 8. DARWIN 2 Summary of primary and secondary outcomes a week 12 and 24 (NRI [ITT Population])

Efficacy assessment	**Week**	**Filgotinib q.d Dose Groups**			**Placebo (n=72)**
		50g (n=72)	**100 mg (n=70)**	**200mg (n=69)**	
ACR20 responders (%)	12	48 (66.7) ***	46 (65.7) ***	50 (72.5) ***	21 (29.2)
	24	41 (56.9)	55 (78.6)	46 (66.7)	-
ACR50 responders (%)	12	25 (34.7) ***	26 (37.1) ***	30 (43.5) ***	8 (11.1)
	24	24 (33.3)	27 (38.6)	31 (44.9)	-
ACR70 responders (%)	12	6 (8.3)	13 (18.6) **	9 (13.0) *	2 (2.8)
	24	14 (19.4)	18 (25.7)	17 (24.6)	-
ACR/EULAR remission (%)	12	1 (1.4)	3 (4.3)	3 (4.3)	1 (1.4)
	24	6 (8.3)	6 (8.6)	6 (8.7)	-
Number of patients who achieved DAS28-CRP <2.6, %	12	9 (12.5)	10 (14.3)	12 (17.4)	5 (6.9)
	24	14 (19.4)	15 (21.4)	17 (24.6)	-
Patients (n) who achieved DAS28-CRP ≤3.2, %	12	17 (23.6)	19 (27.1)	31 (44.9) ***	10 (13.9)
	24	25 (34.7)	35 (50.0)	29 (42.0)	-
Patients (n) who	12	2 (2.8)	5 (7.1)	5 (7.2)	2 (2.8)

achieved SDAI remission (%)	24	8 (11.1)	8 (11.4)	8 (11.6)	-
Patients (n) who achieved CDAI remission (%)	12	2 (2.8)	4 (5.7)	6 (8.7)	2 (2.8)
	24	9 (12.5)	8 (11.4)	9 (13.0)	-
Change from baseline in HAQ-DI, mean (95%CI)	12	-0.661 (-0.824;-0.498) ***	-0.677 (-0.825; -0.529) ***	-0.739 (-0.888 ;-0.590) ***	-0.226 (-0.363;-0.089)
	24	-0.690 (-0.857;-0.523) **	-0.786 (-0.938;-0.634)	-0.850 (-1.007;-0.693)	-

Pairwise comparisons of each group versus the placebo group using a logistic regression model with factors treatment group, geographical region and prior use of biologics: Hommel-corrected p-value.
Note 1: The denominator for the percentage calculations = the total number of subjects per group with a response (yes or no) at that time point Note 3: Subjects who switched treatment at Week 12 were handled as if they discontinued at Week 12.
* p< 0.05; ** p< 0.01; *** p < 0.001
Note 4 Mean Change in ACR-N and Change from baseline in HAQ-DI are (LOCF [ITT population]) ACR=American College of Rheumatology, twice daily; CDAI= Clinical Disease Activity Index DAS28= Disease Activity Score based on 28 joints and C-reactive protein. CI = confidence interval; EULAR= European League Against Rheumatism HAQ-DI= Health Assessment Questionnaire – Disability Index ITT=Intent-to-Treat; N=number of subjects per group; n=number of subjects with an ACR response; NRI=non-responder imputation; q.d.=*quaque die*, once daily; SDAI= Simplified Disease Activity Index; w= week

A summary of rates of TEAEs in DARWIN 2 up to week 12 and up to week 24 is shown in Table 9 and Table 10 respectively. (10)

Table 9. summary of rates of Treatment-emergent Adverse Events at week 12 (Safety Population)

	Filgotinib q.d Dose Groups			**Placebo (n=72)**
	50g (n=72)	**100 mg (n=72)**	**200mg (n=69)**	
≥1 TEAE (%)	29 (40.3)	23 (32.9)	30 (43.5)	28 (38.9)
≥1 serious TEAE (%)	1 (1.4)	0	3 (4.3)	1 (1.4)
≥1 TE death (%)	0	0	0	0
≥1 treatment-related TEAE (%)	11 (15.3)	7 (10.0)	9 (13.0)	7 (9.7)
≥1 treatment-related serious TEAE (%)	0	0	1 (1.4)	0
≥1 TEAE leading to temporary discontinuation of study medication (%)	2 (2.8)	2 (2.9)	3 (4.3)	1 (1.4)

≥1 TEAE leading to permanent discontinuation of study medication (%)	1 (1.4)	0	1 (1.4)	4 (5.6)

N = Number of subjects per group; n = number of subjects with event; q.d. = *quaque die*, once daily; TE = treatment-emergent; TEAE = treatment-emergent adverse event.
Note 1: The denominator for percentage calculations is the total number of subjects per treatment group in the Safety Population.
Note 2: Treatment-emergent was defined as "started on or after the first intake of study medication".
Note 3: Treatment-related was defined as "at least possibly related to the study drug according to the investigator".
Note 4: TEAE for stopping rule was a TEAE which was a protocol-defined stopping criterion, which is included in the TEAEs leading to permanent study drug discontinuation.

Table 10. Treatment-emergent Adverse Events up to Week 24 in "Continued Groups" (Safety Population)

	Filgotinib q.d Dose Groups		
	Continued filgotinib 50 mg q.d. N=57	**Continued filgotinib 100 mg q.d. N=70**	**Continued filgotinib 200 mg q.d. N=69**
≥1 TEAE (%) (%)	30 (52.6)	31 (44.3)	35 (50.7)
≥1 serious TEAE (%)	2 (3.5)	2 (2.9)	3 (4.3)
≥1 TE death (%)	0	0	0
≥1 treatment-related TEAE (%)	14 (24.6)	12 (17.1)	12 (17.4)
≥1 treatment-related serious TEAE (%)	0	1 (1.4)	1 (1.4)
≥1 TEAE leading to temporary discontinuation of study medication (%)	4 (7.0)	4 (5.7)	4 (5.8)
≥1 TEAE leading to permanent discontinuation of study medication (%)	2 (3.5)	2 (2.9)	2 (2.9)

= Number of subjects per group; n = number of subjects with event; q.d. = *quaque die*, once daily; TE = treatment-emergent; TEAE = treatment-emergent adverse event.
Note 1: The denominator for percentage calculations is the total number of subjects per treatment group in the SafetyPopulation.
Note 2: Treatment-emergent was defined as "started on or after the first intake of study medication".
Note 3: Treatment-related was defined as "at least possibly related to the study drug according to the investigator".
Note 4: TEAE for stopping rule was a TEAE which was a protocol-defined stopping criterion, which is included in the TEAEs leading to permanent study drug discontinuation.
Note 5: "Continued Groups" were defined as "treatment groups in which subjects used the same study medication (GLPG0634) and the same dose of GLPG0634 from the start of the treatment period up to Week 24".

A17. Please confirm that the CS does not provide any data for filgotinib monotherapy (apart from FINCH 3, which is in a MTX-naïve population, and therefore outside the scope).

A17 response: Data from FINCH 3 is the only data presented in the submission that provides evidence for filgotinib as monotherapy (full results in section 2.6 of CS). As mentioned, FINCH 3 investigates filgotinib in an MTX-naïve population, which is not within the scope of this submission. Additionally, as requested, data from the Phase 2 DARWIN 2 study which also provides data for monotherapy is presented in the response to question A16.

Systematic review

A18. In the systematic review were any studies excluded solely due to not being published in English? Please give details.

A18. Answer: There was only one study that was excluded from this review due to non-English language (13). However, studies were limited to English language only in search filters and only studies with an abstract in English would avoid the filter.

A19. In the systematic review can the company justify the date limit of 1999?

A19. Answer: Searches were limited to those later than 1999 as a pragmatic way of limiting search results to focus on newer biologic treatments. This was in alignment with the search strategy used in TA466 (5). In addition, this date aligns with the first use of biologics for Rheumatoid arthritis (14).

Network Meta-analysis

A20. Priority question: Could the company perform NMAs in the populations most comparable to FINCH 1 and FINCH 2 and in line with the scope. These data need to be consistent with the NICE recommended care pathway i.e. only those who have severe disease would be expected to receive a bDMARD, whether due to inadequate response to cDMARDs only or cDMARDs plus a bDMARD. Therefore, please perform the following NMAs:

a) Those who had an inadequate response to MTX, but using only data from those with severe disease including the severe subgroup data from FINCH 1. Including the following comparators: adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept or sarilumab (each with MTX); adalimumab, etanercept, certolizumab pegol, tocilizumab or sarilumab (each as monotherapy); Tofacitinib, baricitinib or upadacitinib (each as monotherapy or in combination with methotrexate)

b) Those who had an inadequate response to bDMARDs, but using only data from those with severe disease including the severe subgroup data from FINCH 2. Including the following comparators: Rituximab in combination with methotrexate; adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept or sarilumab (each with MTX); adalimumab, etanercept, certolizumab pegol, tocilizumab or sarilumab (each as monotherapy); tofacitinib, baricitinib or upadacitinib (each as monotherapy or in combination with methotrexate)

c) Please provide all of the WinBUGS code and data for these NMAs.

A20. Answer:

We checked the trials included in the NMA and found that no studies were carried out in severe RA patients only or reported results for severe patients only. We did note the following two trials in MTX-IR patients which appeared to have been carried out in a mostly severe population:

- One study (Bi et al. 2019) noted that 90% of its population had a DAS28 ESR >5.1. This study was in a Chinese population for CZP+MTX vs. MTX. (15)

- One publication of the REFLEX trial (Keystone et al. 2008) , describes its population as severe; mean baseline DAS = 6.85, but this is not a requirement of the inclusion criteria. (16)

We can confirm that it would not be possible to construct a network for a population restricted to severe RA patients.

A21. Priority question: The WinBUGS code for the analyses of ACR at 12 weeks are missing, for both the MTX-IR and bDMARD-IR networks. Please provide the code for ACR at 12 weeks for both populations.

A21. Answer:

Please find the WinBUGS code for the analyses of ACR 12 weeks for both MTX-IR and bDMARD-IR networks attached.


bDMARD-IR - ACR - W12 - update (dose


MTX-IR - ACR - W12 (dose splitting).odc

A22. There are some treatments in the NMA which are not in the decision problem in Table 1. Peficitinib is included in Table 18 in Appendix D for the MTX-IR population and anakinra is included in Table 19 for the cDMARD-IR population. Neither of these treatments have been specified in the decision problem. Please justify their inclusion in the NMA.

A22. Answer: Peficitinib and anakinra although not included in the NICE scope, are treatment option for patients with rheumatoid arthritis, and so were included for completeness in the ACR at week 12 and week 24 networks in the cDMARD-IR population, respectively.

The NMA results from the ACR at week 12 network are not used to inform efficacy in the economic modelling, therefore, the inclusion of peficitinib does not impact results.

Additionally, anakinra is only connected to the ACR at week 24 network through cDMARDs, therefore, its inclusion does not impact the results of this NMA (see Figure 19 in CS).

A23. Section B.2.9.9 Assessment of Heterogeneity of CS. The company based the assumptions of clinical homogeneity on previous Technology Assessments and so have not performed an assessment of homogeneity. However, does your review contain new or different trials from those in the previous TAs and did they use the same patient groups? Please provide justification for your assumption of clinical homogeneity for each of the MTX-IR and bDMARD-IR analyses based on a review of the baseline patient characteristics of the trials within each network.

A23 response: Due to the volume of work required to allow for an answer, a response was not possible at this time. Gilead are investigating and will provide a response at a later stage.

Section B: Clarification on cost-effectiveness data

Population, intervention, and comparators

B1. Priority question: The CS stated that due to a paucity of studies reporting results stratified by severity, no NMA was performed separately for the moderate and severe populations. Therefore, efficacy for the moderate and severe subgroups was assumed equivalent to treatment effect in the overall moderately to severely active RA NMAs.

a) Please provide evidence that supports the assumption that the treatment effect in the moderate and severe subgroups is similar to the treatment effect in the overall moderately to severely active RA NMAs.

b) Please use the results from the analyses requested in A20 as scenarios in the model.

B1. Answers:

a) Due to the paucity of studies reporting results stratified by severity, it was not possible to conduct an NMA for moderate and severe populations separately. Therefore, the efficacy for the moderate and severe subgroups was assumed equivalent to the treatment effect in the overall moderately to severely active RA NMAs.

This approach is consistent to that taken and accepted by NICE in TA466 and is further supported by a subgroup analysis conducted in FINCH 1 (5). The analysis demonstrated that when compared with the overall moderately-to-severely active population at week 24, filgotinib 200mg showed comparable ACR20, 50 and 70 response rates in the moderate subgroup ([redacted] respectively). Furthermore, at week 52, filgotinib 200mg showed comparable ACR20, 50 and 70 response rates in the moderate subgroup ([redacted], respectively), indicating that filgotinib is similarly effective in both populations. Similarly, in the severe subgroup, when compared with the overall moderate-to-severe population, filgotinib 200mg also showed a comparable ACR20 response rate at week 24 in the severe subgroup ([redacted]). Furthermore, filgotinib 200mg also showed a comparable ACR50 response rate at week 24 in the severe subgroup ([redacted]).

Please refer to section B2.7.2 (moderate subgroup) and Appendix E (severe subgroup) in the submission for further details.

b) As detailed in question A20, as the efficacy data from publications included in the NMA are not stratified by severity (moderate and severe), only NMA's for the overall moderate to severe population were possible. The paucity of data stratified in this way is well established in previous TAs in RA, as such a similar approach to not stratify was taken by the AG in MTA375 and TA466 (5, 17). Therefore, running the analysis requested in A20 is not possible given the data available

B2. Priority question: The CS states that no NMA for monotherapies was performed, as efficacy data were not available for cDMARD-IR and bDMARD-IR populations for filgotinib monotherapy. Therefore, all monotherapies are assumed to have the same relative effect as the corresponding combination therapies.

Please provide evidence that supports the assumption that monotherapies have the same relative effect as the corresponding combination therapies.

B2. Answer:

This approach is in line with that employed in TA466 and is further supported by the committee guidance in MTA375 (5, 17). The guidance indicated that the minority of (cDMARD-IR) patients with severe active rheumatoid arthritis who could not tolerate methotrexate should not be treated differently from other people with severe disease, as far as possible. Therefore, the conclusion of the Committee was that biological DMARDs should be recommended as monotherapy within their marketing authorisation. This economic evaluation assumes a similar rationale be applied to filgotinib monotherapy.

Furthermore, this assumption is supported by data from FINCH 3, which demonstrated that the addition of MTX to filgotinib 200mg produced no marked improvement over filgotinib 200mg monotherapy in an MTX-naïve population (percentage of ACR20 responders were 78.1% and 81.0% in the monotherapy and combination therapy arm, respectively at week 24) supporting the assumption of equivalent efficacy for monotherapy versus combination therapy. For ACR50, filgotinib 200mg monotherapy (58.1%) also showed a numerically comparable response to filgotinib 200mg combination therapy (61.5%). Please see section B2.6.3 for full FINCH 3 results.

Additionally, this assumption was validated with a third-party clinician who confirmed that when considering ACR20 as an outcome, it would acceptable to assume equivalence between combination and monotherapy, in the absence of robust evidence.

B3. Priority question: Table 1 of the CS presents an overview of the Final Scope issued by NICE and how this was addressed in the CS. According to Table 1, several comparators mentioned in the scope and included in the NMA (infliximab, certolizumab pegol, golimumab, tofacitinib) were not included in the economic model (see also question A4).

a) Please clarify which comparators mentioned in the scope were included in the economic model and for which subpopulation.

b) Please justify why comparators listed in the scope, and for which data are available from the NMA, were not included in the economic model.

c) BSC was defined as 'cDMARDs that patients have already received, administered at lower doses' (CS, page 32) and the CS states that: "BSC is assumed to have no treatment effect (i.e. EULAR non-response" (page150). Please clarify precisely how BSC was included in the economic model.

d) Please run scenarios in the economic model where all comparators that were listed in the scope are included.

B3. Answers:

a) The comparators detailed in the NICE scope included in the economic model for each subpopulation are show in Table 11.

Table 11: Comparators detailed in NICE scope that were included in economic model per population

Comparators included in model	
cDMARD-IR population	**bDMARD-IR population**
• FIL (200mg) + csDMARDs • FIL (200mg) monotherapy • ABC (125mg qw) + csDMARDs • BARI + csDMARDs • SARI (200mg q2w) + csDMARDs • ADA (Hulio®) (40mg q2w) + csDMARDs • ETN (Erelzi™) (50mg qw) + csDMARDs • RTX (Rixathon®) (1000mg)+ csDMARDs* • IFX (Inflectra®) (3mg/kg) + csDMARDs • TCZ (162mrg q2w) + csDMARDs • ADA (Hulio®) (40mg q2w) monotherapy • ETN (Erelzi™) (50mg qw) monotherapy • BARI (4mg) monotherapy • TCZ (162mg q2w) monotherapy • ABC (125mg qw) monotherapy • csDMARDs • Intensive csDMARDs** • BSC	• FIL (200mg) + csDMARDs • BARI (4mg) + csDMARDs • SARI (200mg q2w) + csDMARDs • TCZ (162mg q2w) + csDMARDs • RTX (Rixathon®) (1000mg) + csDMARDs • ABC (125mg qw) + csDMARDs • ABC (125mg qw) monotherapy • FIL (200mg) monotherapy • BARI (4mg) monotherapy • TOF monotherapy • csDMARDs • BSC

*included only for the validation against exercise MTA375 **not included in scope

b) The comparators included in the final cost-effectiveness model and treatment sequences were deemed most relevant to UK clinical practise based on NICE treatment guidelines, market share data (Therapy Watch, 2019 data) and through validation by UK rheumatologists to guide on both the most likely drug classes at each line and commonly used molecules within each class seen in clinical practice (18). This approach was taken due to the large

number of treatment sequences permutations possible given the number of comparators in the NICE treatment pathway, which would be both unfeasible to generate given the model run time and impeded interpretation of results to aid decision making given the volume of analysis.

With regard to infliximab, clinician opinion indicated that infliximab is very rarely prescribed in clinical practice with market share data from Therapy Watch confirming that infliximab market share in the UK in 2019 was at 2% in first line (inc. biosimilars)(18). Therefore, infliximab was not included in the modelled sequences. Please note that for the validation exercise against MTA375, infliximab is included in the model for a cDMARD-IR population in order to replicate those analyses. Since MTA375, market share data indicates that the standard of care and treatment pathways have changed due to the introduction of new classes and molecules.

Baricitinib was the most commonly used JAK1 inhibitor, with a market share of 5.4% compared with tofacitinib which had 2.6%. Therefore, in the interest of modelling only the most relevant sequences, baricitinib was included as the JAK1 inhibitor used in the sequences for the relevant populations as defined by the NICE pathway. Additionally, clinician opinion also indicated that baricitinib was the most frequently used JAK1 inhibitor in practise. In population 3a (severe RA patients after failure of first line advanced therapy, MTX ineligible, RTX ineligible) as there are only a limited number of molecules recommended, tofacitinib monotherapy was included.

Similarly, only the most commonly used anti-TNFs were included for analysis. Certolizumab pegol has relatively low usage in the UK as validated by a third-party clinician and supported by market share data. This data indicates that 77% of first line advanced therapy (not mono- and combination-therapy specific) in the UK comprises of an anti-TNF agent, of which 62% is attributable to adalimumab (inc. biosimilars) and etanercept (inc. biosimilars), and that certolizumab has a comparatively low share of 9.2%, therefore certolizumab pegol was not included in the sequences.

Finally, given that the model uses NMA results at 24-weeks and evidence for golimumab is only available in the ACR at 12-week network in the cDMARD-IR population, including golimumab was not feasible. Additionally, clinician opinion indicated that golimumab was rarely used, which was supported by market share data showing a 4.1% share in first line use.

Please note that the market share data presented here is based on an internal data source, Therapy Watch (2019)(18). The original company submission states this data source was used although figures in Document B were taken from a different source in error. The conclusions relating to the treatment sequences are unchanged, as the market shares between sources were comparable (see section B3.2.5 in the CS). The Budget Impact analysis is unaffected. Correct figures are provided in the response to question B11.

c) For the economic modelling, BSC is included as the last line of therapy in all treatment sequences, so that once a patient commences on BSC they remain on this until death, with no discontinuation sampled. BSC is assumed to have no treatment effect (i.e. EULAR non-response), an approach in line with that employed in MTA375 and other recent submission such as TA466 and TA480 (4, 5, 17).

   This taken from MTA375: "*It was assumed that NBT would be associated with no initial EULAR response, unlike MTX where the results from the NMA indicated that MTX had a significant EULAR response*". (17)

   Expert validation during development of the company submission and upadacitinib (ID1400) committee meeting indicated that BSC usually comprises of csDMARDs that patients have previously failed on, although at lower doses. During this appraisal (ID1400), this assumption was argued to bias in favour of the technology because the company product consisted of longer sequences than comparator arms (19). All sequences in this submission are of equal length, hence minimising any potential bias.

d) Due to the number of possible treatment sequence permutations (based on the NICE treatment pathway), the approach taken was to present only the

most clinically relevant sequences to UK practice based on clinician validation and market share data. As detailed in B3 above, the comparators not included in the treatment sequences (but included in the NICE scope) were based on a combination of this information.

B4. Subgroups:
According to Figure 1 of the CS, eight separate relevant patient groups can be distinguished in the scope. However, in the cost-effectiveness analyses (Tables 66-68), a further distinction was made between three subgroups within the “Severe RA patients in first line advanced therapy treatment (MTX eligible)” group, namely: Severe RA, Severe RA (using second line IL-6), and Severe RA (using second line CD80). Please justify why this additional stratification was needed in the cost-effectiveness analyses?

B4. Answer: Population 2b in the CS refers to severe RA who are MTX eligible (i.e. tolerant) patients who are eligible for their first-line advanced therapy. This is the overarching population being analysed. However, given the analysis models sequences, these patients may or may not receive 2L RTX depending on whether they are contraindicated to treatment with RTX. Hence this population branches into two stratifications:

- RTX eligible
    - for who RTX is the NICE recommended 2L treatment option
- RTX Ineligible

RTX ineligible patients (i.e. contraindicated) are eligible for ten potential molecules at the second line. Based on market share data and clinical opinion some molecules were not considered as 2L options based on being most likely to be used as 1L options. Further, based on clinical opinion, anti-TNF cycling was not considered as appropriate as current standard of care. Of the remaining options IL-6 and CD-80 drugs were recommended by clinical experts as the most suitable options at 2L hence sequences were built using either options. There these are not sub-populations rather alternative sequences (2L IL-6 or CD-80) for RTX ineligible patients.

Model structure

B5. Moderate RA patients could become severe over time. In the model these patients do not become eligible for treatments reserved for severe RA patients. This could underestimate the health effects for these patients.

a) Please provide justification for this, and describe the potential impact on the incremental costs and QALYs of this assumption.

b) Please provide an adapted model structure that enables patients in the moderate cDMARD population to receive bDMARD treatment once they progressed to severe RA.

B5. Answer for a) and b): The CEM has been updated as requested and an updated version, including this functionality, has been submitted with this response document.

Methodology consistent with TA10389 and TA485 was applied to allow moderate patients (DAS28 score at baseline between 3.2 and 5.1) to progress to severe disease (DAS28 > 5.1) over time (3, 20). The approach undertaken is consistent with the approach undertaken in TA10389 with minor modifications undertaken to reflect ERG critique. Broadly this methodology includes:

1. Using patient level trial data to estimate the relationship between change in DAS28 and change in HAQ-DI
2. Updating simulated patients' DAS28 scores at every timepoint in the model based on their modelled HAQ-DI trajectory to determine when progression to severe state occurs

Detailed methodology is provided below.

Step 1

The filgotinib CEM, in line with the methodology presented in MTA375 and subsequent technology appraisals in RA (TA466, TA480, TA485, TA10389), tracks HAQ-DI over time (updated at every six-month cycle) but does not model DAS28 scores directly. In order to introduce time dependent changes in DAS28, a

regression analysis was conducted to determine the relationship between DAS28 and HAQ-DI scores.

Consistent with the ERG approach in TA485, change from baseline in DAS28 over time was estimated using change from baseline in HAQ-DI scores (3). In order to estimate the relationship between change in the two variables, patient level data from the FINCH 1 trial was used to inform a regression analysis. Patients with moderately active RA (DAS28 score at baseline between 3.2 and 5.1), who were csDMARD-IR, on any treatment (filgotinib 200mg, filgotinib 100mg, and placebo) were included in the analysis.

A linear mixed model for repeated measures was run for the analysis in line with TA10389. All available data for the [redacted] patients in the moderate subgroup in FINCH 1 was used, which included DAS28 change from baseline, and HAQ-DI change from baseline, at any available timepoint starting from week 2 and up until week 52 (weeks 2, 4, 8, 12, 14, 16, 20, 24, 26, 30, 44, 52). Where data for either HAQ-DI or DAS28 was missing at a single timepoint, both measures were excluded at that timepoint for the patient (0.9% of datapoints). As the FINCH 1 trial allowed for crossover from placebo to filgotinib at week 24, any patients who initiated filgotinib treatment at 24 weeks were reintroduced into the analysis as new patients, using the measures at 24 weeks as the new adjusted baseline values. Given that the analysis considers only the relative change in HAQ-DI and DAS28, which would not be expected to be affected by specific treatments, this approach will increase the data available without introducing bias. Consistent with the approach taken at baseline, crossover patients were excluded from the analysis after week 24 if data at 24 weeks were missing (2 patients).

The model estimated change from baseline in DAS28 as a function of change from baseline in HAQ-DI score using the coefficient estimated in the regression:

$$\Delta_{baseline} DAS28 = Coefficient \times \Delta_{baseline} HAQ$$

In response to the ERG critique of TA10389 where an estimated constant was not included in the regression, this modification of using a random intercept with mean 0 ensures that no change in HAQ-DI results in no change in DAS28.

In addition to the linear mixed model for repeated measures, the inclusion of random effects for the coefficient was explored, providing additional flexibility. The results of this analysis was tested in the CEM as a scenario analysis. Non-linear mixed models were also explored, using a second and third order polynomial, but as the resulting additional coefficients were not significant, these were not considered appropriate for the cost-effectiveness analysis. The results of the base case and scenario analysis are presented in Table 12.

Table 12: Results from the regression analysis: coefficient for estimating change from baseline DAS28 scores as a function of change from baseline HAQ-DI scores

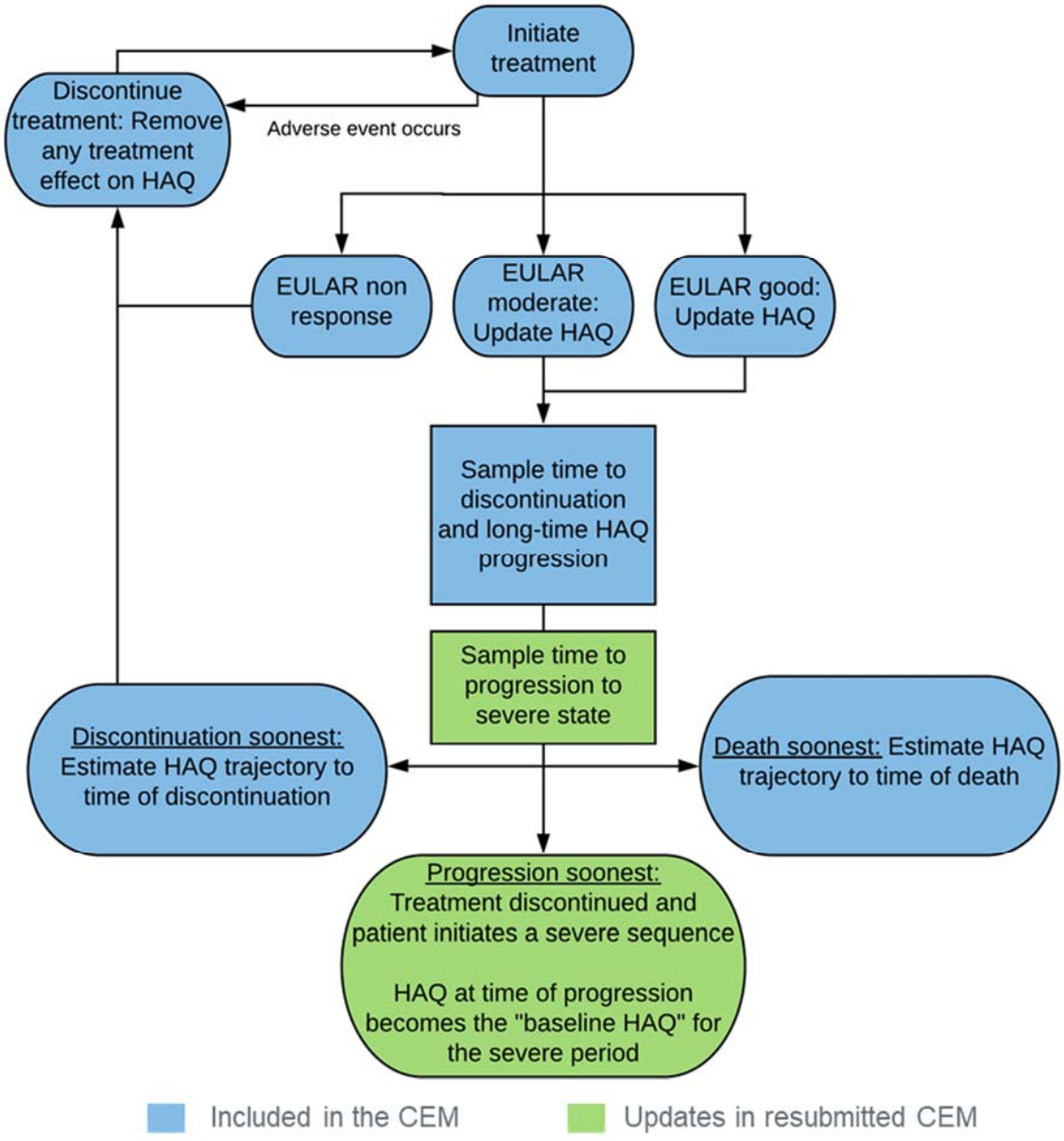
	Coefficient	SE	p-value
Base case: linear mixed model for repeated measures	1.406	0.033	<0.001
Scenario analysis: linear mixed model for repeated measures, including random effects for the change coefficient	1.768	0.052	<0.001
Abbreviations: DAS28, disease activity score 28-joint count; HAQ-DI, health assessment questionnaire – disability index; SE, standard error			

Step 2

In the CEM, moderate patients DAS28 score at each six-monthly cycle is calculated by applying the estimated regression coefficient detailed in Step 1 to the patient's current HAQ-DI, the resulting change in DAS28 score is then applied to the patient's DAS28 score at baseline. Once the DAS28 value exceeds the severe threshold (DAS28 > 5.1), the patient discontinues the current treatment in the moderate sequence, and initiates treatment in the subsequent severe sequence. Upon initiating a severe sequence, the HAQ-DI score at the time of transition becomes the updated base HAQ-DI score for the severe period. Following progression to severe disease and initiating advanced treatment, the model does not allow transition from severe RA to moderate RA. This approach is consistent with TA10389.

A schematic describing a moderate patient's flow through the updated CEM is provided in Figure 1.

Figure 1: Schematic depicting a moderate RA patient flow through the CEM



AE, adverse event; CEM, cost-effectiveness model; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; QoL, quality of life

In order to avoid the potential for moderate patients' DAS28 scores at baseline to be sampled as greater than 5.1 (and thus potentially overestimate progression), the baseline DAS28 scores for the moderate population were sampled using a shifted gamma distribution, shifted such that the maximum sampled score at baseline cannot exceed 5.1. This distribution is calculated based upon the cohort mean DAS28 score at baseline and the standard deviation of the mean. When sampling is

applied using the mean baseline DAS28 scores for the FINCH 1 moderate subgroup ([redacted]), a sizable proportion of patients have a resulting DAS28 score close to the severe threshold (5.1), and therefore patients progressed rapidly. Since this is may not be reflective of the average moderate patient in clinical practice, a more conservative approach is implemented in the base case whereby the midpoint of the moderate DAS28 interval (i.e. a DAS28 score of 4.15, which is the midpoint between the low disease and severe disease activity score thresholds, 3.2 and 5.1) is applied as the mean. For completeness, application of the mean DAS28 from the FINCH 1 trial is explored in a scenario analysis.

The cumulative percentage of BSC patients progressing to a severe state for the different scenarios is presented in Table 13. The base case analysis using the midpoint DAS28 score finds that 5% of moderate patients progress to severe after 2 years, and 24% at 5 years, whereas the analysis using the FINCH 1 trial mean DAS28 for moderate patients finds 26% of patients have progressed after 2 years, and 59% after 5 years.

Kiely et al. reported data on 302 newly diagnosed patients, predominantly treated with csDMARDs or csDMARD combinations, in the ERAN database who were followed up for 2 years (21). The study found that after 2 years 19% of patients had exceeded the DAS28 severe threshold of 5.1. This is notably higher than the base case analysis presented here, and as such, the base case is considered conservative.

Table 13: Cumulative percentage of patients in the CEM progressing to severe RA from moderate RA on BSC

Time	Base case: linear mixed model, gamma using midpoint DAS28 mean	Scenario: linear mixed model with random change coefficient	Scenario: gamma using FINCH 1 DAS28 mean
Year 1	3%	4%	19%
Year 2	5%	7%	26%
Year 3	12%	17%	44%
Year 4	14%	20%	49%
Year 5	24%	33%	59%
Abbreviations: DAS28, disease activity score 28-joint count			

Updated base case cost-effectiveness analyses are presented for the two moderate populations, 1a and 1b: Moderate RA patients after 2 csDMARD failures (MTX ineligible and MTX eligible).

The base case analysis considers severe sequences from the CS: patients in population 1a progress to a sequence for population 2a (severe, cDMARD-IR, MTX ineligible), and patients in population 1b progress to a sequence for population 2b (sever, csDMARD-IR, MTX eligible), both using adalimumab as first line advanced therapy comparator (as the most commonly used advanced therapy in first line). The same severe sequence is used for moderate patients in both filgotinib and BSC arms.

Other severe sequences from the CS are provided as scenario analyses.

Base case sequences

1a. Moderate RA patients after 2 cDMARD failures (MTX ineligible)

Table 14: Treatment sequences considered in moderately active cDMARD-IR patients after two cDMARD failures

Sequence	First-line treatment	Second-line treatment
1	***FIL***	***BSC***
2	PBO/BSC	BSC
Abbreviations: BSC, best supportive care; FIL, filgotinib; PBO, placebo		

Table 15: Severe treatment sequences considered upon progression in moderately active cDMARD-IR patients after two cDMARD failures

Sequence	First-line treatment	Second-line treatment	Third-line treatment
1 & 2	ADA	ABC SC	BSC
Abbreviations: ABC, abatacept; ADA, adalimumab; BSC, best supportive care			

1b. Moderate RA patients after 2 cDMARD failures (MTX eligible)

Table 16: Treatment sequences considered in moderately active cDMARD-IR patients after two cDMARD failures

Sequence	First-line treatment	Second-line treatment
1	***FIL + MTX***	***BSC***
2	PBO/BSC	BSC
Abbreviations: BSC, best supportive care; FIL, filgotinib; MTX, methotrexate; PBO, placebo		

Table 17: Severe treatment sequences considered upon progression in moderately active cDMARD-IR patients after two cDMARD failures

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment
1 & 2	ADA + MTX	RTX + MTX	TCZ SC + MTX	BSC
Abbreviations: ADA, adalimumab; BSC, best supportive care; MTX, methotrexate; RTX, rituximab; TCZ, tocilizumab				

Sequences considered for scenario analyses

1a. Moderate RA patients after 2 cDMARD failures (MTX ineligible)

Table 18: Scenario 1 severe treatment sequences considered upon progression in moderately active cDMARD-IR patients after two cDMARD failures

Sequence	First-line treatment	Second-line treatment	Third-line treatment
1 & 2	ETN	ABC SC	BSC
Abbreviations: ABC, abatacept; BSC, best supportive care; ETN, etanercept			

1b. Moderate RA patients after 2 cDMARD failures (MTX eligible)

Table 19: Scenario 1 severe treatment sequences considered upon progression in moderately active cDMARD-IR patients after two cDMARD failures

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment
1 & 2	ETN + MTX	RTX + MTX	TCZ SC + MTX	BSC
Abbreviations: BSC, best supportive care; ETN, etanercept; MTX, methotrexate; RTX, rituximab; TCZ, tocilizumab				

Table 20: Scenario 2 severe treatment sequences considered upon progression in moderately active cDMARD-IR patients after two cDMARD failures

Sequence	First-line treatment	Second-line treatment	Third-line treatment
1 & 2	ADA + MTX	TCZ SC + MTX	BSC
Abbreviations: ADA, adalimumab; BSC, best supportive care; MTX, methotrexate; TCZ, tocilizumab			

Table 21: Scenario 3 severe treatment sequences considered upon progression in moderately active cDMARD-IR patients after two cDMARD failures

Sequence	First-line treatment	Second-line treatment	Third-line treatment
1 & 2	ETN + MTX	TCZ SC + MTX	BSC
Abbreviations: BSC, best supportive care; ETN, etanercept; MTX, methotrexate; TCZ, tocilizumab			

Table 22 lists the scenario analyses provided for the moderate population. In addition, both one-way and probabilistic sensitivity analyses were undertaken.

Table 22: List of scenario analyses provided for the moderate population analyses

Population 1a	
Scenario number	***Description***
1	Alternative sequence using ETN as first-line advanced therapy
2	Regression estimates based on linear mixed model with random change coefficient
3	Moderate patients sampled using gamma distribution and FINCH 1 DAS28 mean
Population 1b	
Scenario number	***Description***
1	Alternative sequence using ETN as first-line advanced therapy
2	Alternative sequence for RTX contraindicated patients
3	Alternative sequence for RTX contraindicated patients using ETN as first-line advanced therapy
4	Regression estimates based on linear mixed model with random change coefficient
5	Moderate patients sampled using gamma distribution and FINCH 1 DAS28 mean
Abbreviations: DAS28, disease activity score 28-joint count; ETN, etanercept; RTX, rituximab	

Base case results

Consistent with the CS, all base case analyses were conducted by simulating 10,000 patients, using an annual price of [redacted] for filgotinib.

1a. Moderate RA patients after 2 csDMARD failures (MTX ineligible)

The results of the base case analysis for the moderate, MTX ineligible patient population after at least two csDMARD failures are presented in Table 23. Compared to BSC, filgotinib 200mg monotherapy was associated with QALY gains (0.584), and increased costs (£6,918), generating an incremental cost-effectiveness ratio (ICER) of £11,844 per QALY. This is a decrease in ICER of £9,878 compared to the analysis presented in the submission not considering the moderate to severe transition.

Table 23: Two csDMARD failure, MTX ineligible, moderate RA – versus FIL 200mg monotherapy (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	15.810	[redacted]	-	-	-	11,843.53	-
FIL	[redacted]	15.810	[redacted]	6,918.39	0.000	0.584	-	11,843.53
Abbreviations: BSC, best supportive care; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year								

1b. Moderate RA patients after 2 csDMARD failures (MTX eligible)

The results of the base case analysis for the moderate, MTX eligible patient population after at least two csDMARD failures are presented in Table 24. Compared to BSC, filgotinib 200mg combination therapy was associated with QALY gains (0.565), and increased costs (7,855), generating an incremental cost-effectiveness ratio (ICER) of £13,909 per QALY. This is a decrease in ICER of £8,015 compared to the analysis presented in the submission not considering the moderate to severe transition.

Table 24: Two csDMARD failure, MTX ineligible, moderate RA – versus FIL 200mg monotherapy (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	15.810	[redacted]	-	-	-	13,908.64	-
FIL + MTX	[redacted]	15.810	[redacted]	7,855.22	0.000	0.565	-	13,908.64

Abbreviations: BSC, best supportive care; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year

Scenario analysis results

1a. Moderate RA patients after 2 csDMARD failures (MTX ineligible)

Table 25: Results from scenario analyses for the moderate RA populations

Population 1a: Moderate RA patients after 2 csDMARD failures (MTX ineligible)	
Scenario	***ICER (£/QALY)***
Base case	11,843.53
Scenario 1: Alternative sequence using ETN as first-line advanced therapy	11,606.92
Scenario 2: Regression estimates based on linear mixed model with random change coefficient	7,906.89
Scenario 3: Moderate patients sampled using gamma distribution and FINCH 1 DAS28 mean	Dominant
Population 1b: Moderate RA patients after 2 csDMARD failures (MTX eligible)	
Scenario number	***ICER (£/QALY)***
Base case	13,908.64
Scenario 1: Alternative sequence using ETN as first-line advanced therapy	13,564.37
Scenario 2: Alternative sequence for RTX contraindicated patients	14,567.80
Scenario 3: Alternative sequence for RTX contraindicated patients using ETN as first-line advanced therapy	14,189.14
Scenario 4: Regression estimates based on linear mixed model with random change coefficient	10,592.96
Scenario 5: Moderate patients sampled using gamma distribution and FINCH 1 DAS28 mean	1,849.88
Abbreviations: DAS28, disease activity score 28-joint count; ETN, etanercept; RTX, rituximab	

Conclusion

The incorporation of moderate-to-severe progression in moderate activity patients (MTX eligible and MTX ineligible) results in substantially lower ICER results across analyses compared with the cost-effectiveness estimates in the original CS where this transition was not permitted.

As explained above a conservative approach has been implemented and thus if alternative approaches were implemented, for example greater rates of disease progression, further reductions in the ICER may be plausibly expected.

Treatment effectiveness

B6. Priority question: Patient profiles used in model**:**

a) Patient characteristics used in the model are shown in CS Table 44. Please elaborate on which of these characteristics are actually used in the model, and how.

b) Patient profiles appear to be pre-generated and hard-coded in the model and the model then draws from these pre-generated patient profiles. Please clarify the methods used for generating these patient profiles and provide justification.

c) Please provide the code used for generating these patient profiles as well as their description, so that a different set of patient profiles can be generated.

B6. Answers:

a) All the baseline characteristics presented in CS Table 44 are used in the model. These are detailed below:

- **Age:** Age is used to determine the time of death at model initiation. After the initial phase, it is used to determine the HAQ trajectory for both patients on bDMARDs (using a mapping from MTA375), and for patients on csDMARDs/BSC (using a mapping from Norton et al.). Age is also used as an input variable for the mapping from Hernandez-Alava et al. to determine the utility accrued in each cycle.

- **Proportion female:** Sex is used to determine the time of death at model initiation. After the initial phase, it is used to determine the HAQ trajectory for both patients on bDMARDs (using a mapping from MTA375), and for patients on csDMARDs/BSC (using a mapping from Norton et al.). Sex is also used as an input variable for the mapping

from Hernandez-Alava et al. to determine the utility accrued in each cycle.

- **Duration of disease:** After the initial phase, duration of disease is used to determine the HAQ trajectory for both patients on bDMARDs (using a mapping from MTA375), and for patients on csDMARDs/BSC (using a mapping from Norton et al.).

- **Number of prior DMARDs:** After the initial phase, number of prior DMARDs is used to determine the HAQ trajectory for patients on bDMARDs (using a mapping from MTA375).

- **Baseline HAQ-DI:** As described in section B3.3.5 of the CS, mortality was adjusted for by using hazard ratio associated with baseline HAQ-DI scores. It was assumed that only the baseline HAQ-DI score was important for predicting mortality, in line with the approach taken in MTA375. The HAQ-DI score at baseline is additionally used to determine the HAQ-score at 6-months. Patients experience an initial reduction based on their treatment response group, as described in section B3.3.3.

- **Baseline pain (VAS):** Baseline pain from the input baseline characteristics is used to provide the utility at baseline, using the mapping from Hernandez-Alava et al. Throughout the model, the pain parameter is dependent on HAQ-DI progression.

- **IMD quartile:** After the initial phase, IMD is used to determine the HAQ-DI trajectory for patients on csDMARDs/BSC (using a mapping from Norton et al.). This parameter is sourced from Norton et al. and has been used in previous technical appraisals in RA.

- **Weight:** The base weight is used to calculate treatment costs for IV administrated treatments. It is not updated throughout the model.

- **DAS28:** After the initial phase, the baseline DAS28 is used to determine the HAQ trajectory for both patients on bDMARDs (using a

mapping from MTA375), and for patients on csDMARDs/BSC (using a mapping from Norton et al.). DAS28 at baseline is also used as an input variable for the latent class model from Hernandez-Alava et al. to determine the utility accrued in each cycle.

- **RF (positive):** After the initial phase, presence of RF is used to determine the HAQ trajectory for patients on csDMARDs/BSC (using a mapping from Norton et al.). This is a binary variable; hence sampled patients are sampled a presence of RF based on the proportion provided in the baseline characteristics inputs.

- **ACR (positive):** After the initial phase, the ACR is used to determine the HAQ trajectory for patients on csDMARDs/BSC (using a mapping from Norton et al.). This parameter is sourced from Norton et al. and represents the proportion of patients fulfilling the 1987 ACR criteria of RA, based on the ERAS database. This is a binary variable, hence sampled patients are sampled based on the proportion provided for the baseline characteristics.

b) The patient profiles were pre-generated using summary baseline characteristics from the FINCH trials, and provided in Table 44 in the CS. The code is included in the model, `GenerateRandomCohort`. Additionally, the model includes a functionality in the front end to generate a new patient cohort by executing this macro. Steps to generating a new cohort are detailed in c).

Values were sampled from the following distributions:

- Normal distribution for weight and age
- Variables expected to be positively skewed were sampled using gamma distribution for duration: duration of disease, disease activity score (DAS28), health assessment questionnaire disability index (HAQ-DI) and number of prior DMARDs
- As the pain variable has a limited range (from 0 to 100), a beta distribution was used for sampling baseline pain

Sampled values were bounded, where appropriate. DAS28 was restricted to values ranging from 2 to 10, which are the minimum and maximum values of the scale. Similarly, HAQ-DI scores were restricted to values ranging from 0 to 3, and additionally, by an increment of 0.125, as was done in MTA375 (17). Patients were assumed to be adults between 18 and 100 years of age.

c) In the *Main Setting* sheet, in the *Patient and Treatment Characteristic* section, there is a built-in option to generate a random patient cohort, using summary baseline characteristics.

    a. Select “Randomly generated (MTX-IR)” in cell E83

    b. Provide the summary baseline characteristics for the cohort in cells E102:E112 and G102:G112.

    c. Select the distributions used for the sampling using cells I102:I112. Note that only continuous outcomes have alternative distribution to select from. Other outcomes are marked “NA”.

    d. Click the button *“Generate patient level data”* below the summary baseline characteristics input cells.

The macro `GenerateRandomCohort` is used to sample the cohort using a selection of Normal, Gamma and Beta distribution as selected by the user. The sampled patient level data can be viewed in the *Patient level data* sheet in columns BK through BU. Note that when this functionality is used to run the model, the treatment inputs for the MTX-IR population are applied during a model run. The selected cohort baseline characteristics for running the model can be viewed in columns C through M.

B7. Priority question: The company have used the mapping algorithm developed by Stevenson et al in MTA375 to map ACR response rates available from the trials to EULAR response rates.

a) Please provide inputs (please clarify whether the single model results from the NMA are used), code and results of this analysis.

b) Table 46 in the CS does not match the data inputs in the model. Please explain this deviation and provide a corrected version of the model or Table 46 in the report, highlighting what has changed.

B7. Answers:

a) In order to use the results of the ACR NMA for inputs in the model, the following steps are used.

I. The modelled probabilities of ACR response for cDMARDs (Table 24) and bDMARDs (Table 27) are used as input for the mapping. The modelled probabilities of response are based on an assumed probability of achieving the first level of response (e.g. ACR20) in the reference treatment group. The assumed probability was based upon conducting a meta-analysis (MA) of responses within the reference treatment arms of included studies, as outlined within NICE DSU guidelines, and detailed in B2.9.13.

II. Data from the VARA database (sourced from MTA375) for the relationship between EULAR and ACR responses is converted to a matrix of probabilities. The data is summarised in Table 26.

Table 26: The relationship between EULAR responses and ACR responses in the VARA database. Sourced from MTA375 (17).

EULAR	Less	ACR20	ACR50	ACR70
None	755	4	2	0
Moderate	136	27	2	2
Good	57	26	10	2

III. As the modelled probabilities from the NMA are the probabilities of achieving at least each response (and thus includes patients achieving a better response), the modelled percentage of patients achieving ACR70 are subtracted from the ACR50 response group, and the modelled percentage of patients achieving ACR50 are subtracted from the ACR20 response group. Thus, the response groups are defined as

mutually exclusive, and probabilities of belonging to each group are calculated.

IV. The probabilities of belonging to each ACR response group in III. are converted to probabilities of belonging to each EULAR response group, using the mapping from MTA375. Please refer to rows K:M in the attached sheet *NMA ACR results converted to EULAR* labelled "Conversion".

NMA ACR results converted to EULAR.x

b) Table 46 in the CS mistakenly includes incorrect efficacy inputs for filgotinib 200mg. A corrected Table 46 is presented below. Table 27 details all the inputs used for the base case cost-effectiveness analysis.

Table 27: Probability of achieving a given response based on 24-week ACR data converted to EULAR.

Treatment	cDMARD-IR population			bDMARD-IR population		
	No response	Moderate response	Good response	No response	Moderate response	Good response
FIL (200mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABC (125 mg qw) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA (40mg q2w) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BAR (4mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN (50mg qw) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX (1000mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAR (200mg q2w) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ (162mg q2w) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
csDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABC, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; BAR, baricitinib; bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug ; ETN, etanercept; IR, insufficient response; MTX, methotrexate; qw, once a week; q2w, once every two weeks; q4w, once every four weeks; RTX, rituximab; SAR, sarilumab; TCZ, tocilizumab;

* A comparison was not possible in the NMA.

Results

B8. Priority question: Application of HAQ-DI scores in the model: the CS states that the HAQ-DI score is assumed to be constant for non-responders to bDMARDs, which is in contrast to Figure 36 in the CS, which is derived from MTA375. Furthermore, the ERG wishes to request more information on the application of the Norton et al latent class model for patients receiving cDMARDs.

a) The assumption that the HAQ-DI score remains constant for bDMARD non-responders may under-estimate health-related quality of life (HRQoL) and over-estimate costs of bDMARD non-responders in the first 6 months, favouring those treatments that have smaller proportions of non-responders. Please provide justification for this assumption, and an assessment of its impact in scenario analysis.

b) Please explain how the Norton et al latent class HAQ-DI progression model for the cDMARD population was incorporated in the model, also explaining whether each patient was assigned a class, or whether each patient followed an average trajectory based on their probabilities of being in each class (as detailed in TA466). Please incorporate the latter approach, if not done so already.

c) Please provide more detail on how the patient baseline characteristics from the FINCH trials were combined with the estimates reported by Norton et.al., and provide an overview of baseline patient characteristics (similar to Table 44 of the CS) of the FINCH trials by each latent class used.

d) Please tabulate the numbers used in Figures 36 & 37 by EULAR response category (Figure 36) and latent class (Figure 37).

e) Please elaborate on the potential inaccuracy / bias introduced by calculating average HAQ-DI progressions over time between two events and estimating HRQoL and costs based on this.

B8. Answers:

a) The analysis included within the CS uses the British society of rheumatology biologics register (BSRBR) analysis conducted by the in MTA375 (Stevenson et al) to estimate long term HAQ progression for patients on bDMARDs (17). This approach is consistent with other recent TAs (TA466 and TA480)(4, 5).

   The review group in MTA375 only conducted statistical analysis for those patients who had good or moderate EULAR response but did not conduct any formal analysis for patients who had no EULAR response as they are assumed to have treatment stopped after 6 months (in accordance with NICE guidelines) (17, 22). The cost-effectiveness analyses in MTA375 and subsequent TAs, as well as this submission, apply this same assumption for non-responders.

   To Gilead's knowledge the BSRBR dataset was only available to the NICE assessment group and Gilead is unable to conduct further analysis using this data. Robust scenario analyses testing this assumption is therefore not possible.

b) The present analysis employs the latent class analysis of HAQ-DI progression by Norton et al (as modified and used by the AG in MTA375) to patients receiving cDMARDs in the first 15 years, after which HAQ-DI progression is assumed to remain stable (17, 23). This approach is in line with that employed in MTA375,TA466 and TA480(4, 5, 17). Full details of the statistical analysis conducted by the AG in MTA375 can be found on pg254-257 of Stevenson et al.

   The Norton et al. latent class analysis of HAQ-DI progression (as modified and used by the AG in MTA375) identifies four classes of patients, whose HAQ-DI progresses in different ways while receiving treatment with cDMARDs. These classes are low, moderate, high and severe HAQ progression. Norton et al. presents the results of an analysis that predicts which class a patient will be in based on their baseline characteristics (23).

In this analysis (in line with MTA375,TA466 and TA480) as patients' initial HAQ-DI response at Month 6 (based on the EULAR response) is assessed, the latent class method is not directly used. Instead, the method employed by the Assessment group in MTA375 (applied in MTA375,TA466 and TA480) is used and the HAQ-DI change from the value at Year 1 in each class, weighted by the probability of being in each class, is applied. The value at Year 1 is used instead of the value at Month 6, as it is assumed that all HAQ-DI improvements occur in the initial 6 months of treatment and allows the HAQ-DI scores in the latent classes to plateau. The baseline characteristics from the FINCH trials (table 44 of CS) are multiplied by their respective covariates from the Norton et al analysis conducted in MTA375 (shown below).

In line with TA466, each patient follows an average trajectory based on their probabilities of being in each class. Therefore, the current approach is consistent with TA466 and no changes are required.

The values used to produce probabilities for membership of each latent class, based on baseline characteristics, are shown in Table 28. These are defined relative to the low progression class; therefore, this does not appear in the table. These parameters can be found in the VBA code of the model in the macro `generateConvTraj`.

Table 28. Predictors of class membership – Norton et al class analysis (23)

Variable	Moderate		High		Severe	
	Parameter	SE	Parameter	SE	Parameter	SE
Constant	-3.50	0.62	-6.69	0.66	-12.06	1.10
Age	0.03	0.01	0.04	0.01	0.08	0.01
Female	0.84	0.20	1.69	0.21	1.98	0.27
DAS28	0.30	0.08	0.57	0.08	0.80	0.09
Disease duration (years)	0.38	0.02	0.55	0.02	0.50	0.02
Rheumatoid factor positive	0.21	0.24	0.32	0.25	0.30	0.29
ACR criteria	0.28	0.23	0.41	0.24	0.94	0.32
Socio-economic status (IMD)	0.99	0.37	1.12	0.34	1.43	0.38

c) All available baseline characteristics (the categories of which are shown in response B8.b above) from the FINCH trials were used, with those not available taken from Norton et al (ACR positive criteria and IMD). The baseline characteristics detailed in table 44 of the CS are multiplied by their respective covariates from the MTA375 AG analysis of Norton et al (described in B8.b above) to provide a probability of each patient being in each class. A weighted average of these classes then determines patients HAQ trajectory.

Given that the analysis from the Norton et al does not segment patients into a single definitive class, rather assigning a probability of being in each class, segmenting the FINCH trial data in this way is not possible.

d) Figure 36 was obtained directly from MTA375 as an illustrative example of the findings from the BSRBR study by Stevenson et al, showing the average HAQ in the sample by EULAR response (17). As the BSRBR data used by the AG in MTA375 is not available to Gilead tabulating the values is not possible.

Similarly, Figure 37 is an illustrative figure obtained from Norton et al, to demonstrate the four latent classes identified by this study. Tabulating the data is not possible as the original data used to produce this figure is not available.

e) After a patient has progressed to the maintenance phase from the initial phase, a HAQ-DI trajectory is created based on whether the patient is treated with a bDMARD (using a mapping from MTA375), or cDMARD/BSC (using a mapping from Norton et al.). Additionally, the next event, i.e. time of death and time of discontinuation is determined. The model then compares which of these events occurs first, and executes the macro `endMaint`. Within that macro, the utility for every cycle from the start of the maintenance phase is determined, and the patient accrues QALYs at 6 monthly intervals until the next event (discontinuation or death).

The mapping from MTA375 is based on data from the BSRBR database which measures HAQ at 6-monthly intervals, and provided estimates very close to the observed HAQ changes. Thus, estimating utilities on a 6 monthly

basis is considered to introduce minimal bias considering the data available, and the cycle length of 6 months is consistent with the cost-effectiveness analysis conducted in MTA375 (17).

B9. Time to treatment discontinuation (TTD): please justify the assumption that all biologic treatments have the same treatment duration (only depending on response, thereby assuming that response is the only predictor of discontinuation).

B9. Answer: The time to treatment discontinuation parametric survival models, as detailed in section B3.3.4, are taken from the analysis described in MTA375 (pg.257-259) based on data from the BSRBR database (17). Establishing separate covariates for the individual biologic therapies was considered by the MTA375 assessment group. Some therapies were excluded due to paucity of data, and only IFX, ADA and ETN were considered appropriate for the analysis. However, the Assessment Group concluded that although the duration of treatment for those on ETN and ADA was significantly shorter than for IFX, this was likely to be due to the times at which therapies became available in the UK. Thus, due to the lack of data, and owing to this potential confounding, separate terms for individual therapies in the cost-effectiveness analysis were not adopted (17).

Similarly, for cDMARDs there was also limited data on the duration of response. Based on the assumption that the safety profile of cDMARDs is likely to be no worse than biologics used in combination with a cDMARD, the assessment group concluded that the survival duration for each EULAR response category for bDMARDs would be applicable for cDMARDs.

Thus, in line with the analysis conducted in MTA375, treatment discontinuation is assumed to be only dependent on initial EULAR treatment response category for all treatments in the CEM (except BSC). This approach has also been adopted by subsequent technical appraisals in RA (TA10389, TA480, and TA466) (4, 5, 19).

B10. Efficacy assumptions:

For some treatments (TCZ SC, ABC SC combination therapies and TOF monotherapy), the efficacy could not be informed by the NMA. The company therefore used some additional efficacy assumptions (Table 47 of the CS).

a) For TCZ SC + MTX, no data was available from the cDMARD-IR NMA. Therefore, the company assumed the efficacy to be equal to TCZ SC + MTX bDMARD-IR NMA. However, a visual inspection of the data presented in Table 46 indicates that the response rates (24-week ACR data converted to EULAR) between the cDMARD-IR population and the bDMARD-IR population in general do not correspond well. Please justify why you expect that the relative efficacy would not significantly differ for TCZ SC + MTX in these different settings?

b) For ABC SC + MTX, no data was available from the bDMARD-IR NMA. Therefore, the company assumed the efficacy to be equal to ABC IC + MTX cDMARD-IR NMA. For the same reasons as stated in B9.a, please justify why you expect that the relative efficacy would not significantly differ through for ABC SC + MTX in these different settings?

B10. Answers:

a) For TCZ SC, no efficacy data were available from the cDMARD-IR NMA, and thus assumptions were required for inclusion in the CEM. Previous technical appraisals in RA have required similar assumptions, and the assumption applied in the CS is based on the one applied in TA466. In TA466, the same efficacy results were applied across populations to model treatments where inclusion in the bDMARD-IR NMA were not feasible (5). The recently published TA10389 assumed that the efficacy of TCZ SC monotherapy (in the cDMARD-IR population) was the same as the TCZ IV monotherapy (in the cDMARD-IR population). However, comparing SC and IV treatments from the NMA used in this submission showed a substantial difference between mean efficacy estimates of ABC SC and ABC IV in the cDMARD-IR population (see Figure 28 of the CS), and in the mean efficacy estimates of TCZ SC and TCZ IV in the bDMARD-IR population (see Figure 31 of the CS), suggesting that assuming equivalence between IV and SC treatments may not be appropriate. However, Gilead acknowledge that EULAR response rates are likely to decline by line of treatment.

b) For ABC SC, no efficacy data were available in the bDMARD-IR NMA, and thus an assumption was required for inclusion in the CEM. Using the same arguments as in a), the results from the cDMARD-IR NMA were applied.

B11. Subsequent treatment data:

The company stated that "the treatment sequences used in this submission are in keeping with treatments suggested by NICE guidelines and have been validated using both market share data and clinical expert validation". Please provide more detailed information on how the treatment sequences for the different subgroups were determined.

B11. Answer: The treatments considered for inclusion in the treatment sequences modelled were determined by the NICE treatment pathway (shown in figure 2 of the CS). Based on this, in combination with market share data (therapy watch, 2019) and through validation by a UK rheumatologist to guide on both the most likely drug classes at each line and most commonly used molecules within each class seen in clinical practise (18). This approach was taken due to the large number of treatment sequences permutations possible given the number of comparators in the NICE treatment pathway, which would be both unfeasible to generate given the model run time and impeded interpretation of results to aid decision making given the volume of analysis.

<u>Population 2:cDMARD-IR</u>

2a) *Severe RA patients in first line advanced therapy treatment of (MTX ineligible)*

Market share data indicates 77% of 1L advanced therapy (not mono- and combination-therapy specific) in the UK comprises of an anti-TNF agent, of which 21% and 40% is attributable to ADA and ETN (including biosimilars), respectively. BAR is the most commonly used JAK in 1L advanced therapy, contributing 5.4% in the UK compared 2.6% for TOF. Finally, TCZ accounts for 9.1% of all 1L therapies and clinical expert opinion indicated its use in 1L would be mostly in monotherapy. Given 1L and 2L monotherapy options are largely the same, it was agreed that ABT would be the most likely 2L option and that anti-TNF cycling is not a clinically preferred approach. Throughout analyses, subcutaneous formulations were selected

based on clinical preference. This appropriateness of this selection was validated by clinical experts.

2b) *Severe RA patients in first line advanced therapy treatment (MTX eligible)*
For patients who are MTX eligible and RTX is tolerated the rationale for the choice of 1L comparators is as per population 2a, with the omission of TCZ based on clinical opinion as described above. At 3L clinical expert opinion indicated that TCZ would be the most utilised option and that SAR should only be modelled if there are significant differences in costs as its usage is expected to be low.

This appropriateness of this selection was validated by clinical experts. For patients who are MTX eligible but RTX is contraindicated (or not tolerated) the rationale for 1L treatments is as per Table 38. At 2L, anti-TNF cycling is not considered appropriate (see above) although clinical expert opinion indicated that 2L options could include IL-6 or CD-80 agents. TCZ was preferred to SAR as the 2L option based on clinical opinion and 2L market share data (15.5% vs. 1%, respectively).

2bi) Severe RA (MTX eligible, RTX contraindicated)
For patients who are MTX eligible but RTX is contraindicated (or not tolerated) the rationale for 1L treatments as above. At 2L, anti-TNF cycling is not considered appropriate (see above) although clinical expert opinion indicated that 2L options could include IL-6 or CD-80 agents. TCZ was preferred to SAR as the 2L option based on clinical opinion and 2L market share data (15.5% vs. 1%, respectively).

<u>Population 3: bDMARD-IR</u>
3a*) Severe RA patients after failure of first line advanced therapy treatment (MTX ineligible, RTX ineligible)*
Comparators were selected in line with the NICE treatment pathway. A limited number of molecules are recommended as 2L advanced treatments. Anti-TNF agents were not included based on clinical expert feedback that anti-TNF cycling is not an optimal treatment approach. All other recommended drug classes are included.

3b) *Severe RA patients after failure of first line advanced therapy treatment (MTX eligible, RTX ineligible)*

As per clinical advice, the most commonly used agent in each class (at 2L) was selected. Anti-TNFs were excluded as described above.

Severe RA patients after failure of first line advanced therapy (MTX eligible, RTX eligible)

The only guideline recommended option is RTX. TCZ was preferred to SAR as the appropriate final active therapy based on clinical advice and market share.

Severe RA patients after failure of rituximab in combination with methotrexate

After failure of RTX, TCZ and SAR are the only guideline recommend options.

Additionally, further rationale relating to the exclusion of infliximab, certolizumab pegol, golimumab, tofacitinib from a number of sequences can be found in the response to QB3.b.

Please note that the market share data presented here is based on an internal data source, Therapy Watch (2019) (18). The IL market share data is shown below (Table 29). The original company submission states this data source was used although figures in Document B were taken from a different source in error. The conclusions relating to the treatment sequences are unchanged, as the market shares between sources were comparable (see section B3.2.5 in the CS). The Budget Impact analysis is unaffected. Correct figures provided below.

Table 29. 1L market share data (therapy watch,2019) accessed 27/03/2020 (18)

Molecule	Market share (2019)
Xeljanz	2.61%
Olumiant	5.40%
RTX biosimilar	2.65%
MabThera	1.03%
Orencia	1.73%
Kevzara	0.49%

RoActemra	9.11%
Simponi	4.14%
Cimzia	9.24%
IFX biosimilar	1.38%
Remicade	0.66%
ADA biosimilar	9.31%
Humira	12.04%
ETN biosimilar	34.30%
Enbrel	5.92%

Adverse events

B12. In the model, rates of adverse events (AE) – serious infections – were based on those identified as part of the Singh et al. [CS REF #160] Cochrane review, and were dependent on the class of therapy, rather than being treatment-specific. In the CS it is further stated that "Although the approach represents a simplification of the disease and safety profile of RA therapies, this is considered a conservative approach, as filgotinib is considered to have a favourable safety and tolerability profile in patients with moderately to severely active RA".

a) Please justify this assumption by providing evidence that it is reasonable to assume that AEs depend on class of therapy rather than individual treatments.

b) Please provide evidence supporting the claim that "filgotinib is considered to have a favourable safety and tolerability profile in patients with moderately to severely active RA" compared to other bDMARDs.

B12. Answers:

a) This assumption has been previously accepted by NICE, and was applied in recent technology appraisals in RA (MTA375, TA10389, TA485 and TA466)(3, 5, 17, 19). In TA480, an odds ratio relative to tofacitinib was applied, but similar effect estimates are not available for filgotinib (4). Previous models have shown that adverse events are not a significant driver of cost-effectiveness and have therefore either taken a simplistic approach or

assumed no impact and have not modelled them. Additionally, a scenario analysis presented in section B3.8.2 in the CS demonstrated that separating JAK AE rates from other bDMARDs, and varying AE rate, had minimal impact on the results.

b) The CEM only considers serious infections, consistent with the methodology applied in TA375. Adverse events rates from the FINCH 1 trial provide data compared to the active comparator in this trial, adalimumab. At week 24, which is most the relevant time point from a modelling perspective, rates of serious infectious adverse events were comparable (whilst being numerically favourable for filgotinib) for filgotinib against adalimumab, with rates of 1.7% (filgotinib 200mg), 1.7% (filgotinib 100mg) and 2.5% (adalimumab). Additionally, herpes zoster rates, an important AE related to therapies in RA, showed comparable (but numerically favourable for filgotinib) between treatment arms 0.4% (fil 200mg), 0.4% (filgotinib 100mg) and 0.6% (adalimumab). At week 24, one patient experienced an opportunistic infection in the adalimumab arm, with no one in the filgotinib arm doing so.

   At week 52, rates of serious infectious adverse events were 2.7% (filgotinib 200mg), 2.7% (filgotinib 100mg) and 3.1% for adalimumab. Additionally, for herpes zoster, showed broadly comparable rates between treatment arms, with 1.3% (filgotinib 200mg), 0.8% (filgotinib 100mg) and 0.6% (Adalimumab). Two subjects (0.6%) in the adalimumab arm experienced an AE of opportunistic infection, with no patients experiencing this in either filgotinib treatment arms. Overall, the incidence of serious adverse events was also comparable between treatment arms; 7.4% (filgtonib 200mg), 8.3% (filgotinib 100mg) and 6.8% (adalimumab).

Health-related quality of life

B13. Utility values in the model are estimated using a mapping algorithm by Hernandez-Alava et al mapping from HAQ-DI and pain scores to EQ-5D scores, as was done in MTA375. The VAS pain-score used in the mapping algorithm is derived

from the HAQ-DI and is also used as a separate input in the same mapping algorithm.

a) As stated in MTA375, adding pain as an additional explanatory variable improves model fit, because HAQ-DI and pain are not perfectly correlated. However, it is questionable whether these advantages are also applicable when pain is estimated only based on the HAQ-DI (and not based on actual patient data), as is done in the company's model. Please justify the derivation of VAS pain scores from the HAQ-DI score and the use of both estimates in the mapping function (i.e. given that these pain VAS scores also depend on the same HAQ-DI scores) and consider not using pain as an explanatory variable in the mapping algorithm.

b) Please add a scenario in which the VAS pain scores at baseline are used to estimate utility values.

c) Please use baseline HAQ-DI scores to estimate baseline VAS pain scores (based on the function provided in table 52 in the CS) and compare these scores to the empirical patient level data.

d) Please provide details and justification for using the method to estimate the 'current pain' parameter in the VBA model.

e) It appears that estimated utility values are set to 1 in the model when the utility value exceeds 0.883 (the largest plausible EQ-5D-5L score below perfect health). This potentially over-estimates the utility values in treated patients. The ERG considers it preferable to not alter utility values resulting from the mapping algorithm. Please provide justification for the company's approach and implement the ERG's preferred approach in the model.

B13. Answers:

a) The approach in the CEM is consistent with the approach in MTA375. Pain is one of the five domains in the EQ-5D instrument and contributes the greatest weight to the summary score, and analyses conducted in Hernandez-Alava et al. demonstrated that it is important to include pain as a separate explanatory variable in estimating EQ-5D from HAQ-DI (24). Tracking pain separately in

the model would add to its complexity, and the mapped relationship between HAQ-DI and pain is estimated using data from the National Databank for Rheumatic Diseases based on over 100,000 observations (17). As such, Gilead consider it appropriate to be consistent with this approach, as previous analyses have shown that other methods give poorer estimates.

b) This scenario has been implemented in the submitted model as requested, using the base pain score for each patient throughout the model simulation. A switch is included in cell I85 in the *Main Settings* sheet.

The result of this scenario for population 2b (severe, csDMARD-IR, MTX tolerant, RTX tolerant) is provided below. Costs are equivalent to the CS base case, while QALYs increase for each treatment.

Table 30: Base case and scenario analysis: csDMARD-IR, MTX eligible, RTX eligible, severe RA population – versus FIL 200mg in combination with MTX

Base case						
First-line treatment	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER vs FIL (£/QALY)**	**ICER incremental (£/QALY)**
FIL + MTX	[redacted]	[redacted]	-	-	-	-
ADA + MTX	[redacted]	[redacted]	18,263.14	-0.011	Dominated	Dominated
ETN + MTX	[redacted]	[redacted]	4,100.90	0.064	418,614.42 SW	63,661.88
BAR + MTX	[redacted]	[redacted]	7,638.94	-0.033	1,466,495.03 SW	Dominated
Scenario analysis						
First-line treatment	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER vs FIL (£/QALY)**	**ICER incremental (£/QALY)**
FIL + MTX	[redacted]	[redacted]	-	-	-	-
ADA + MTX	[redacted]	[redacted]	18,263.14	-0.008	Dominated	Dominated
ETN + MTX	[redacted]	[redacted]	4,100.90	0.047	580,751.14 SW	162,658.82
BAR + MTX	[redacted]	[redacted]	7,638.94	-0.024	2,030,674 SW	Dominated

Abbreviations: ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

c) Baseline HAQ-DI for each cohort in the model were mapped to pain values using the function provided in Table 52 of the CS. The comparison of the

appropriate sampled cohorts and the baseline characteristics from FINCH 1 and FINCH 2 are provided in Table 31.

Table 31: Baseline HAQ-DI scores from the CEM mapped to pain scores, compared to trial baseline pain scores

Cohort	Model mean (SD)	Trial mean (SD)
cDMARD-IR (moderate subgroup) FINCH 1 subgroup data	38 (14.3)	50 (20.6)
cDMARD-IR (severe subgroup) FINCH 1 subgroup data	49 (12.5)	70 (16.7)
bDMARD-IR FINCH 2	47 (13.4)	67 (21.0)

d) The *currentPain* parameter is estimated from the mapping described in function provided in table 52 in the CS. It is used as an input variable for the mapping from Hernandez-Alava et al. to determine the utility accrued in each cycle, consistent with the approach in MTA375. As detailed in a), this parameter is estimated using an analysis on the correlation between HAQ-DI and pain scores described in MTA375, based on over 100,000 observations from the National Databank for Rheumatic Diseases. The baseline pain can either be found by using this mapping on baseline HAQ-DI score, or by using the baseline characteristics input provided in the front end. The approach taken can be selected in cell E85 in the *Main Settings* sheet.

e) The VBA code in the submitted CEM has been updated so that utility values exceeding 0.883 are not rounded to 1. This update does not affect the base case results which are equivalent to the results included in the submission.

B14. In the model, only adverse events after 6 months are included, which results in a utility decrement of 0.156. Please justify this assumption.

B14. Answer: Adverse events are only applied in the first 6 month of initiating treatment, and not in the subsequent maintenance phase. Based on MTA375, it was assumed that patients would not switch to a subsequent treatment within 6 months of initiating a treatment, and that any adverse event would be monitored before changing treatment at 6 months (17).

Consistent with the cost-effectiveness analysis in MTA375 and other recent technical appraisals in RA (TA10389, TA485, TA480, TA466) (3-5, 19), a simple approach to adverse event modelling, considering serious infections only, was taken as described in section B3.4.4. The utility decrement is sourced from MTA375 (17).

Costs and resource use

B15. In the model, costs are applied six-monthly and are separated for initial treatment (including any loading doses) and maintenance treatment. However, time spent in the maintenance period is based on a time to event function.

a) Please justify why costs were applied six-monthly given that the maintenance period could be assumed as a continuous time variable.

b) Please elaborate on the implications of using 6-monthly costing (e.g. does this lead to rounding of costs to the closest 6-months period).

B15. Answers:

a) The time to discontinuation is based on parametric survival models as detailed in section B3.3.4. of the CS, and calculates the number of days until discontinuation. However, as the HAQ-DI trajectory is calculated on a 6-monthly basis, and used to accrued utilities, the time of discontinuation is rounded to the nearest 6-month cycle. Applying 6-monthly cycles is consistent with the cost-effectiveness analysis in MTA375, and other recent technical appraisals in RA (TA10389, TA485, TA480, TA466)(3-5, 17, 19). Additionally, 6 months is the NICE recommended follow up for review of RA drugs (22).

b) During the maintenance phase, costs are calculated by using the number of 6-monthly periods from the start of the phase, until the next event. When a patient discontinues or dies during any cycle, the number of this cycle is used as the time of event. Events are modelled as follows.

- Adverse events only occur within the initial 6 months. If an adverse event occurs, patients accrue costs of treatment for the whole period, in addition to adverse event costs.
- If a patient dies during the initial 6 months, they are assumed to accrue no costs or utilities.
- As described in the response to question B20, the time at which death occurs is sampled base on a survival curve and rounded to a 6 month period.
- Time to discontinuation is calculated using the macro `sampletimeOfDiscontinue` and then rounded to the number of the next 6 monthly period.

Since same rounding approach is applied to both intervention and comparator, and both up- and down-rounding is applied, this approach is unlikely to bias the average model outputs or notably impact the incremental results. Further this approach is consistent with the cost-effectiveness analysis conducted in MTA375 and other recent TAs approved by NICE (TA10389, TA485, TA480, TA466) (3-5, 17, 19).

Results

B16. Sensitivity analyses:

a) Please provide tabulated results for all deterministic scenario analyses (including expected life-years, QALYs and costs for filgotinib and each comparator).

b) The probabilistic sensitivity analysis (PSA) does not appear to include time to treatment discontinuation (TTD) and the HAQ-DI trajectory. Please provide

clarification on this and, if these are indeed not included, include these estimates in the PSA (for TTD in a way that it can be different for each treatment in one PSA run).

c) The PSA does not seem to take into account the response rates using the joint posterior distribution from the NMA (instead of just drawing from the response probability distribution separately). Please implement response rates using the joint posterior distribution from the NMA in the model.

d) 500 simulated patients per PSA replication is likely insufficient to achieve stable results. Please provide your thoughts on the validity of the probabilistic results, any diagnostics performed, and, if needed, a larger number of simulations

B16. Answer:

a) Tabulated results for the scenario analyses presented in section B3.8.2 of the CS are included in Table 32 through Table 34. The analyses for the moderate population were updated based on the updated moderate cost-effective analysis as described in question B5. Additionally, it should be noted that the originally submitted model had an error in the code for the alternative utility mapping scenario. This has been corrected in the resubmitted model and results of the corrected analyses are presented below.

Table 32: Results of deterministic scenario analyses for the moderate population: csDMARD-IR, MTX eligible, RTX eligible, severe RA (filgotinib combination therapy vs. BSC)

Scenario	FIL			BSC			Incremental			Incremental NMB
	LY	QALY	Total cost (£)	LY	QALY	Total cost (£)	LY	QALY	Total cost (£)	
Horizon 20 years	12.380	[redacted]	[redacted]	12.380	[redacted]	[redacted]	0.000	[redacted]	[redacted]	1,259.72
FIL efficacy (95% CI): Lower	15.815	[redacted]	[redacted]	15.815	[redacted]	[redacted]	0.000	[redacted]	[redacted]	904
FIL efficacy (95% CI): Upper	15.815	[redacted]	[redacted]	15.815	[redacted]	[redacted]	0.000	[redacted]	[redacted]	1,126

ETN efficacy (95% CI): Lower	15.815	[redacted]	[redacted]	15.815	[redacted]	[redacted]	0.000	[redacted]	[redacted]	935
ETN efficacy (95% CI): Upper	15.815	[redacted]	[redacted]	15.815	[redacted]	[redacted]	0.000	[redacted]	[redacted]	935
Adverse event rate (-20%)	15.815	[redacted]	[redacted]	15.815	[redacted]	[redacted]	0.000	[redacted]	[redacted]	920
Adverse rate (+20%)	15.815	[redacted]	[redacted]	15.815	[redacted]	[redacted]	0.000	[redacted]	[redacted]	788
Adverse events from FINCH trials	15.815	[redacted]	[redacted]	15.815	[redacted]	[redacted]	0.000	[redacted]	[redacted]	1,057.89
Efficacy from FINCH trials	15.815	[redacted]	[redacted]	15.815	[redacted]	[redacted]	0.000	[redacted]	[redacted]	2,289.13
Admin costs (-20%)	15.815	[redacted]	[redacted]	15.815	[redacted]	[redacted]	0.000	[redacted]	[redacted]	922
Admin costs (+20%)	15.815	[redacted]	[redacted]	15.815	[redacted]	[redacted]	0.000	[redacted]	[redacted]	948
Monitoring costs	15.815	[redacted]	[redacted]	15.815	[redacted]	[redacted]	0.000	[redacted]	[redacted]	1,062

(-20%)										
Monitoring costs (+20%)	15.815	[redacted]	[redacted]	15.815	[redacted]	[redacted]	0.000	[redacted]	[redacted]	807
Hospital cost (-20%)	15.815	[redacted]	[redacted]	15.815	[redacted]	[redacted]	0.000	[redacted]	[redacted]	621
Hospital cost (+20%)	15.815	[redacted]	[redacted]	15.815	[redacted]	[redacted]	0.000	[redacted]	[redacted]	1,248
Adverse event costs (-20%)	15.815	[redacted]	[redacted]	15.815	[redacted]	[redacted]	0.000	[redacted]	[redacted]	943
Adverse event costs (+20%)	15.815	[redacted]	[redacted]	15.8151	[redacted]	[redacted]	0.000	[redacted]	[redacted]	926
Adverse utility decrement (-20%)	15.815	[redacted]	[redacted]	15.8151	[redacted]	[redacted]	0.000	[redacted]	[redacted]	937
Adverse utility decrement (+20%)	15.815	[redacted]	[redacted]	15.8151	[redacted]	[redacted]	0.000	[redacted]	[redacted]	932
Discount rate 0%	26.429	[redacted]	[redacted]	26.4290	[redacted]	[redacted]	0.000	[redacted]	[redacted]	194

Discount rate 6%	12.005	[redacted]	[redacted]	12.0045	[redacted]	[redacted]	0.000	[redacted]	[redacted]	871
Linear HAQ-DI progression based on Malottki et al. 2011	15.815	[redacted]	[redacted]	15.8151	[redacted]	[redacted]	0.000	[redacted]	[redacted]	10,843.60
Utility mapping algorithm based on Malottki et al. 2011	15.815	[redacted]	[redacted]	15.8151	[redacted]	[redacted]	0.000	[redacted]	[redacted]	8,095.48

Abbreviations: BSC, best supportive care; CI, confidence interval; FIL, filgotinib; HAQ-DI, Health Assessment Questionnaire – Disability Index; LY, life year; NMB, net monetary benefit; QALY, quality adjusted life year

Table 33: Results of deterministic scenario analyses for csDMARD-IR, MTX eligible, RTX eligible, severe RA (filgotinib combination therapy vs. ETN combination therapy)

Scenario	FIL	ETN	Incremental	Incremental

	LY	QALY	Total cost (£)	LY	QALY	Total cost (£)	LY	QALY	Total cost (£)	NMB
Horizon 20 years	11.826	[redacted]	[redacted]	11.826	[redacted]	[redacted]	0.000	[redacted]	[redacted]	20,018.32
FIL efficacy (95% CI): Lower	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	22,025.05
FIL efficacy (95% CI): Upper	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	22,470.27
ETN efficacy (95% CI): Lower	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	22,209.27
ETN efficacy (95% CI): Upper	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	22,061.21
Adverse event rate (-20%)	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	22,116.17
Adverse rate (+20%)	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	22,064.57
Adverse events from FINCH	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	22,544.14

trials										
Admin costs (-20%)	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	21,973.14
Admin costs (+20%)	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	22,244.83
Monitoring costs (-20%)	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	22,134.12
Monitoring costs (+20%)	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	22,083.85
Hospital cost (-20%)	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	22,143.28
Hospital cost (+20%)	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	22,074.70
Adverse event costs (-20%)	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	22,110.32
Adverse event costs (+20%)	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	22,107.66

Adverse utility decrement (-20%)	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	22,109.37
Adverse utility decrement (+20%)	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	22,108.60
Discount rate 0%	23.621	[redacted]	[redacted]	23.621	[redacted]	[redacted]	0.000	[redacted]	[redacted]	30,677.66
Discount rate 6%	11.307	[redacted]	[redacted]	11.307	[redacted]	[redacted]	0.000	[redacted]	[redacted]	18,554.05
Linear HAQ-DI progression based on Malottki et al. 2011	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	21,243.04
Utility mapping algorithm based on Malottki et al. 2011	14.655	[redacted]	[redacted]	14.655	[redacted]	[redacted]	0.000	[redacted]	[redacted]	21,283.66

Abbreviations: CI, confidence interval; ETN, etanercept; FIL, filgotinib; HAQ-DI, Health Assessment Questionnaire – Disability Index; LY, life year; NMB, net monetary benefit; QALY, quality adjusted life year

Table 34: Results of deterministic scenario analyses for bDMARD-IR, MTX eligible, RTX ineligible, severe RA (filgotinib combination therapy vs. ABC combination therapy)

Scenario	FIL			ABC			Incremental			Incremental NMB
	LY	QALY	Total cost (£)	LY	QALY	Total cost (£)	LY	QALY	Total cost (£)	
Horizon 20 years	11.330	[redacted]	[redacted]	11.330	[redacted]	[redacted]	0.000	[redacted]	[redacted]	63,335.37
FIL efficacy (95% CI): Lower	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	69,057.25
FIL efficacy (95% CI): Upper	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	69,150.36
ABC efficacy (95% CI): Lower	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	65,790.14
ABC efficacy (95% CI): Upper	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	70,089.09
Adverse event rate (-20%)	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	69,357.46
Adverse rate	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	68,537.38

(+20%)										
Adverse events from FINCH trials	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	69,778.89
Admin costs (-20%)	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	68,984.94
Admin costs (+20%)	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	69,336.97
Monitoring costs (-20%)	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	69,172.44
Monitoring costs (+20%)	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	69,149.47
Hospital cost (-20%)	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	69,262.41
Hospital cost (+20%)	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	69,059.50
Adverse event costs (-20%)	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	69,160.96

Adverse event costs (+20%)	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	69,160.96
Adverse utility decrement (-20%)	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	69,160.96
Adverse utility decrement (+20%)	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	69,160.96
Discount rate 0%	21.349	[redacted]	[redacted]	21.349	[redacted]	[redacted]	0.000	[redacted]	[redacted]	94,458.07
Discount rate 6%	10.703	[redacted]	[redacted]	10.703	[redacted]	[redacted]	0.000	[redacted]	[redacted]	58,267.21
Linear HAQ-DI progression based on Malottki et al. 2011	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	67,487.81
Utility mapping algorithm based on Malottki et al. 2011	13.676	[redacted]	[redacted]	13.676	[redacted]	[redacted]	0.000	[redacted]	[redacted]	67,379.31

Abbreviations: ABC, abatacept; CI, confidence interval; FIL, filgotinib; HAQ-DI, Health Assessment Questionnaire – Disability Index; LY, life year; NMB, net monetary benefit; QALY, quality adjusted life year

b) **Answer to b and c:** The PSA has been updated to include additional parameters as requested by the ERG.

The parameters for the time to treatment discontinuation curves for patients achieving moderate and good EULAR response were not available from MTA375, and as such, the published curve was digitised as described in section B3.3.4 in the CS. The PSA has been updated by applying a uniform distribution allowing variation of +/- 20% to the discontinuation curves. This simplified approach was applied in the absence of accurate parameter and variance estimates.

The joint posterior distribution from the NMA has been added to the model and is sampled in the updated PSA. Four additional sheets, labelled “CODA” are included in the resubmitted model which provide the response rates from joint posterior distribution. The PSA VBA code has been updated to randomly sample response rates based on these data.

The initial reduction in HAQ scores for patients with treatment response was varied in the CS PSA using a normal distribution. Following the initial period, the HAQ-DI trajectory (for both csDMARDs and bDMARDs) is calculated using a mapping based on analyses performed by the assessment group in MTA375. The PSA does not sample this curve since variance parameters for inclusion into the PSA are not available, consistent with recent submissions in RA (TA10389, TA485, TA480). However, this mapping is well established, and has been applied by the assessment group in MTA375, as well as subsequent technical appraisals (3, 4, 17, 20).

Furthermore, the model has been updated to vary additional parameters beyond the parameters varied in the originally submitted model, described in section B3.8.1 in the CS. These include time to discontinuation, monitoring costs, adverse event costs, adverse event disutilities, and DAS28 progression coefficient. The inputs for the updated PSA are summarised in

Table 35.

It should be noted that Table 73 in the CS mistakenly listed that a gamma distribution was used for hospital costs. A lognormal distribution is applied in the CEM. This has been corrected in

Table 35.

Table 35: Summary of inputs used for the updated probability sensitivity analysis

Parameter	CS section	Distribution	Description
Efficacy			
Proportion of good/moderate responders by treatment	B3.3.2	NMA CODA	Treatment effects in terms of EULAR response (no response, moderate response, good response) were varied using random draws from the joint posterior distribution of the 24-week NMA results.
Initial HAQ-DI reduction	B3.3.2	Normal	Mean HAQ-DI and standard error reported in MTA375 were used to vary response. Standard error was sampled from a normal distribution.
Treatment discontinuation			
Time to discontinuation curves for good/moderate responders	B3.3.4	Uniform	The published curve in MTA375 was digitised, and used to fit a generalised gamma survival curve. A multiplier varying the output by 20% was sampled using a uniform distribution.
Hazard ratios			
Survival hazard ratios	B3.3.5	Lognormal	HRs were sourced from Michaud et al. with a 95% CI (25). CIs were used to sample HRs using a lognormal distribution.
Costs			
Hospitalisation costs	B3.5.3	Lognormal	Hospital costs were taken from MTA375. However, no measure of uncertainty nor breakdown of costs was reported. Therefore, a standard error of 1/10th costs was assumed for each category and costs were sampled from a lognormal distribution.
Monitoring costs	B3.5.3	Lognormal	Monitoring costs were taken from MTA375. However, no measure of uncertainty nor breakdown of costs was reported. Therefore, a standard error of 1/10th costs was assumed and costs were sampled from a lognormal distribution.
Adverse event costs	B3.5.4	Lognormal	Adverse event costs were taken from MTA375. However, no measure of uncertainty nor breakdown of costs was reported. Therefore, a standard error of 1/10th costs was assumed and costs were sampled from a lognormal distribution.
Utilities			
Adverse event disutilities	B3.4.4	Beta	Adverse event disutilities were taken from MTA375. However, no measure of uncertainty nor breakdown of costs was reported. Therefore, a standard error of 1/10th costs was assumed and utilities were sampled from a beta distribution.
Moderate to severe progression coefficient			
Coefficient for DAS28 progression	Included post-submission	Normal	A regression was performed to estimate the relationship between DAS28 and HAQ-DI scores was performed as described in question B5. The standard error from the regression was used for sampling from a normal distribution.

Abbreviations: CI, confidence interval; CODA, convergence diagnostic and output analysis; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire – Disability Index; HR, hazard ratio; NMA, network meta-analysis

Results from the updated PSA are provided below. The overall variation is greater than in the original CS, which is to be expected when additional parameters are varied. The conclusion of the analysis, in addition to the analysis provided in the CS is that the base case ICERs are robust to plausible variation.

Probabilistic sensitivity analysis results

1a. Moderate RA patients after 2 csDMARD failures (MTX ineligible)

The results of the PSA are presented in Table 36, with a cost-effectiveness acceptability curve in Figure 2 and a cost-effectiveness plane in Figure 3. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, filgotinib had a 55.4% probability of being the optimal treatment. At a WTP of £30,000, this increased to 77.9%.

Table 36: Two csDMARD failures, MTX ineligible, moderate RA – versus FIL 200mg monotherapy (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	15.819	[redacted]	-	-	-	14,212.93	-
FIL	[redacted]	15.819	[redacted]	8,078.12	0.000	0.568	-	14,212.93

Abbreviations: BSC, best supportive care; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year

Figure 2. Two csDMARD failures, MTX ineligible, moderate RA – CEAC for PSA

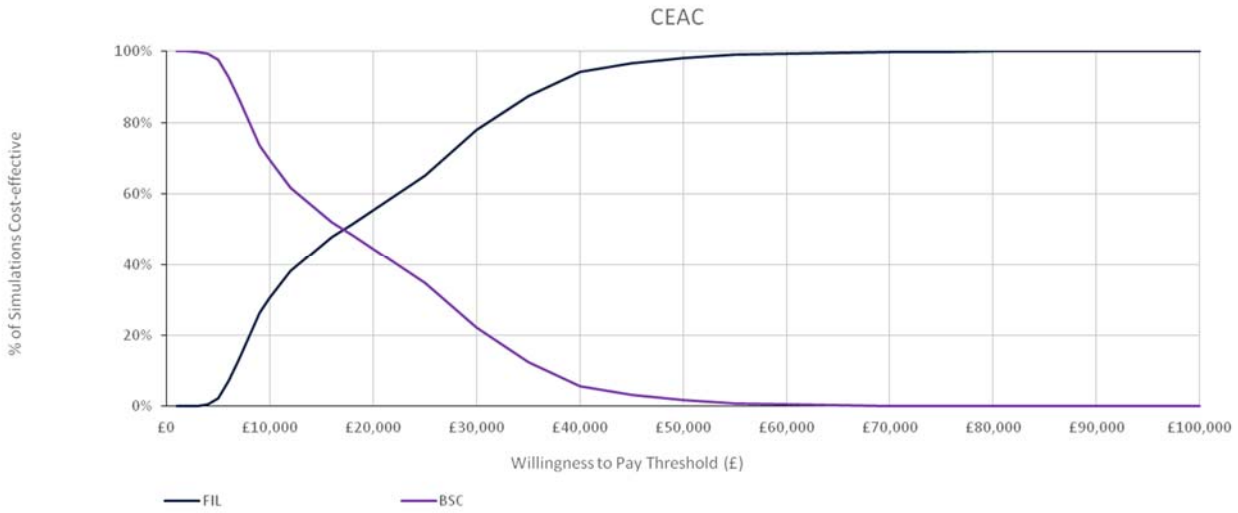
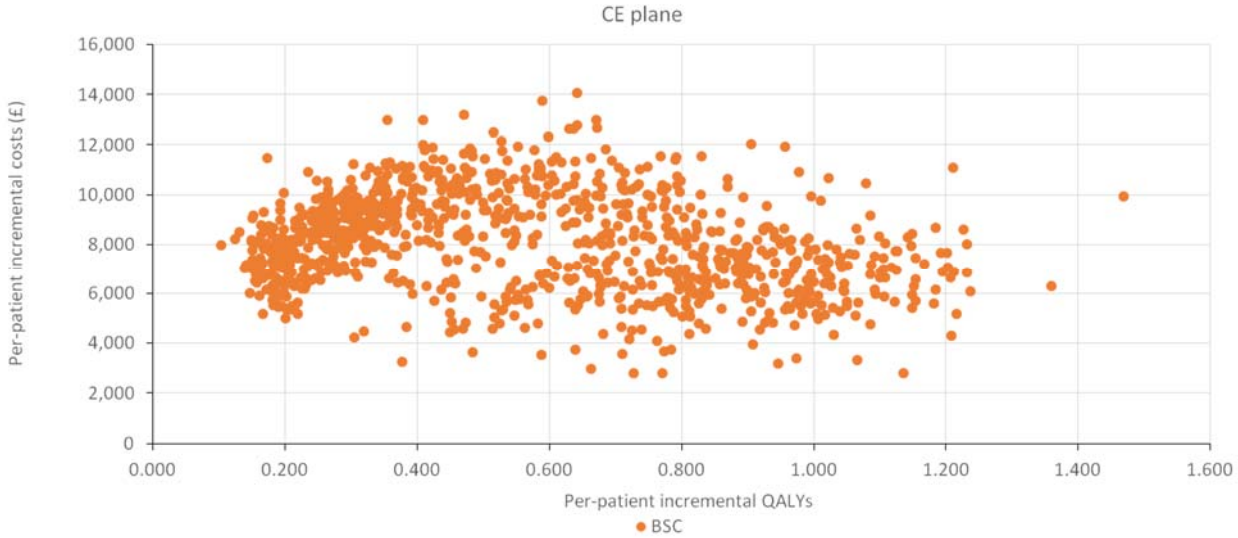


Figure 3. Two csDMARD failures, MTX ineligible, moderate RA – CE plane for PSA: filgotinib vs BSC



1b. Moderate RA patients after 2 csDMARD failures (MTX eligible)

The results of the PSA are presented in Table 37, with a cost-effectiveness acceptability curve in Figure 4 and a cost-effectiveness plane in Figure 5. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, filgotinib had a 56.6% probability of being the optimal treatment. At a WTP of £30,000, this increased to 81.9%.

Table 37: Two csDMARD failures, MTX eligible, moderate RA – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	15.819	[redacted]	-	-	-	15,472.11	-
FIL + MTX	[redacted]	15.819	[redacted]	8,530.02	0.000	0.551	-	15,472.11
Abbreviations: BSC, best supportive care; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year								

Figure 4. Two csDMARD failures, MTX eligible, moderate RA – CEAC for PSA

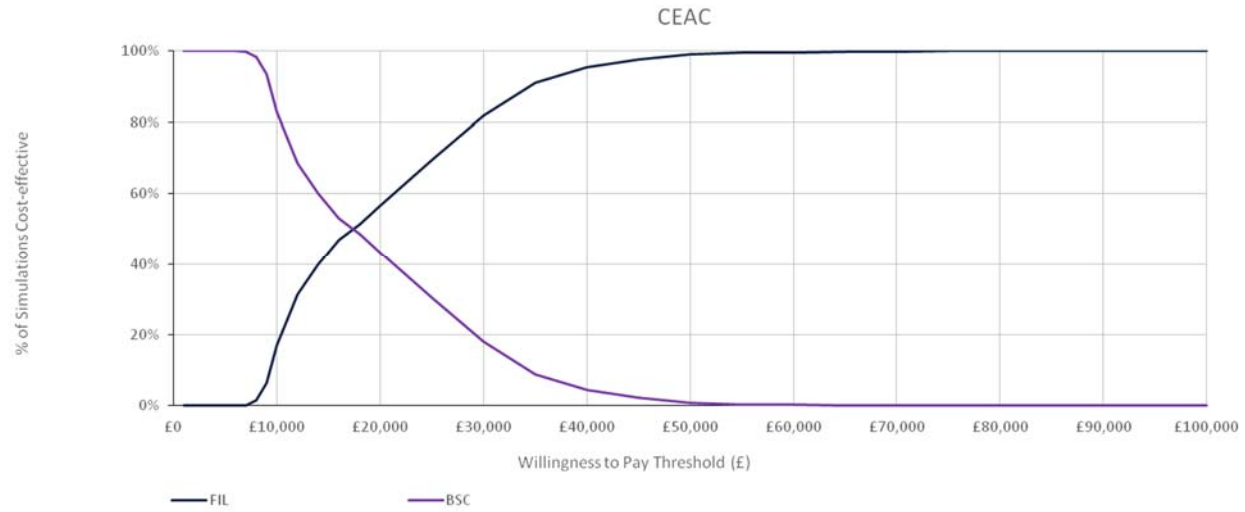
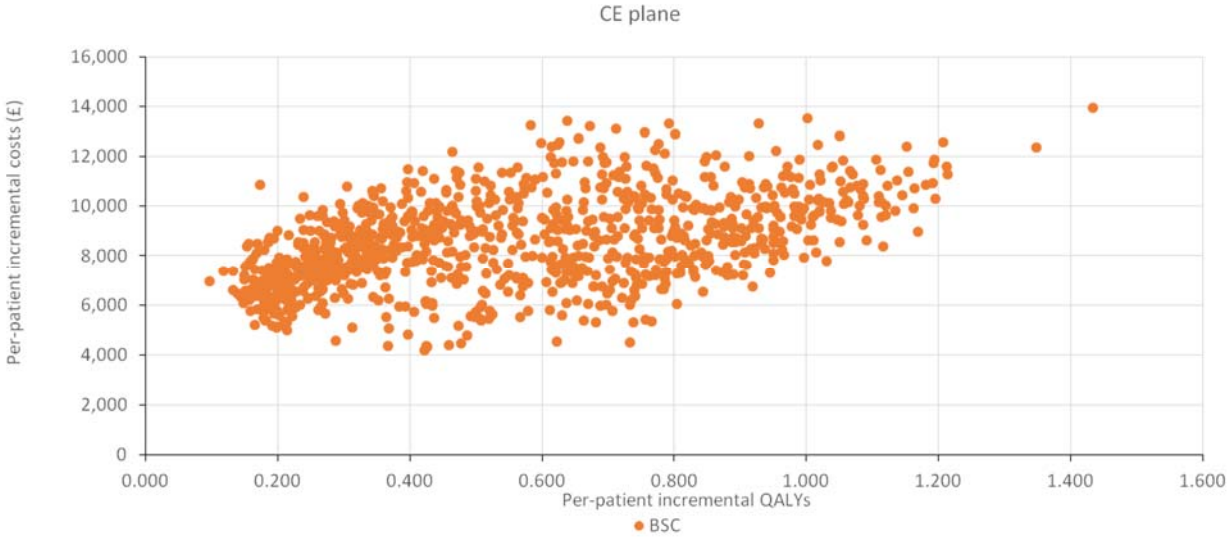


Figure 5. Two csDMARD failures, MTX eligible, moderate RA – CE plane for PSA: filgotinib vs BSC



2a. Severe RA patients in first line advanced therapy treatment of (MTX ineligible)

The results of the PSA are presented in Table 38, with a cost-effectiveness acceptability curve in Figure 6 and a cost-effectiveness plane in Figure 7. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 38: csDMARD-IR, MTX ineligible, severe RA – versus FIL 200mg monotherapy (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL	[redacted]	14.656	[redacted]	-	-	-	-	-
ADA	[redacted]	14.656	[redacted]	19,000.52	0.000	-0.015	Dominated	Dominated
ETN	[redacted]	14.656	[redacted]	3,131.55	0.000	0.080	339,852.38 SW	39,247.72
BAR	[redacted]	14.656	[redacted]	8,590.23	0.000	-0.038	1,144,187.39 SW	Dominated
TCZ	[redacted]	14.656	[redacted]	5,343.79	0.000	-0.056	Dominated	Dominated

Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; TCZ, tocilizumab

Figure 6. csDMARD-IR, MTX ineligible, severe RA – CEAC for PSA

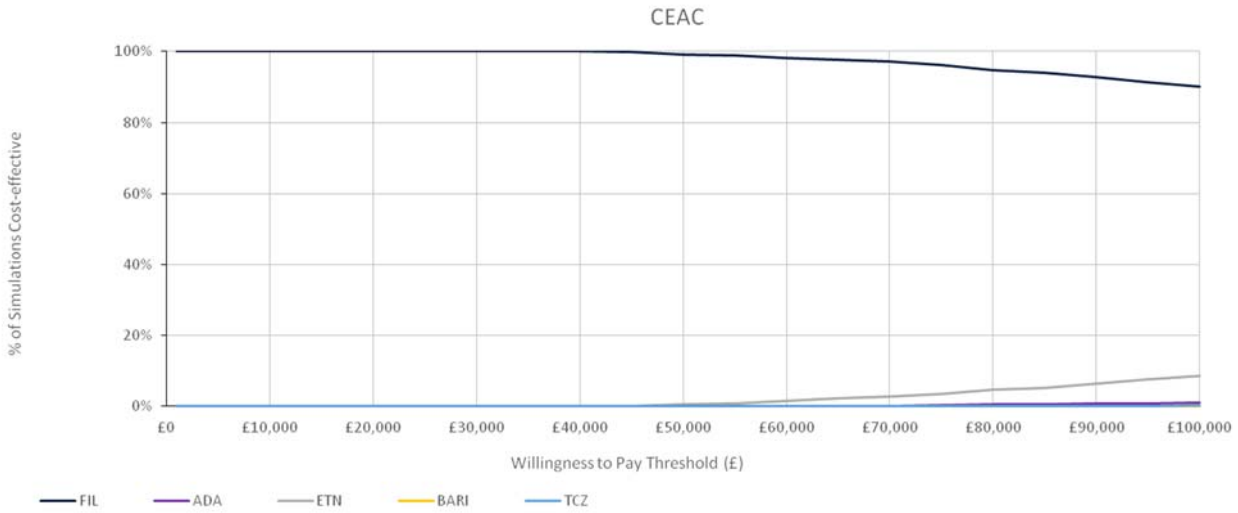
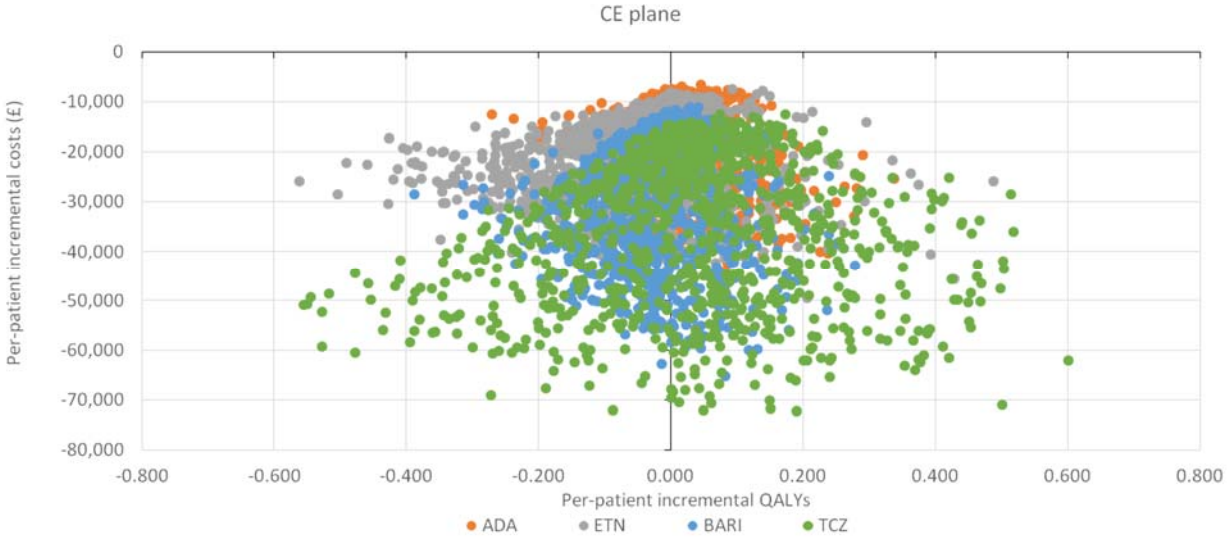


Figure 7. csDMARD-IR, MTX ineligible, severe RA – CE plane for PSA: filgotinib vs comparators



2b. Severe RA patients in first line advanced therapy treatment (MTX eligible)

The results of the PSA for the RTX eligible population are presented in Table 39, with a cost-effectiveness acceptability curve in Figure 8 and a cost-effectiveness plane in Figure 9. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 39: csDMARD-IR, MTX eligible, RTX eligible, severe RA – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.656	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.656	[redacted]	18,936.62	0.000	-0.010	Dominated	Dominated
ETN + MTX	[redacted]	14.656	[redacted]	3,923.82	0.000	0.055	501,202.82 SW	71,1138.43
BAR + MTX	[redacted]	14.656	[redacted]	8,220.29	0.000	-0.026	1,604,482.15 SW	Dominated

Abbreviations: ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Figure 8. csDMARD-IR, MTX eligible, RTX eligible, severe RA – CEAC for PSA

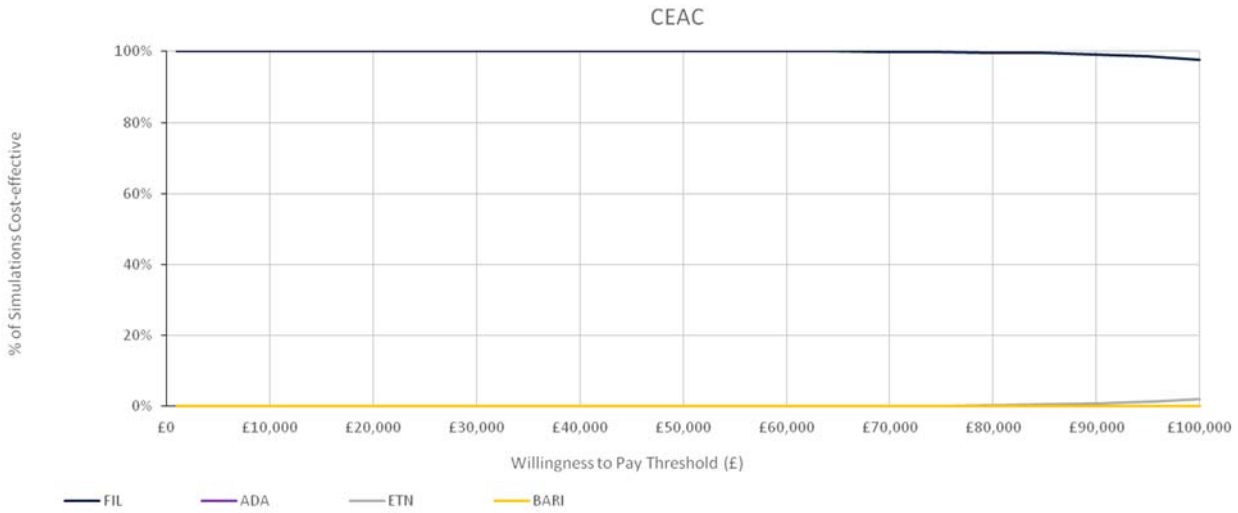
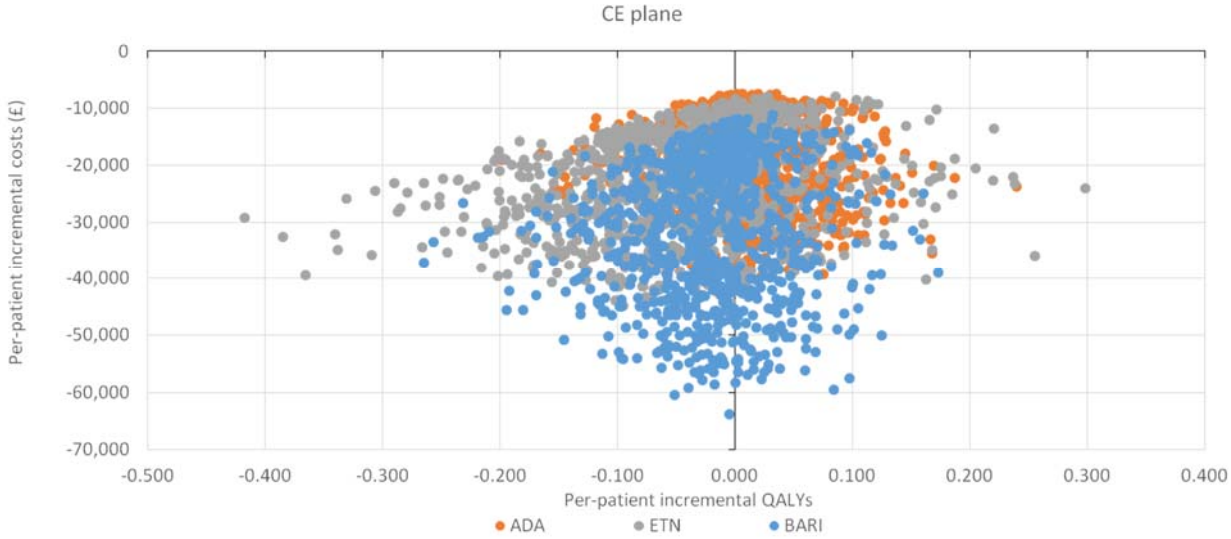


Figure 9. csDMARD-IR, MTX eligible, RTX eligible, severe RA – CE plane for PSA: filgotinib vs comparators



The results of the PSA for the RTX contraindicated population (using second line IL-6) are presented in Table 40, with a cost-effectiveness acceptability curve in Figure 10, and a cost-effectiveness plane in Figure 11. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 40: csDMARD-IR, MTX eligible, RTX contraindicated, severe RA (using second line IL-6) – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.656	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.656	[redacted]	18,837.16	0.000	-0.015	Dominated	Dominated
ETN + MTX	[redacted]	14.656	[redacted]	4,505.20	0.000	0.087	324,055.96 SW	51,666.32
BAR + MTX	[redacted]	14.656	[redacted]	7,953.94	0.000	-0.041	1,020,838.36 SW	Dominated

Abbreviations: ADA, adalimumab; BAR, baricitinib; ETN, etanercept; FIL, filgotinib; IL-6, interleukin 6; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Figure 10. csDMARD-IR, MTX eligible, RTX contraindicated, severe RA, second line IL-6 – CEAC for PSA

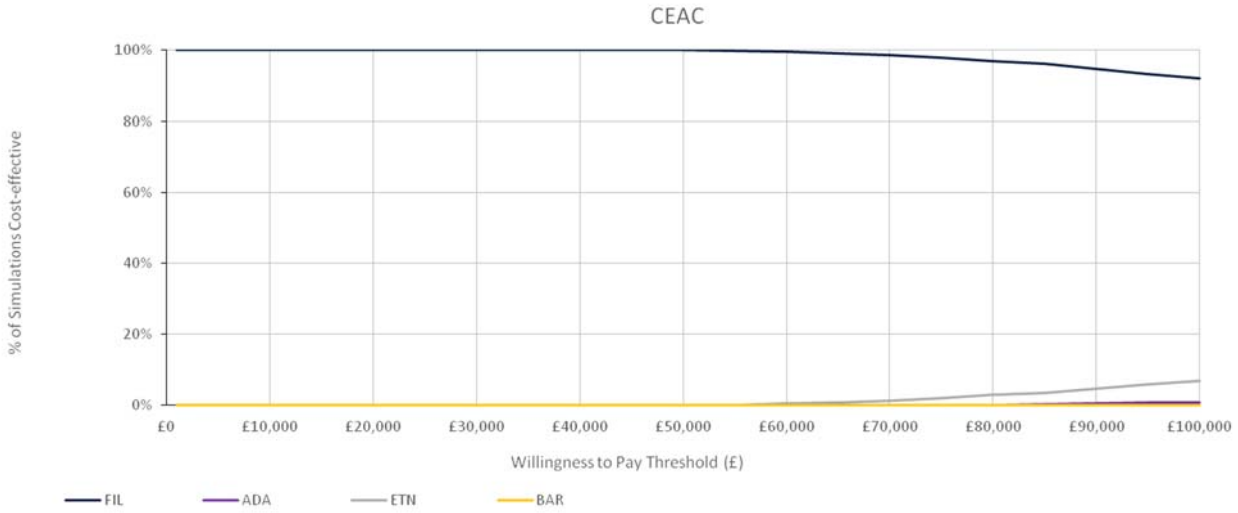
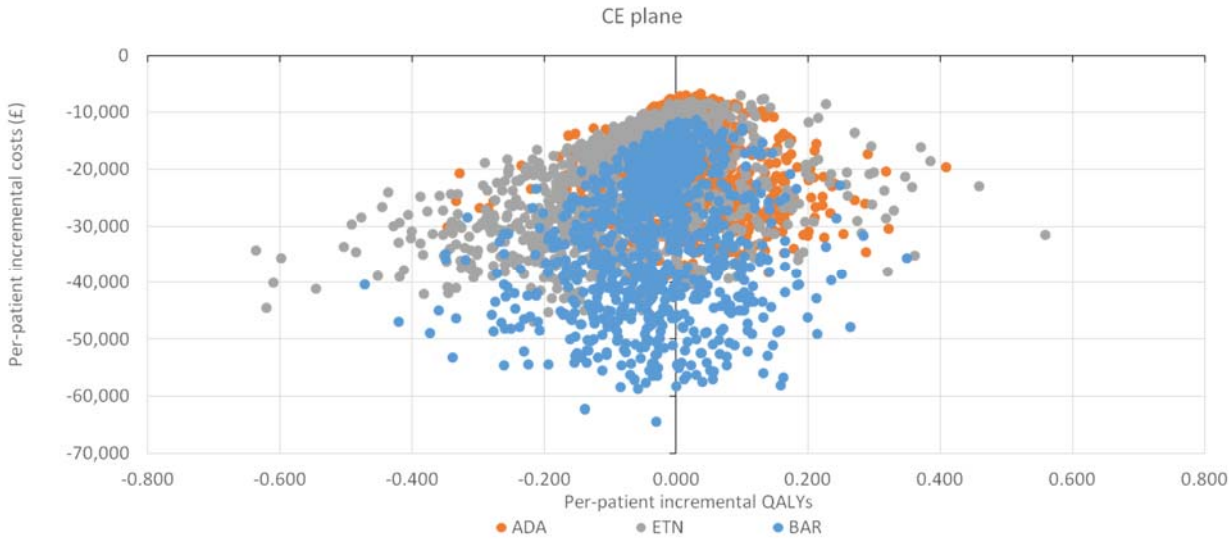


Figure 11. csDMARD-IR, MTX eligible, RTX contraindicated, severe RA, second line IL-6 – CE plane for PSA: filgotinib vs comparators



The results of the PSA for the RTX contraindicated population (using second line CD80) are presented in Table 41, with cost-effectiveness acceptability curve in Figure 12, and cost-effectiveness planes in Figure 13. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 41: csDMARD-IR, MTX eligible, RTX contraindicated, severe RA (using second line CD80) – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.656	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.656	[redacted]	18,998.38	0.000	-0.015	Dominated	Dominated
ETN + MTX	[redacted]	14.656	[redacted]	3,143.66	0.000	0.080	340,005.53 SW	39,399.53
BAR + MTX	[redacted]	14.656	[redacted]	8,584.29	0.000	-0.038	1,144,337.70 SW	Dominated

Abbreviations: ADA, adalimumab; BAR, baricitinib; CD80, cluster of differentiation 80; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Figure 12. csDMARD-IR, MTX eligible, RTX contraindicated, severe RA, second line CD80 – CEAC for PSA

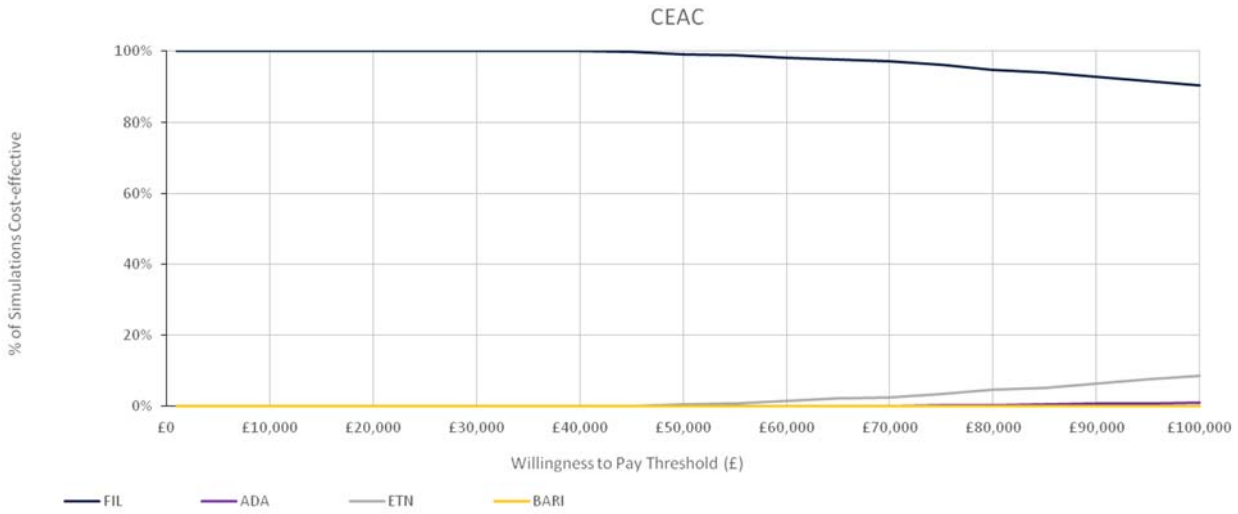
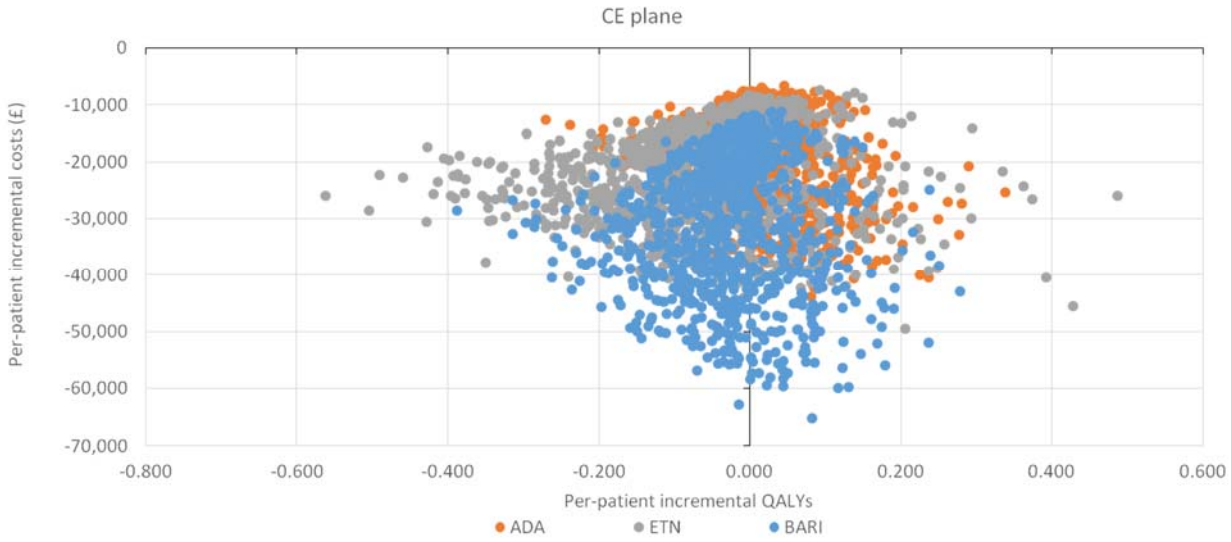


Figure 13. csDMARD-IR, MTX eligible, RTX contraindicated, severe RA, second line CD80 – CE plane for PSA: filgotinib vs comparators



3a. Severe RA patients after failure of first line advanced therapy treatment (MTX ineligible, RTX ineligible)

The results of the PSA are presented in Table 42, with a cost-effectiveness acceptability curve in Figure 14 and a cost-effectiveness plane in Figure 15. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 42: bDMARD-IR, MTX ineligible, RTX ineligible, severe RA – versus FIL 200mg monotherapy (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL	[redacted]	13.675	[redacted]	-	-	-	-	-
TOF	[redacted]	13.675	[redacted]	18,647.81	0.000	-0.114	Dominated	Dominated
BAR	[redacted]	13.675	[redacted]	5,898.79	0.000	0.000	Dominated	-
ABC	[redacted]	13.675	[redacted]	41,873.87	0.000	0.238	533,378.84 SW	175,633.24

Abbreviations: ABC, abatacept; BAR, baricitinib; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; TOF, tofacitinib

Figure 14. bDMARD-IR, MTX ineligible, RTX ineligible, severe RA – CEAC for PSA

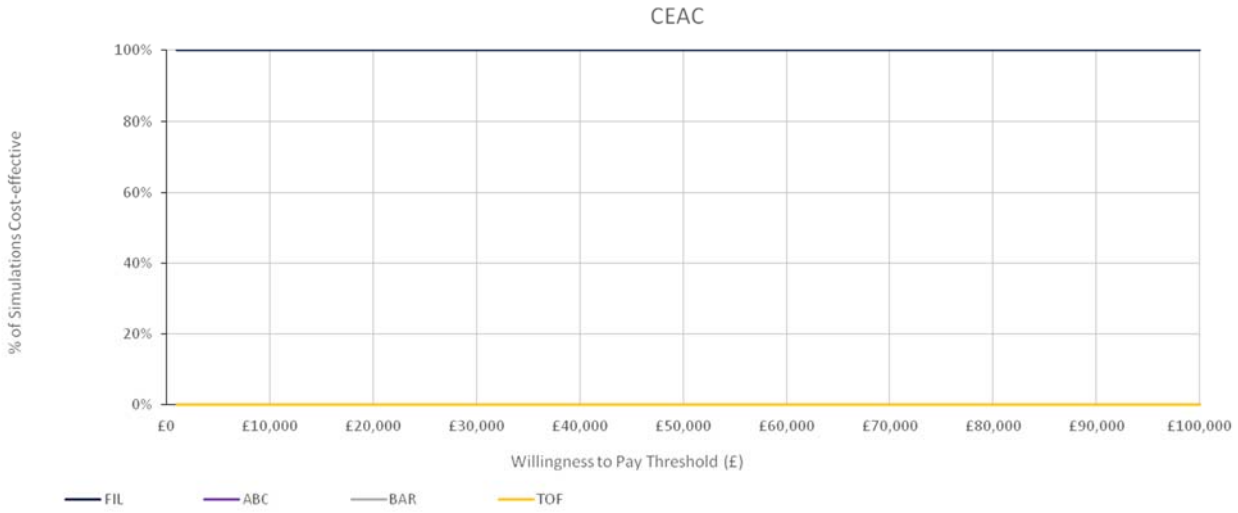
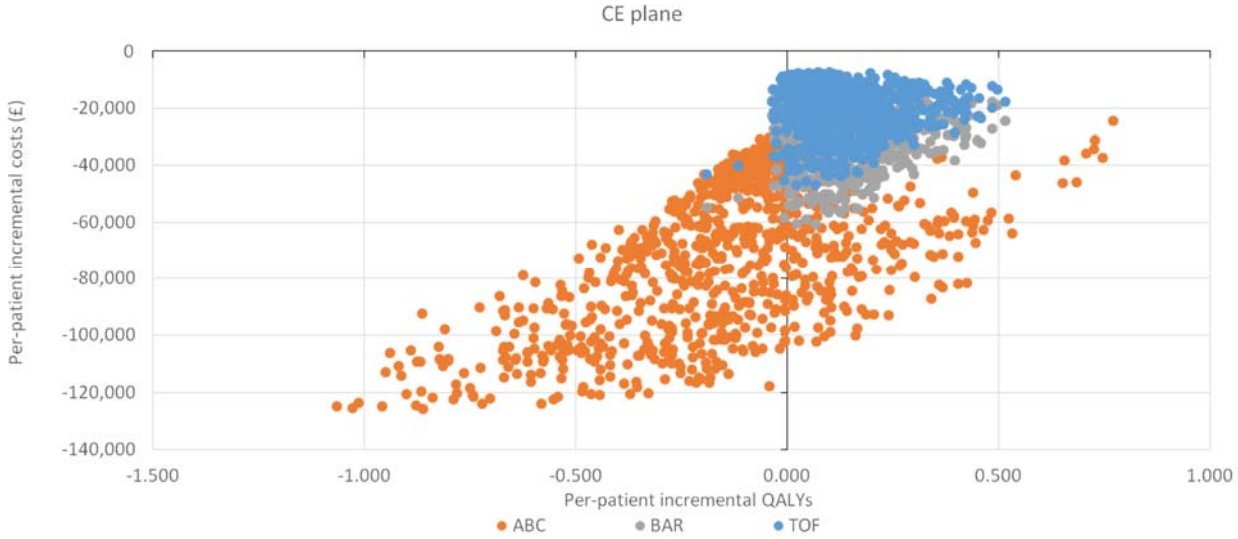


Figure 15. bDMARD-IR, MTX ineligible, RTX ineligible, severe RA – CE plane for PSA: filgotinib vs comparators



3b. Severe RA patients after failure of first line advanced therapy treatment (MTX eligible, RTX ineligible)

The results of the PSA are presented in Table 43, with a cost-effectiveness acceptability curve in Figure 16 and a cost-effectiveness plane in Figure 17. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 43: bDMARD-IR, MTX eligible, RTX ineligible, severe RA – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.675	[redacted]	-	-	-	-	-
BAR + MTX	[redacted]	13.675	[redacted]	24,527.93	0.000	-0.114	Dominated	Dominated
TCZ + MTX	[redacted]	13.675	[redacted]	6,638.88	0.000	0.008	Dominated	782,127.40
SAR + MTX	[redacted]	13.675	[redacted]	69.40	0.000	0.006	Dominated	10,725.91
ABC + MTX	[redacted]	13.675	[redacted]	35,204.18	0.000	0.223	533,539 SW	157,542.76
Abbreviations: ABC, abatacept; BAR, baricitinib; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life-year; SAR, sarilumab; TCZ, tocilizumab								

Figure 16. bDMARD-IR, MTX eligible, RTX ineligible, severe RA – CEAC for PSA

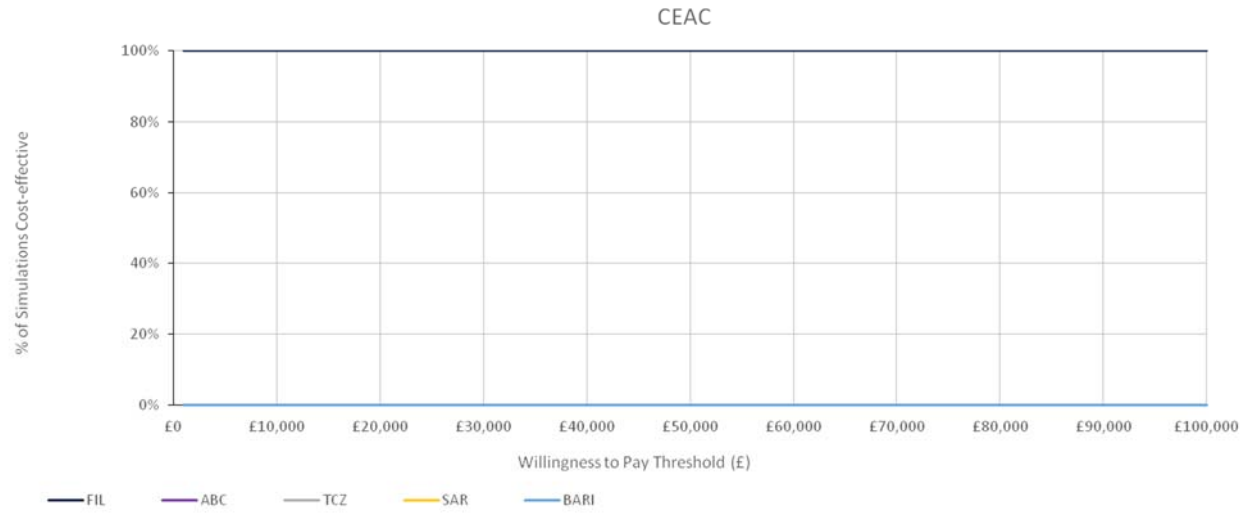
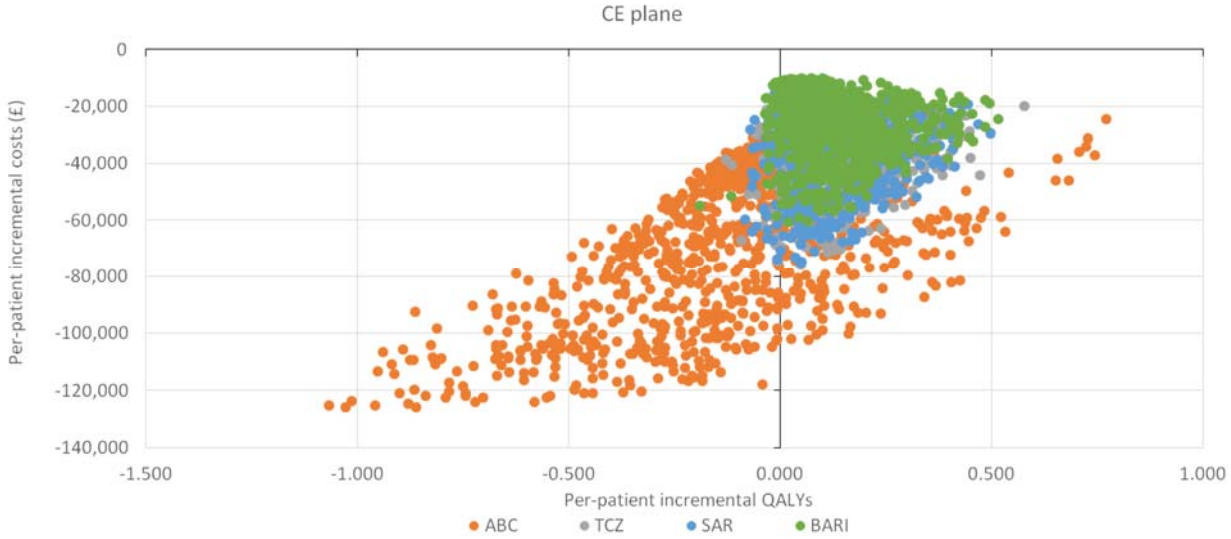


Figure 17. bDMARD-IR, MTX eligible, RTX ineligible, severe RA – CE plane for PSA: filgotinib vs comparators



4. Severe RA patients after failure of first line advanced therapy (MTX eligible, RTX eligible)

The results of the PSA are presented in Table 44, with a cost-effectiveness acceptability curve in Figure 18 and a cost-effectiveness plane in Figure 19. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 44: bDMARD-IR, MTX eligible, RTX eligible, severe RA – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.675	[redacted]	-	-	-	-	-
RTX + MTX	[redacted]	13.675	[redacted]	14,816.63	0.000	0.006	2,670,868.09 SW	2,670,868.09
Abbreviations: FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; RTX, rituximab;								

Figure 18. bDMARD-IR, MTX eligible, RTX eligible, severe RA – CEAC for PSA

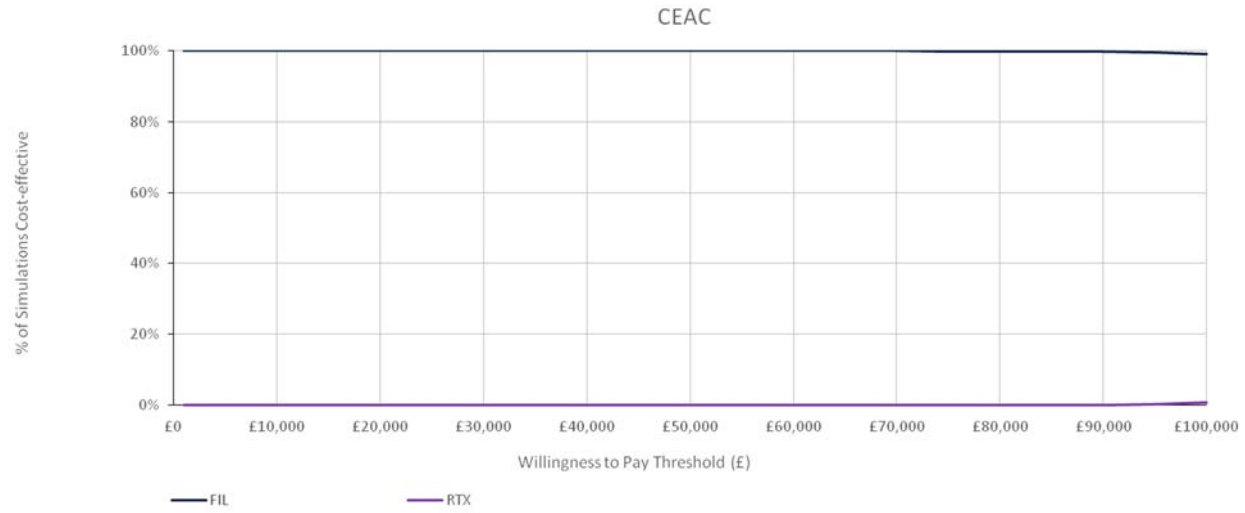
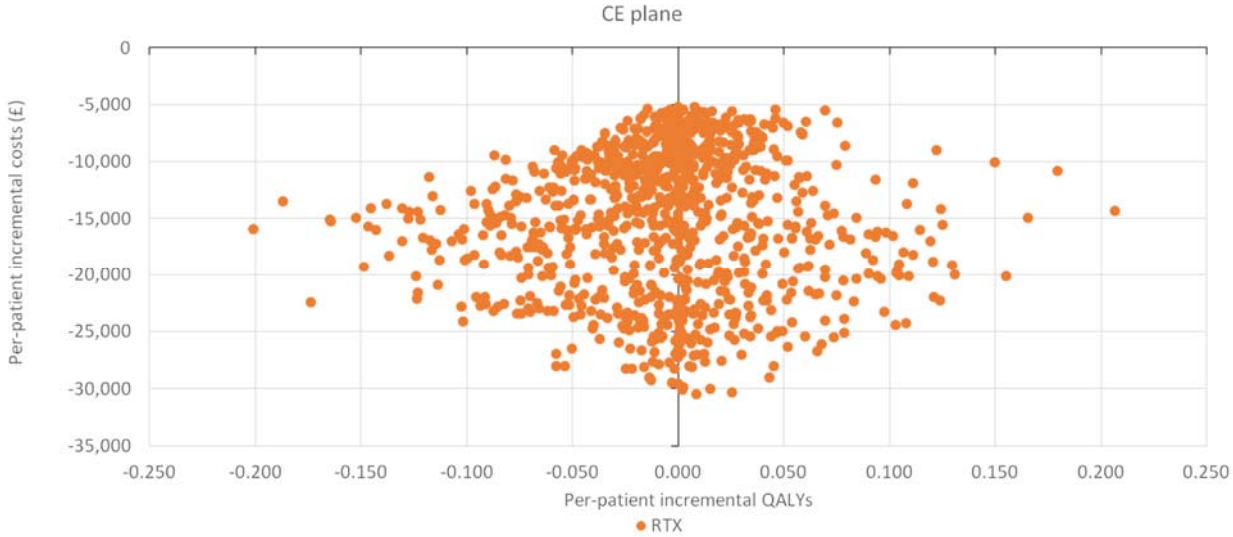


Figure 19. bDMARD-IR, MTX eligible, RTX eligible, severe RA – CE plane for PSA: filgotinib vs RTX



5. Severe RA patients after failure of rituximab in combination with methotrexate

The results of the PSA are presented in Table 45, with a cost-effectiveness acceptability curve in Figure 20 and a cost-effectiveness plane in Figure 21. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 45: bDMARD-IR, MTX eligible, RTX IR, severe RA – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.675	[redacted]	-	-	-	-	-
TCZ + MTX	[redacted]	13.675	[redacted]	31,166.81	0.000	-0.105	Dominated	Dominated
SAR + MTX	[redacted]	13.675	[redacted]	69.40	0.000	0.006	Dominated	10,725.91
Abbreviations: FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; SAR, sarilumab; TCZ, tocilizumab								

Figure 20. bDMARD-IR, MTX eligible, RTX IR, severe RA – CEAC for PSA

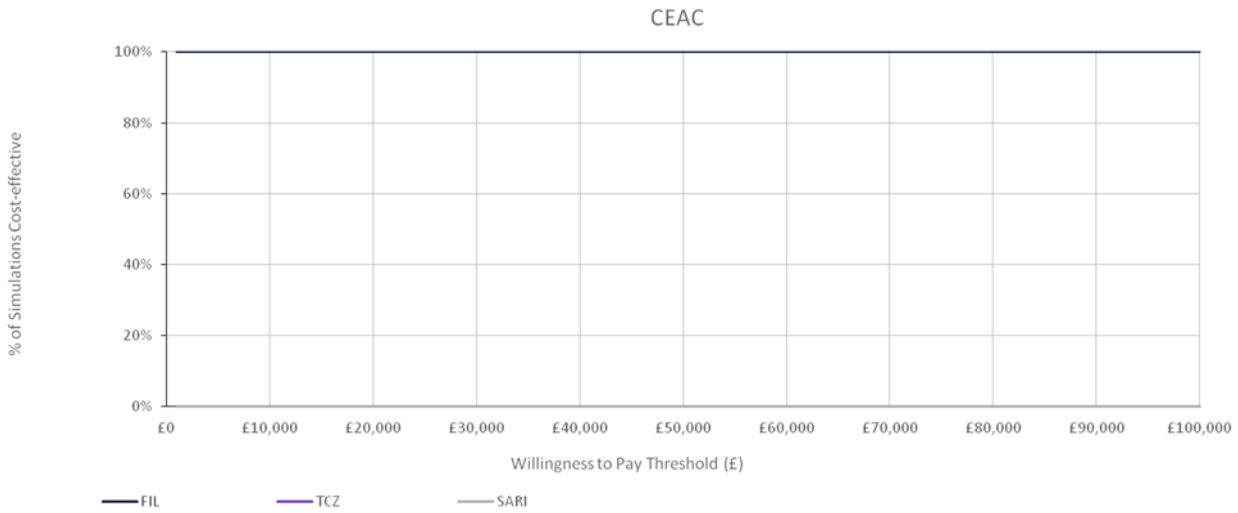
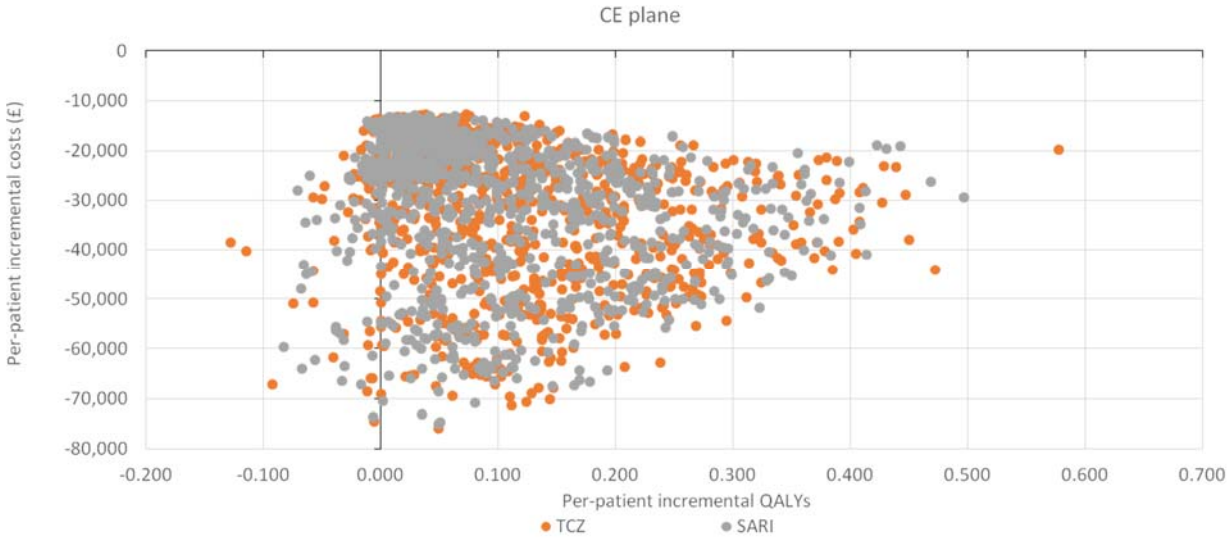


Figure 21. bDMARD-IR, MTX eligible, RTX IR, severe RA – CE plane for PSA: filgotinib vs comparators



d) The PSA results presented in the submission included 500 simulated patients per arm, and used 1,000 sampling loops. Although the base case analyses included 10,000 patients, the computational burden of the model necessitates a pragmatic approach when conducting probabilistic analyses. The approach applied, reducing the number of sampled patients compared to the base case, is consistent with recent submissions in RA. Further, the PSA results are consistent with the base case results, which implies that sufficient amount of sampling was provided.

Additionally, PSA convergence was assessed by means of visual inspection of convergence plots for each analysis, which are included for PSA analyses in the CEM. A convergence plot for filgotinib versus adalimumab for population 2b (severe, csDMARD-IR, MTX tolerant, RTX tolerant) is provided in Figure 22, and a convergence plot for filgotinib versus BSC for population 1b (moderate, csDMARD-IR, MTX tolerant) in Figure 23.

Figure 22: ICER convergence plot for filgotinib versus adalimumab

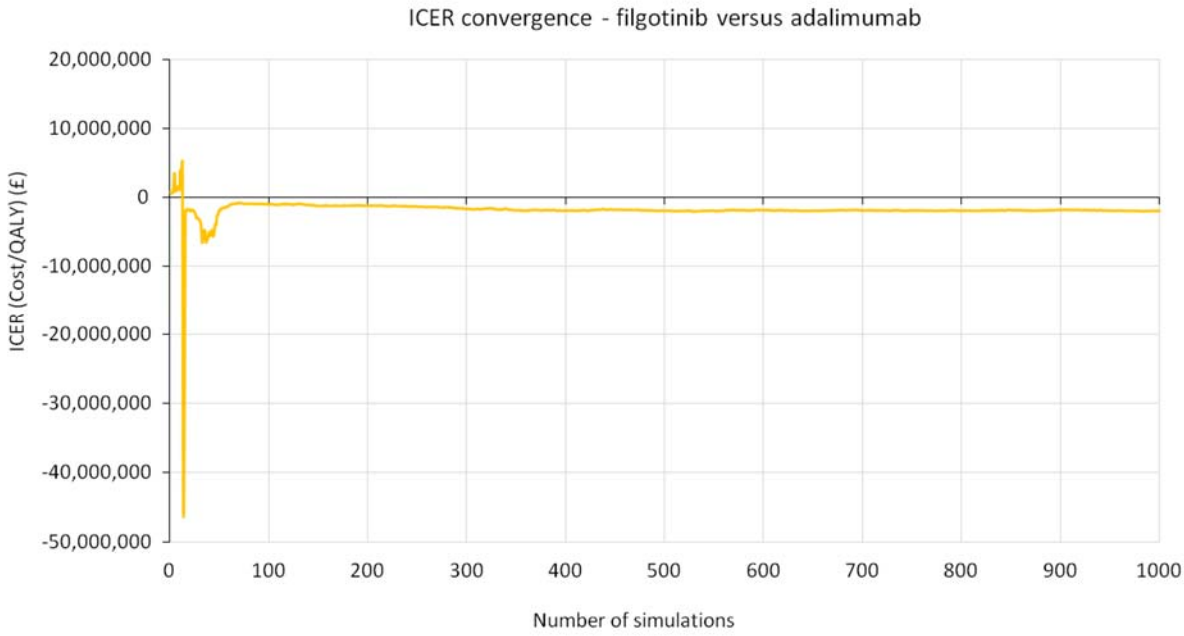
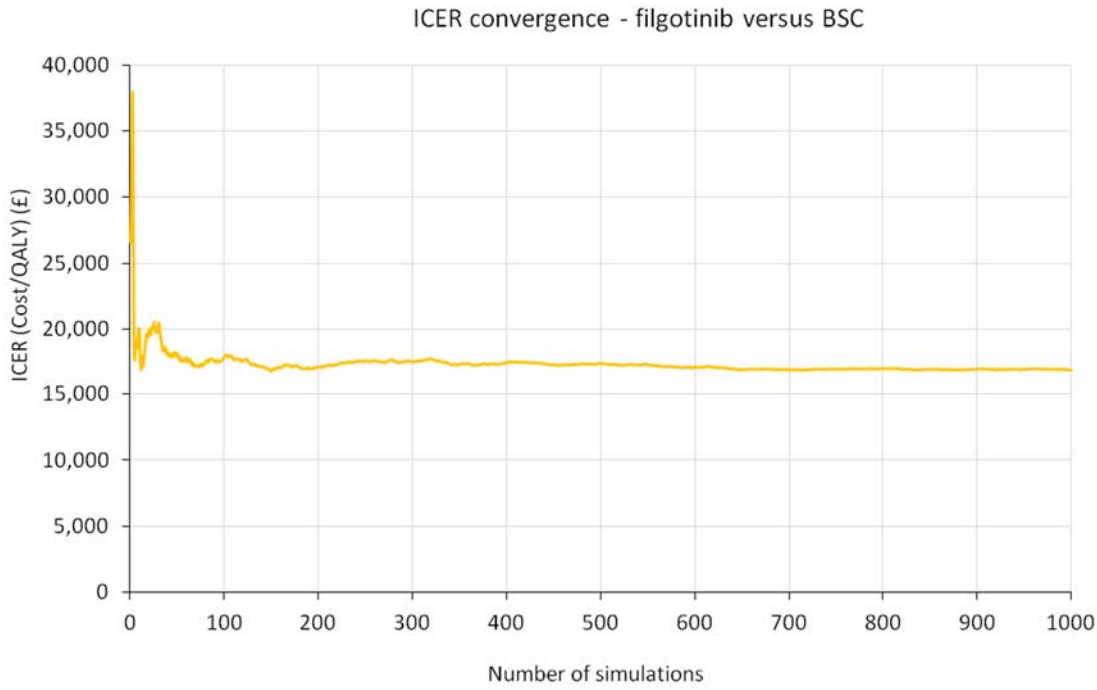


Figure 23: ICER convergence plot for filgotinib versus BSC



Model validation and face validity check

B17. Priority question: Given the availability of many cost-effectiveness models for the comparators in this therapeutic area, cross-validation to other models is important. As described in section 3.10 of the CS, the company made some efforts to cross-validate to other models. However, not all relevant information is presented.

a) Please provide a model file that enables creation of the following output items (in addition to existing ones): for each patient: duration of each treatment sequence, times at which events happen for each event (AE, treatment discontinuation for all treatments, death), HAQ-DI scores at event times, utility scores at event times, costs at event times.

b) In the CS, it is mentioned that “model outputs were individually validated against their input equations for both survival and treatment discontinuation”. Please provide this information.

c) It is further stated in the CS that “a review was carried out to ensure the model operates as expected over the full range of inputs” and “to ensure consistency, parameter estimations within the model were checked against

estimates generated by spreadsheet-based duplicated models". Please provide the results from both validation approaches.

d) In the CS it is stated that "model programming, calculations and inputs have also been reviewed". Please provide information whether this reviewer was involved in creating the model or whether it was an independent assessor.

e) In the CS it is stated that the model was externally validated by an independent third-party clinician. Please provide more background of this third-party clinician. Furthermore, please elaborate on what specific aspects of the model this external validation was focused. Please share the results of this validation, if available.

f) Please provide cross-validation for all relevant input parameters (e.g. cost inputs, utility inputs, HAQ-DI scores, change in HAQ-DI over time, treatment sequences, and EULAR response rates for relevant comparators, proportions of responders stratified as good, moderate, none, time to treatment discontinuation, excess mortality) and the corresponding inputs with MTA375.

g) Please provide cross-validation of the parameters described in the CS and the additional ones requested above not only for MTA375 but also for the more recent STAs TA466 & TA480.

h) Please compare the utility values identified in the literature review to the ones used in the model (at various times throughout the model).

B17. Answer:

a) Five additional sheets are included in the resubmitted model. These are named "Detailed output", followed by arm number. Details for each treatment for all simulated patients from the are displayed after each model run. These include:
   - *Patient experiences AE:* indicator whether a patient experiences an AE on the treatment
   - *Time to treatment disc (years):* time on treatment before a patient discontinues

- *Severe:* indicator as to whether a patient progresses to a severe state on the treatment (moderate cohort only)
- *Time to severe progression (year):* time on treatment before a patient progresses and initiates a severe sequence (moderate cohort only)
- *Patient dies during treatment:* indicator whether a patient dies on treatment
- *Time to death (years):* time until a patient dies
- *Initial response:* patient's initial EULAR response to treatment (1 – None, 2 – Moderate, 3 – Good)
- *Base DAS:* a patient DAS28 score upon entering the model
- *Current DAS:* a patient's DAS score upon progressing to a severe state, shown if a patient progresses during treatment (moderate cohort only)
- *Base HAQ:* a patient's HAQ-DI score upon entering the model
- *HAQ at event:* a patient's HAQ-DI score at time of event
- *HAQ after event (bounce back):* a patient's HAQ-DI score upon initiating the next treatment in the sequence, after HAQ-DI improvement on the current treatment has been removed
- *Utility at event:* a patient's utility at time of event
- *Cumulative costs, LYs and QALYs*
- *Model time:* time that has passed in the model upon time of event

b) **Answer for B17. b) and c):** The validation described in both parts b and c is as follows:

The cost effectiveness model (CEM) has sub-models for sampling patient specific estimates of:

- HAQ progression on conventional therapy
- HAQ progression on advanced therapy
- Time to treatment discontinuation
- Utility based on HAQ-DI score
- Pain score based on HAQ-DI score
- Time to death

To ensure that each of these sub-models is implemented correctly within the CEM and aligned to the source evidence, each sub-model was recreated

within an Excel spreadsheet, parameterised with patient characteristics from the source publication and the output visualised. The outputs were then compared with the results in the source publication to ensure the models were parameterised correctly. Where possible, the outputs from the CEM were compared with the models created in MS Excel to check implementation.

Please find the results of this validation attached.

Model outputs validation.docx

d) This reviewer was not involved in creating the model, but was an independent assessor.
e) The model approach was externally validated by an independent third-party clinician, whom has been involved in another recent TA in RA, ID1400. As the economic modelling methodology in RA is well established given MTA375 and other recent TAs e.g. TA466,TA480 and TA485, this validation focused on the overall modelling approach and any areas were any recent clinical validation would be most appropriate.

   Specific aspects of the model approach which were validated with the clinician were the overall model structure (in line with MTA375 and recent TAs), the assumption that the relative effects of combination therapy were equivalent to monotherapy, confirming that the HAQ trajectory approach for cDMARDs and bDMARDs employed in MTA375 (and this present analysis) was still valid from a clinical perspective. Additionally, the proposed treatment sequences for each population and relevance of specific comparators to UK clinical practise including what the most common treatments were likely to be were also validated.
f) **Answer for B17. f) and g):** The cross validation of parameters between MTA375, TA466 and TA480 is shown in Table 46.

Table 46. Cross-validation of parameters (MTA375, TA480 and TA466)

Factor	Previous appraisals			Current appraisal	
	MTA375 (2016) (17)	**TA480 (2017) (4)**	**TA466 (2017) (5)**	**Chosen values**	**Justification**
Model type	Patient-level CEA model using DES structure			Patient-level CEA model using DES structure	Consistent with previous models, and MTA375
Initial change HAQ-DI scores upon EULAR response	Values modelled from BSRBR data	Values in line with MTA375 BSRBR analysis ,see section 5.3.2.2 in TA480	Values in line with MTA375 BSRBR analysis, see section 5.3 in TA466	In line with MTA375,TA480 and TA466	Consistent with previous models, and MTA375
Change in HAQ-DI scores over time	**bDMARDs –** Statistical analysis (autoregressive latent trajectory model) based on data from the BSRBR database (available to the AG only) was used to relevant estimate parameters. See pg251 of MTA375 (Stevenson et al) **cDMARDs –** Modified analysis based on the approach by Norton et al. See page 254 of Stevenson et al.	**bDMARDs –** In line with AG approach in MTA375 **cDMARDs –** In line with AG approach in MTA375 (Norton et al latent class analysis)	**bDMARDs –** In line with AG approach in MTA375 **cDMARDs –** In line with AG approach in MTA375 (Norton et al latent class analysis)	**bDMARDs** – Parameters used in line with those in MTA375 (Stevenson et al) and also TA480 and TA466 **cDMARDs –** Approach in line with MTA375 approach and TA466, TA480	Consistent with previous models, and MTA375
Mortality based on HAQ-DI category	HRs based on AG analysis of Michaud el al. See table 171 in Stevenson et al.	HRs associated with each HAQ category were based those from MTA375. See table 114 in TA480	HRs associated with each HAQ category were based on those from MTA375. See table 108 in TA466	In line with MTA375, TA466 and TA480	Established approach in RA economical evaluations, and in line with MTA375
EULAR response rates	Please see figure 102 and 103 and chapter 3 in Stevenson et al	Response rates marked AIC in CS (See section 4.10.5.4 in TA480)	Response rates marked AIC in TA480 (Table 106 & 107)	Based on filgotinib NMA, comparison with TA466 and TA480 was not possible	The relative efficacy of filgotinib should be derived from the present NMA
Discontinuation	Duration of treatment was estimated using the BSRBR database, with separate analysis for good and moderate EULAR response. Range of parametric survival models fit (gamma chosen). See pg258 of Stevenson et al.	Based on parametric survival analysis on tofacitinib clinical trial data (Scan, Solo, Standard and Step). Separate analysis conducted for good and moderate responders in MTA375. See section 5.3.2.4 in TA480	In line with MTA375. Plots from MTA375 for continuation on therapy were digitised and parametric models fit (Weibull chosen). See Pg.253 of TA466	In line with MTA375. Model as parameters were not published in MTA375, therefore curves were digitized and a survival curve fit (Gamma, in line with MTA375)	Approach in line with MTA375 was deemed the most robust

Source of utilities	HAQ-DI values are mapped to EQ-5D utility using algorithm designed by Hernandez-Alva et al. 2013	HAQ-DI values are mapped to EQ-5D utility using algorithm designed by Hernandez-Alva et al. 2012 (24)(4)(4)(4)(4)(4)(22)(21)(20)(19)(20)(20)(20)(20)(20)(20)(20)(20)(20)(20)(20)(20)(20)(20)(20)(20)(20)(20)(19)(19)(19)(18)(18)(18)(18)(18)(17)(16)(15)(14)(14)(13)(13)(12)(11)(11)(11)(11)(10)	HAQ-DI values are mapped to EQ-5D utility using algorithm designed by Hernandez-Alva et al. 2013	HAQ-DI values are mapped to EQ-5D utility using algorithm designed by Hernandez-Alva et al. 2013	Established approach in RA economical evaluations, and in line with MTA375
Source of costs	TA247 NHS reference costs 2011-2012 Malottki et al. 2011	British National Formulary 2016 NHS Reference Costs 2015–16 and 2010-11 PSSRU 2016 Malottki et al 2011	British National Formulary 2016 MTA375 MIMS 2016	MTA375 MIMS 2019	Use of latest drug pricing data, as well as inflated costs from the most relevant model, MTA375
Treatment sequences	Please see table 159-162 in MTA375 (Stevenson et al)	Please see table 96-98 in TA480	Please see table 103 – 105 in TA466	Sequences based on NICE treatment pathway, with most relevant sequences determined based on market share and by a third-party clinician	The most relevant sequences based on the most up to date clinician opinion and market share data
Abbreviations: CEA, cost-effectiveness analysis; DES, discrete event simulation; HAQ-DI, Health Assessment Questionnaire – Disability Index; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit; PSS, Personal Social Services; QALY, quality adjusted life year; RA, rheumatoid arthritis; TA, technology appraisal; UK, United Kingdom. Molecules assessed in TAs: TA480, tofacitinib; TA466, baricitinib;					

h) The utility values identified in the literature review (see Appendix H of CS) can be found in Table 47. Additionally, this table includes the FINCH I and FINCH II trials. Aggregated data for the FINCH 1 (overall cohort) and FINCH 2 were mapped to utility values and averaged using an EQ-5D-5L value set for England described in Devlin et al., accessed from the EuroQoL website (26). The baseline characteristics of the sampled cohort in the model, for cDMARD-IR (overall population, moderate only, and severe only, using baseline characteristics from FINCH 1), and bDMARD-IR (using baseline

characteristics from FINCH 2) were mapped to utilities, using the Hernandez-Alava et al mapping used in the base case. Note that as the model utilities are found using a mapping algorithm based on baseline characteristics, and as such comparison with studies of different cohorts are hard to interpret. The table from Appendix H includes baseline utilities, and as such, only baseline utilities from the model are provide

Table 47. Baseline utilities of studies identified in the HRQoL literature review compared to the FINCH trials, and baseline utilities used in the model base case.

Model								
Population					**Baseline utilities**			
MTX-IR (moderate to severe)					0.455			
MTX-IR (moderate)					0.481			
MTX-IR (severe)					0.306			
bDMARD-IR					0.419			
Studies								
Study Reference	**Study Design**	**Country of Study**	**Population**	**Sample Size**	**Interventions and Comparators**	**EQ-5D-3L, Baseline Mean (SD)**	**EQ-5D-5L, Baseline Mean (SD)**	**EQ-VAS, Baseline Mean (SD)**
Filgotinib FINCH I (NCT02889796)	Trial (randomised)	Various (see Table 6 in CS)	MTX-IR Moderate-severe RA (DAS >3.2)	1755	FIL + MTX ADA + MTX Placebo (MTX)	-	0.530	-
Filgotinib FINCH II (NCT02873936)	Trial (randomised)	Various (see Table 6 in CS)	bDMARD-IR Moderate-severe RA (DAS >3.2)	448	FIL + MTX Placebo (MTX)	-	0.531	-
Patients recruited from 22 tertiary hospitals from 2012-2013 Bae (2018)(27)	Observational	South Korea	Moderate RA (DAS: 3.2 - 5.1)	557	Mixed DMARDs	0.5 (0.28)	-	-
			Severe RA (DAS: >5.1)	110	Mixed DMARDs	0.4 (0.35)	-	-
SWITCH (NCT01295151) Brown (2018)(28)	Trial (randomised)	UK	MTX-IR Moderate-severe RA (DAS >3.2)	37	RTX + MTX	0.36 (0.33)	-	-
				36	ABT + MTX	0.34 (0.33)	-	-
				40	TNFi + MTX	0.42 (0.29)	-	-
DREAM (registry) Buitinga (2012)(29)	Observational	Netherlands	MTX-IR Moderate-severe RA (DAS >3.2)	278	TNFi	0.46 (0.29)	-	-
GO-MORE (NCT00975130) Dasgupta (2014)(30)	Trial (non-randomised)	International	MTX-IR Moderate-severe RA (DAS >3.2)	3,268	GOL + csDMARD	0.42 (0.33)	-	-
PRESERVE (NCT00565409) Edwards (2019)(31)	Trial (randomised)	International	MTX-IR Moderate RA (DAS: 3.2 - 5.1)	827	ETN + MTX	0.6 (0.2)	-	-
BSRBR (registry) Morgan (2015)(32)	Observational	UK	MTX-IR Severe RA (DAS >5.1)	329	ADA + csDMARD	-	-	45.56 (20.72)
T2T (NCT01578850) Pavelka (2016)(33)	Trial (randomised)	International	MTX-IR Moderate-severe RA (DAS >3.2)	163	ETN + MTX	0.4 (0.3)*		20.4
				168	PBO + MTX	0.4 (0.3)*		20.8
TACIT (MREC	Trial (randomised)	UK	MTX-IR	101	TNFi	0.35 (0.3)	-	-

07/Q0505/57) Scott (2014)(34)			Severe RA (DAS >5.1)	104	csDMARD	0.39 (0.31)	-	-
RA-BEACON (NCT01721044) Smolen (2016)(35)	Trial (randomised)	International	bDMARD-IR Moderate-severe RA (DAS >3.2)	174	BARI + csDMARD	-	0.461 (0.233)	46.0 (20.8)
				177	BARI + csDMARD	-	0.427 (0.26)	47.4 (24.3)
				176	PBO + csDMARD	-	0.433 (0.25)	47.8 (22.4)
ARAD (Australian Rheumatology Association Database) Staples (2011)(36)	Observational	Australia	MTX-IR and bDMARD-naïve Severe RA (DAS >5.1)	437	TNFi + csDMARD	0.42 (0.31)	-	-
NCT00960440 Strand (2015)(37)	Trial (randomised)	International	bDMARD-IR Moderate-severe RA (DAS >3.2)	131	TOF + MTX	0.38 (0.34)	-	-
				134	TOF + MTX	0.47 (0.32)	-	-
				129	PBO + MTX	0.38 (0.33)	-	-
SELECT NEXT (NCT02675426) Strand (2019c)(38)	Trial (randomised)	International	MTX-IR Moderate-severe RA (DAS >3.2)	221	UPA + csDMARD	-	0.6 (0.3)	49.6 (21.3)
				219	UPA + csDMARD	-	0.6 (0.3)	49.0 (22.0)
				221	PBO + csDMARD	-	0.6 (0.2)	51.4 (21.5)
SELECT BEYOND (NCT02706847) Strand (2019d)(39)	Trial (randomised)	International	bDMARD-IR Moderate-severe RA (DAS >3.2)	163	UPA + csDMARD	-	-	50.7 (23.0)
				160	UPA + csDMARD	-	-	51.8 (21.8)
				166	PBO + csDMARD	-	-	49.7 (24.9)
BIOPSY registry (KCT0000097) Sung (2017)(40)	Observational	Korea	MTX-IR Moderate-severe RA (DAS >3.2)	356	bDMARD	0.4 (0.3)	-	-
KORONA registry (KCT0000086) Sung (2017)(40)	Observational	Korea	MTX-IR Moderate-severe RA (DAS >3.2)	586	csDMARD	0.6 (0.3)	-	-
FIRST ACT-SC Tanaka (2018)(41)	Observational	Japan	MTX-IR and bDMARD-naive Moderate-severe RA (DAS >3.2)	167	TCZ + csDMARD	0.60 (0.14)	-	-
				154	TCZ + csDMARD	0.56 (0.15)	-	-
				160	csDMARD	0.66 (0.14)	-	-
				148	csDMARD	0.65 (0.16)	-	-
NR Traki (2014)(42)	Observational	Morocco	MTX-IR and bDMARD-naive Moderate-severe RA (DAS >3.2)	29	TCZ	0.24	-	50
TEMPO Van der Heijde (2006)(43)	Trial (randomised)	International	MTX-IR Moderate-severe RA (DAS >3.2)	228	MTX	-	-	38.2 (20.3)
				223	ETN	-	-	42.1 (21.7)
				231	ETN + MTX	-	-	40.3 (22.4)

*EQ-5D variant (3L or 5L) not specified

- EQ-5D: EuroQol 5-dimensions; 3L: EQ-5D 3-level; 5L: EQ-5D 5-level; VAS: EQ-5D visual analogue scale; SD: standard deviation; RA: rheumatoid arthritis; DAS: disease activity score modified to include the 28 diarthrodial joint count; MTX: methotrexate; MTX-IR: MTX inadequate responders; DMARD: disease modifying anti-rheumatic drug; csDMARD: conventional synthetic DMARD; bDMARD: biological DMARD; bDMARD-IR: bDMARD inadequate responders; PBO: placebo; BARI: baricitinib; ETN: etanercept; ADA: adalimumab; UPA: upadacitinib; ABT: abatacept; TNFi: tumour necrosis factor inhibitor; TCZ: tocilizumab; TOF: tofacitinib; RTX: rituximab; GOL: golimumab.

B18. Priority question: The ERG would like to see external validation between clinical studies and the modelled outcomes.

a) For validation purposes, please enable in the model (and PSA) the following comparisons, using data derived directly from FINCH 1:

- FIL200+MTX vs MTX (=BSC) for moderate RA from FINCH 1 (cDMARD-IR population)

- FIL200+MTX vs ADA+MTX for severe RA from FINCH 1 (cDMARD-IR population)

b) Please provide a comparison between modelled outcomes and similar outcomes that can be retrieved from the FINCH 1 & FINCH 2 trials? For example, this could focus on time to treatment discontinuation and treatment sequences (i.e. frequencies of failed treatments), and proportion of good, moderate and none-responders.

c) Please use the algorithms of Hernandez-Alava et al. and Malottki et al. to estimate (baseline) utilities in the model and compare these values to empirical data from the FINCH I and FINCH II trials.

B18. Answers:

a) The requested treatments have been added to the model for both the csDMARD-IR moderate and severe population using subgroup data directly from the FINCH 1 and 2 trials. As results from the NMA posterior distributions are not available, the PSA uses a Dirichlet distribution for sampling.

b) The model was run for 10,000 patients using baseline characteristics for the severe and moderate subgroups, and EULAR response rates reported at week 24 from FINCH 1. FIL 200mg was compared with placebo using FINCH 1 moderate subgroup data, and to adalimumab using the FINCH 1 severe subgroup data.

   The proportion of simulated EULAR responders at 24 weeks from the CEM is consistent with the trial input data. Discontinuation varies somewhat between

trial and CEM outputs, however, as no data for discontinuation was available for each subgroup, the trial discontinuation data used for comparison is data from the overall moderate to severely active disease cohort.

Table 48: Comparison between FINCH trial data and modelled outcomes, for moderate RA patients

Proportion of EULAR responders at week 24						
Treatment	**FINCH 1 moderate subgroup data**			**Output from CEM**		
	None	**Moderate**	**Good**	**None**	**Moderate**	**Good**
FIL200mg + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation at week 24						
Treatment	**FINCH 1 data (data for the moderate subgroup not available)**			**Output from CEM**		
FIL200mg + MTX	10.9%			9.1%		
Placebo+ MTX	18.1%*			15.7%		
Abbreviations: CEM, cost-effectiveness model; EULAR, European League Against Rheumatism; FIL, filgotinib; MTX, methotrexate						

*Patients discontinued placebo at week 24, thus the last available timepoint before a crossover, week 20, is presented here

Table 49: Comparison between FINCH trial data and modelled outcomes, for severe RA patients

Proportion of EULAR responders at week 24						
Treatment	**FINCH 1 severe subgroup data**			**Output from CEM**		
	None	**Moderate**	**Good**	**None**	**Moderate**	**Good**
FIL200mg + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation at week 24						
Treatment	**FINCH 1 data (data for the severe subgroup not available)**			**Output from CEM**		
FIL200mg + MTX	10.9%			5.9%		
ADA + MTX	11.1%			12.0%		
Abbreviations: ADA, adalimumab; CEM, cost-effectiveness model; EULAR, European League Against Rheumatism; FIL, filgotinib; MTX, methotrexate						

a) Empirical EQ-5D-5L data from the FINCH I and II data were used for comparisons. Aggregated data for the FINCH I (overall cohort) and FINCH II were mapped to utility values and averaged using an EQ-5D-5L value set for England described in Devlin et al., accessed from the EuroQoL website (26). The baseline characteristics of the sampled cohort in the model, for cDMARD-IR (overall population, not stratified by severity, using baseline characteristics from FINCH I), and bDMARD-IR (using baseline characteristics from FINCH II) were mapped to utilities, using both Hernandez-Alava et al. and Malottki et al. These approaches are included in the CEM.

   Table 50 summarises the average utility outputs from the trials and the model. Compared to Malottki et al., the mapping from Hernandez-Alava et al., which is used for the base case, gives an estimate closer to the trial outputs.

Table 50: Average utility outputs from the FINCH trials, and the two mappings included in the model

Average utilities	cDMARD-IR (FINCH I)	bDMARD-IR (FINCH II)
From trial	0.530	0.531
Output from model using mapping from Hernandez-Alava et al.	0.455	0.419
Output from model using mapping from Malottki et al.	0.351	0.328

Model implementation

B19. Please provide a justification for the use of 10,000 simulated patients. Please provide diagnostics such as a figure demonstrating mean outcomes (costs and QALYs) vs. the number of patients (i.e. visual inspection of stochastic uncertainty); and by means of a mathematical estimation.

B19. Answer: Diagnostics comparing filgotinib and adalimumab were performed by running analysis on 30,000 sampled patients. Diagnostic plots are provided below in Figure 24 and Figure 25. For 10,000 patients, the standard error for the sampled incremental costs and incremental QALYs were 5.7388 and 0.0001, respectively. For 30,000 patients, the standard errors reduce to 2.1137 and <0.0001, respectively. A sample of 10,000 patients was chosen as a trade-off between model stability and run-time.

Figure 24: Incremental costs convergence – filgotinib versus adalimumab

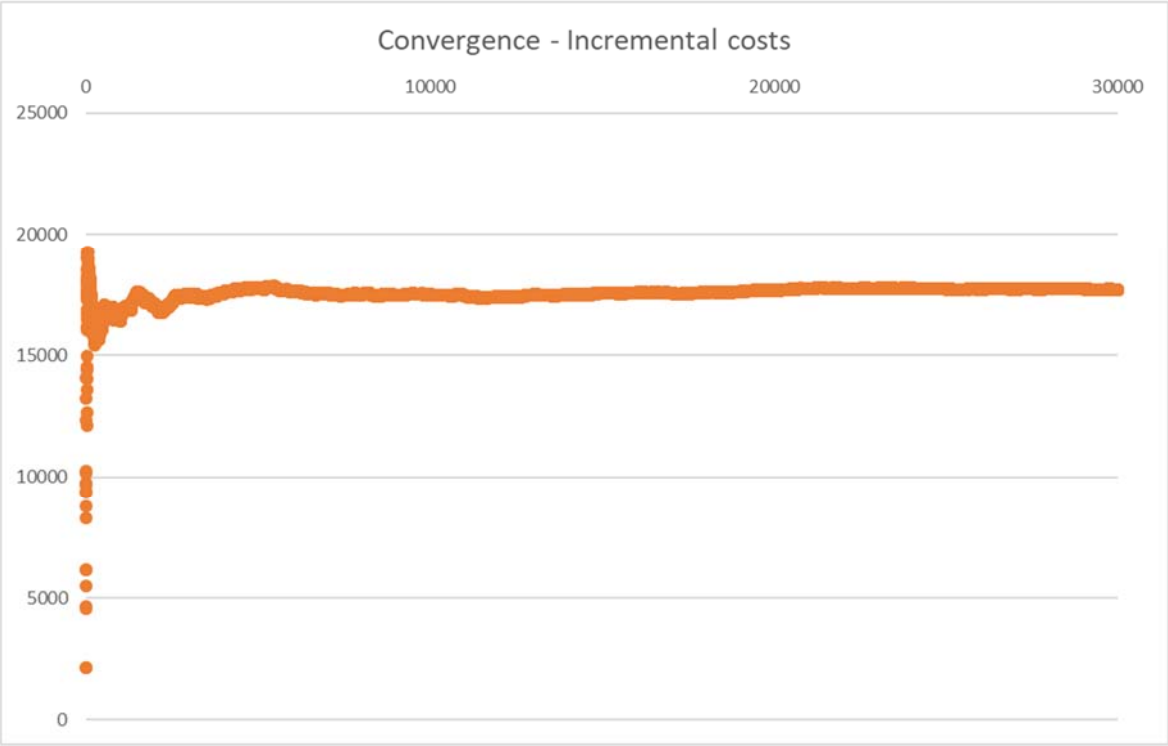
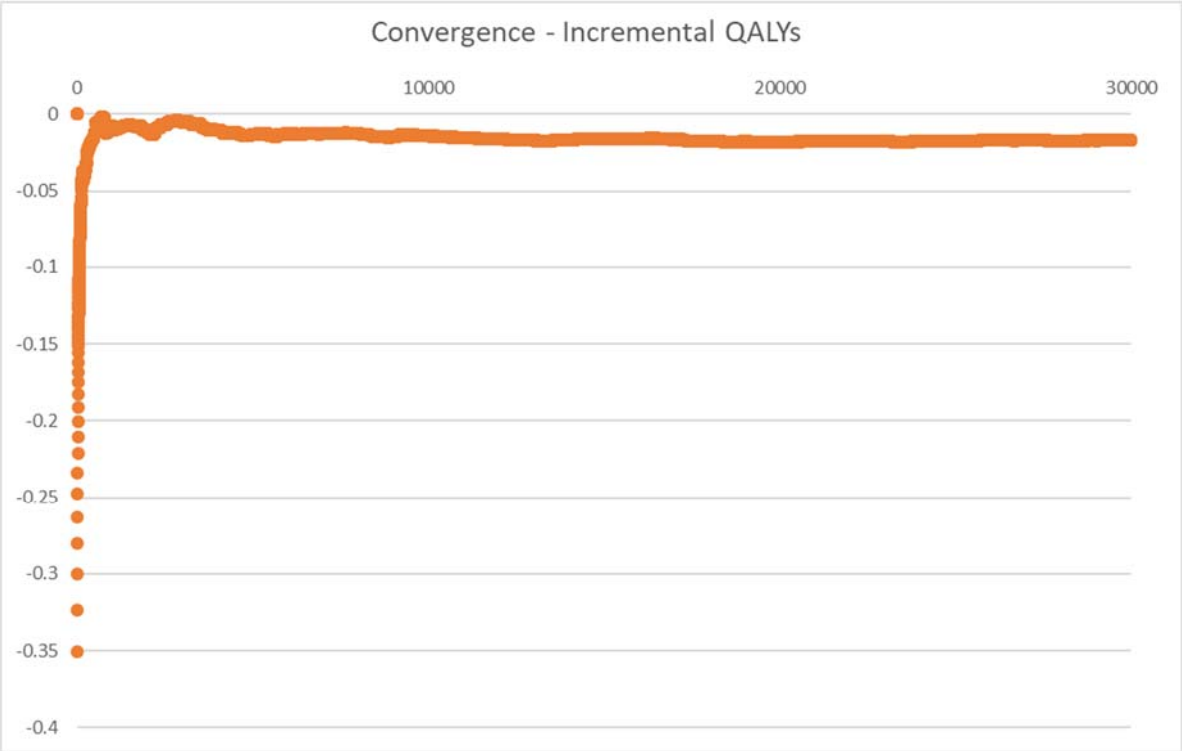


Figure 25: Incremental QALYs convergence – filgotinib versus adalimumab



B20. It is not fully clear to the ERG how mortality is calculated within the model. Please elaborate on how the time of death is selected from the individual survival curve (VBA code: *timeOfDeath = Round((((Application.Match(rands(1, j, 3), survCurve, -1)) - 1) * 2) + rands(1, j, 4), 0)*).

B20. Answer: When a patient is sampled, they are assigned a survival curve based on age, sex, and baseline HAQ-DI score as described in section B3.3.5 of the CS . The array survCurve is an array of probabilities in a descending order of a patient being alive at every year elapsed in the model, starting from their current age. After sampling this curve, the code timeOfDeath = Round((((Application.Match(rands(1, j , 3), survCurve, -1)) - 1) * 2) + rands(1, j, 4), 0)) assigns the patient a cycle number representing time of death.

Application.Match(rands(1, j, 3), survCurve, -1) looks up a randomly assigned value randomly assigned to each patient (j is the patient iterator) e between 0 and 1 and finds the smallest value that is greater than or equal to that value in the *survCurve* matrix. It then returns the position of this value, which is an integer corresponding to years elapsed from their baseline age.

Subtracting 1 from the position returned by the Match method allows for death at time 0, i.e. the assumption that patients that die in the first 6 months accrue no costs or QALYs (Table 62 of the CS) first 6 months.

As this integer corresponds to number of years elapsed until death, and the cycle length in the model is 6 months, this is then multiplied by 2 to convert the output to a cycle number. Then this value is a multiple of 2, corresponding to a whole year. In order to allow for death in either the first or second 6 months of any given year, a random variable between 0 and 1 is then added., and f Finally, the total is rounded to the nearest integer, corresponding to the nearest cycle.

References

1. Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, et al. THE EFFECT OF ENGLISH-LANGUAGE RESTRICTION ON SYSTEMATIC REVIEW-BASED META-ANALYSES: A SYSTEMATIC REVIEW OF EMPIRICAL STUDIES. International Journal of Technology Assessment in Health Care. 2012;28(2):138-44.
2. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). 2019.
3. National Institute for Health and Care Excellence. Overview | Sarilumab for moderate to severe rheumatoid arthritis | Guidance | NICE.
4. National Institute for Health and Care Excellence. Overview | Tofacitinib for moderate to severe rheumatoid arthritis | Guidance | NICE.
5. National Institute for Health and Care Excellence. Overview | Baricitinib for moderate to severe rheumatoid arthritis | Guidance | NICE.
6. Namour F, Fagard L, Van der Aa A, Harrison P, Xin Y, Tasset C. Influence of age and renal impairment on the steady state pharmacokinetics of filgotinib, a selective JAK1 inhibitor. Br J Clin Pharmacol. 2018;84(12):2779-89.
7. Humphreys JH, Verstappen SMM, Hyrich KL, Chipping JR, Marshall T, Symmons DPM. The incidence of rheumatoid arthritis in the UK: comparisons using the 2010 ACR/EULAR classification criteria and the 1987 ACR classification criteria. Results from the Norfolk Arthritis Register. Annals of the Rheumatic Diseases. 2013;72(8):1315-20.
8. Kearsley-Fleet L, Davies R, De Cock D, Watson KD, Lunt M, Buch MH, et al. Biologic refractory disease in rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Annals of the Rheumatic Diseases. 2018:annrheumdis-2018-213378.
9. Gilead. Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 24 Weeks in Combination with Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug(s) (csDMARDs) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Biologic DMARD(s) Treatment (FINCH 2). Clinical Study Report. 2020.
10. Kavanaugh A, Kremer J, Ponce L, Cseuz R, Reshetko O, Stanislavchuk M, et al. Filgotinib (GLPG0634/GS-6034), an oral selective JAK1 inhibitor, is effective as monotherapy in patients with active rheumatoid arthritis: results from a randomised, dose-finding study (DARWIN 2). 2017;76(6):1009-19.
11. Westhovens R, Taylor, P. C., Alten, R., Pavlova, D., Enriquez-Sosa, F., Mazur, M., ... & Harrison, P. Filgotinib (GLPG0634/GS-6034), an oral JAK1 selective inhibitor, is effective in combination with methotrexate (MTX) in patients with active rheumatoid arthritis and insufficient response to MTX: results from a randomised, dose-finding study (DARWIN 1). Annals of the Rheumatic Diseases. 2017;76(6), 998-1008.
12. Gilead. A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib

Administered for 52 Weeks Alone and in Combination with Methotrexate (MTX) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are Naive to MTX Therapy (FINCH 3). Clinical Study Report. 2020.
13. Montoya N, Gómez L, Vélez M, Rosselli D. Costos directos del tratamiento de pacientes con artritis reumatoide en Medellín, Colombia. Revista Colombiana de Reumatología. 2011;18:26-33.
14. Curtis JR, Singh JA. Use of biologics in rheumatoid arthritis: current and emerging paradigms of care. Clin Ther. 2011;33(6):679-707.
15. Bi L, Li Y, He L, Xu H, Jiang Z, Wang Y, et al. Efficacy and safety of certolizumab pegol in combination with methotrexate in methotrexate-inadequate responder Chinese patients with active rheumatoid arthritis: 24-week results from a randomised, double-blind, placebo-controlled phase 3 study. (0392-856X (Print)).
16. Keystone E, Burmester Gr Fau - Furie R, Furie R Fau - Loveless JE, Loveless Je Fau - Emery P, Emery P Fau - Kremer J, Kremer J Fau - Tak PP, et al. Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. (0004-3591 (Print)).
17. Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J, et al. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. Health Technol Assess. 2016;20(35):1-610.
18. Therapy Watch. 2019.
19. Excellence NIfHaC. Single Technology Appraisal: Upadacitinib for previously treated moderate to severe active rheumatoid arthritis [ID1400]. Committee Papers. 2019.
20. National Institute for Health and Care Excellence. Single Technology Appraisal: Upadacitinib for previously treated moderate to severe active rheumatoid arthritis [ID1400]. Committee Papers. 2019.
21. Kiely PD, Jayakumar K, Norton S, Williams R, Walsh D, Young A, editors. Relation between year 1 DAS28 status and 2 year disease activity, function and employment in DMARD treated RA patients in the Early Rheumatoid Arthritis Network (ERAN). Rheumatology; 2009: OXFORD UNIV PRESS GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND.
22. Excellence NIfHaC. Rheumatoid arthritis in adults: management. NICE guideline [NG100]. 2018.
23. Norton S, Fu B, Scott DL, Deighton C, Symmons DP, Wailoo AJ, et al. Health Assessment Questionnaire disability progression in early rheumatoid arthritis: systematic review and analysis of two inception cohorts. Semin Arthritis Rheum. 2014;44(2):131-44.
24. Hernandez Alava M, Wailoo A, Wolfe F, Michaud K. The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis. Rheumatology (Oxford). 2013;52(5):944-50.
25. MICHAUD K, VERA-LLONCH M, OSTER G. Mortality Risk by Functional Status and Health-related Quality of Life in Patients with Rheumatoid Arthritis. The Journal of Rheumatology. 2012;39(1):54-9.

26. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. Health Econ. 2018;27(1):7-22.
27. Bae SC, Cho SK, Won S, Lee HS, Lee SH, Kang YM, et al. Factors associated with quality of life and functional disability among rheumatoid arthritis patients treated with disease-modifying anti-rheumatic drugs for at least 6 months. International journal of rheumatic diseases. 2018;21(5):1001-9.
28. Brown S, Everett CC, Naraghi K, Davies C, Dawkins B, Hulme C, et al. Alternative tumour necrosis factor inhibitors (TNFi) or abatacept or rituximab following failure of initial TNFi in rheumatoid arthritis: the SWITCH RCT. Health Technol Assess. 2018;22(34):1-280.
29. Buitinga L, Braakman-Jansen LM, Taal E, Kievit W, Visser H, van Riel PL, et al. Comparative responsiveness of the EuroQol-5D and Short Form 6D to improvement in patients with rheumatoid arthritis treated with tumor necrosis factor blockers: results of the Dutch Rheumatoid Arthritis Monitoring registry. Arthritis Care Res (Hoboken). 2012;64(6):826-32.
30. Dasgupta B, Combe B, Louw I, Wollenhaupt J, Zerbini CA, Beaulieu A, et al. Patient and physician expectations of add-on treatment with golimumab for rheumatoid arthritis: relationships between expectations and clinical and quality of life outcomes. Arthritis Care Res (Hoboken). 2014;66(12):1799-807.
31. Edwards CJ, Roshak K, Bukowski JF, Pedersen R, Thakur M, Borlenghi C, et al. Efficacy and Safety of Etanercept in Elderly Patients with Rheumatoid Arthritis: A Post-Hoc Analysis of Randomized Controlled Trials. Drugs Aging. 2019;36(9):853-62.
32. Morgan C, McBeth J, Cordingley L, Watson K, Hyrich KL, Symmons DP, et al. The influence of behavioural and psychological factors on medication adherence over time in rheumatoid arthritis patients: a study in the biologics era. Rheumatology (Oxford). 2015;54(10):1780-91.
33. Pavelka K, Akkoc N, Al-Maini M, Zerbini C, Bao C, Karateev D, et al. Maintenance of remission with combination etanercept-DMARD therapy versus DMARDS alone in active rheumatoid arthritis: results of an international treat-to-target study with a double-blind, placebo-controlled maintenance phase. Journal of clinical rheumatology Conference: 19th pan american league of associations for rheumatology congress Panama. 2016;22(3):127-8.
34. Scott DL, Ibrahim F, Farewell V, O'Keeffe AG, Ma M, Walker D, et al. Randomised controlled trial of tumour necrosis factor inhibitors against combination intensive therapy with conventional disease-modifying antirheumatic drugs in established rheumatoid arthritis: the TACIT trial and associated systematic reviews. Health Technol Assess. 2014;18(66):i-xxiv, 1-164.
35. Smolen JS, Kremer JM, Gaich CL, DeLozier AM, Schlichting DE, Xie L, et al. Patient-reported outcomes from a randomised phase III study of baricitinib in patients with rheumatoid arthritis and an inadequate response to biological agents (RA-BEACON). Annals of the rheumatic diseases (no pagination), 2016. 2016;Date of Publication: October 31.
36. Staples MP, March L, Lassere M, Reid C, Buchbinder R. Health-related quality of life and continuation rate on first-line anti-tumour necrosis factor therapy among rheumatoid arthritis patients from the Australian Rheumatology Association Database. Rheumatology (Oxford). 2011;50(1):166-75.

37. Strand V, Burmester GR, Zerbini CA, Mebus CA, Zwillich SH, Gruben D, et al. Tofacitinib with methotrexate in third-line treatment of patients with active rheumatoid arthritis: patient-reported outcomes from a phase III trial. Arthritis care & research. 2015;67(4):475-83.
38. Strand V, Pope J, Tundia N, Friedman A, Camp HS, Pangan A, et al. Upadacitinib improves patient-reported outcomes in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying antirheumatic drugs: results from SELECT-NEXT. Arthritis research & therapy. 2019;21(1):272-.
39. Strand V, Schiff M, Tundia N, Friedman A, Meerwein S, Pangan A, et al. Effects of upadacitinib on patient-reported outcomes: results from SELECT-BEYOND, a phase 3 randomized trial in patients with rheumatoid arthritis and inadequate responses to biologic disease-modifying antirheumatic drugs. Arthritis research & therapy. 2019;21(1):263-.
40. Sung YK, Cho SK, Kim D, Choi CB, Won S, Bang SY, et al. Comparative effectiveness of treatment options after conventional DMARDs failure in rheumatoid arthritis. Rheumatology international. 2017;37(6):975-82.
41. Tanaka Y, Kameda H, Saito K, Kaneko Y, Tanaka E, Yasuda S, et al. Effect of subcutaneous tocilizumab treatment on work/housework status in biologic-naïve rheumatoid arthritis patients using inverse probability of treatment weighting: FIRST ACT-SC study. Arthritis Research and Therapy. 2018;20(1).
42. Traki L, Rostom S, Tahiri L, Bahiri R, Harzy T, Abouqal R, et al. Responsiveness of the EuroQol EQ-5D and Hospital Anxiety and Depression Scale (HADS) in rheumatoid arthritis patients receiving tocilizumab. Clinical Rheumatology. 2014;33(8):1055-60.
43. van der Heijde D, Klareskog L, Singh A, Tornero J, Melo-Gomes J, Codreanu C, et al. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. Annals of the rheumatic diseases. 2006;65(3):328-34.

Appendices

Appendix 1

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Filgotinib for treating moderate-to-severe rheumatoid arthritis [ID1632]

Document B

Company evidence submission

File name	Version	Contains confidential information	Date
ID1632_Filgotinib_STA_Document B_v5.0_AIC_CIC	6.0	Yes	29th June, 2020

Contents

Tables and figures

List of abbreviations

Abbreviation	Definition
ABA	Abatacept
ACPA	Anti-citrullinated protein antibodies
ACR	American College of Rheumatology
ADA	Adalimumab
AIMS	Arthritis Impact Measurement Scales
ATP	Adenosine triphosphate
BAR	Baricitinib
bDMARD	Biological disease modifying antirheumatic drugs
CCP	Cyclic citrullinated peptide
CDAI	Clinical disease activity index
CI	Confidence interval
CSA	Clinically suspect arthralgia
cDMARDs	Conventional disease modifying antirheumatic drugs
CVD	Cardiovascular disease
CZP	Certolizumab pegol
DALY	Disability-adjusted life years
DAS	Disease Activity Score
DMARD	Disease modifying antirheumatic drugs
EQ-5D	EuroQol five dimension
EMEA	Europe, Middle East and Africa
ERAN	Early rheumatoid arthritis network
ESR	Erythrocyte sedimentation rate
ET	Early termination
ETA	Etanercept
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy
GOL	Golimumab
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire Disability Index
HRQoL	Health-related quality of life
IC50	Half maximal inhibitory concentration
IFX	Infliximab
JAK	Janus kinase
MACE	Major adverse cardiovascular events
MCS	Mental component of the SF-36 survey
MTX	Methotrexate
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

Abbreviation	Definition
PCS	Physical component of the SF-36 survey
PDUS	Power Doppler ultrasound
PSS	Personal Social Services
SDAI	Simplified Disease Activity Index
tsDMARDs	Targeted synthetic DMARDs
QALY	Quality-adjusted life years
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RTX	Rituximab
SF-36	36-item Short Form Survey
SLR	Systematic literature review
SmPC	Summary of product characteristics
STATs	Signal transducers and activators of transcription
TA	Technology Appraisal
TOC	Tocilizumab
TOF	Tofacitinib
UK	United Kingdom
US	United States
ULN	Upper limit of normal

Appendix 1

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

B.1.1 Decision problem

The Marketing Authorisation application for filgotinib was submitted to the European Medicines Agency (EMA) in [redacted] and is currently under review.

Filgotinib is a targeted synthetic disease modifying antirheumatic drug (tsDMARD) and, together with biological DMARDs (bDMARDs), is considered an advanced therapy for rheumatoid arthritis (RA).

The Marketing Authorisation for filgotinib is expected to be as monotherapy or in combination with methotrexate (MTX) for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to, or who are intolerant to, one or more (DMARDs), including conventional or biological DMARDs.

This submission covers filgotinib's full anticipated Marketing Authorisation, including the following populations:

Two populations in moderately active RA:

1a. As monotherapy after two or more cDMARD failures in patients who are MTX ineligible

1b. As combination therapy with MTX after two or more cDMARD failures in patients who are MTX eligible

Four populations in severely active RA, for patients who are MTX eligible:

2b. As combination therapy with MTX as first-line advanced therapy[1]

[1] Advanced therapy refers to bDMARDs and targeted DMARDs (tsDMARDs) and is used throughout this document to refer to these treatments as one group

3b. As combination therapy with MTX, after failure of first-line advanced therapy in patients who are RTX ineligible or intolerant

4. As combination therapy with MTX, after first-line advanced therapy failure in patients who are RTX eligible

5. As combination therapy with MTX, after failure of RTX in combination with MTX

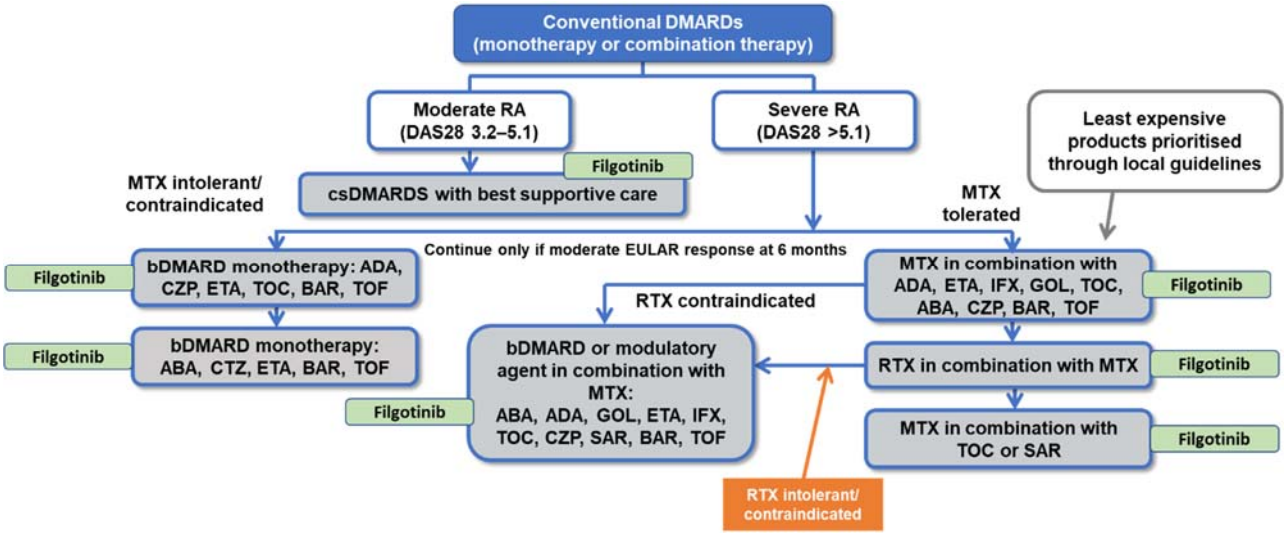
Two populations in severely active RA, for patients who are MTX ineligible:

2a. As monotherapy, used as first-line advanced therapy

3a. As monotherapy, after failure of first-line advanced therapy

The expected position of filgotinib within the current treatment pathway is represented in Figure 1.

Figure 1. Positioning of filgotinib within current NICE treatment pathway



ADA=adalimumab; ABA=abatacept; BAR=baricitinib; CZP=certolizumab pegol; DAS=Disease Activity Score; DMARD=Synthetic disease modifying antirheumatic drugs; ETA=etanercept; GOL=golimumab; IFX=infliximab; MTX=Methotrexate; RA=Rheumatoid arthritis; RTX=Rituximab; TOC=tocilizumab; TOF=tofacitinib;

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

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderately to severely active rheumatoid arthritis who have had an inadequate response to, or who are intolerant of one or more DMARDs, including conventional or biological DMARDs	Adults with moderately to severely active, active RA whose disease has responded inadequately to two or more cDMARDs, or who are intolerant to DMARDs, including conventional or biologic DMARDs. The specific populations modelled in the cost-effectiveness analysis are: Filgotinib for moderately active RA: 1a. As monotherapy after two or more cDMARD failures in patients who are MTX ineligible 1b. As combination therapy with MTX after two or more cDMARD failures in patients who are MTX eligible Filgotinib in combination with MTX for severely active RA, for patients who are MTX eligible: 2b. As combination therapy with MTX as first-line advanced therapy[2] 3b. As combination therapy with MTX, after failure of first-line advanced therapy in patients who are RTX ineligible or intolerant 4. As combination therapy with MTX, after first-line advanced	The populations included within the submission is within the NICE scope. However, in the moderately active RA population the company submission is limited to patients following two or more cDMARD failures, this restriction is applied on the basis of clinical opinion and expected cost-effectiveness.

[2] Advanced therapy refers to bDMARDs and targeted DMARDs (tsDMARDs) and is used throughout this document to refer to these treatments as one group

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		therapy failure in patients who are RTX eligible 5. As combination therapy with MTX, after failure of RTX in combination with MTX Filgotinib for severely active RA, for patients who are MTX ineligible: 2a. As monotherapy, used as first-line advanced therapy 3a. As monotherapy, after failure of first-line advanced therapy	
Intervention	Filgotinib (as monotherapy or in combination with other conventional DMARDs, including methotrexate)	Aligned with NICE scope	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Comparator(s)	For moderately active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs: • Combination of two or more conventional DMARDs (including methotrexate and at least one other DMARD, such as sulfasalazine and leflunomide) • Conventional DMARD monotherapy with dose escalation • Best supportive care For severely active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs: • Biological DMARDs in combination with methotrexate (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept or sarilumab) • Adalimumab, etanercept, certolizumab pegol, tocilizumab or sarilumab (each as monotherapy) • Tofacitinib, baricitinib or upadacitinib (each as monotherapy or in combination with methotrexate) For severely active rheumatoid arthritis that has not responded adequately to therapy with DMARDs including at least one TNF inhibitor: • Rituximab in combination with methotrexate	For moderately active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs: • Best supportive care For severely active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs: MTX intolerant patients: • Adalimumab, etanercept, tocilizumab or baricitinib (each as monotherapy) MTX tolerant patients: • Biological DMARDs in combination with methotrexate (adalimumab, etanercept, baricitinib) For severely active rheumatoid arthritis that has not responded adequately to therapy with bDMARDs including at least one TNF inhibitor: When rituximab is contraindicated or withdrawn due to adverse events, MTX is not tolerated or is contraindicated: • Abatacept, baricitinib or tofacitinib (each as monotherapy) When rituximab is contraindicated or withdrawn due to adverse events, MTX tolerated and is not contraindicated: • Abatacept, baricitinib or tofacitinib in combination with methotrexate When rituximab is tolerated, MTX is tolerated:	Comparators in the model were applied based on currently reimbursed treatments and availability of evidence to inform comparisons, comparisons are consistent with previous Technology Appraisals. Real-world data and expert opinion, in conjunction with NICE guidance for the treatment of RA, were used to inform treatment sequences, which are reflective of current clinical practice.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	When rituximab is contraindicated or withdrawn due to adverse events: • Adalimumab, etanercept, infliximab, abatacept tocilizumab, certolizumab pegol, golimumab or sarilumab (each in combination with methotrexate) • Tofacitinib, baricitinib, or upadacitinib (each in combination with methotrexate) When methotrexate is contraindicated or withdrawn due to adverse events: • Adalimumab, etanercept, certolizumab pegol or sarilumab (each as monotherapy) • Tofacitinib, baricitinib, or upadacitinib (each as monotherapy) When the disease has not responded adequately to therapy with rituximab in combination with methotrexate: • Tocilizumab, sarilumab (each in combination with methotrexate) • Upadacitinib (in combination with methotrexate)	• Rituximab in combination with MTX When the disease has not responded adequately to therapy with rituximab in combination with methotrexate: • Tocilizumab or sarilumab, both in combination with MTX	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • disease activity • physical function • joint damage, pain • mortality • fatigue • radiological progression • extra-articular manifestations of disease • adverse effects of treatment • health-related quality of life.	Aligned with final NICE scope (except where noted). Outcome measures considered in the analysis: • disease activity (American College of Rheumatology - ACR20, ACR50, ACR70, European League Against Rheumatism (EULAR) response, Disease Activity Score (DAS28) • physical function (HAQ-DI) • pain, fatigue • mortality • radiological progression • adverse effects of treatment • health-related quality of life.	Extra-articular manifestations of disease were not captured in the FINCH trial programme and therefore could not be included within this submission. In line with previous economic models with RA appraised by NICE, including MTA375, fatigue was not modelled in the economic analysis.
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	Aligned with NICE scope	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator technologies and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar products should be taken into account.		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • moderate disease activity (DAS28 between 3.2 and 5.1) • severe active disease (DAS28 greater than 5.1)	Aligned with NICE scope	NA

NICE=National Institute for Health and Care Excellence; NA=Not applicable; DMARD=Synthetic disease modifying antirheumatic drugs; ACR=American College of Rheumatology; European League Against Rheumatism HAQ=Health Assessment Questionnaire; HAQ-DI=Health Assessment Questionnaire Disability Index; FACIT-F=Functional Assessment of Chronic Illness Therapy; DAS=Disease Activity Score; QALY=Quality-adjusted life years;

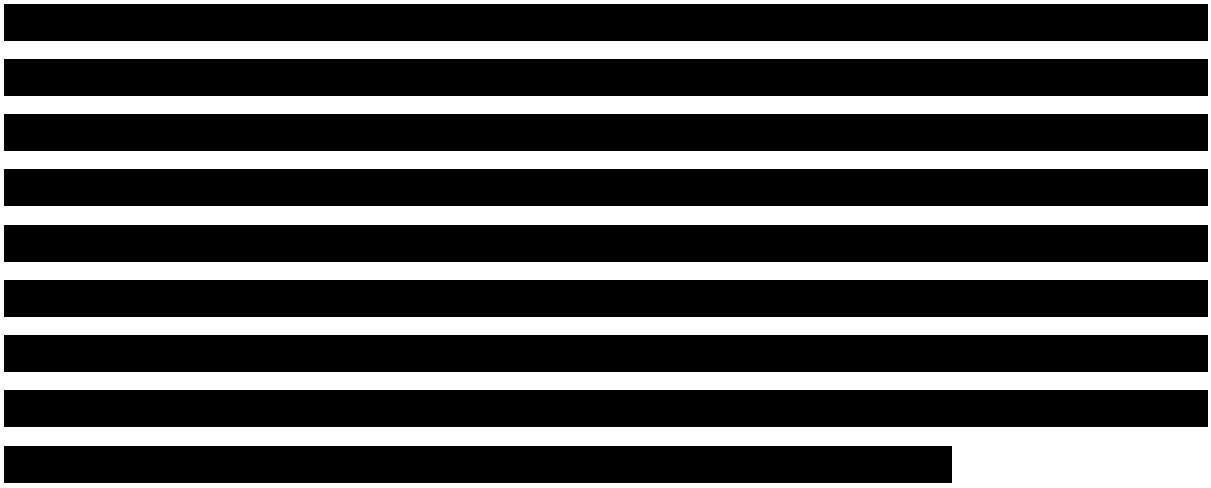
B.1.2 Description of the technology being appraised

The main characteristics of filgotinib are summarised in Table 2. For the full draft summary of product characteristics (SmPC) (1), see Appendix C.

B.1.2.1 Mechanism of action

Filgotinib is a potent reversible JAK inhibitor with a selectivity for JAK1. Cytokines associated with JAK1 are involved in the inflammatory signalling pathway that drives RA progression. Targeted inhibition of JAK1 could reduce dominant inflammatory cytokine signalling involved in RA, whilst limiting impact on normal physiological function. Filgotinib and its active metabolite contribute to its pharmacodynamic effects, with similar JAK1 selectivity.

Filgotinib modulates the signalling pathway by preventing the phosphorylation and activation of STATs by JAKs, thereby supressing immune cell activity and pro-inflammatory cytokine signalling (1). In addition, neither filgotinib nor its active metabolite induce or inhibit cytochrome P450 enzymes or inhibit critical drug transporter enzymes, including P-glycoprotein (2). Therefore, the potential for drug-drug interactions is low, which means filgotinib can be administered with commonly used RA drugs without the need for dose adjustments (2).



B.1.2.2 Technology being appraised

Table 2. Technology being appraised

UK approved name and brand name	Filgotinib (brand name to be confirmed)
Mechanism of action	Filgotinib is a potent, selective ATP-competitive and reversible inhibitor of JAK1. It modulates the cytokine signalling pathway by preventing the phosphorylation and activation of STATs by JAK. For a detailed overview of the mechanism of action, see section B.1.2.1.
Marketing Authorisation/CE mark status	The Marketing Authorisation application for filgotinib in the treatment of adults with RA was submitted to the European Medicines Agency in [redacted]. The anticipated date of regulatory approval is[redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Filgotinib is indicated as monotherapy or in combination with MTX for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to, or who are intolerant to, one or more disease-modifying antirheumatic drugs (DMARDs). Contraindications: • Hypersensitivity to the active substance or to any of the excipients • Pregnancy For the full draft SmPC, see Appendix C.
Method of administration and dosage	The recommended dose is one 200mg tablet once a day. A dose of 100mg of filgotinib once daily is recommended for patients with severe renal impairment (Creatinine clearance 15 to 30 mL/min). Filgotinib may be used as monotherapy or in combination

	with MTX.
Additional tests or investigations	No additional investigations outside of routine clinical management of RA. For the full SmPC, see Appendix C.
List price and average cost of a course of treatment	£863.10 per bottle of 30 200mg tablets Equivalent to £10,508.24 per year
Patient access scheme (if applicable)	[redacted]

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

B.1.3.1 Disease overview

Signs and symptoms

Rheumatoid arthritis is a common autoimmune disease that is associated with progressive disability, systemic complications, early death, and socioeconomic costs (3). Swelling and tenderness of the joints and degradation of synovial tissue (4, 5) leading to joint damage is an important manifestation of RA. However, RA does not exclusively affect the joints. Extra-articular systemic manifestations can include: ocular, pulmonary, skin, cardiac, vascular, renal, haematological, neurological, gastrointestinal. These manifestations also worsen as disease progresses.

Although at early stages of the disease there is no evidence of joint destruction, RA has an impact even at this stage: the main symptoms of early RA are pain and fatigue. Without adequate treatment the disease is associated with progressive joint damage and disability, both of which are irreversible (3). However, even at the moderately active stage of disease, patients' burden is significant, with joint damage and disability accumulating over time if no remission or low disease activity can be achieved. These patients also experience reduced quality of life and represent a substantial burden to healthcare systems.

As a progressive disease, the burden of RA increases with time, with worsening symptoms and increasingly irreversible joint damage. As a systemic disease, multiple organs of the body are typically affected, adding to the clinical burden.

RA also leads to a variety of complications, many of which are related to the chronic inflammation associated with the disease (6).

Diagnosis

The European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) criteria are widely used by rheumatologists to confirm the diagnosis (4, 7).

These criteria include assessment of joint damage or impairment, levels of serum markers, anti-citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF), acute phase reactants: C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (4, 7), and duration of symptoms.

Stratification by severity

Disease activity is classified by composite scoring systems. DAS28 is primarily used in UK, and includes the following variables:

- In 28 specified joints
- Tender joint count (TJC)
- Swollen joint count (SJC)
- High sensitive C reactive Protein (hsCRP) or erythrocyte sedimentation rate (ESR) value
- Patient global health assessment on a 0-100 visual analogue scale

DAS28 cut-off points used for stratifying disease by severity are presented in Table 3 (8).

Table 3. DAS28 cut off points for disease activity categories

DAS28 score	Disease activity
DAS28 <2.6	Remission
DAS28 <3.2	Low disease activity (LDA)
DAS28 3.2 - 5.1	Moderate disease activity (MDA)
DAS28 >5.1	High disease activity / Severe disease (HDA)

DAS, Disease Activity Score; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity.

Source: Fransen et al, 2004 (8)

B.1.3.2 Epidemiology

Prevalence

RA is the most common inflammatory arthritis (9), with an estimated global prevalence of 0.24% (10). It develops more frequently in women (estimated global prevalence of 0.35%) than in men (estimated global prevalence of 0.13%) (10). Prevalence estimates for the UK have been reported as 1.16% in women and 0.44% in men (11), yielding an overall population-level estimate of 0.81%. Based on current population figures (12), this equates to approximately 400,000 prevalent adult patients in England and Wales.

A 2016 report suggests that in the in UK, 87% of the total RA population is diagnosed, and the percentage of diagnosed patients being treated is 76% (13), putting the estimated number of diagnosed and treated patients at approximately 300,000.

Incidence

The UK-specific incidence rate of RA has been reported to be 40 per 100,000 persons per year in a report published in 2013 (14), with a markedly higher (54 per 100,000 persons, 95% confidence interval [CI]: 44.5 to 64.7) incidence in women than in men (25 per 100,000 persons, 95% CI: 18.1 to 32.4) (14). Using the above rates and latest population figures (12), approximately 20,000 new adult patients are estimated to be diagnosed with RA each year in England and Wales.

Moderately to severely active patients

Out of the total RA patient pool, market research suggests 39% are estimated to have moderately active disease (or around 120,000 in England and Wales), while the proportion of severely active RA patients are estimated to be 29% (approximately 90,000) (15). A study of UK patients in the Early RA Network (ERAN), a cohort of newly diagnosed RA patients receiving cDMARDs, showed the rate of patients progressing from moderately to severely active disease was 19% over a two-year period (16), which translates to approximately 12,000 patients in England and Wales a year who progress to severely active disease.

B.1.3.3 Disease burden

Clinical burden

The clinical burden of RA is substantial. Improvements made in therapies in recent years led to reduced disease severity overall; a study by Diffin et al (17), studying patients from Norfolk Arthritis Register (NOAR), found a significant association between year of presentation and lower DAS scores[3]. However, a substantial proportion of RA patients have moderately to severely active disease activity. RA can progressively lead to irreversible joint damage and disability (18, 19). As a progressive disease, the burden of RA increases with time, with worsening symptoms and increasingly irreversible joint damage. As a systemic disease, multiple organs of the body are typically affected, adding to the clinical burden.

Disease progression

As detailed above, a study of patients in the ERAN patient network showed the rate of patients progressing from moderately to severely active disease to be 19% over a two-year period (16). A recent UK multi-centre, retrospective non-interventional study concluded that many patients with moderately active RA had received multiple cDMARDs, suggesting there may be a lack of suitable, effective treatments following failure of cDMARDs (20).

EULAR guidelines identify key prognostic factors that may be used to identify patients more likely to progress to severe disease activity. According to the guidelines (21), these include persistently moderate or high disease activity despite cDMARDs, failure of two or more cDMARDs, high levels of RF/ACPA, high disease activity, early joint damage, and high swollen joint count. A recent retrospective single centre study from the UK, involving 207 patients (22), aimed to identify moderately active RA patients with poor functional outcomes found that baseline Health Assessment Questionnaire – Disability Index (HAQ-DI) score was the dominant predictor of 12-month HAQ-DI, implying those who had more significant disability at baseline remained so during the full period– suggesting a need among

[3] In the study, calendar year of presentation to NOAR was significantly associated with lower DAS28 scores over time [Y = 4.51 + (–0.56 x year) + (0.44 x year2)]

moderately active RA patients for additional treatments that effectively treat their disease (22). The poor functional outcomes of patients assessed in the study also highlight the fact that even moderately active RA is associated with substantial joint destruction and disability – which is exacerbated with progression of disease.

Disease complications and comorbidities

RA is a multisystem disease that can affect several organ systems, leading to a variety of complications, many of which are related to the chronic inflammation associated with the disease (6). These comorbidities, particularly cardiovascular disease (CVD), can lead to serious clinical events, reduced health related quality of life (HRQoL), and death (23). The 2014 COMORA study (6) evaluated the prevalence of comorbidities in RA patients and found that hypertension and dyslipidaemia were most prevalent. Other comorbidities that have been found to occur with greater frequency in patients with RA compared with the general population include depression, lung cancer, lymphoma, infections, and the RA-related complications osteoporosis and osteoporotic fractures.

Other potentially serious non-CV related comorbidities prevalent in RA patients include anaemia, psychiatric disorders, malignancies, and diabetes (6).

Mortality

RA patients are at an increased risk of mortality, partly due to the increased rate of comorbidities described previously, and partly due to the interplay between inflammation and disease activity (23-25). A 2016 study by Michaud et al (24) reported age- and sex-standardised mortality incidence rates (per 100 person-years) from RA registries; finding a UK mortality incidence rate of 0.8 per 100 person-years. Within the same UK RA registry, cardiovascular mortality was 0.2 per 100 person-years (24), highlighting RA patients' high risk for CV-related mortality.

Humanistic burden

In addition to its clinical burden, RA is also associated with a substantial humanistic burden, reducing the HRQoL of patients as measured using a range of disease-

specific and generic assessments. A 2014 literature review (26),which included 31 studies (including two from the UK) with a total of 22,335 patients, investigated the effects of RA on HRQoL as measured by the 36-item Short Form survey (SF-36) questionnaire. Results of this study show worse mean scores for the physical component (PCS) of the survey than the mental component (MCS), the mean pooled HRQoL score for PCS was 34.1 (95% CI: 22.0, 46.1) and the mean score for MCS was 45.6 (95% CI: 30.3, 60.8) (100 represents best possible QoL) (26).

Another study highlighting the high burden of RA was published in 2019 by Safiri et al (27). In it, the authors analysed RA-specific data from the 2017 Global Burden of Disease study. The age-standardised rate of RA disability-adjusted years (DALYs) per 100,000 population was 43.3 (95% CI 33.0 to 54.5) globally, underscoring that RA leads to a substantial number of healthy life years lost (27).

Economic burden

The economic burden of RA is substantial, estimated by Lundkvist et al in 2008 to be up to €45.3 billion across all European countries, including direct, indirect and informal care costs (28). Overall, the mean annual cost per patient was estimated at around €13,500 in Europe, of which medical costs and medications represent approximately one third. The remaining two thirds are from outside the healthcare sector (production losses contribute 32%, informal care 19% and non-medical costs 14%) (32). UK-specific cost estimates from this study showed a total cost of €16,502 (£11,116 at 2007 exchange rates (29) the cost year reported from the study), with 61% (£6,793) representing direct costs and 39% (£4,323) indirect costs.

B.1.3.4 Current treatment guidelines

Recommendations for the management of RA are available from international guidelines such as EULAR (21), as well as national guidelines for England, published by NICE (30).

EULAR guidelines

The 2019 update to the EULAR guidelines was published in early 2020 (21). At diagnosis, the guidelines first recommend methotrexate, as first-line treatment, unless contraindicated to use other cDMARDs (combined with short-term glucocorticoids). If at three months there is an improvement, treatment is recommended to be continued.

For patients not responding to treatment or achieving target, recommendations are stratified by the presence or absence of poor prognostic factors. If the treatment target is not achieved after six months, a change to another bDMARD or JAK inhibitor is recommended, from the same class or a different one.

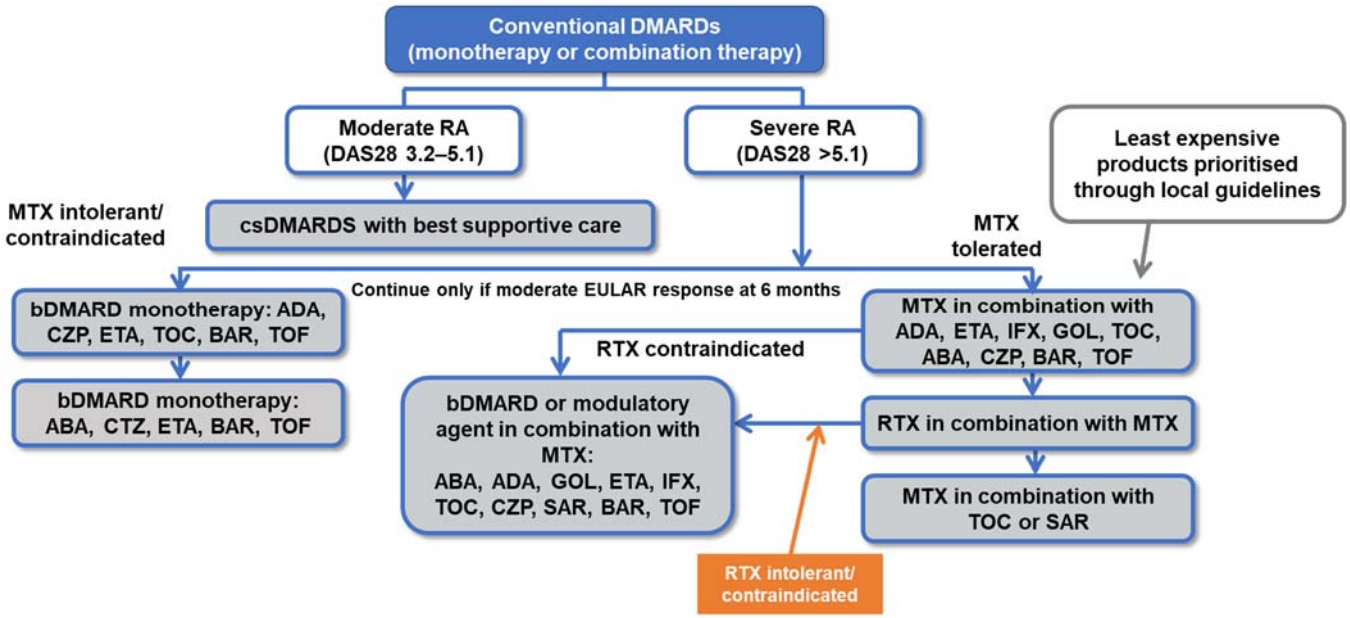
A notable difference between EULAR guidelines and NICE guidelines is that, in addition to severely active RA patients, they recommend considering advanced therapies in moderate disease activity, following failure of two cDMARDs, or after one cDMARD in patients with poor prognostic factors (detailed earlier in section B.1.3.3 on Disease burden).

NICE guidelines

The NICE clinical guidance [NG100] for the management of RA in adults was published in 2009 and most recently updated in 2018 (30). The current version provides guidance on pharmacotherapy options as well as exercise and physical and occupational therapy (30).

The clinical pathway of pharmacological care, recommended by the NICE guidelines, is presented in Figure 2.

Figure 2. Current NICE treatment guidance on treatment of moderately to severely active RA



ADA=adalimumab; ABA=abatacept; BAR=baricitinib; CZP=certolizumab pegol; DAS=Disease Activity Score; DMARD=Synthetic disease modifying antirheumatic drugs; ETA=etanercept; GOL=golimumab; IFX=infliximab; MTX=Methotrexate; RA=Rheumatoid arthritis; RTX=Rituximab; TOC=tocilizumab; TOF=tofacitinib;

Source: NICE 2009 clinical guideline: 2018 update [NG100] (30)

Newly diagnosed and moderately active patients

For newly diagnosed patients, cDMARDs (preferably MTX, or alternatively leflunomide or sulfasalazine) as monotherapy are the recommended first-line treatments, ideally within three months of onset of persistent symptoms. For those who do not respond to this treatment, treatment dose is escalated, or a combination therapy is given with another cDMARD, preferably including MTX. Alternatively,

leflunomide, sulfasalazine or hydroxychloroquine should be offered in combination in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved despite dose escalation. From this point, current recommendations differentiate between moderately active (DAS28 score of 3.2-5.1) and severely active (DAS28 score greater than 5.1) RA patients, with the recommended treatments dependent upon this classification.

For moderately active RA patients, NICE guidelines currently recommend further cDMARDs (oral MTX, leflunomide, sulfasalazine or hydroxychloroquine) in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved despite dose escalation.

Where combination therapies are not appropriate (in the case of comorbidities or pregnancy), cDMARD monotherapy is recommended.

After the failure of two cDMARDs, there is a notable lack of clinical options with current NICE guidance, presenting an unmet need for additional therapeutic options, particularly as a subset of these patients are at risk of progressing to severely active disease. The only remaining treatment option is best supportive care, comprising of cDMARDs that patients have already received, administered at lower doses.

Severely active RA

For severely active RA patients in whom disease has not responded to intensive combination therapy with cDMARDs, NICE guidance recommends bDMARDs (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept and sarilumab) or tsDMARDs/JAK inhibitors (baricitinib and tofacitinib) in combination with MTX, unless intolerant or contraindicated. For those who are intolerant or for whom MTX is contraindicated, adalimumab, etanercept, certolizumab pegol, tocilizumab, baricitinib, sarilumab or tofacitinib are recommended, as monotherapy.

Where severely active RA patients do not show adequate response to advanced treatments, a combination of RTX and MTX is recommended.

Where RTX is contraindicated or withdrawn because of adverse events, advanced therapies (adalimumab, etanercept, infliximab, abatacept, golimumab, tocilizumab, certolizumab pegol, sarilumab, tofacitinib and baricitinib) are recommended, in combination with MTX.

For those who are not eligible for MTX and have failed first-line advanced therapy, advanced therapies are recommended to be used as monotherapy (adalimumab, etanercept, certolizumab pegol, sarilumab, tocilizumab, tofacitinib and baricitinib).

Finally, for those patients who have not responded to treatment with RTX and MTX, tocilizumab and sarilumab, in combination with MTX, are recommended by NICE guidance.

Key differences between NICE and EULAR Guidelines

NICE currently only recommends the use of advanced therapies in severely active RA patients, following failure of intensive combination therapy or at least two cDMARDs. In contrast, the recently updated EULAR guidelines recommend advanced therapies for moderately or severely active patients, following failure of two cDMARDs, or after one cDMARD in patients with other poor prognostic factors detailed earlier in section the Disease burden section (see B.1.3.3).

Related NICE Technology Appraisals

A summary of all related NICE Technology Appraisals (TAs) is presented in Table 4.

Table 4. Summary of related NICE Technology Appraisals

Technology and indication	Year
Published Technology Appraisals	
Sarilumab for moderately to severely active rheumatoid arthritis (NICE TA485) (31)	2017
Tofacitinib for moderately to severely active rheumatoid arthritis (NICE TA480) (32)	2017
Baricitinib for moderately to severely active rheumatoid arthritis (NICE TA466) (33)	2017
Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor (NICE TA415) (34)	2016 (reviewed in 2019)
Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (NICE MTA375 (previously TA130, TA186 and TA280) (35)	2016
Tocilizumab for the treatment of rheumatoid arthritis (NICE TA247) (36)	2012

Technology and indication	Year
Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease modifying anti-rheumatic drugs (NICE TA225) (37)	2011
Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (NICE TA195) (38)	2010
Appraisals in development	
Upadacitinib for treating moderately to severely active rheumatoid arthritis (NICE TA guidance [ID1400]) (39)	Expected 2020
Sirukumab for previously treated moderately to severely active rheumatoid arthritis (NICE TA guidance [ID1002]) (40)	Suspended appraisal
Rituximab for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs (NICE TA guidance [ID333]) (41)	Suspended appraisal

DMARD=Synthetic disease modifying antirheumatic drug; NICE= National Institute for Health and Care Excellence; TA= Technology Appraisal

B.1.3.5 Unmet need with current treatments

The unmet need of patients with RA includes issues such as: efficacy, safety and tolerability, patient preference, and treatment options for patients with moderately active disease.

Efficacy issues

The aim of RA treatment is to achieve remission, or, alternatively, to remain in a low disease activity state. Therefore, it is crucial that patients have adequate and timely response to their treatments, but treatment failure (defined as lack of response) is among the main challenges with current treatments for a considerable number of patients. Though the advent of bDMARDs has brought options with improved efficacy to the treatment of RA, many patients still either do not achieve response or lose response to therapy over time. A study of 13,502 UK RA patients (42), published in 2018, investigated biologic refractory disease among patients in the British Society for Rheumatology Biologics Register. Data showed that 6.4% of all RA patients were classified as bDMARD refractory (defined as being exposed to at least three different classes of bDMARD), a substantial portion of patients (38%) reported lack of efficacy.

Safety and tolerability issues

Currently available treatments in RA have notable safety and tolerability issues. Firstly, infections are among the common side effects of both corticosteroids and biologic treatments. This is in addition to the underlying immune disfunction due to

the disease process itself (i.e. immunological alteration), disability and immobility, and the perioperative infection risk associated with joint surgery (43, 44). For example, currently available JAK inhibitors are associated with an increased rate of herpes zoster infection (45).

Exposure to cDMARDs, bDMARDs and currently available JAK inhibitors is associated with AEs such as serious infections, malignancies, deep vein thrombosis (DVT) and pulmonary embolism (PE) (46-52). In addition, current treatment strategies may worsen patients' existing comorbidities or extra-articular manifestations (51-56).

Patients with RA have a higher risk of cardiovascular complications, including heart failure, myocardial infarction, stroke, DVT and PE than those without the disease, which is thought to be linked to the inflammatory disease process (53-55). This risk may be worsened by treatment with non-selective JAK inhibitors, for example baricitinib carries a special warning for risk of venous thromboembolism (VTE) and PE (51), and a post-marketing study of tofacitinib found a statistically significantly increased risk of PE in patients treated with tofacitinib (56).

A recent analysis found that AEs were the cause of discontinuation for 8% to 22% of patients who stopped bDMARD therapy (57, 58). In a 2017 study by Li et al (57), involving 572 RA patients from the UK, France, and Germany, adverse effects were the reason for stopping etanercept treatment in 21.6% of patients. Furthermore, among the reasons for choosing a second biologic treatment, tolerability was named frequently among patients choosing TNF inhibitors (15.2%), and non-TNF biologics alike (22.5%) (57).

Patient preference

Patient preference presents challenges with some of the current RA treatment options: oral therapy is preferable to an injection for a substantial portion of RA patients (59, 60). A 2013 survey of 1,400 patients with RA in France, the UK, Germany, Italy, Spain, Belgium, Sweden and the Netherlands found that 79% would prefer to take a tablet twice daily over an IV infusion or a subcutaneous injection (53).

A common reason for patients preferring oral treatments is needle phobia, which currently presents challenges for some patients. A survey of 250 RA patients from the US, published in 2015, indicated that a considerable portion (6.8%) of patients who discontinued their treatments (etanercept, adalimumab, certolizumab, or golimumab) pointed to fear of needles as the primary reason (61).

Lack of treatment options in moderately active RA

A considerable unmet need exists within the current RA treatment landscape in the UK for moderately active RA patients. Current NICE recommendations (30), as outlined previously in section B.1.3.4, do not provide any further therapeutic options for moderately active RA patients who fail cDMARDs, the only option remaining is best supportive care, which is considered to provide little therapeutic benefit to patients. Only patients who have severely active disease are currently eligible for advanced treatments to control their disease progression, with disease progression carrying an increased risk of a range of comorbidities and increasing disease burden - clinical, humanistic and economic alike, as detailed previously in section B.1.3.3.

In the UK the majority of moderately active RA patients do not achieve a satisfactory clinical response with currently available therapies. Sustained clinical remission is only achieved by 20%-40% of patients and long-term remission (>1 year) is only achieved by 3% to 14% of patients (62, 63). Sustained inflammation contributes to cartilage damage and bone erosion, affecting up to 80% of patients within one year of diagnosis (3, 64). Patients with persistent moderately active disease have also been shown to experience functional decline (as measured by HAQ-DI), suggesting that these patients could benefit from more advanced therapy (3, 64).

At present, in the UK, advanced therapies are licensed by EMA but not recommended by NICE for treatment of patients with moderately active RA. The current lack of flexibility to allow clinicians to tailor the use of advanced therapy to the needs of patients may result in poorer long-term outcomes (65), with patients remaining on cDMARDs rather than switching to more effective treatment strategies leaving them at greater risk of disease progression (66).

Filgotinib is a potent reversible JAK inhibitor with a selectivity for JAK1. Cytokines associated with JAK1 are involved in the inflammatory signalling pathway that drives RA progression. Targeted inhibition of JAK1 could reduce dominant inflammatory cytokine signalling involved in RA, whilst limiting impact on normal physiological function. Filgotinib and its active metabolite contribute to its pharmacodynamic effects, with similar JAK1 selectivity.

B.1.3.6 Positioning of filgotinib within current the clinical pathway

As described in section B1.1. Filgotinib is a tsDMARD and can be used after failure of cDMARDs in moderately to severely active RA patients. Its oral method of administration is also preferred by patients, as well as avoiding the need for training for administration or refrigerated storage associated with IV or SC treatments.

B.1.4 Equality considerations

No equality issues were identified in relation to filgotinib.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

Two systematic literature reviews (SLRs) were conducted to determine the clinical efficacy of existing interventions for the treatment of moderately to severely active RA for:

- Patients who had intolerance or inadequate response to prior conventional synthetic disease-modifying antirheumatic drugs (cDMARDs) including MTX.
- Patients who had intolerance or inadequate response to previous biologic disease modifying anti-rheumatic drugs (bDMARD-IR).

Comprehensive literature searches were undertaken in electronic databases (MEDLINE, Embase and The Cochrane Library) for studies published between 1st January 1999 and 8th of August 2018, as well as conference proceedings and websites of national reimbursement and Health technology assessment organisations. An update searched these databases from 08 August 2018 to 18 September 2019. Data from eligible studies was extracted and assessed for methodological quality and applicability.

In total, the reviews identified 191 publications describing 139 trials that met review inclusion criteria for clinical effectiveness of interventions for the treatment of moderately to severely active RA. Among these, four trials and five publications were related to filgotinib.

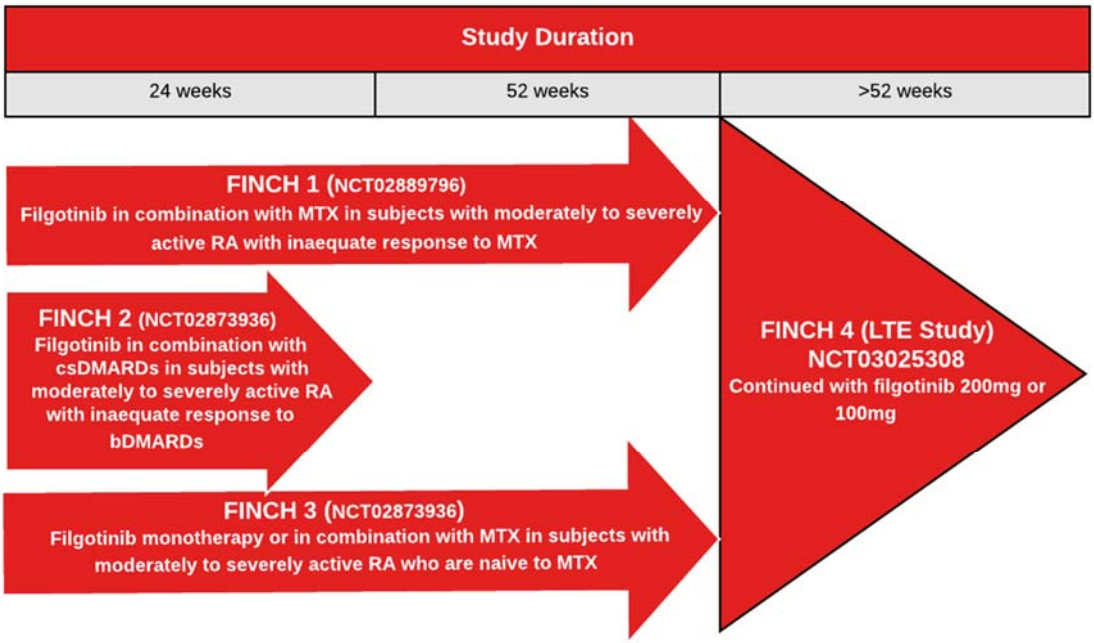
See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

Filgotinib (both in combination with MTX and as monotherapy) has been well-studied and characterised through an extensive clinical trial programme. Three Phase 3 studies, FINCH 1, 2 and 3 inform the safety and efficacy in three distinct populations. The clinical effectiveness evidence from the three FINCH trials is detailed in Table 5.

A long-term extension (LTE) study (FINCH 4) to characterise the long-term safety and efficacy of filgotinib is currently underway, further details are provided in section B.2.11. An overview of the filgotinib phase 3 clinical trial programme can be found in Figure 3.

Figure 3. Overview of the filgotinib clinical trial programme



DMARDs, disease modifying anti-rheumatic drugs; bDMARDs, biologic DMARDs, csDMARDs, conventional synthetic DMARDS; LTE, long-term extension; MTX, methotrexate; RA, rheumatoid arthritis

The primary endpoint for both FINCH 1 and FINCH 2 was the proportion of subjects achieving a 20% improvement in American College of Rheumatology response (ACR20) at week 12. The primary endpoint in FINCH 3 was the proportion of subjects achieving an ACR20 response at week 24.

The results of FINCH 3 were included in the Marketing Authorisation application for filgotinib to the European Medicine Agency (EMA) and are therefore presented in sections 2.2 to 2.6. FINCH 3 was not included in the economic model because participants in this trial were naïve to MTX and therefore were not within the scope of this submission.

Table 5. Clinical effectiveness evidence: FINCH 1, FINCH 2 and FINCH 3

Study	FINCH 1, (NCT02889796) (1)	FINCH 2, (NCT02873936) (2)	FINCH 3, (NCT02886728) (3)
Study design	Randomised, double-blind, placebo- and active-controlled, multicentre, parallel assignment, 52-week Phase 3 trial	Randomised, double-blind, placebo-controlled, multicentre, parallel assignment, 24-week Phase 3 trial	Randomised, double-blind, placebo- and active-controlled, multicentre, parallel assignment, 52-week, Phase 3 trial
Population	Adults with moderately to severely active RA who have inadequate response to ongoing stable MTX dose	Adults with moderately to severely active RA despite ongoing therapy with 1 or 2 cDMARD(s) and who have had an inadequate response or are intolerant to at least one biologic DMARD (bDMARD).	Adults with moderately to severely active RA who were MTX-naïve
Intervention(s)	**Filgotinib 200mg** • Filgotinib 200mg once daily • Placebo-to-match (PTM) filgotinib 100mg once daily • PTM adalimumab -subcutaneous injection every 2 weeks **Filgotinib 100mg** • Filgotinib 100mg once daily • PTM filgotinib 200mg once daily • PTM adalimumab subcutaneous injection every 2 weeks	**Filgotinib 200mg** • Filgotinib 200mg tablet • PTM filgotinib 100mg tablet administered orally, once daily **Filgotinib 100mg**: • Filgotinib 100mg tablet • PTM filgotinib 200mg tablet, administered orally, once daily	**Filgotinib 200mg + MTX** • Filgotinib 200mg once daily • PTM filgotinib 100mg once daily + MTX up to 20 mg once weekly **Filgotinib 100mg + MTX** • Filgotinib 100mg once daily • PTM filgotinib 200mg once daily + MTX up to 20 mg once weekly **Filgotinib 200mg monotherapy** • Filgotinib 200mg once daily • PTM filgotinib 100mg once daily • PTM MTX once weekly
Comparator(s)	**Active comparator** • Adalimumab 40 mg subcutaneous injection every 2 weeks • PTM filgotinib 200mg once daily • PTM filgotinib 100mg once daily **Placebo**	**Placebo** • PTM filgotinib 200mg tablet • PTM filgotinib 100mg tablet, administered orally, once daily	**MTX monotherapy** • PTM filgotinib 200mg once daily • PTM filgotinib 100mg once daily • MTX up to 20 mg once weekly

	• PTM filgotinib 200mg once daily • PTM filgotinib 100mg once daily • PTM adalimumab subcutaneous injection every 2 weeks		
Background treatment	Subjects must have had ongoing treatment with a stable dose of MTX as described below: • Use of oral MTX on a continuous basis for at least 12 weeks prior to Day 1 and on a stable prescribed dose of 7.5 mg to 25 mg/weekly for at least 4 weeks prior to Day 1. • Stable doses of <7.5 mg/week were allowed only in the presence of intolerance or toxicity to higher doses or where higher doses were prohibited by the local label or local clinical practice. • Doses >25 mg weekly were not permitted during the study.	All subjects continued to receive a stable dose of a permitted protocol-specified cDMARD (MTX, hydroxychloroquine, sulfasalazine, or leflunomide).	Less than 3 months with conventional synthetic disease modifying antirheumatic drugs (cDMARDs) other than MTX or hydroxychloroquine.
Trial supports application for Marketing Authorisation?	Yes	Yes	Yes
Trial used in the economic model?	Yes	Yes	No
Rationale for use/non-use in the model	Pivotal trial in relevant patient population	Pivotal trial in relevant patient population	Patients naïve to MTX, are out of the scope of this appraisal.
Reported outcomes specified in the decision problem	• Disease activity (American College of Rheumatology - ACR20, ACR50, ACR70, • **European League Against Rheumatism (EULAR) response,** • **Disease Activity Score (DAS28)**	• Disease activity (American College of Rheumatology - ACR20, ACR50, ACR70, • **European League Against Rheumatism (EULAR) response,** • **Disease Activity Score (DAS28)**	• Disease activity (American College of Rheumatology - ACR20, ACR50, ACR70, • **European League Against Rheumatism (EULAR) response,** • **Disease Activity Score (DAS28)**

	• **physical function (HAQ-DI)** • pain • mortality • fatigue (FACIT-F) • radiological progression (mTSS) • adverse effects of treatment • health-related quality of life.	• **physical function (HAQ-DI)** • pain • mortality • fatigue (FACIT-F) • radiological progression (mTSS) • adverse effects of treatment • health-related quality of life.	• **physical function (HAQ-DI)** • pain • mortality • fatigue (FACIT-F) • radiological progression (mTSS) • adverse effects of treatment • health-related quality of life.
All other reported outcomes	Additional endpoints included changes in individual ACR components, other composite measures of disease activity (e.g., ACR-N% improvement [ACR-N], Clinical Disease Activity Index [CDAI], Simplified Disease Activity Index [SDAI]), and additional patient reported outcomes, including measures of health-related quality of life: • SF-36 • EQ-5D • WPAI-RA at day 1 and at weeks 4, 12, 24, 36, and 52, or at ET (if applicable)	Additional endpoints included changes in individual ACR components, other composite measures of disease activity (e.g., ACR-N% improvement [ACR-N], Clinical Disease Activity Index [CDAI], Simplified Disease Activity Index [SDAI]), and additional patient reported outcomes, including measures of health-related quality of life: • SF-36 • EQ-5D • WPAI-RA at day 1 and at weeks 4 (Treatment satisfaction questionnaire for medication excluded), 12, 24, at ET (if applicable)	Additional endpoints included changes in individual ACR components, the ACR N% improvement (ACR-N) response, change from baseline in Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI), low disease activity (LDA) per CDAI and SDAI criteria, remission per CDAI and SDAI criteria, Boolean remission per TJC28 criteria, the proportion of subjects with no radiographic progression from baseline, and additional patient-reported outcomes, including measures of health-related quality of life: • SF-36 • WPAI-RA • EQ-5D on day 1 and at weeks 4, 12, 24, 36, and 52, and at ET (if applicable).

ACR, American College of Rheumatology; CDAI, clinical disease activity index; DAS, disease activity score; DMARDs, disease modifying anti-rheumatic drugs; bDMARDs, biologic DMARDs, cDMARDs, conventional DMARDS; EQ-5D, EuroQol five dimension; ET, early termination; EULAR, European League Against Rheumatism; FACIT-F, functional assessment of chronic illness therapy-fatigue; HAQ-DI, health assessment questionnaire disability index; LDA, low disease activity; mTSS, modified Total Sharp Score; MTX, methotrexate; NA, not applicable; PTM, placebo-to-match; RA, rheumatoid arthritis; SDAI, simplified disease activity index; SF-36, 36-item short form survey; WPAI, work productivity and activity impairment.

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

A summary of the methods used in the three pivotal FINCH trials is provided in Table 6 below.

Table 6. Comparative summary of trial methodology

Trial no. (acronym)	NCT02889796 (FINCH 1) (1)	NCT02873936 (FINCH 2) (2)	NCT02886728 (FINCH 3) (3)
Trial design	52-week randomised, double-blind, placebo- and active-controlled, multicentre, Phase 3 study. Patients were randomised in a 3:3:2:3 ratio to receive MTX and: • Filgotinib (200mg) or • Filgotinib (100mg) or • Adalimumab (40mg) or • Placebo Randomisation was stratified by geographic region, prior exposure to bDMARDs and presence of RF or anti-CCP antibodies at screening and was carried out using a computerised interactive web response system. Treatment assignments should have remained blinded unless that knowledge was necessary to determine emergency medical care for the subject. The rationale for unblinding must have been clearly explained in source documentation and on the Case Report Form (CRF), along with the date on which the treatment assignment was unblinded.	24-week randomised, double-blind, placebo-controlled, multicentre, Phase 3 study. Patients were randomised in a 1:1:1 ratio to receive a stable dose of cDMARD (MTX, hydroxychloroquine, sulfasalazine, or leflunomide) and: • Filgotinib (200mg) or • Filgotinib (100mg) or • Placebo Randomisation was stratified by geographic region, number of bDMARDs previously exposed to (<3 or ≥3), and the presence of RF or anti-CCP antibody at screening and was carried out using a computerised IXRS system. Treatment assignments should have remained blinded unless that knowledge was necessary to determine emergency medical care for the subject. The rationale for unblinding must have been clearly explained in source documentation and on the Case Report Form (CRF),	52-week randomised, double-blind, placebo- and active-controlled, multicentre, Phase 3 study. Patients were randomised using a 2:1:1:2 ratio to receive: • Filgotinib (200mg) + MTX (up to 20mg) or • Filgotinib (100mg) + MTX (up to 20mg) or • Filgotinib (200mg) or • MTX (up to 20mg) Randomisation was stratified by geographic region and presence of either RF or anti-CCP antibody at screening and was carried out using an interactive web response system. Treatment assignments should have remained blinded unless that knowledge was necessary to determine emergency medical care for the subject. The rationale for unblinding must have been clearly explained in source documentation and on the Case Report Form (CRF), along with the date on which the treatment assignment was unblinded. The investigator was requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

Trial no. (acronym)	NCT02889796 (FINCH 1) (1)	NCT02873936 (FINCH 2) (2)	NCT02886728 (FINCH 3) (3)
	The investigator was requested to contact the Gilead medical monitor promptly in case of any treatment unblinding. At week 14, patients who had not achieved at least 20% improvement from baseline in both Swollen Joint Count (SJC) and Tender Joint Count (TJC) discontinued investigational study drug dosing but continued with study visits and assessments per protocol. All patients meeting this criterion who discontinued from investigational therapy received standard of care treatment for their RA (as determined by the investigator). At week 24, all patients assigned to placebo were reassigned 1:1 to either filgotinib 100mg + MTX or filgotinib 200mg + MTX in a blinded fashion and continued in the study per protocol up to week 52. Subjects previously randomized to filgotinib 100 or 200 mg or adalimumab continued on their original randomization group. All patients who continued on study drug were evaluated for loss of therapeutic response from week 30 through week 52. Patients failing to maintain at least a 20% improvement from baseline in TJC and SJC, (which was confirmed at two consecutive visits), discontinued from	along with the date on which the treatment assignment was unblinded. The investigator was requested to contact the Gilead medical monitor promptly in case of any treatment unblinding. At week 14, patients who had not achieved at least 20% improvement from day 1 in both SJC66 and TJC68 discontinued study drugs, but continued study visits and assessments, and received SoC treatment for RA. All patients who attained responder status at week 14 continued on their assigned study drugs, in a blinded fashion, to week 24. Upon completion of the 24-week dosing period all patients, regardless of response, who had not discontinued the study drug due to toxicity were given the option to screen for enrolment in a separate long-term extension study (FINCH 4). The Full Analysis Set (FAS) included all subjects who were randomized into the study and received at least 1 dose of study drug. The FAS was the primary analysis set for efficacy analyses. The Safety Analysis Set (SAS) included all subjects who received at	At week 24, patients who had not achieved at least a 20% improvement from day 1 in both SJC and TJC discontinued the investigational study drug dosing but continued with study visits and assessments per protocol. All patients meeting this criterion who discontinued from investigational therapy received standard of care treatment as determined by the investigator. Subjects who achieved at least a 20% improvement in SJC and TJC at Week 24 continued the dosing regimen to which they were randomized and were evaluated for loss of therapeutic response from Week 30 through week 52. Subjects who failed to maintain at least a 20% improvement from Day 1 in TJC and SJC (confirmed at 2 consecutive visits) discontinued investigational study drug dosing to receive standard of care treatment for RA as determined by the investigator, but continued with study visits and assessments per protocol Upon completion of the 52-week treatment period, subjects who had not discontinued assigned study drug or had not met the criteria for loss of therapeutic response had the option to enter a long-term extension (LTE) study (FINCH 4). Subjects who did not enter the LTE study completed the Posttreatment Week 4 visit after the last dose of study drug. The Full Analysis Set (FAS) included all randomized subjects who received at least 1 dose of study drug. The FAS was the primary analysis set for efficacy analyses.

Trial no. (acronym)	NCT02889796 (FINCH 1) (1)	NCT02873936 (FINCH 2) (2)	NCT02886728 (FINCH 3) (3)
	investigational study drug therapy but continued with study visits and assessments per protocol. All patients meeting this criterion who discontinued from investigational study drug dosing received standard of care treatment for their RA as determined by the investigator and were not eligible for enrolment in the separate Long-Term Extension (LTE) study (FINCH 4). At completion of the 52-week dosing period, subjects who had not discontinued assigned study drug dosing, were provided the option to enrol into the LTE Study GS-US-417-0304.(4). The primary analysis set for efficacy analyses was the Full Analysis Set (FAS), which included all randomized subjects who received at least 1 dose of study drug The Safety Analysis Set (SAS) included all subjects who received at least 1 dose of study drug. This was the primary analysis set for safety analyses.	least 1 dose of study drugs. This was the primary analysis set for safety analyses.	The Safety Analysis Set (SAS) included all subjects who received at least 1 dose of study drug. This was the primary analysis set for safety analyses.
Eligibility criteria for participants	• Age ≥18 years (≥20 years in Japan) • Met 2010 ACR/EULAR criteria for RA and were ACR functional class I–III • ≥6 swollen joints and ≥6 tender joints at screening and	• Aged ≥18 years • Met 2010 ACR/EULAR criteria for RA and were ACR functional class I-III • Had ≥6 swollen joints and ≥6 tender joints at screening and on Day 1	• Age ≥18 years • Met 2010 ACR/EULAR criteria for RA and were ACR functional class I–III • ≥6 swollen joints and ≥6 tender joints at screening and on Day 1 • Met at least one of the following parameters at screening:

Trial no. (acronym)	NCT02889796 (FINCH 1) (1)	NCT02873936 (FINCH 2) (2)	NCT02886728 (FINCH 3) (3)
	on Day 1 • At least one of the following parameters at screening: ≥1 documented joint erosion on radiographs of the hands, wrists or feet by central reading and a positive result for RF or anti-CCP antibodies ≥3 documented joint erosions on radiographs of the hands, wrists or feet by central reading if both RT and anti-CCP antibodies were negative Serum CRP ≥6 mg/L Underwent treatment with oral MTX for at least 12 weeks prior to Day 1, at a stably prescribed dose	• Undergoing treatment with 1 or 2 cDMARDs at a stable dose • Prior inadequate response or intolerance to at least one bDMARD	o Positivity for RF or anti-CCP antibodies per central laboratory, or o CRP ≥4 mg/L based on central laboratory value, or o ≥1 document joint erosion of the hands, wrists or feet on radiographs by central reading • Naïve to MTX or have had limited prior treatment with MTX (≤3 doses of MTX ≤25 mg, with the last dose occurring at least 28 days prior to Day 1)
Settings and locations where the data were collected	This study was conducted at 303 study centres in: **Group A:** Australia, Belgium, Germany, Canada, Ireland, Israel, Italy, Netherlands, New Zealand, Republic of Korea, South Africa, Spain, United Kingdom, and the United States **Group B:** Bulgaria, Czech Republic, Hungary, India, Poland, Romania,	This study was conducted at 114 sites in: **Group A:** Australia, Belgium, France, Germany, Israel, Italy, Netherlands, South Korea, Spain, Switzerland, United Kingdom, and the United States **Group B:** Czech Republic, Hungary, Poland	This study was conducted in over 227 sites in: **Group A:** Australia, Belgium, Canada, France, Germany, Ireland, Israel, Italy, Netherlands, New Zealand, Republic of Korea, Singapore, South Africa, Spain, Sweden, Switzerland, United Kingdom, and the United States **Group B:** Bulgaria, Croatia, Czech Republic,

Trial no. (acronym)	NCT02889796 (FINCH 1) (1)	NCT02873936 (FINCH 2) (2)	NCT02886728 (FINCH 3) (3)
	Russian Federation, Serbia, Slovakia, Ukraine, **Group C:** Argentina, Mexico **Group D:** Hong Kong, Taiwan, Thailand, **Group E:** Japan	**Group C:** Argentina, Mexico **Group D:** China (originally planned but no subjects were screened or enrolled from China). **Group E:** Japan	Estonia, Georgia, Hungary, India, Latvia, Moldova, Poland, Romania, Russian Federation, Serbia, Slovakia, and Ukraine **Group C:** Argentina, Brazil, Chile, Colombia, Mexico, Peru, and Puerto Rico **Group D:** China, Hong Kong, Malaysia, Philippines, Taiwan, Thailand, and Vietnam **Group E:** Japan
Trial drugs	**Interventions:** • Filgotinib 200mg + MTX + placebo (n=477), • Filgotinib 100mg + MTX + placebo (n=480) **Comparators:** • Adalimumab + MTX + placebo (n=325), • placebo + MTX (n=475).	**Interventions:** • Filgotinib 200mg + placebo + cDMARD(s) (n=148), • Filgotinib 100mg + placebo +cDMARD(s) (n=153) **Comparators:** • placebo + cDMARD(s) (n=148).	**Interventions:** • Filgotinib 200mg + placebo + MTX (n=417), • Filgotinib 100mg+ placebo + MTX (n=207), • Filgotinib 200mg + placebo (n=210) **Comparators:** • MTX + placebo (n=418).
Permitted and disallowed concomitant medications	Concomitant therapies taken for treatment of pre-existing conditions continued during the study provided they were in accordance with the inclusion and exclusion criteria. It was preferred that these medications were continued without variation of dose or regimen during the study, as much as possible. All non-RA medication used within 30 days of consent (including any changes) were to be documented in the eCRF. All prior medication(s) used in the treatment for RA were documented in the eCRF Prohibited concomitant medications (and their wash out period as applicable) while on study drug included:	Concomitant therapies taken for treatment of pre-existing conditions could continue during the study provided they were in accordance with the inclusion and exclusion criteria. It was preferred that these medications were continued without variation of dose or regimen during the study, as much as possible. All non-RA medication used within 30 days of consent (including any changes) were to be documented in the eCRF. All prior medication used for treatment of RA, were to be documented in the eCRF. Prohibited concomitant medications (and their wash out period as applicable) while on study drugs	Concomitant therapies taken for treatment of pre-existing conditions could continue during the study provided they were in accordance with the inclusion and exclusion criteria. It was preferred that these medications were continued without variation of dose or regimen during the study, as much as possible. All non-RA medications used within 30days of consent (including any changes) were to be documented in the eCRF. All prior medications used for treatment of RA were to be documented in the eCRF. Prohibited concomitant medications (and their wash out period as applicable) while on study drug included: • Use of cDMARDs (other than the study-provided MTX/PTM MTX or ongoing hydroxychloroquine ≤400mg/day or

Trial no. (acronym)	NCT02889796 (FINCH 1) (1)	NCT02873936 (FINCH 2) (2)	NCT02886728 (FINCH 3) (3)
	• Use of any DMARDs, other than background MTX and anti-malarial' s • Use of oral or injectable gold within 4weeks prior to Day1 • Use of sulfasalazine within 4weeks prior to Day1 • Use of Azathioprine within 4weeks prior to Day1 • Use of D-penicillamine within 4weeks prior to Day1 • Use of cyclosporine within 4 weeks prior to Day1 • Use of leflunomide within 8 weeks prior to Day1 or a minimum 4weeks prior to Day1 if after 11days of standard cholestyramine therapy. • Use of any cytotoxic agent, including chlorambucil, cyclophosphamide, nitrogen mustard, and other alkylating agents. • Use of any JAK inhibitor or other small molecule immunomodulator • Use of any injectable corticosteroids and receipt of an intra-articular or parenteral corticosteroid injection within 4 weeks prior to day 1 was prohibited. • Use of potent P-glycoprotein inducers (e.g. rifampin,	included: • Any DMARD(s), other than the ones specified above • Oral or injectable gold within 4weeks prior to Day1 • Azathioprine within 4weeks prior to Day1 • D penicillamine within 4weeks prior to Day1 • Cyclosporine within 8weeks prior to Day1 • Any cytotoxic agent, including chlorambucil, cyclophosphamide, nitrogen mustard, and other alkylating agents. • Use of any other JAK inhibitor or other small molecule immunomodulator • Any injectable corticosteroids and receipt of an intra-articular or parenteral corticosteroids injection within 4 weeks prior to Day1 is prohibited. • Potent P-gp inducers (e.g. rifampin, phenytoin, carbamazepine, and St. John's wort) within 3weeks prior to Day1	chloroquine≤250mg/day) • Use of any bDMARD • Use of any cytotoxic agent, including chlorambucil, cyclophosphamide, nitrogen mustard, and other alkylating agents • Use of any other JAK inhibitor or other small molecule immunomodulator • Use of any injectable corticosteroids and receipt of an intra-articular or parenteral corticosteroid injection within 4weeks prior to Day1 • Use of potent P-glycoprotein inducers (e.g. rifampin, phenytoin, carbamazepine, and St. John's wort) within 3 weeks prior to Day1

Trial no. (acronym)	NCT02889796 (FINCH 1) (1)	NCT02873936 (FINCH 2) (2)	NCT02886728 (FINCH 3) (3)
	phenytoin, carbamazepine, and St. John's wort) within 3weeks prior to Day1		
Primary outcomes	The primary efficacy endpoint was the proportion of subjects who achieved an ACR20 response at week 12	The primary efficacy endpoint was the proportion of subjects who achieved an ACR20 response at week 12.	The primary efficacy endpoint was the proportion of subjects who achieved an ACR20 response at week 24.
Key secondary outcomes (including scoring methods and timings of assessments)	The key secondary efficacy endpoints were: • Proportion of subjects who achieved DAS28-CRP≤3.2 at week 12 versus placebo and versus adalimumab • Change from baseline in the HAQ-DI score at week 12 versus placebo • Proportion of subjects who achieve DAS28-CRP<2.6 at week 24 versus placebo and adalimumab • Change from baseline in mTSS at week 24 versus placebo	The key secondary efficacy endpoints were: • Proportion of subjects who achieved DAS28-CRP≤3.2 at week 12 • Change from baseline in the HAQ-DI score at week 12	The key secondary efficacy endpoints were: • Change from baseline in the HAQ-DI score at week 24 • Proportion of subjects who achieved DAS28-CRP<2.6 at week24 • Change from baseline in mTSS at week 24
Other secondary outcomes	Other secondary efficacy endpoints included: • Change from baseline in the mTSS at week 52 • The proportion of subjects who achieved an ACR50 and ACR70 response at weeks 4, 12, 24, and 52, an ACR20 response at weeks 4, 24, and 52, and an ACR20/50/70	Other secondary efficacy endpoints included: • The proportion of subjects who achieved an ACR50 response at weeks 4 and 24, an ACR70 response at weeks 4 and 12, an ACR20 response at weeks 4 and 24, and ACR20/50/70 response rates over time from day 1 through week 2	Other secondary efficacy endpoints included: • Change from baseline in mTSS at week 52 • The proportion of subjects who achieved ACR50 and ACR70 responses at weeks 4, 12, 24, and 52, and ACR20 response at weeks 4, 12, and 52, and ACR20/50/70 responses over time from day 1 through week 52 • Change from baseline in individual

Trial no. (acronym)	NCT02889796 (FINCH 1) (1)	NCT02873936 (FINCH 2) (2)	NCT02886728 (FINCH 3) (3)
	response over time from day 1 through week 52 • Change from baseline in individual components of the ACR response at weeks 4, 12, 24, and 52, and over time from day 1 through week 52 • The proportion of subjects who achieved change (i.e., decrease) in HAQ-DI of ≥ 0.22 at weeks 4, 12, 24, and 52, and over time from day 1 through week 52 • Change from baseline in DAS28-CRPat weeks 4, 12, 24, and 52, and over time from day 1 through week 52 • The proportion of subjects who achieved DAS28-CRP≤ 3.2 at weeks 4, 24, and 52, and over time from day 1 through week 52 • The proportion of subjects who achieved DAS28-CRP< 2.6 at weeks 4, 12, and 52, and over time from day 1 through week 52 • ACR-N and EULAR response at weeks 4, 12, 24, and 52, and over time from day 1 through week 52 • Change from baseline in CDAI at weeks 4, 12, 24, and 52, and over time from day 1 through week 5	• Change from baseline in individual components of the ACR response at weeks 4, 12, and 24 and over time from day 1 through week 24 • The proportion of subjects who achieved a decrease in HAQ-DI of ≥ 0.22 at weeks 4, 12 and 24, and over time from day 1 through week 24 • Change from baseline in DAS28-CRPat weeks 4, 12, and 24, and over time from day 1 through week 2 • The proportion of subjects who achieved DAS28-CRP≤ 3.2 at weeks 4 and 24, and over • time from day 1 through week 24The proportion of subjects who achieved DAS28-CRP< 2.6 at weeks 4 and 12, and over • time from day 1 through week 24 ACR-N and EULAR response at weeks 4, 12, and 24, and over time from day 1 through week 24 • Change from baseline in CDAI at weeks 4, 12, and 24, and over time from day 1 through week 24 • Change from baseline in SDAI at weeks 4, 12, and	components of the ACR response at weeks 4, 12, 24, and 52, and over time from day 1 through week 52 • The proportion of subjects who achieved change (i.e., decrease) in HAQ-DI of ≥ 0.22 at weeks 4, 12, 24, and 52, and over time from day 1 through week 52 • Change from baseline in DAS28-CRPat weeks 4, 12, 24, and 52, and over time from day 1 through week 52 • The proportion of subjects who achieved DAS28-CRP≤ 3.2 at weeks 4, 12, 24, and 52, and over time from day 1 through week 52 • The proportion of subjects who achieved DAS28-CRP< 2.6 at weeks 4, 12, and 52, and over time from day 1 through week 52 • ACR-N and European League Against Rheumatism (EULAR) response at weeks 4, 12, 24 and 52, and over time from day 1 through week 52

Trial no. (acronym)	NCT02889796 (FINCH 1) (1)	NCT02873936 (FINCH 2) (2)	NCT02886728 (FINCH 3) (3)
	• Change from baseline in SDAI at weeks 4, 12, 24, and 52, and over time from day 1 through week 24 • The proportion of subjects with no radiographic progression from baseline at weeks 24 and absolute value and change from baseline in SF-36, FACIT-Fatigue, and the EQ-5D at weeks 4, 12, 24 (except for SF-36 PCS and FACIT-Fatigue), and 52, and over time from day 1 through week 52 • Absolute value and change from baseline in WPAI-RA at weeks 4, 12, 24, and 52, and over • time from day 1 through week 52	24, and over time from day 1 through week 24 • Absolute value and change from baseline in SF-36, FACIT-Fatigue score, and the EQ-5D over time at weeks 4, 12, and 24 (except for SF-36 PCS and FACIT-Fatigue score), and over time from day 1 through week 24 • Absolute value and change from baseline in WPAI-RA at weeks 4, 12, and 24, and over time from day 1 through week 24	

ACR, American College of Rheumatology; CCP, citric citrullinated peptide; CDAI, clinical disease activity index; CRF, case report form, CRP, C-reactive protein; DAS, disease activity score; DMARDs, disease modifying anti-rheumatic drugs; bDMARDs, biologic DMARDs, cDMARDs, conventional DMARDS; EQ-5D, EuroQol five dimension; ET, early termination; EULAR, European League Against Rheumatism; FACIT-F, functional assessment of chronic illness therapy-fatigue; FAS, full analysis set; HAQ-DI, health assessment questionnaire disability index; IXRS, interactive web response system; JAK, Janus kinase; LDA, low disease activity; mTSS, modified Total Sharp Score; MTX, methotrexate; NA, not applicable; PCS, Physical Component Summary; PTM, placebo-to-match; RA, rheumatoid arthritis; RF, Rheumatoid factor; SDAI, simplified disease activity index; SF-36, 36-item short form survey; SJC, Swollen joint count; SoC, Standard of care; TJC, Tender joint count; WPAI, work productivity and activity impairment.

Table 7 shows the baseline characteristics of study patients for FINCH 1, FINCH 2 and FINCH 3. Within the three studies that constitute the pivotal registrational clinical programme, demographics and other baseline characteristics were well-balanced across the different treatment arms and can be considered broadly generalisable to those of patients seen in NHS clinical practice in England.

The characteristics of the population across each arm of FINCH 1 were well aligned. The main differences between FINCH 1 arms were:

- Sex at birth: 20.2% of patients were male in the filgotinib 200mg arm versus 16.9% in the filgotinib 100mg arm.
- Race: 20.0% of patients were Asian in the adalimumab arm versus 25.7% in the filgotinib 200mg arm. 70.5% were White in the adalimumab arm versus 65.7% in the filgotinib 200mg arm.
- Duration of RA since diagnosis: 8.0 years in the adalimumab group and 7.3 years in the filgotinib 200mg group

Similarly, the characteristics of patients within FINCH 2 and FINCH 3 were well balanced. The main differences were seen in sex at birth; in FINCH 2, 22.2% of patients were male in the filgotinib 100mg arm and 18.2% were male in the placebo arm. In FINCH 3, 21.0% of patients were male versus 25.0% in the MTX monotherapy arm.

Table 7. Baseline characteristics of patients in FINCH 1 (filgotinib + MTX; MTX-IR; SAS), FINCH 2 (filgotinib + cDMARD; bDMARD-IR; SAS) and FINCH 3 (filgotinib + MTX; MTX naïve; SAS)

Baseline characteristic	NCT02889796 (FINCH 1) (1)				NCT02873936 (FINCH 2) (2)			NCT02886728 (FINCH 3) (3)			
	filgotinib 200mg (n=475)200mg	filgotinib 100mg (n=480)100mg	Adalimumab (n=325)	placebo (n=475)	filgotinib 200mg (n=147)	filgotinib 100mg (n=153)	placebo (n=148)	filgotinib 200mg + MTX (n=416)	filgotinib 100mg + MTX (n=207)	filgotinib 200mg monotherapy (n=210)	MTX monotherapy (n=416)
Age, mean (SD)	52 (12.8)	53 (12.6)	53 (12.9)	53 (12.8)	56 (12.5)	55 (12.0)	56 (12.1)	53 (13.8)	54 (12.6)	52 (13.9)	53 (13.7)
Sex at birth, n (%)											
Male	96 (20.2%)	81 (16.9%)	59 (18.2%)	84 (17.7%)	27 (18.4%)	34 (22.2%)	27 (18.2%)	91 (21.9%)	49 (23.7%)	44 (21.0%)	104 (25.0%)
Female	379 (79.8%)	399 (83.1%)	266 (81.8%)	391 (82.3%)	120 (81.6%	119 (77.8%)	121 (81.8%)	325 (78.1%)	158 (76.3%)	166 (79.0%)	312 (75.0%)
Ethnicity											
Hispanic or Latino	67 (14.1%)	71 (14.8)	54 (16.6)	70 (14.7%)	0%	0%	0%	93 (22.4%)	40 (19.3%)	45 (21.4%)	84 (20.2%)
Not Hispanic or Latino	404 (85.1%)	399 (83.1%)	268 (82%)	400 (84.2%)	0%	0%	0%	322 (77.4%)	167 (80.7%)	165 (78.6%)	332 (79.8%)
Not permitted	4 (0.8%)	10 (2.1%)	3 (0.9%)	5 (1.1%)	100%	100%	100%	1 (0.2%)	0	0	0
Race, n (%)											
American Indian or Alaskan Native	27 (5.7%)	27(5.6%)	20 (6.2%)	29 (6.1%)	7 (4.8%)	9 (5.9%)	10 (6.8%)	26 (6.3%)	12 (5.8%)	18 (8.6%)	33 (7.9%)

Asian	122 (25.7%)	115 (24.0%)	65 (20.0%)	109 (22.9%)	15 (10.2%)	20 (13.1%)	15 (10.1%)	90 (21.6%)	51 (24.6%)	47 (22.4%)	85 (20.4%)
Black or African American	6 (1.3%)	7 (1.5%)	10 (3.1%)	12 (2.5%)	14 (9.5%)	12 (7.8%)	21 (14.2%)	15 (3.6%)	8 (3.9%)	8 (3.8%)	14 (3.4%)
Native Hawaiian or Pacific Islander	1 (0.2%)	0	0	2 (0.4%)	NA	NA	NA	1 (0.2%)	0	1 (0.5%)	3 (0.7%)
White	312 (65.7%)	324 (67.5%)	229 (70.5%)	319 (67.2%)	110 (74.8%)	109 (71.2%)	97 (65.5%)	278 (66.8%)	132 (63.8%)	135 (64.3%)	278 (66.8%)
Other	7 (1.5%)	6 (1.3%)	1 (0.3%)	3 (0.6%)	1 (0.7%)	3 (2.0%)	2 (1.4%)	6 (1.4%)	4 (1.9%)	0	3 (0.7%)
*Not permitted**	0	1 (0.2%)	0	1 (0.2%)	0	0	3 (2.0%)	0	0	1 (0.5%)	0
BMI, mean kg/m^2 (SD)	26.7 (5.67)	26.4 (5.80)	26.9 (5.97)	27.0 (5.91)	30.5 (7.89)	30.3 (7.66)	29.8 (7.25)	27.6 (6.35)	27.8 (6.25)	27.5 (6.49)	27.9 (6.54)
Mean duration of RA from diagnosis, years (SD)	7.3 (7.39)	8.5 (8.22)	8.0 (7.40)	7.3 (7.24)	12.6 (9.48)	12.0 (7.74)	12.6 (10.30)	1.9 (3.57)	2.3 (4.71)	2.6 (6.26)	2.3 (5.52)
RF positive, n (%)	352 (74.1%)	362 (75.4%)	241 (74.2%)	365 (76.8%)	104 (70.7)	107 (69.9)	92 (62.2)	282 (67.8%)	141 (68.1%)	137 (65.2%)	288 (69.2%)
Anti-CCP positive, n (%)	380 (80.0%)	381 (79.4%)	253 (77.8%)	378 (79.6%)	99 (67.3%)	113 (73.9%)	105 (70.9%)	287 (69.0%)	143 (69.1%)	133 (63.3%)	292 (70.2%)
RF positive + anti-CCP positive, n (%)	331 (69.7%)	332 (69.2%)	219 (67.4%)	333 (70.1%)	91 (61.9%)	102 (66.7%)	84 (56.8%)	252 (60.6%)	122 (58.9%)	112 (53.3%)	258 (62.0%)
Concurrent oral corticosteroid use on first dose date, n (%)											
No	246 (51.8%)	251 (52.3%)	185 (56.9%)	258 (54.3%)	79 (53.7%)	85 (55.6%)	77 (52.0%)	273 (65.6%)	119 (57.5%)	121 (57.6%)	242 (58.2%)
Yes	229 (48.2%)	229 (47.7%)	140 (43.1%)	217 (45.7%)	68 (46.3%)	68 (44.4%)	71 (48.0%)	143 (34.4%)	88 (42.5%)	89 (42.4%)	174 (41.8%)
Mean dose, mg/day (SD)	6.2 (3.42)	6.1 (2.49)	5.9 (2.22)	5.9 (2.52)	6.4 (2.70)	6.3 (2.58)	6.2 (2.69)	6.6 (2.34)	7.2 (2.86)	6.6 (2.24)	6.5 (2.33)
Concurrent MTX use on first dose date, n (%)											
Mean dose, mg/week (SD)	15.3 (4.94)	15.5 (4.81)	15.4 (4.79)	14.9 (4.52)	15.5 (5.12)	16.2 (5.58)	15.5 (5.02)	NA	NA	NA	NA

Prior exposure to cDMARDs other than MTX, n (%)											
Yes	NA	NA	NA	NA	NA	NA	NA	73 (17.5%)	38 (18.4%)	35 (16.7%)	76 (18.3%)
No	NA	NA	NA	NA	NA	NA	NA	343 (82.5%)	169 (81.6%)	175 (83.3%)	340 (81.7%)
Prior exposure to MTX, n (%)											
Yes	NA	NA	NA	NA	NA	NA	NA	29 (7.0%)	14 (6.8%)	15 (7.1%)	24 (5.8%)
No	NA	NA	NA	NA	NA	NA	NA	387 (93.0%)	193 (93.2%)	195 (92.9%)	392 (94.2%)
SJC 66, mean (SD)	15 (8.5)	15 (8.5)	16 (8.4)	16 (8.5)	18 (12.5)	17 (12.4)	17 (9.7)	16 (9.8)	16 (9.3)	16 (9.7)	16 (9.4)
TJC 68, mean (SD)	25 (13.5)	25 (13.4)	24 (13.2)	24 (13.5)	28 (16.1)	26 (15.4)	27 (15.5)	26 (14.5)	25 (13.9)	26 (13.7)	26 (13.8)
SJC 28, mean (SD)	11 (5.2)	11 (5.2)	11 (5.0)	11 (5.0)	12 (6.3)	12 (6.0)	12 (6.0)	11 (5.6)	11 (5.3)	11 (5.9)	12 (5.6)
TJC 28, mean (SD)	15 (6.4)	15 (6.7)	15 (6.3)	15 (6.4)	16 (7.7)	15 (6.8)	16 (6.9)	15 (6.6)	15 (6.9)	15 (6.8)	15 (6.5)
HAQ-DI total score, mean (SD)	1.59 (0.611)	1.55 (0.625)	1.59 (0.600)	1.63 (0.613)	1.70 (0.656)	1.64 (0.683)	1.65 (0.633)	1.52 (0.622)	1.56 (0.654)	1.56 (0.655)	1.60 (0.625)
DAS28-CRP, mean (SD)	5.8 (0.88)	5.7 (0.95)	5.7 (0.88)	5.7 (0.91)	5.9 (1.03)	5.9 (0.98)	5.9 (0.86)	5.7 (0.99)	5.7 (1.04)	5.8 (0.94)	5.7 (1.00)
FACIT-Fatigue, mean (SD)	27.6 (10.68)	27.8 (10.60)	27.2 (10.20)	26.9 (10.34)	24.2 (11.47)	23.7 (12.30)	25.4 (10.89)	28.3 (10.93)	27.3 (11.92)	27.3 (10.90)	27.1 (10.72)
Patient's Pain Assessment, mean (SD)	65 (20.4)	64 (20.1)	64 (19.5)	66 (19.0)	66 (21.6)	67 (21.7)	68 (19.9)	64 (22.0)	67 (22.1)	67 (18.4)	66 (21.4)
Patient's Global Assessment Disease Activity, mean (SD)	67 (19.2)	65 (19.7)	67 (19.1)	68 (18.7)	68 (20.6)	69 (20.2)	70 (18.0)	65 (21.0)	66 (21.6)	68 (19.2)	66 (21.0)
Physician Global Assessment Disease Activity, mean (SD)	66 (16.0)	65 (16.5)	67 (15.5)	66 (16.2)	69 (17.6)	68 (18.7)	66 (16.7)	66 (17.0)	68 (16.3)	66 (14.4)	67 (16.8)
SDAI, mean, (SD)	41.2 (12.26)	40.2 (12.79)	40.6 (11.88)	41.2 (12.37)	43.4 (14.64)	42.6 (14.16)	43.0 (12.33)	41.3 (13.41)	41.0 (13.53)	41.8 (13.09)	41.9 (13.39)

CDAI, mean (SD)	39.5 (11.85)	38.6 (12.23)	39.2 (11.51)	39.6 (11.66)	41.7 (14.23)	40.4 (13.23)	41.4 (12.00)	39.5 (12.77)	39.2 (12.69)	40.0 (12.63)	40.2 (12.50)
hsCRP, mean mg/L (SD)	16.13 (21.005)	16.74 (22.982)	14.56 (18.003)	16.25 (24.051)	17.21 (18.275)	21.49 (28.206)	16.42 (18.321)	18.04 (25.289)	17.72 (27.419)	17.32 (23.228)	16.86 (24.353)

*Not permitted: local regulators did not allow collection of race or ethnicity information; ACR, American College of Rheumatology; BMI, body mass index; CCP, citric citrullinated peptide; CDAI, clinical disease activity index; CRF, case report form, CRP, C-reactive protein; DAS, disease activity score; DMARDs, disease modifying anti-rheumatic drugs; bDMARDs, biologic DMARDs, cDMARDs, conventional DMARDS; EQ-5D, EuroQol five dimension; ET, early termination; EULAR, European League Against Rheumatism; FACIT-F, functional assessment of chronic illness therapy-fatigue; FAS, full analysis set; HAQ-DI, health assessment questionnaire disability index; IR, inadequate response; IXRS, interactive web response system; JAK, Janus kinase; LDA, low disease activity; mTSS, modified Total Sharp Score; MTX, methotrexate; NA, not applicable; PCS, Physical Component Summary; PTM, placebo-to-match; RA, rheumatoid arthritis; RF, Rheumatoid factor; SAS, safety analysis set; SD, standard deviation; SDAI, simplified disease activity index; SF-36, 36-item short form survey; SJC, Swollen joint count; SoC, Standard of care; TJC, Tender joint count; WPAI, work productivity and activity impairment.

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

The statistical analysis methods and definitions of study groups used in the three pivotal FINCH trials are described in Table 8 below.

Table 8. Summary of statistical analysis in RCTs

Trial no. (acronym)	**NCT02889796 (FINCH 1) (1)**	**NCT02873936 (FINCH 2) (2)**	**NCT02886728 (FINCH 3) (3)**
objective	To evaluate the effects of filgotinib versus placebo for the treatment of signs and symptoms of rheumatoid arthritis (RA) as measured by the proportion of subjects achieving an American College of Rheumatology 20% improvement response (ACR20) at week 12.	To evaluate the effects of filgotinib versus placebo for the treatment of signs and symptoms of rheumatoid arthritis (RA) as measured by the proportion of subjects achieving an American College of Rheumatology 20% improvement (ACR20) response at week 12	To evaluate the effects of filgotinib (GS-6034, formerly GLPG0634) in combination with MTX versus MTX monotherapy for the treatment of signs and symptoms of rheumatoid arthritis (RA) as measured by the proportion of subjects achieving an American College of Rheumatology 20% improvement (ACR20) at week 24
Statistical analysis for primary endpoints	The primary efficacy endpoint was the proportion of subjects who achieved an ACR20 response at week 12. For the primary analysis, the ACR20 response rate at week 12 for filgotinib 200mg was compared with placebo for a superiority test at the 2-sided 0.05-level. A logistic regression analysis with treatment groups and stratification factors in the model was used. Subjects who did not have sufficient measurements to establish efficacy at week 12 were considered non-responders (i.e., non-responder imputation	The primary endpoint for the study was the proportion of subjects who achieved an ACR20 response at week 12. The primary analyses consisted of a superiority test of filgotinib 200mg compared with placebo based on the primary endpoint. Superiority was tested at the 2-sided 0.05-level. A logistic regression analysis with treatment groups and stratification factors in the model was used. Subjects who did not have sufficient measurements to establish efficacy at week 12 were	The primary efficacy endpoint was the proportion of subjects who achieved an ACR20 response at week24. For the primary analysis, the ACR20 response rate at week 24 for filgotinib200mg+ MTX was compared with MTX monotherapy for a superiority test at the 2-sided 0.05-level. A logistic regression analysis with treatment groups and stratification factors in the model was used. Subjects who did not have sufficient measurements to establish efficacy at week 24 were considered as

Trial no. (acronym)	NCT02889796 (FINCH 1) (1)	NCT02873936 (FINCH 2) (2)	NCT02886728 (FINCH 3) (3)
	[NRI]).	considered non-responders (i.e., non-responder imputation [NRI]).	non-responders (i.e., non-responder imputation [NRI]).
Sample size, power calculation	Sample size was determined based on the superiority test of filgotinib 200mg compared with placebo based on the change from baseline in mTSS at week 24. When assuming a difference of 0.4 between the 2 groups and a common standard deviation of 1.85, 450 subjects in each group were required to obtain 90% power at a 2-sided 0.05-level. This sample size provided over 95% power to detect an increase in ACR20 response rate of 45%to 65% between the placebo control group and the filgotinib group, respectively, using a 2-sided 0.05-level test. Based on Liu 2014 (4), 450 subjects in each of the filgotinib 200mg group and placebo group, and 300 subjects in the adalimumab group, the sample size provided over 90% power at a 2-sided 0.05 significance level to demonstrate that filgotinib 200mg preserved more than 50% of the effect of adalimumab with respect to the response rate of DAS28 (CRP)≤3.2 at week 12, assuming both filgotinib 200mg and adalimumab groups have similar response rates of DAS28(CRP)≤3.2. Given this study had a placebo group, assay sensitivity was established through a direct comparison of adalimumab to placebo. The total planned sample size was 1650 (450 each for the filgotinib 200mg, filgotinib 100mg, and placebo	Sample size was determined based on the superiority test of filgotinib compared with placebo on the change from baseline in HAQ-DI at week 12. When assuming a difference of 0.25 between the 2 groups and a common standard deviation of 0.645, 141 subjects in each of the filgotinib groups and placebo control group were required to obtain 90% power at a 2-sided 0.05-level. A sample size of 141 subjects in each of the filgotinib groups and placebo control group provided over 90% power to detect an increase in ACR20 response rate of 25% to 45% between the placebo control group and the filgotinib groups respectively, using a 2-sided 0.05-level test. In summary, the total planned sample size was 423 (141 subjects in each treatment group).	Sample size was determined based on the superiority test of filgotinib200mg+ MTX compared with MTX monotherapy based on the change from baseline in mTSS at week 24. When assuming a difference of 0.62 between the 2 groups on change from baseline in mTSS at week 24 and a common standard deviation (SD) of 2.7, 400subjects in the filgotinib 200mg+MTX group and 400subjects in the MTX monotherapy group were required to obtain 90% power at a 2-sided 0.05-level. The total planned sample size was 1200 subjects (400subjects in the filgotinib200mg+ MTX group, 200 subjects in the filgotinib100mg+ MTX group, 200subjects in the filgotinib200mg monotherapy group, and 400 subjects in the MTX monotherapy group). This sample size provided over 90% power to detect a difference in the ACR20 response rate of 62% to 78% between the MTX monotherapy group and the filgotinib groups, respectively, using a 2-sided 0.05-level test.

Trial no. (acronym)	NCT02889796 (FINCH 1) (1)	NCT02873936 (FINCH 2) (2)	NCT02886728 (FINCH 3) (3)
	groups, and 300 for the active comparator group).		
Data management, patient withdrawals	The Gilead medical monitor was to be consulted prior to discontinuation of study drug when medically feasible. Per protocol subjects were supposed to permanently discontinue study drug in the following instances: • Any opportunistic infection • Any serious infection that required antimicrobial therapy or hospitalization, or any infection that met serious adverse events (SAE) reporting criteria • Complicated herpes zoster infection (with multidermatomal, disseminated, ophthalmic, or central nervous system involvement) • Evidence of active HCV during the study, as evidenced by HCV RNA positivity • Evidence of active HBV during the study, as evidenced by HBV DNA positivity • Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromised the subject's ability to continue study-specific procedures or was considered to not be in the subject's best interest • Non-responder at week 14 or at 2	The Gilead medical monitor was to be consulted prior to discontinuation of study drugs when medically feasible. Subjects could have withdrawn nor have been removed from treatment for any of the following reasons: • Any opportunistic infection • Any serious infection that required antimicrobial therapy or hospitalization, or any infection that met serious adverse event (SAE)reporting criteria. • Complicated herpes zoster infection (with multidermatomal, disseminated, ophthalmic, or CNS involvement) • Evidence of active HCV during the study, as evidenced by HCV RNA positivity • Evidence of active HBV during the study, as evidenced by HBV DNA positivity • Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromised the subject's ability to continue study-specific procedures or was considered to not be in the	The Gilead medical monitor was to be consulted prior to discontinuation of study drug when medically feasible. Per protocol subjects were supposed to permanently discontinue study drug in the following instances: • Any opportunistic infection • Any serious infection that required antimicrobial therapy or hospitalization, or any infection that met serious adverse events (SAE) reporting criteria • Complicated herpes zoster infection (with multidermatomal, disseminated, ophthalmic, or central nervous system involvement) • Evidence of active HCV during the study, as evidenced by HCV RNA positivity • Evidence of active HBV during the study, as evidenced by HBV DNA positivity • Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromised the subject's ability to continue study-specific procedures or

Trial no. (acronym)	NCT02889796 (FINCH 1) (1)	NCT02873936 (FINCH 2) (2)	NCT02886728 (FINCH 3) (3)
	consecutive visits after week 30 Subject requested to discontinue for any reason • Subject non-compliance Pregnancy during the study Discontinuation of the study at the request of Gilead, a regulatory agency, or an IRB/IEC • Subject use of prohibited concurrent therapy may have triggered discontinuation of study drug; consultation should have been made with the Gilead medical monitor. • Laboratory criteria: After becoming aware of any of the abnormal laboratory changes occurring at any one time described below, an unscheduled visit (i.e., sequential visit) should have occurred to retest within 3 to 7days (except creatinine, which should have been retested 7-14 days apart). • Two sequential neutrophil counts <750 neutrophils/mm3 (SI: <0.75x10^9 cells/L) • Two sequential platelet counts <75,000 platelets/mm3 (SI: <75.x10^9 cells/L) • Two sequential AST or ALT elevations >3xULN and ≥1 total bilirubin value >2xULN or accompanied by symptoms consistent with hepatic injury.	subject's best interest • Subject request to discontinue for any reason • Subject noncompliance • Pregnancy during the study (see Appendix16.1.1, Section 7.7.2.1and Appendix 5) • Discontinuation of the study at the request of the sponsor, a regulatory agency, an IRB, or an IEC • Subject use of prohibited concurrent therapy could trigger discontinuation of study drugs; consultation was to be made with the Gilead Medical Monitor. • Laboratory criteria: After becoming aware of any of the following abnormal laboratory changes occurring at any 1time, an unscheduled visit (i.e. sequential visit) was to occur to reassess within 3 to 7days (except creatinine, which was to be retested within 7 to14days): • Two sequential neutrophil counts <750neutrophils/mm3 (SI: <75.x10^9 cells/L) • Two sequential l platelet counts <75,000platelets/mm3 (SI: <75x10^9 cells/L)	was considered to not be in the subject's best interest • Non-responder at week 14 or at 2consecutive visits after Week30 Subject requested to discontinue for any reason • Subject non-compliance Pregnancy during the study Discontinuation of the study at the request of Gilead, a regulatory agency, or an IRB/IEC • Subject use of prohibited concurrent therapy may have triggered discontinuation of study drug; consultation should have been made with the Gilead medical monitor. • Laboratory criteria: After becoming aware of any of the abnormal laboratory changes occurring at any one time described below, an unscheduled visit (i.e., sequential visit) should have occurred to retest within 3 to 7days (except creatinine, which should have been retested 7-14 days apart). • Two sequential neutrophil counts <750 neutrophils/mm3 (SI: <75x10^9 cells/L) • Two sequential platelet counts

Trial no. (acronym)	NCT02889796 (FINCH 1) (1)	NCT02873936 (FINCH 2) (2)	NCT02886728 (FINCH 3) (3)
	• Two sequential AST or ALT elevations >5xULN • Two sequential values for estimated creatinine clearance <35 mL/min based on the Cockroft-Gault formula Handling of dropouts or missing data: In general, missing data were not imputed unless methods for handling missing data were Specified in the sensitivity and supportive analyses.	Handling of dropouts or missing data: In general, missing data were not imputed unless methods for handling missing data were Specified in the sensitivity and supportive analyses.	<75,000 platelets/mm3 (SI: <75.x10^9 cells/L) • Two sequential AST or ALT elevations >3xULN and ≥1 total bilirubin value >2xULN or accompanied by symptoms consistent with hepatic injury. • Two sequential AST or ALT elevations >5xULNTwo sequential values for estimated creatinine clearance <35 mL/min based on the Cockroft-Gault formula Handling of dropouts or missing data: In general, missing data were not imputed unless methods for handling missing data were Specified in the sensitivity and supportive analyses.

ACR, American College of Rheumatology; CCP, citric citrullinated peptide; CDAI, clinical disease activity index; CRF, case report form, CRP, C-reactive protein; DAS, disease activity score; DMARDs, disease modifying anti-rheumatic drugs; bDMARDs, biologic DMARDs, cDMARDs, conventional DMARDS; EQ-5D, EuroQol five dimension; ET, early termination; EULAR, European League Against Rheumatism; FACIT-F, functional assessment of chronic illness therapy-fatigue; FAS, full analysis set; HAQ-DI, health assessment questionnaire disability index; IXRS, interactive web response system; JAK, Janus kinase; LDA, low disease activity; mTSS, modified Total Sharp Score; MTX, methotrexate; NA, not applicable; PCS, Physical Component Summary; PTM, placebo-to-match; RA, rheumatoid arthritis; RF, Rheumatoid factor; SDAI, simplified disease activity index; SF-36, 36-item short form survey; SJC, Swollen joint count; SoC, Standard of care; TJC, Tender joint count; WPAI, work productivity and activity impairment.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The quality assessment of the FINCH 1, FINCH 2 and FINCH 3 trials is presented in Table 9. In general, the three pivotal FINCH trials were designed and carried out following a robust methodology. Randomisation was performed so that baseline characteristics of patients were homogeneous across treatment groups. Both patients and investigators remained blinded throughout the studies.

Table 9 Quality assessment results for RCTs

Trial no. (acronym)	**NCT02889796 (FINCH 1)**	**NCT02873936 (FINCH 2)**	**NCT02886728 (FINCH 3)**
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes

B.2.6 Clinical effectiveness results of the relevant trials

2.6.1 FINCH 1

FINCH 1 (1) met its primary endpoint, demonstrating superiority of filgotinib 200mg over placebo measured by proportion of patients achieving ACR20 response at week 12 (76.6% [72.7%, 80.5%] versus 49.9% [45.3%, 54.5%] for placebo) (p<0.001). Filgotinib 200mg + MTX and filgotinib 100mg + MTX also demonstrated statistically significantly better efficacy over placebo for a number of key efficacy endpoints including ACR20, ACR50 and ACR70, change from baseline in HAQ-DI, the proportion of patients achieving DAS28-CRP <2.6 (remission), the proportion of patients achieving DAS28-CRP ≤3.2 (LDA) and change from baseline in mTSS (radiographic progression). Further detail is given in the sections below.

ACR20/50/70 response

At week 12, the proportion of patients who achieved an ACR20 response was statistically significantly higher in the filgotinib 200mg (76.6% [72.7%, 80.5%]) and filgotinib 100mg (69.8%) groups compared with placebo (49.9% [45.3%, 54.5%]) (p<0.001 for both). This was also demonstrated for filgotinib 200mg versus adalimumab (70.5% [65.3%, 75.6] (p=0.046). Similarly, the proportion of patients who achieved an ACR50 response was statistically significantly higher in the filgotinib 200mg (47.2% [42.6%, 51.8%]) and filgotinib 100mg (36.5% [32.0%, 40.9%]) groups compared with placebo (19.8% [16.1%, 23.5%]); (p <0.001 for both). This was also demonstrated for filgotinib 200mg versus adalimumab (35.1% [29.7%, 40.4%]) (p<0.001). Finally, the proportion of patients achieving ACR70 response was also statistically significantly higher in the filgotinib 200mg (26.1% [22.1%, 30.2%]) and filgotinib 100mg (18.5% [15.0%, 22.1%]) groups compared with placebo (6.7% [4.4%, 9.1%]); (p <0.001 for both). This was also demonstrated for filgotinib 200mg versus adalimumab (14.2% [10.2%, 18.1%]) (p<0.001).

At week 24, the proportion of patients who achieved an ACR20 response was statistically significantly higher in the filgotinib 200mg (78.1% [74.3%, 81.9%]) and filgotinib 100mg (77.7% [73.9%, 81.5%]) groups compared with placebo (59.2% [54.6%, 63.7%]) (p <0.001 for both). Compared with adalimumab (74.5% [69.6%,

79.4%]), filgotinib 200mg (78.1% [74.3%, 81.9%]) demonstrated a numerically higher ACR20 response at week 24 (p=0.21). Similarly, the proportion of patients who achieved an ACR50 response was statistically significantly higher in the filgotinib 200mg (57.9% [53.3%, 62.4%]) and filgotinib 100mg (52.7% [48.1%, 57.3%]) groups compared with placebo (33.3%); (p <0.001 for both). Compared with adalimumab (52.3% [46.7%, 57.9%]), filgotinib 200mg (57.9% [53.3%, 62.4%]) demonstrated a numerically higher ACR50 response rate at week 24 (p=0.11). Finally, the proportion of patients achieving ACR70 response was also statistically significantly higher in the filgotinib 200mg (36.2% [31.8%, 40.6%]) and filgotinib 100mg (29.6% [25.4%, 33.8%]) groups compared with placebo (14.9% [11.6%, 18.3%]); (p <0.001 for both). The proportion of patients who achieved an ACR70 response was also statistically significantly higher in the filgotinib 200mg compared with the adalimumab group (29.5% [24.4%, 34.7%]) (p =0.042).

Figure 4, Figure 5 and Figure 6 show ACR20, ACR50 and ACR70 over time. These demonstrate filgotinib's rapid onset of action, as well as the maintenance of response across the 52-week study period.

Figure 4. ACR20 response by study visit, FAS

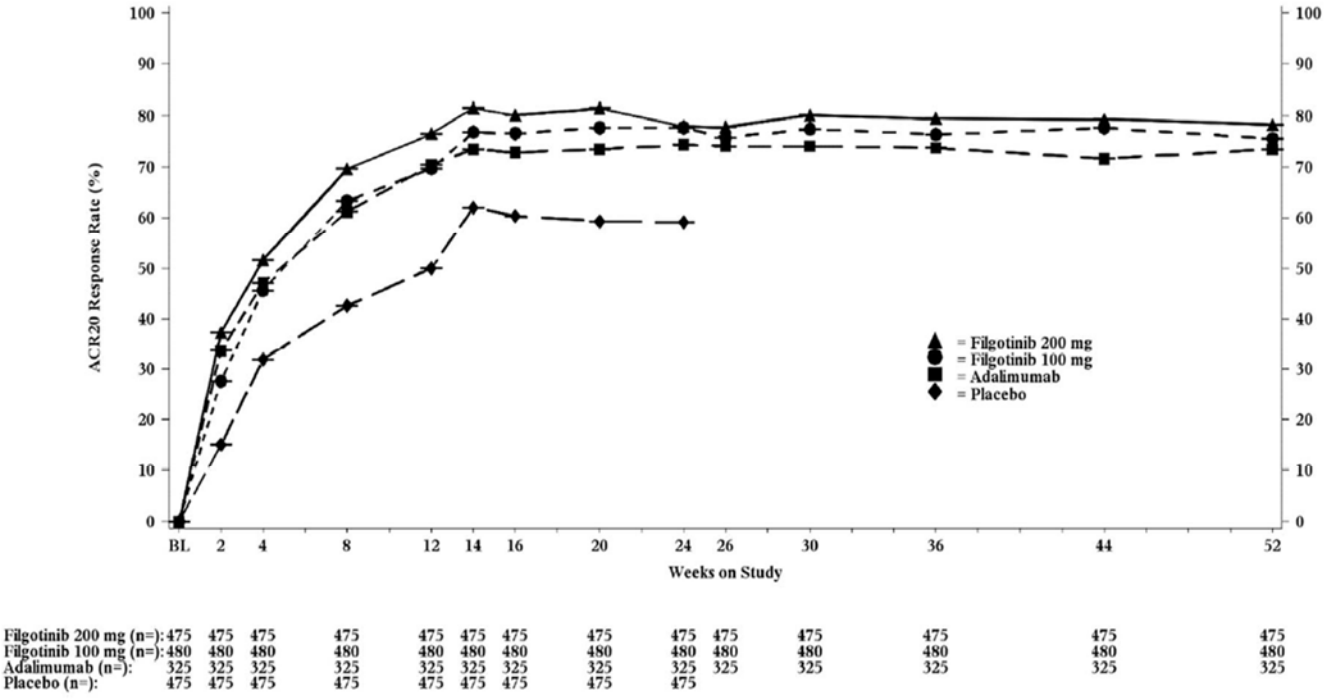
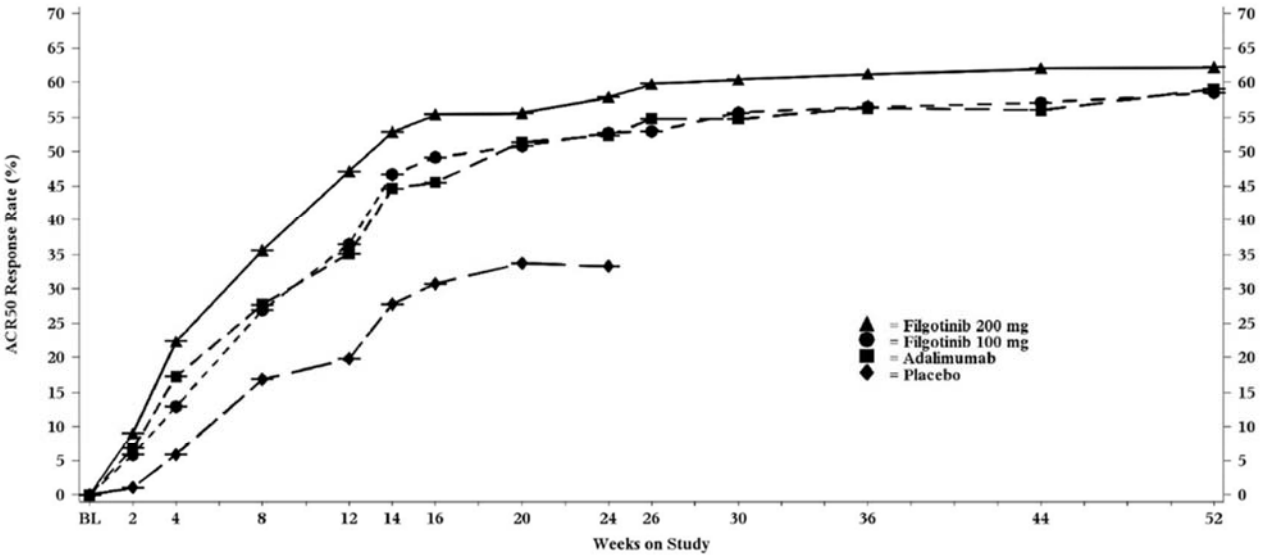
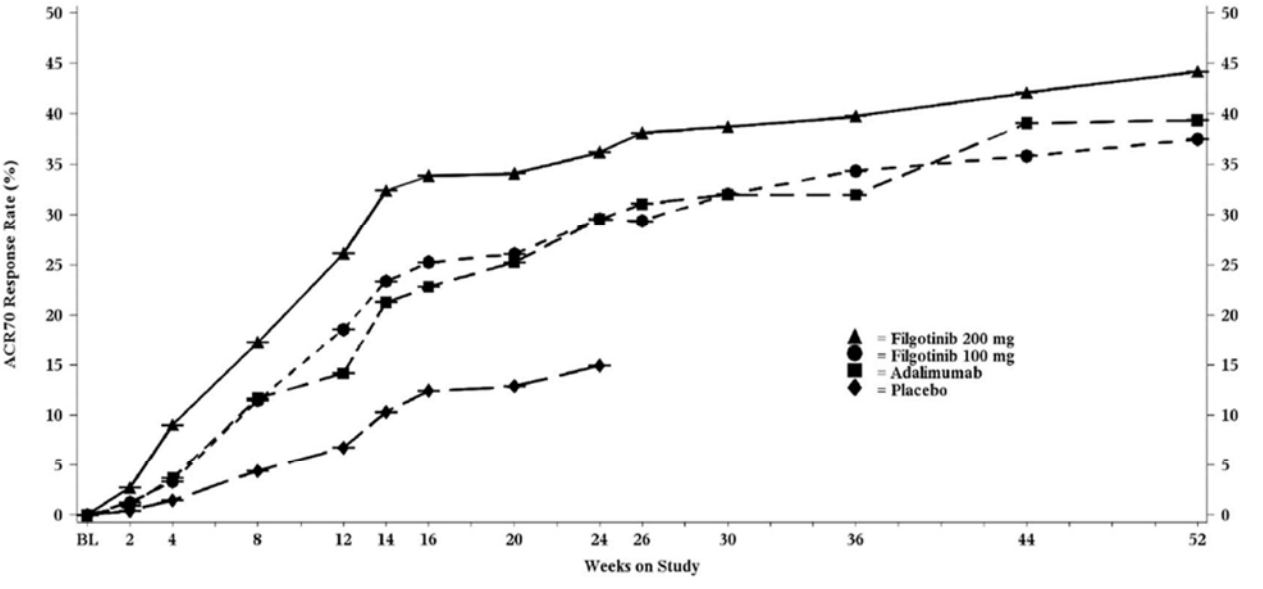


Figure 5. ACR50 response by study visit, FAS



Filgotinib 200 mg (n=):	475	475	475	475	475	475	475	475	475	475	475	475	475	475
Filgotinib 100 mg (n=):	480	480	480	480	480	480	480	480	480	480	480	480	480	480
Adalimumab (n=):	325	325	325	325	325	325	325	325	325	325	325	325	325	325
Placebo (n=):	475	475	475	475	475	475	475	475	475					

Figure 6. ACR70 response by study visit, FAS



Filgotinib 200 mg (n=):	475	475	475	475	475	475	475	475	475	475	475	475	475	475
Filgotinib 100 mg (n=):	480	480	480	480	480	480	480	480	480	480	480	480	480	480
Adalimumab (n=):	325	325	325	325	325	325	325	325	325	325	325	325	325	325
Placebo (n=):	475	475	475	475	475	475	475	475	475					

Proportion of subjects who achieved DAS28-CRP <2.6 (remission)

At week 12, the proportion of patients achieving DAS28-CRP <2.6 was statistically significantly higher in the filgotinib 200mg (34.1% [29.7%, 38.5%]) and filgotinib 100mg (23.8% [19.8%, 27.7%]) groups compared with placebo (9.3% [6.6%, 12.0%]) (p <0.001 for both). This was also demonstrated for filgotinib 200mg versus adalimumab (23.7%) (p <0.001).

Similarly, at week 24, the proportion of patients achieving DAS28-CRP <2.6 was statistically significantly higher in the filgotinib 200mg (48.4% [43.8%, 53.0%]) and in the filgotinib 100mg (35.2% [30.8%, 39.6%]) groups compared with placebo (16.2% [12.8%, 19.6%]) (p <0.001 for both). This was also demonstrated for filgotinib 200mg versus adalimumab (35.7% [30.3%, 41.1%]) (p <0.001).

Proportion of subjects who achieved DAS28-CRP ≤3.2 (LDA)

At week 12, the proportion of patients achieving DAS28-CRP ≤3.2 was statistically significantly higher in the filgotinib 200mg (49.7% [45.1%, 54.3%]) and filgotinib 100mg (38.8% [34.3%, 43.2%]) groups compared with placebo (23.4% [19.5%, 27.3%]) (p <0.001 for both). This was also demonstrated for filgotinib 200mg versus adalimumab (43.5% [37.8%, 48.9%]) (p<0.001).

Similarly, at week 24, the proportion of patients achieving DAS28-CRP ≤3.2 was statistically significantly higher in the filgotinib 200mg (60.6%) and filgotinib 100mg (53.1% [48.6%, 57.7%]) groups compared with placebo (33.7% [29.3%, 38.0%]) (p <0.001 for both). This was also demonstrated for filgotinib 200mg versus adalimumab (50.5% [44.9%, 56.1%]) (p <0.001).

EULAR response

At week 12, filgotinib 200mg (51.4%) and filgotinib 100mg (39.2%) demonstrated a higher or comparable percentage of patients achieving a good EULAR response compared with placebo (24.6%) and when compared with adalimumab (44.8%).

At week 24, filgotinib 200mg (68.4%) and filgotinib 100mg (59.7%) demonstrated a higher percentage of patients achieving a good EULAR response compared with placebo (41.8%) and when compared with adalimumab (58.0%).

Change from baseline in HAQ-DI (physical function)

At week 12, a statistically significantly greater mean change from baseline in HAQ-DI was shown in the filgotinib 200mg (−0.69 [-0.77, -0.62]) and filgotinib 100mg (−0.56 [-0.65, -0.50]) groups compared with placebo (−0.42 [-0.48, -0.33]) (p <0.001 for both). This was also demonstrated for filgotinib 200mg versus adalimumab (-0.61[-0.68, -0.52]) (p=0.018). Of note, a reduction of -0.22 is considered a minimum clinically important difference (MCID) for HAQ-DI.

At week 24, a statistically significantly greater mean change from baseline in HAQ-DI was shown in the filgotinib 200mg (−0.82 [-0.90, -0.75]) and filgotinib 100mg (−0.75[-0.82, -0.67]) groups compared with placebo (−0.62 [-0.63, -0.48]) (p <0.001 for both). Compared with adalimumab (-0.78 [-0.85, -0.68]), filgotinib 200mg showed a numerically greater improvement in HAQ-Di at week 24 (p=0.15).

Change from baseline in mTSS (radiographic progression)

At week 24, filgotinib 200mg (0.13 [-0.04, 0.31]) and filgotinib 100mg (0.17 [-0.02, 0.33]) showed significantly less radiographic progression, measured as change from baseline in mTSS, when compared with placebo (0.37 [0.22, 0.59]) (p <0.001 for both). Compared with adalimumab (0.16 [-0.01, 0.38]), filgotinib 200mg showed less radiographic progression (p=0.54).

Results of additional secondary endpoints from FINCH 1 including Quality of Life as measured by SF-36 and additional patient reported outcome measures (pain and fatigue) are presented in Table 10.

Table 10. Summary of secondary efficacy outcomes, FINCH 1

Efficacy assessment	Week	Filgotinib 200 mg + MTX (n=475)	Filgotinib 100 mg + MTX (n=480)	Adalimumab + MTX (n=325)	Placebo + MTX (n=475)
Change from baseline in HAQ-DI, mean [95%CI] (SD)	12	−0.69 ***†# [-0.77, -0.62] (0.613)	−0.56 *** [-0.65, -0.50] (0.564)	−0.61 [0.68, -0.52] (0.559)	−0.42 [-0.48, -0.33] (0.544)
	24	-0.82 (0.632)*** [-0.90, -0.75]	−0.75 (0.597)*** [-0.65, -0.50]	-0.78 (0.632) [-0.85, -0.68]	−0.62 (0.598) [-0.63, -0.48]
EULAR response %	12	51.4%	39.2%	44.8%	24.6%
	24	68.4%	59.7%	58.0%	41.8%
Proportion of patients who achieved DAS28-CRP <2.6, % [95%CI]	12	34.1***†††#a [29.7%, 38.5%]	23.8***††#a [19.8%, 27.7%]	23.7 [19.8%, 27.7%]	9.3 [6.6%, 12.0%]
	24	48.4***#†††#a [43.8%, 53.0%]	35.2***#†††#a [30.8%, 39.6%]	35.7 [30.3%, 41.1%]	16.2 [12.8%, 19.6%]
Proportion of patients who achieved DAS28-CRP ≤3.2, % [95%CI]	12	49.7***#[††††a] [45.1%, 54.3%]	38.8***# [34.3%, 43.2%]	43.4 [37.8%, 48.9%]	23.4 [19.5%, 27.3%]
Change from baseline in mTSS, mean [95%CI] (SD)	24	0.13 *** [-0.04, 0.31] (0.937)	0.17 *** [-0.02, 0.33] (0.905)	0.16 [-0.01, 0.38] (0.948)	0.37 [0.22, 0.59] (1.408)
Change from baseline in SF-36 PCS, mean [95%CI] (SD)	12	9.2 *** # [†#] [8.6, 10.8] (8.10)	8.5 ***# [8.0, 10.2] (7.72)	8.4 [7.4, 9.8] (7.89)	5.8 [4.8, 7.1] (7.10)
Change from baseline in FACIT-Fatigue score, mean [95%CI] (SD)	12	9.2 ***# [-20.0, 38.0] (9.82)	9.1 ***# [-24.0, 39.0] (10.15)	8.8 [-17.0, 33.0] (9.19)	6.8 [-20.0, 40.0] (9.89)
Change from Baseline in Subject's pain assessment mean [95%CI] (SD)	12	-31 *** [-36, -30] (26.9)	-29 *** [-34, -28] (25.3)	-27 [-33, -26] (23.6)	-21 [-24, -18] (26.0)

*P<0.05; **P<0.01; ***P<0.001; versus placebo. †P<0.05; ††P<0.01; †††P<0.001; versus adalimumab. #P value is nominal. Square brackets indicate analyses versus adalimumab. ADA=adalimumab; DAS28-CRP=Disease Activity Score based on 28 joints and C reactive protein value; FACIT=Functional Assessment of Chronic Illness Therapy; FIL=filgotinib; HAQ-DI=Health Assessment Questionnaire-Disability Index; mTSS=modified total Sharp score; MTX=methotrexate; NR=not reported; placebo=placebo; QD=once per day; SD=standard deviation; SF-36 PCS=36-item Short Form Health Survey Physical Component Summary. SOURCE: Gilead Data on File. FINCH 1 CSR. 2019 (1)

2.6.2 FINCH 2

FINCH 2 (2) met its primary endpoint, superiority of filgotinib 200mg compared to placebo as measured by the proportion of patients achieving ACR20 response at week 12 (66.0% [58.0%, 74.0%] and 31.1% [23.3%, 38.9%] ; (p<0.001)). Filgotinib 200mg and filgotinib 100mg also demonstrated statistically significantly better efficacy over placebo for several key efficacy endpoints including ACR20, ACR50 an ACR70, change from baseline in HAQ-DI (physical function), as well as proportion of

patients achieving remission and LDA as measured by DAS28-CRP <2.6 and DAS28-CRP ≤3.2 respectively. Further details are provided in the sections below.

ACR20/50/70 response

At week 12, the proportion of patients who achieved an ACR20 response was statistically significantly higher in the filgotinib 200mg (66.0% [58.0%, 74.0%]) and filgotinib 100mg (57.5% [49.4%, 65.7%]) groups compared with placebo (31.1% [23.3%, 38.9%]) (p<0.001 for both). Similarly, the proportion of patients who achieved an ACR50 response was statistically significantly higher in the filgotinib 200mg (42.9% [34.5%, 51.2%]) and filgotinib 100mg (32.0% [24.3%, 39.7%]) groups compared with placebo (14.9%); (p <0.001 for both). Finally, the proportion of patients who achieved an ACR70 response was statistically significantly higher in the filgotinib 200mg (21.8% [14.8%, 28.8%]) and filgotinib 100mg (14.4% [8.5%, 20.3%]) groups compared with placebo (6.8% [2.4%, 11.1%]); (p <0.001 and p=0.036, respectively).

At week 24, the proportion of patients achieving an ACR20 response was statistically significantly higher in the filgotinib 200mg (69.4% [61.6%, 77.2%]) and filgotinib 100mg (54.9% [46.7%, 63.1%]) groups compared with placebo (34.5% [26.5%, 42.5%]); (p <0.001 for both). Similarly, the proportion of patients who achieved an ACR50 response was statistically significantly higher in the filgotinib 200mg (45.6% [37.2%, 54.0%]) and filgotinib 100mg (35.3% [27.4%, 43.2%]) compared with placebo (18.9% [12.3%, 25.6%] of responders); (p <0.001 and p=0.002, respectively). Finally, the proportion of patients who achieved ACR 70 response was also statistically significantly higher in the filgotinib 200mg (32.0% [24.1%, 39.9%]) and filgotinib 100mg (20.3% [13.6%, 27.0%]) groups compared with placebo (8.1% [3.4%, 12.8%]); (p <0.001 and p=0.004, respectively).

An overview of the ACR20/50/70 response rates over time is presented in Figure 10, Figure 11 and Figure 12, demonstrating rapid onset of activity for filgotinib 200mg and 100mg doses.

Figure 7. ACR20 Response Rates by study visit week (NRI; Full Analysis Set)

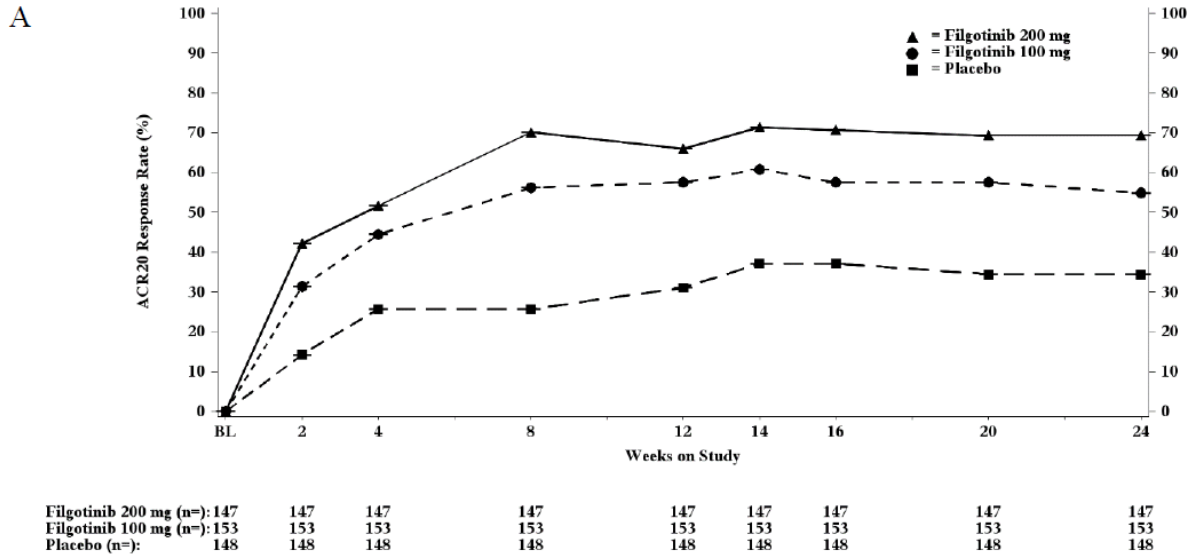


Figure 8. ACR50 Response Rates by study visit week (NRI; Full Analysis Set)

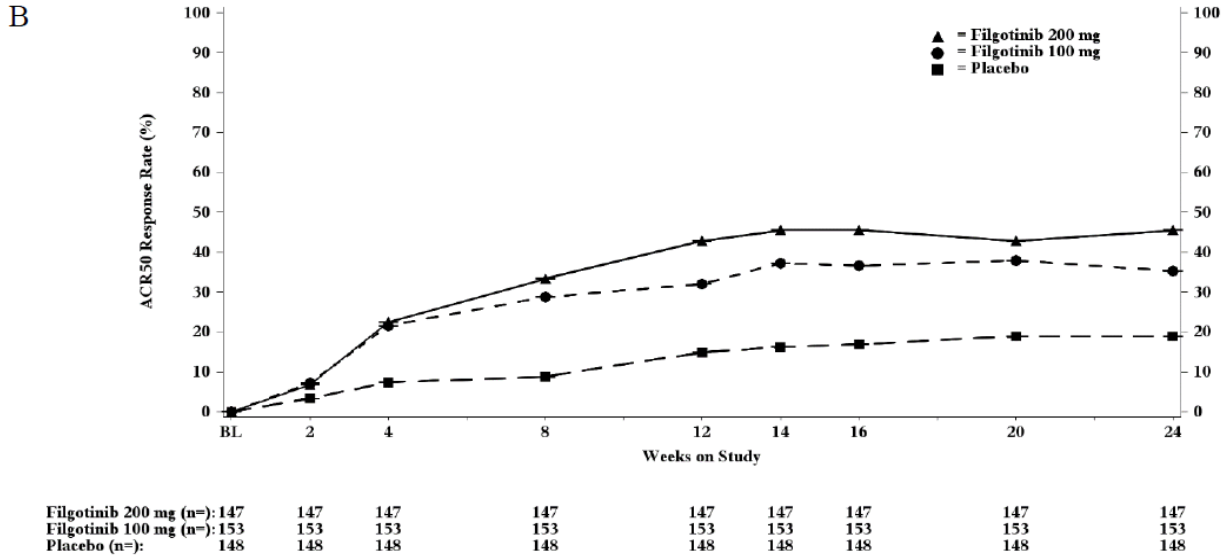
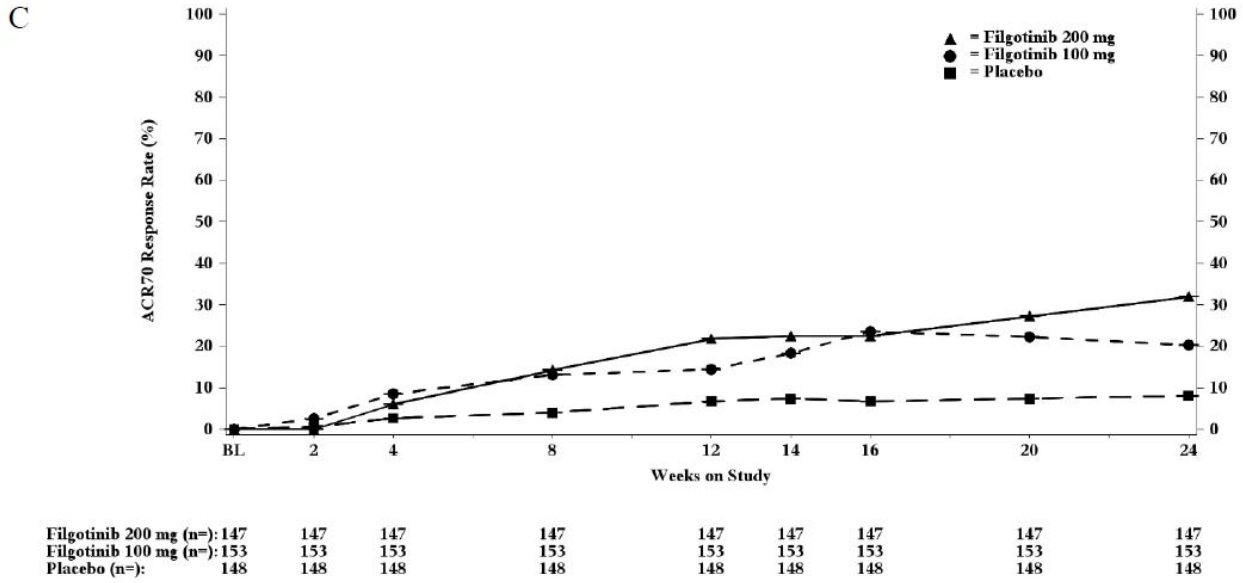


Figure 9. ACR70 Response Rates by study visit week (NRI; Full Analysis Set)



Proportion of subjects who achieved DAS28-CRP <2.6 (remission)

At week 12, the proportion of patients achieving DAS28-CRP <2.6 was statistically significantly higher in the filgotinib 200mg (24.8% [16.7%, 31.8%]) and filgotinib 100mg (28.5% [20.5%, 36.4%]) groups compared with placebo (9.4% [3.9%, 14.8%]) (p=0.001 and p <0.001, respectively).

Similarly, at week 24, the proportion of patients achieving DAS28-CRP <2.6 was statistically significantly higher in the filgotinib 200mg (30.6% [22.8%, 38.4%]) and filgotinib 100mg (26.1% [18.9%, 33.4%]) groups compared with placebo (12.2% [6.6%, 17.8%]) (p<0.001 and p=0.003, respectively).

Proportion of subjects who achieved DAS28-CRP ≤3.2 (LDA)

At week 12, the proportion of patients achieving DAS28-CRP ≤3.2 was statistically significantly higher in the filgotinib 200mg (40.8% [32.5%, 49.1%]) and filgotinib 100mg (37.3% [29.3%, 45.2%]) groups compared with placebo (15.5% [9.4%, 21.7%]) (p <0.001 for both).

Similarly, at week 24, the proportion of patients achieving DAS28-CRP ≤3.2 was statistically significantly higher in the filgotinib 200mg (48.3% [39.9%, 56.7%]) and

filgotinib 100mg (37.9% [29.9%, 45.9%]) groups compared with placebo (20.9% [14.1%, 27.8%]) (p <0.001 and p=0.001 respectively).

EULAR response

At week 12, filgotinib 200mg (42.6%) and filgotinib 100mg (40.9%) demonstrated a higher percentage of patients achieving a good EULAR response compared with placebo (18.0%).

At week 24, filgotinib 200mg (57.9%) and filgotinib 100mg (52.3%) demonstrated a higher percentage of patients achieving a good EULAR response compared with placebo (35.2%).

Change from baseline in HAQ-DI (physical function)

At week 12, a statistically significantly greater mean change from baseline in HAQ-DI was shown in the filgotinib 200mg (−0.55 [-0.61, -0.40]) and filgotinib 100mg (−0.48 [-0.56, -0.35]) groups compared with placebo (−0.23 [-0.30, -0.08]) (p <0.001 for both).

Key secondary endpoints in FINCH 2 are summarised in Table 11.

Table 11. Summary of secondary efficacy outcomes, FINCH 2

Efficacy assessment	Time point	Filgotinib QD dose groups		Placebo + cDMARDs (n=148)
		200 mg + cDMARD(s) (n=147)	100 mg + cDMARD(s) (n=153)	
Change from baseline in the HAQ-DI score (mean change, SD) (95%CI)	week 12	-0.55 (0.590) *** [-0.61, -0.40]	-0.48 (0.602) *** [-0.56, -0.35]	-0.23 (0.547) [-0.30, -0.08]
EULAR response %	week 12	42.6	40.9	18.0
	week 24	57.9	52.3	35.2
Proportion of patients who achieved DAS28-CRP ≤3.2 (%)	week 12	40.8*** [32.5%, 49.1%]	37.3*** [29.3%, 45.2%]	15.5 [9.4%, 21.7%]
	week 24	48.3*** [39.9%, 56.7%]	37.9*** [29.9%, 45.9%]	20.9 [14.1%, 27.8%]
Change from baseline in SF-36 PCS score mean change, [95%CI] (SD)	week 12	[redacted]	[redacted]	[redacted]

Proportion of patients who achieved DAS28-CRP <2.6 (%) [95%CI]	week 12	24.3*** [16.7%, 31.8%]	28.5*** [20.5%, 36.4%]	9.4 [3.9%, 14.8%]
	week 24	30.6*** [22.8%, 38.4%]	26.1** [18.9%, 33.4%]	12.2 [6.6%, 17.8%]
Change from baseline in FACIT-fatigue score (mean change, [95%CI] (SD)	week 12	[redacted]	[redacted]	[redacted]
Change from Baseline in Subject's pain assessment mean [95%CI] (SD)	week 12	[redacted]	[redacted]	[redacted]

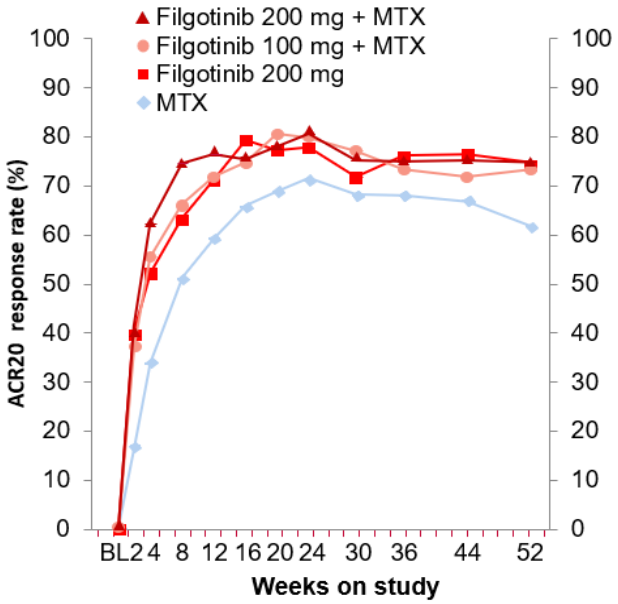
*P<0.05; **P<0.01; ***P<0.001; versus placebo.
cDMARD=conventional synthetic disease-modifying antirheumatic drug; DAS28-CRP=Disease Activity Score based on 28 joints and C reactive protein value; FACIT=Functional Assessment of Chronic Illness Therapy; HAQ-DI=Health Assessment Questionnaire-Disability Index; placebo=placebo; QD=once per day; SD=standard deviation; SF-36 PCS=36-item Short Form Health Survey Physical Component Summary. SOURCE: Gilead Data on File. FINCH 2 CSR. 2019 (2)

2.6.3 FINCH 3

FINCH 3 (3) met its primary endpoint, with study results demonstrating the superiority of filgotinib 200mg + MTX over MTX monotherapy in ACR20 response at week 24 (81.0% [77.1%, 84.9%] and 71.4% [66.9%, 75.9%] respectively) (p<0.001). ACR20 response rate at week 24 was numerically higher for filgotinib 200mg monotherapy (78.1% [72.3%, 83.9%]) as compared to MTX monotherapy (p=0.058). Filgotinib 200mg monotherapy demonstrated statistically significant improvements over MTX monotherapy for ACR50 and ACR70 responses at week 24, as well as for the proportions of patients who achieved remission measured by DAS28-CRP <2.6 (54.1% [49.2%, 59.0%] versus 29.1% [24.6%, 33.6%] for MTX monotherapy [p<0.001]), change from baseline in radiographic progression mTSS (0.21 versus 0.51 (mean−0.29 [−0.61, 0.02]) for MTX monotherapy [p=0.068]) and for the change in physical function HAQ-DI score (-0.94 [-1.06, -0.93] versus -0.79 [-1.06, -0.93] for MTX monotherapy[p<0.001]).

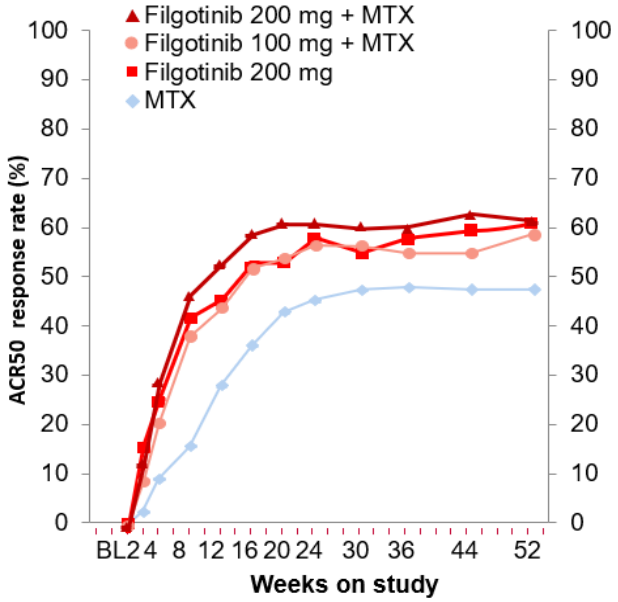
Figure 10, Figure 11 and Figure 12 show ACR20, ACR50 and ACR70 over time. These demonstrate filgotinib's rapid onset of action, as well as the maintenance response across the 52-week study period.

Figure 10. ACR20 response rates by visit through week 52, Full analysis set



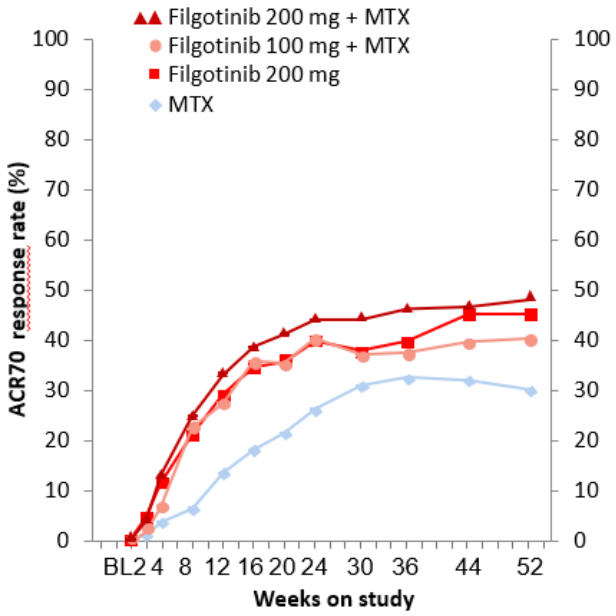
ACR, American College of Rheumatology, MTX, methotrexate

Figure 11. ACR50 response rates by visit through week 52, Full analysis set



ACR, American College of Rheumatology, MTX, methotrexate

Figure 12. ACR70 response rates by visit through week 52, Full analysis set



ACR, American College of Rheumatology, MTX, methotrexate

ACR 20/50/70 response rates for filgotinib monotherapy compared to MTX monotherapy

ACR20 response rates were higher in the filgotinib 200mg monotherapy group compared with the MTX monotherapy group at all study visits starting at week 2 through week 52, with statistically significantly higher response rates at these visits, except at weeks 24 and 30. For ACR50 response, filgotinib 200mg monotherapy (58.1% [51.2%, 65.0%]) also demonstrated superiority compared with MTX monotherapy (45.7% [40.8%, 50.6%]), (p=0.003). The superiority of filgotinib 200mg monotherapy (40.0% [33.1%, 46.9%]) compared with MTX monotherapy (26.0% [21.6%, 30.3%]); was demonstrated again for ACR70 (p<0.001).

ACR 20/50/70 response rates for filgotinib monotherapy and filgotinib combination therapy

The study was not powered to compare statistical differences across the filgotinib combination and monotherapy arms. However, a similar proportion of patients on filgotinib 200mg monotherapy (78.1% [72.3%, 83.9%]) and filgotinib 200g combination therapy (81.0% [77.1%, 84.9%]) achieved ACR20 at week 24. For ACR50, filgotinib 200mg monotherapy (58.1% [51.2%, 65.0%]) also showed a numerically comparable response to filgotinib 200mg combination therapy (61.5%

[56.7%, 66.3%]). Finally, for ACR70 at week 24, filgotinib 200mg monotherapy (40.0% [33.1%, 46.9%]) also demonstrated a numerically comparable response to filgotinib 200mg combination therapy (43.8% [38.9%, 48.6%]).

Key secondary endpoints in FINCH 3 are summarised in Table 12.

Table 12. Summary of secondary efficacy outcomes, FINCH 3

Efficacy assessment	Time point	Filgotinib 200 mg + MTX (n=416)	Filgotinib 100 mg + MTX (n=207)	Filgotinib 200 mg monotherapy (n= 210)	MTX monotherapy (n=416)
Change from baseline in HAQ-DI, mean (SD)	week 24	−0.94 *** [-1.06, -0.93] (0.722)	−0.90 (0.675) –[1.01, -0.84] **	−0.89 (0.631) *# [-0.99, -0.82]	−0.79 (0.634) [-0.86, -0.74]
EULAR response	week 24	75.7	66.8	68.9	50.5
DAS28-CRP <2.6, %	week 24	54.1*** [49.2%, 59.0%]	42.5*** [**35.5%, 49.5%]**	42.4***# [35.5%, 49.3%]	29.1 [24.6%, 33.6%]
Change from baseline in mTSS, mean (SD)	week 24	0.21 (1.682) **–** [0.14, 0.40]	0.22 (1.530) – [0.21, 0.48]	−0.04 (1.710) **# [-0.47, 0.24]	0.51 (2.892) [0.17, 0.71]
Change from baseline in SF-36, mean (SD)	week 24	12.3 ***# [11.8, 13.6] (8.89)	11.1 *# [10.2, 12.6] (9.00)	10.4 [9.5, 11.8] (9.09)	9.7 [8.9, 10.7] (8.62)
Change from baseline in FACIT-Fatigue score, mean (SD)	week 24	10.6 10.2, 12.4] (11.50)	11.4 [9.9, 12.8] (11.26)	10.2 [8.9, 11.8] (11.37)	10.1 [8.9, 11.1] (11.19)
Change from Baseline in Subject's pain assessment mean (SD	week 24	-41 *** [-45, -39] (28.0)	-37 [-41, -34] (27.8)	-39 [-42, -35] (26.1)	-34 [-37, -31] (27.6)

*P<0.05; **P<0.01; ***P<0.001; versus MTX monotherapy. #P value is nominal.
DAS28-CRP=Disease Activity Score based on 28 joints and C reactive protein value; FACIT=Functional Assessment of Chronic Illness Therapy; HAQ-DI=Health Assessment Questionnaire-Disability Index; mTSS=modified total Sharp score; MTX=methotrexate; SD=standard deviation; SF-36 PCS=36-item Short Form Health Survey Physical Component Summary.
SOURCE: Gilead Data on File. FINCH 3 CSR. 2019 (3)

B.2.7 Subgroup analysis

A post-hoc subgroup analysis of FINCH 1 was conducted for patients with moderate disease activity at baseline (as defined by DAS28 score 3.2 to 5.1 inclusive at baseline). Filgotinib was compared with the corresponding subgroup of patients receiving comparator treatments (i.e. adalimumab and placebo). This analysis was conducted only in FINCH 1 to allow separate analysis of patients with moderate disease activity with inadequate response to cDMARD and are naïve to bDMARD and JAK inhibitors in the economic model. In total, [redacted] patients [redacted] in FINCH 1 had moderate disease activity at baseline.

B.2.7.1 Baseline characteristics

Baseline characteristics for all treatment arms in the moderately active RA subgroup are presented in Table 13. Overall, the baseline characteristics of the patients in the moderate subgroup analysis are similar to the overall population, mostly female [redacted] with an average age of [redacted] years, and an average duration of RA of [redacted] years.

Table 13. Baseline characteristics for the moderate RA subgroup in the FINCH 1 trial (SAS)

Parameter	Filgotinib 200mg + MTX (n=104)	Filgotinib 100mg + MTX (n=121)	Adalimumab + MTX (n=72)	Placebo + MTX (n=128)	Total (n=425)
Age (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of RA (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
hsCRP (mg/L), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RF-positive, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 cDMARD, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥2 cDMARDs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
bDMARD-naïve, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DAS28 (CRP), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SJC66, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TJC68, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SGA (mm), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGA (mm), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain (mm), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

bDMARD, biologic disease-modifying antirheumatic drug; cDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28 (CRP), Disease Activity Score for 28 joints with C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; hsCRP, high sensitivity C-reactive protein; placebo, placebo; PGA, Physician's Global Assessment of Disease Activity; RA, rheumatoid arthritis; RF, rheumatoid factor; SAS, safety analysis set; SD, standard deviation; SGA, Subject's Global Assessment of Disease Activity; SJC66, swollen joint count based on 66 joints; TJC66, tender joint count based on 68 joints.

B.2.7.2 Moderate subpopulation – Efficacy results

The results of the analyses for the moderate subpopulation are presented in the sections below. For a range of endpoints, the subgroup analyses demonstrated that results for the overall moderately to severely active population, and the moderate sub-population were comparable.

ACR20/50/70 at week 12

At week 12, results showed that for filgotinib 200mg, a statistically significantly higher proportion of patients achieved ACR20 response compared with patients receiving placebo in the moderate subgroup ([redacted]) and a numerically higher proportion of patients than for adalimumab ([redacted]). Additionally, for filgotinib 100mg, a statistically significantly higher proportion of patients achieved ACR20 response compared with placebo ([redacted]) and a numerically higher proportion of patients than for adalimumab ([redacted] versus [redacted]). Full results, including ACR50 and ACR70 at week 24 are shown in Figure 14 below.

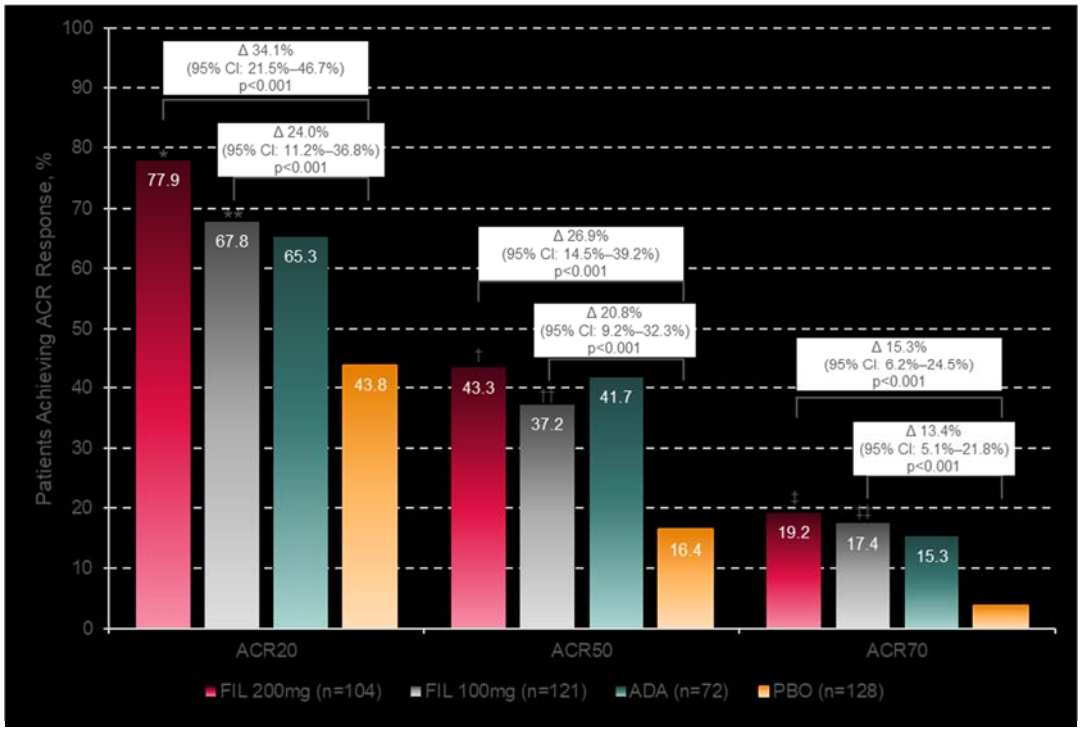
At week 12, results showed that for both filgotinib 200mg and filgotinib 100mg, a statistically significantly higher proportion of patients achieved ACR50 response compared with patients receiving placebo in the moderate subgroup ([redacted] for both). In the comparison with adalimumab, a numerically comparable proportion of patients achieved ACR50 response, for both filgotinib 200mg ([redacted]), and filgotinib 100mg ([redacted]).

At week 12, results showed that for both filgotinib 200mg and filgotinib 100mg, a statistically significantly higher proportion of patients achieved ACR70 response compared with patients receiving placebo in the moderate subgroup ([redacted]). In the comparison with adalimumab, a numerically comparable proportion of patients achieved ACR70 response, for both filgotinib 200mg and filgotinib 100mg ([redacted]

[redacted]).

When compared with the overall moderately to severely active population in FINCH 1, at week 12, filgotinib 200mg showed comparable ACR20, 50 and 70 response rates in the moderate subgroup ([redacted] respectively), indicating that filgotinib is similarly effective in both populations.

Figure 13 ACR20, ACR50 and ACR70 responses at week 12 – Moderate disease activity subgroup



ACR20/50/70 at week 24

At week 24, results showed that for filgotinib 200mg, a statistically significantly higher proportion of patients achieved ACR20 response compared with patients receiving placebo in the moderate subgroup ([redacted]) and a numerically higher proportion of patients than for adalimumab ([redacted]). Additionally, for

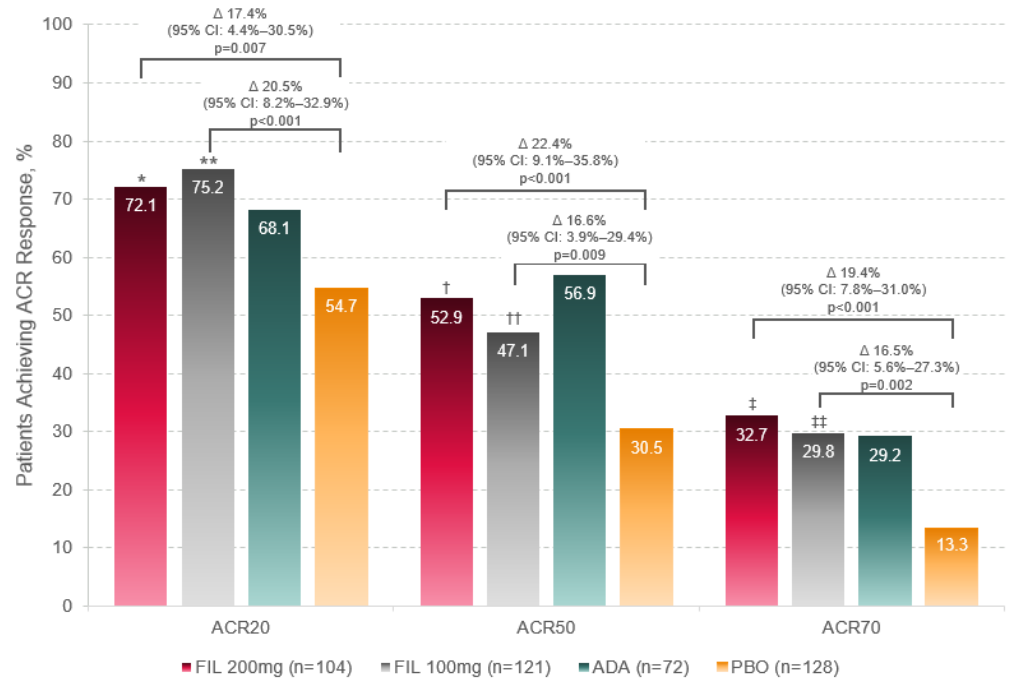
filgotinib 100mg, a statistically significantly higher proportion of patients achieved ACR20 response compared with placebo ([redacted]) and a numerically higher proportion of patients than for adalimumab ([redacted]versus [redacted]). Full results, including ACR50 and ACR70 at week 24 are shown in Figure 14 below.

At week 24, results showed that for both filgotinib 200mg and filgotinib 100mg, a statistically significantly higher proportion of patients achieved ACR50 response compared with patients receiving placebo in the moderate subgroup ([redacted]). In the comparison with adalimumab, a numerically comparable proportion of patients achieved ACR50 response, for both filgotinib 200mg ([redacted]), and filgotinib 100mg ([redacted]).

At week 24, results showed that for both filgotinib 200mg and filgotinib 100mg, a statistically significantly higher proportion of patients achieved ACR70 response compared with patients receiving placebo in the moderate subgroup ([redacted]). In the comparison with adalimumab, a numerically comparable proportion of patients achieved ACR70 response, for both filgotinib 200mg and filgotinib 100mg ([redacted]).

When compared with the overall moderately to severely active population in FINCH 1, at week 24, filgotinib 200mg showed comparable ACR20, 50 and 70 response rates in the moderate subgroup ([redacted]respectively), indicating that filgotinib is similarly effective in both populations.

Figure 14. ACR20, ACR50 and ACR70 at week 24 – Moderate disease activity subgroup



ADA, adalimumab; CI, confidence interval; FIL, filgotinib; PBO, placebo

* p=0.62 vs ADA; ** p=0.32 vs ADA; † p=0.65 vs ADA; †† p=0.23 vs ADA; ‡ p=0.74 vs ADA; ‡‡ p=1.00 vs ADA

ACR20/50/70 at week 52

At week 52, results showed that for both filgotinib 200mg and filgotinib 100mg, a numerically comparable proportion of patients achieved ACR20 response compared with patients receiving adalimumab in the moderate subgroup ([redacted]). For filgotinib 200mg and filgotinib 100mg, a numerically comparable proportion of patients also achieved ACR50 compared with adalimumab ([redacted]), and ACR70 compared with adalimumab ([redacted]).

When compared with the overall moderately to severely active RA population in FINCH1, at week 52, filgotinib 200mg showed comparable ACR20, 50 and 70 response rates in the moderate subgroup ([redacted]

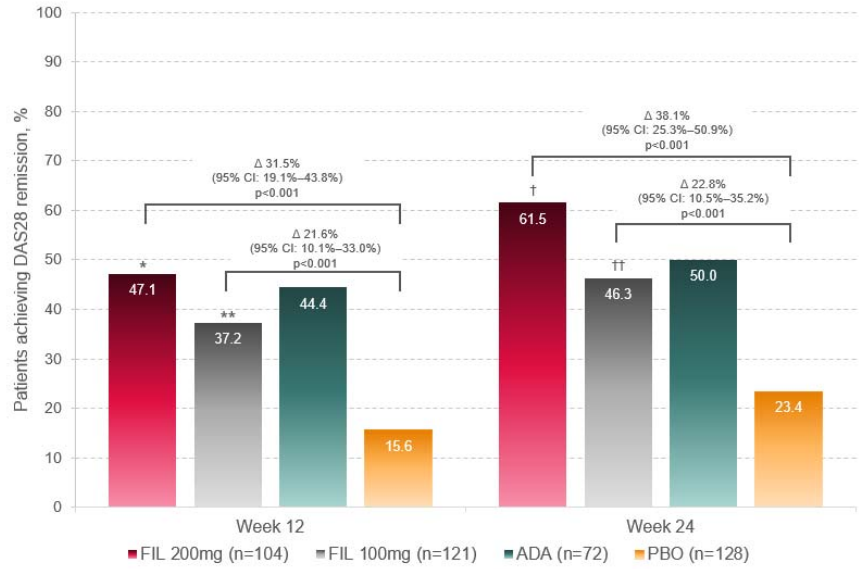
[redacted]), indicating that filgotinib is similarly effective in both populations.

DAS28 (CRP) <2.6 (remission) at week 12 and 24

The results of the moderate subgroup analysis for clinical remission (defined by a DAS28-CRP <2.6) at week 24 showed that for filgotinib 200mg, a [redacted] of patients achieved remission versus placebo ([redacted]) and a numerically higher proportion of patients achieved remission versus adalimumab ([redacted]). The results for patients achieving a DAS28-CRP <2.6 at both 12 and 24 weeks are presented in Figure 15 below.

When compared with the overall moderately to severely active RA population, a [redacted] of moderate filgotinib 200mg subgroup patients achieved DAS28 (CRP) <2.6 response at week 24 than in the total population ([redacted] See section 2.6.1 for full details.

Figure 15. DAS28 (CRP) <2.6 at weeks 12 & 24 – Moderate disease activity subgroup



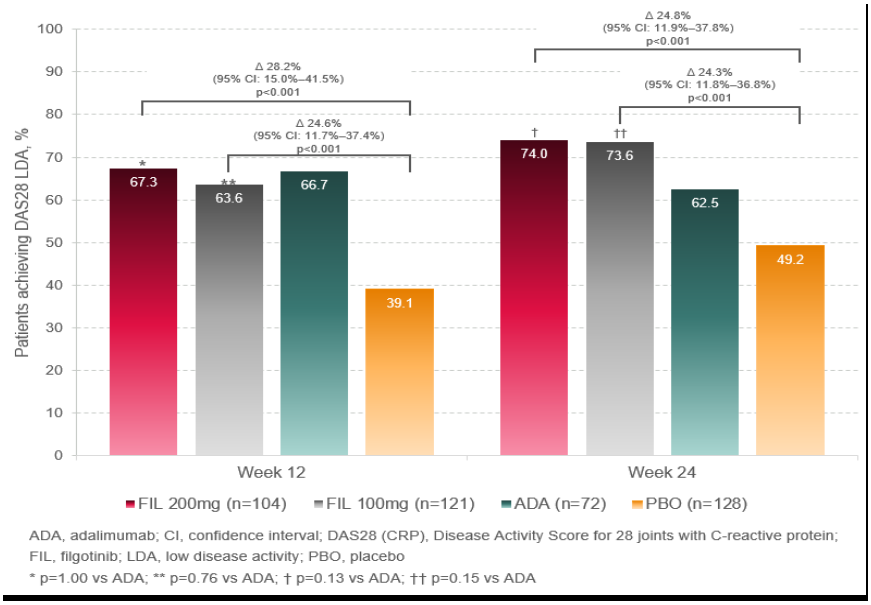
ADA, adalimumab; CI, confidence interval; DAS28 (CRP), Disease Activity Score for 28 joints with C-reactive protein; FIL, filgotinib; PBO, placebo

* p=0.76 vs ADA; ** p=0.36 vs ADA; † p=0.16 vs ADA; †† p=0.66 vs ADA

DAS28 (CRP) ≤3.2 (LDA) at week 12 and 24

For the secondary outcome, low disease activity (LDA), as defined by DAS28-CRP ≤3.2, for filgotinib 200mg, a [redacted] in the moderate subgroup ([redacted]) and [redacted] of patients achieved LDA versus adalimumab ([redacted]) at 24 weeks. Detailed results for both filgotinib 200mg and 100mg at week 12 and 24 are shown in Figure 16 below.

Figure 16. DAS28 (CRP) ≤3.2 at weeks 12 & 24 – moderate disease activity subgroup



ADA, adalimumab; CI, confidence interval; DAS28 (CRP), Disease Activity Score for 28 joints with C-reactive protein; FIL, filgotinib; LDA, low disease activity; PBO, placebo

* p=1.00 vs ADA; ** p=0.76 vs ADA; † p=0.13 vs ADA; †† p=0.15 vs ADA

EULAR at week 24

For the secondary outcome, EULAR response at week 24, filgotinib 200mg demonstrated a [redacted] in the moderate subgroup ([redacted]) and when compared with adalimumab [redacted] at week 24.

When compared with the overall moderately to severely active RA population included in FINCH 1, a [redacted] of moderate filgotinib 200mg subgroup patients achieved a good EULAR response than in the overall population ([redacted]) at week 24. Detailed EULAR response results at 24 weeks are shown in Table 14 below.

Table 14. EULAR responses at week 24 – moderate disease activity subgroup

Parameter	Filgotinib 200mg (n=104)	Filgotinib 100mg (n=121)	Adalimumab (n=72)	Placebo (n=128)
Week 24, n	[redacted]	[redacted]	[redacted]	[redacted]
Good response	[redacted]	[redacted]	[redacted]	[redacted]
Moderate response	[redacted]	[redacted]	[redacted]	[redacted]
No response	[redacted]	[redacted]	[redacted]	[redacted]

Overall, the efficacy results for the moderate subgroup are comparable to the results of the overall FINCH 1 population presented in B2.6. Sub-population results for patients in FINCH 1 with severely active RA are presented in Appendix E.

B.2.8 Meta-analysis

In order to compare the efficacy of filgotinib to the comparators specified in the NICE scope, a network meta-analysis (NMA) was conducted. Whilst a meta-analysis of RCT's was theoretically feasible, performing a comprehensive NMA allows for a more precise estimation of relative treatment effects, therefore no meta-analysis was performed. Please see section B.2.9 below for details on the NMA.

B.2.9 Indirect and mixed treatment comparisons

A network-meta analysis (NMA) was performed to inform the economic model for the assessment of the cost-effectiveness of filgotinib relative to the other treatments in RA. Studies for this were identified from a systematic literature review using criteria in line with previous NICE appraisals in RA (TA466 (1), TA485 (2) and MTA375 (3), with the final set of studies included in the NMA selected in line with previous NICE appraisals (see Appendix D for full details). In line with the NICE scope, separate NMAs were conducted in the cDMARD-IR and bDMARD-IR populations, with ACR at week 12 and 24, and EULAR at 24 weeks the primary outcomes considered. As the FINCH 1 (cDMARD-IR) and FINCH 2 (bDMARD-IR) trials did not include filgotinib monotherapy arms, an NMA for monotherapy was not feasible. Additionally, studies in RA do not frequently stratify results by moderate and severe disease, rather reporting results across moderate to severe RA. Therefore, separate NMAs for moderate and severe RA were also not feasible.

B.2.9.1 Search strategy

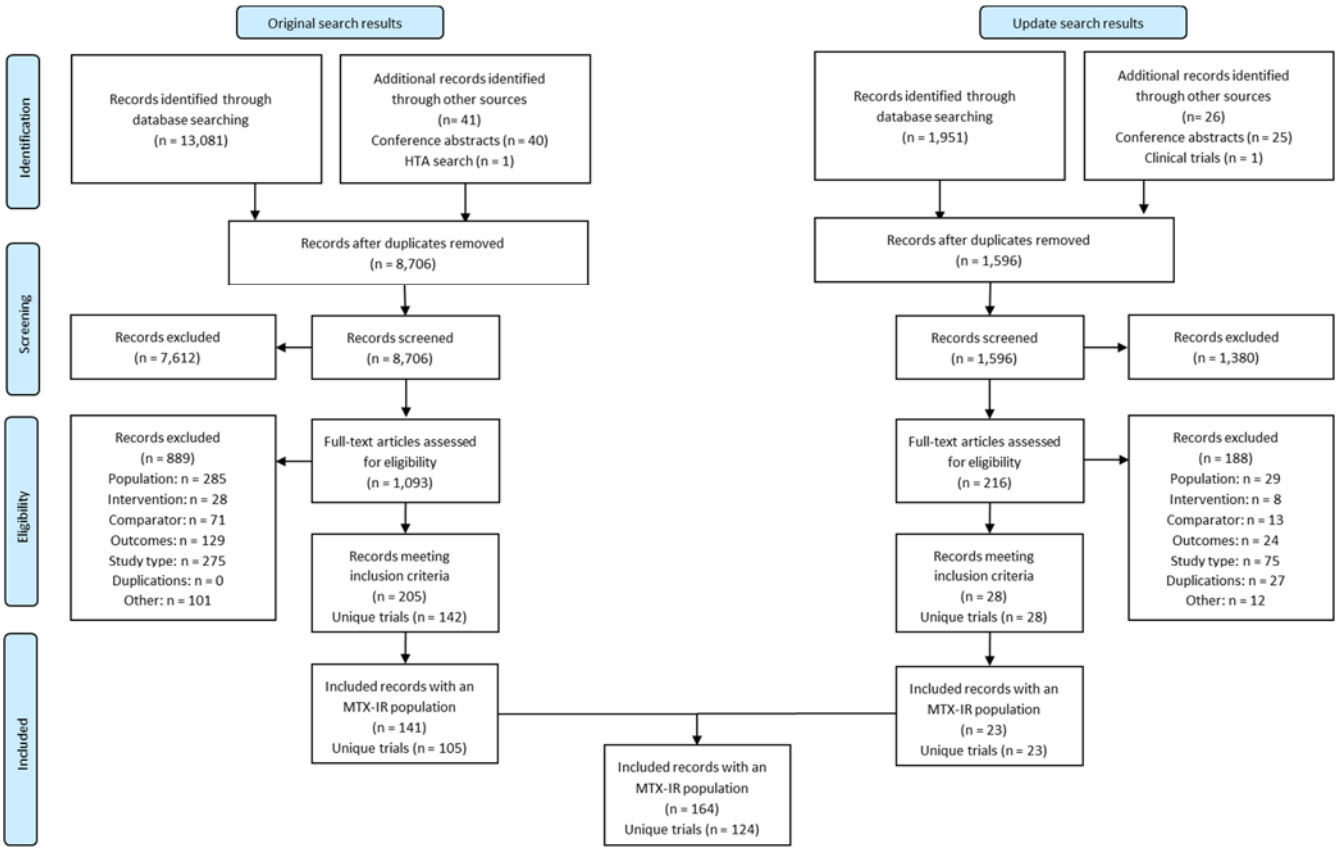
Two systematic literature reviews (SLRs) were conducted, one in the cDMARD-IR population and one in the bDMARD-IR population, across the following databases; MEDLINE, Embase and the Cochrane library (please see Appendix D). The objectives of the SLRs were to identify relevant clinical data from the published literature regarding the clinical effectiveness of filgotinib and other treatments for RA based on the clinical outcomes outlined by the NICE scope. The original review was conducted in August of 2018 with a subsequent update in September 2019. Note that while the SLR considered safety outcomes, safety outcomes frequently focused on the most commonly reported AEs and data for specific AEs tend not be reported consistently across studies, therefore an NMA for safety was not performed.

Studies identified in the SLR were independently assessed by one reviewer in order to ascertain whether they met the pre-defined inclusion and exclusion criteria for the review based on the population, intervention, comparator, outcomes and study design (PICOS). The PICOS criteria was designed to align with the following NICE appraisals: TA466 (1), TA485 (2) and MTA375 (3), and is detailed in Appendix D.

B2.9.2 Trials included in the SLR: cDMARD-IR

Overall, a total of 124 unique studies were eligible for inclusion across the original review and subsequent update (conducted on the 18th September 2019) for cDMARD-IR patients. A PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) diagram (Figure 17) shows the overall flow of studies across the original review and update.

Figure 17. PRISMA flow diagram for the clinical SLR for the cDMARD-IR population

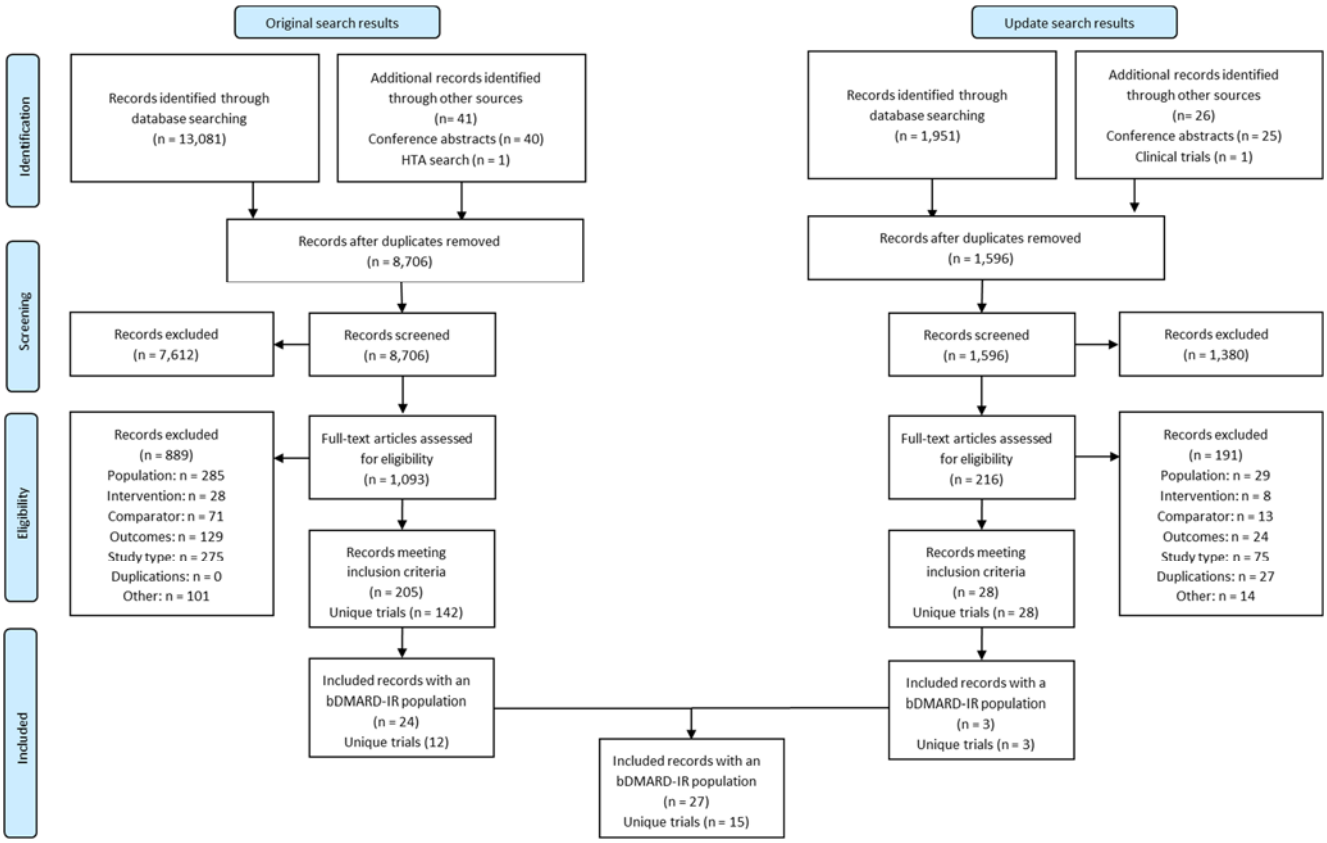


B2.9.3 Trials included in the SLR: bDMARD-IR

In total, 27 publications representing 15 unique trials were identified by the SLR, as presented in the PRISMA diagram in

Figure 18.

Figure 18. PRISMA flow diagram for the clinical SLR for the bDMARD-IR population



B2.9.4 Studies selected for the NMA

To further refine the results of the SLR to more closely meet the requirements of the decision problem and produce relevant networks, several studies from each SLR were excluded in the NMA. The list of studies excluded from each NMA along with associated reasons are available in Appendix D.

The final number of studies included in each NMA are shown below:

- **cDMARD-IR population:** A total of 50 unique trials from the 124 unique trials identified in the SLR were included, with 73 studies excluded.
- **bDMARD-IR population:** A total of 10 unique trials in the final networks from the 15 identified in the SLR were included, with 5 studies excluded.

A summary of the studies included in the evidence networks for each outcome in the cDMARD-IR population is presented in Table 15 and for the bDMARD-IR population

in Table 16 below. The list of studies excluded from the NMA along with the reasons for exclusions can be found in Appendix D.

Table 15: Summary of studies included for each NMA outcome - cDMARD-IR

Trial	Treatment	ACR 12-week inclusion	ACR 24-week inclusion	EULAR 24-week inclusion
Abe et al. (1)	IFX (3mg/kg) +cDMARDs	✓	×	×
	cDMARDs	✓	×	×
AIM (2)	ABT (10mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
ATTEST, (NCT00095147) (3)	ABT	×	✓	×
	IFX (3mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
Baek et al. (4)	TCZ (8mg/kg)	×	✓	✓
	cDMARDs	×	✓	✓
Beals et al. (5)	IFX (3mg/kg) +cDMARDs	✓	×	×
	cDMARDs	✓	×	×
Chen et al. (6)	ADA (40mg/kg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
Cohen et al. (7)	ANK (100mg) +cDMARDs	×	✓	×
	cDMARDs	×	✓	×
DANCER (8) (9)	RTX (1000mg)	×	✓	✓
	cDMARDs	×	✓	✓
DARWIN 1 (10)	FIL (100mg) + cDMARDs	✓	×	×
	FIL (200mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
Etanercept 309 (11)	ETN + intensive cDMARDs	×	✓	×
	cDMARDs	×	✓	×
EXXELERATE (12)	CZP + cDMARDs	✓	×	×
	ADA (40mg/kg) + cDMARDs	✓	×	×
FINCH 1	FIL (100mg)/ (200mg) + cDMARDs	✓	✓	✓

Trial	Treatment	ACR 12-week inclusion	ACR 24-week inclusion	EULAR 24-week inclusion
	ADA + cDMARDs	✓	✓	✓
	cDMARDs	✓	✓	✓
GOFURTHER (13-15)	GLM (2mg/kg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
J-RAPID (NCT00791999) (16)	CZP (400mg) + cDMARDs	✓	×	✓
	CZP (200mg) + cDMARDs	✓	×	✓
	cDMARDs	✓	×	✓
KAKEHASI (17, 18)	SARI (200mg) +cDMARDs	✓	✓	×
	SARI (150mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×
Keystone et al. (19)	ADA (40mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
Kim et al. (20)	ADA (40mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
Kremer et al. (21)	Intensive cDMARDs	×	✓	×
	cDMARDs	×	✓	×
Lim et al. (22)	TCZ (8mg/kg)	×	✓	✓
	cDMARDs	×	✓	✓
MOBILITY (23-25)	SARI (150mg) + cDMARDs	×	✓	×
	SARI (200mg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
NCT00345748 (26)	ABT (10mg/kg) + cDMARDs	×	✓	×
	ABT (2mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
NCT00405275 (27)	ETN (50mg) + HCQ (400mg)	×	✓	×
	SSZ (1-2mg) + HCQ (400mg)	×	✓	×

Trial	Treatment	ACR 12-week inclusion	ACR 24-week inclusion	EULAR 24-week inclusion
NCT00413660	TOF (5mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
NCT00544154 (28)	CZP (400mg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
NCT00603512 (29)	TOF (5mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
NCT00993317 (30)	CZP (200mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×
I4V-MC-JADA (NCT01185353) (31)	BARI (4mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
NCT01313208 (32)	ETN (50mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
NCT01554696 (33)	PFT (25, 50, 100, 150mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
NCT01710358 (34, 35)	BARI (4mg) + cDMARDs	✓	✓	×
	ADA (40mg/kg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×
NCT01758198 (36)	ABT (10mg/kg) +cDMARDs	×	✓	×
	cDMARDs	×	✓	×
NCT02557100	ADA (40mg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
OPTION (37)	TCZ (8mg/kg) + cDMARDs	×	✓	✓
	TCZ (4mg/kg) + cDMARDs	×	✓	✓
	cDMARDs	×	✓	✓
RA-BUILD (38)	BARI (4mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×

Trial	Treatment	ACR 12-week inclusion	ACR 24-week inclusion	EULAR 24-week inclusion
RA0025 (39)	CZP + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
RA-BALANCE (40)	BARI (4mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
RAJ3 (41)	PFT (50mg) + cDMARDs	✓	×	×
	PFT (100mg) + cDMARDs	✓	×	×
	PFT (150mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
RAJ4 (41)	PFT (100mg) + cDMARDs	✓	×	×
	PFT (150mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
RAPID 1 (42)	CZP (400mg) + cDMARDs	×	✓	×
	CZP + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
RAPID 2, (NCT00175877) (43)	CZP (400mg) + cDMARDs	×	✓	×
	CZP + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
RA-SCORE(44)	RTX (1000mg) + cDMARDs	×	✓	✓
	cDMARDs	×	✓	✓
SARIL-RA-MOBILITY (45)	SARI (150mg) q2w / qw + cDMARDs	✓	×	×
	SARI (200mg) qw + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
SELECT-COMPARE (46)	UPA (15mg) + cDMARDs	✓	✓	×
	ADA (40mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×
SELECT-NEXT(47, 48)	UPA (15mg) +cDMARDs	✓	×	×

Trial	Treatment	ACR 12-week inclusion	ACR 24-week inclusion	EULAR 24-week inclusion
	cDMARDs	✓	×	×
SELECT-SUNRISE	UPA (15mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
SERENE (49)	RTX (1000mg) + cDMARDs	×	✓	✓
	cDMARDs	×	✓	✓
Smolen et al.	UPA (15mg) +cDMARDs	✓	×	×
	UPA (30mg) +cDMARDs	✓	×	×
	cDMARDs	✓	×	
Tanaka et al.(50)	BARI (4mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
TOWARD (51)	TCZ (8mg/kg)	×	✓	✓
	cDMARDs	×	✓	✓
Weinblatt et al. (52)	ETN (25mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×

ABT, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; ANK, anakinra; BARI, baricitinib; CRP, C-reactive protein; cDMARDs, conventional synthetic disease modifying anti-rheumatic drug, CZP, certolizumab pegol; DAS28, disease activity score; ETN, etanercept; EULAR, European League Against Rheumatism; FIL, filgotinib; GLM, golimumab; IFX, infliximab; PFT, peficitinib; qw, weekly; q2w, biweekly; RTX, rituximab; SAR, sarilumab; TCZ, tocilizumab; TOF, tofacitinib; tsDMARD, targeted synthetic disease modifying anti-rheumatic drug; UPA, upadacitinib.

Table 16: Summary of studies included for each NMA outcome – bDMARD-IR

Trial	Treatment	ACR 12-week inclusion	ACR 24-week inclusion	EULAR 24-week inclusion
ATTAIN (53)	ABT (10mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
BREVACTA (54)	TCZ (162mg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
FINCH 2 (55)	FIL (100mg) + cDMARDs	✓	✓	✓
	FIL (200mg) + cDMARDs	✓	✓	✓

	cDMARDs	✓	✓	✓
NCT01147341 (56)	CZP (400mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
ORAL-STEP	TOF (5mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
RA-BEACON (57, 58) (59)	BARI (4mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×
RADIATE (60)	TCZ (8mg/kg) + cDMARDs	×	✓	✓
	TCZ (4mg/kg) + cDMARDs	×	✓	✓
	cDMARDs	×	✓	✓
REFLEX (61, 62)	RTX (1000mg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
SELECT-BEYOND (63)	UPA (15mg) + cDMARDs	✓	×	×
	UPA (30mg) + cDMARDs	×	×	×
	cDMARDs	✓	×	×
TARGET (64)	SARI (150mg) + cDMARDs	✓	✓	×
	SARI (200mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×

ADA, adalimumab; BARI, baricitinib; cDMARD, conventional synthetic disease modifying anti-rheumatic drug; CZP, certolizumab pegol; ETN, etanercept; FIL, filgotinib; GLM, golimumab; IFX, infliximab; RTX, rituximab; SARI, sarilumab; TOF, tofacitinib; UPA, upadacitinib

B2.9.5 Evidence networks

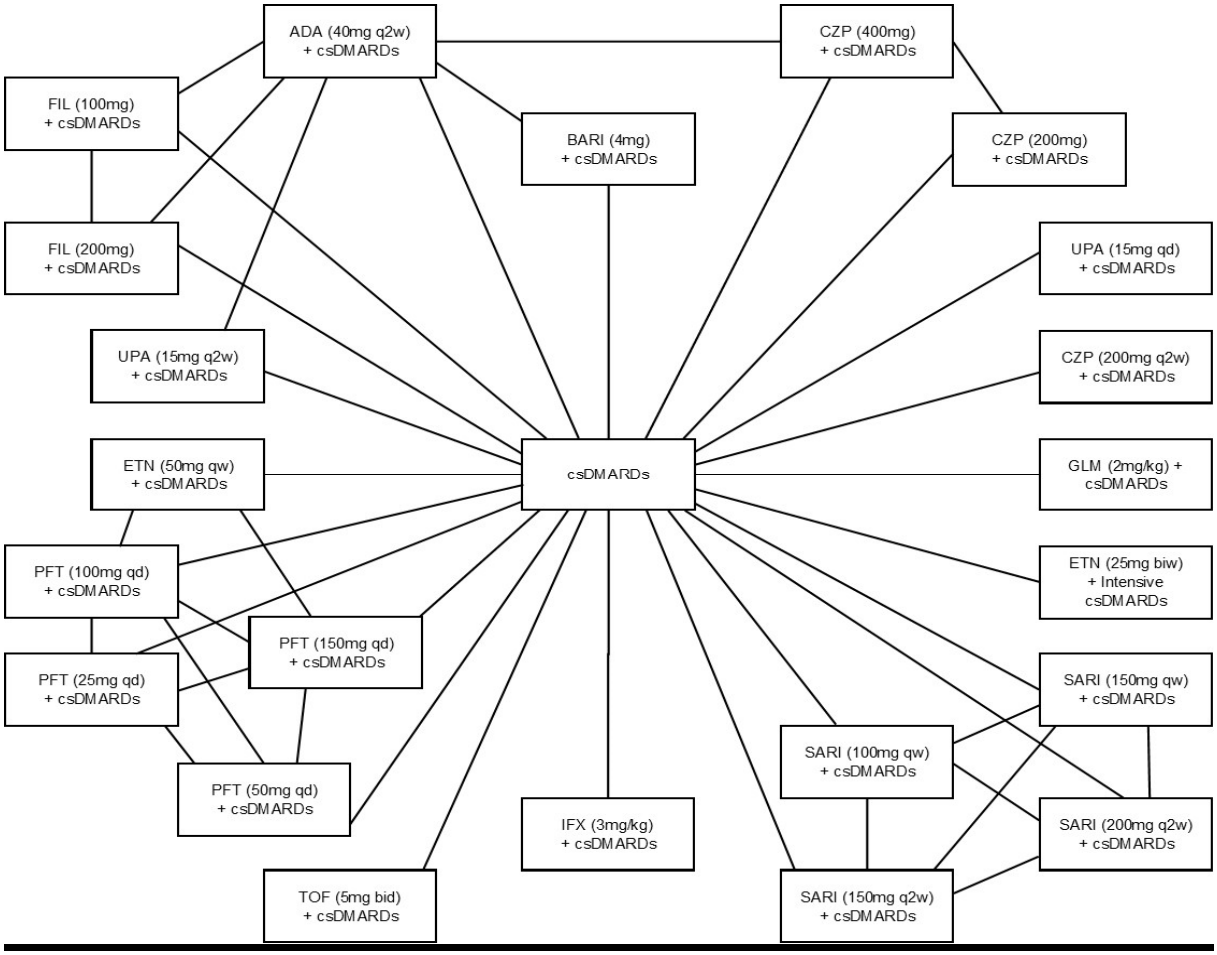
Evidence networks for each outcome for the cDMARD-IR and bDMARD-IR populations are presented in the section below.

Both bDMARDs and cDMARDs may be administered as monotherapy or in combination with cDMARDs. As the only evidence available for filgotinib in the FINCH 1 and FINCH 2 studies was in combination with cDMARDs, only combination therapies were included in the NMA.

cDMARD-IR

The evidence network for ACR at weeks 12 and 24 are presented in Figure 19 and Figure 20 below. The analysis network for ACR at week 12 comprised 23 treatments across 27 studies, which were connected via the common comparator of cDMARDs.

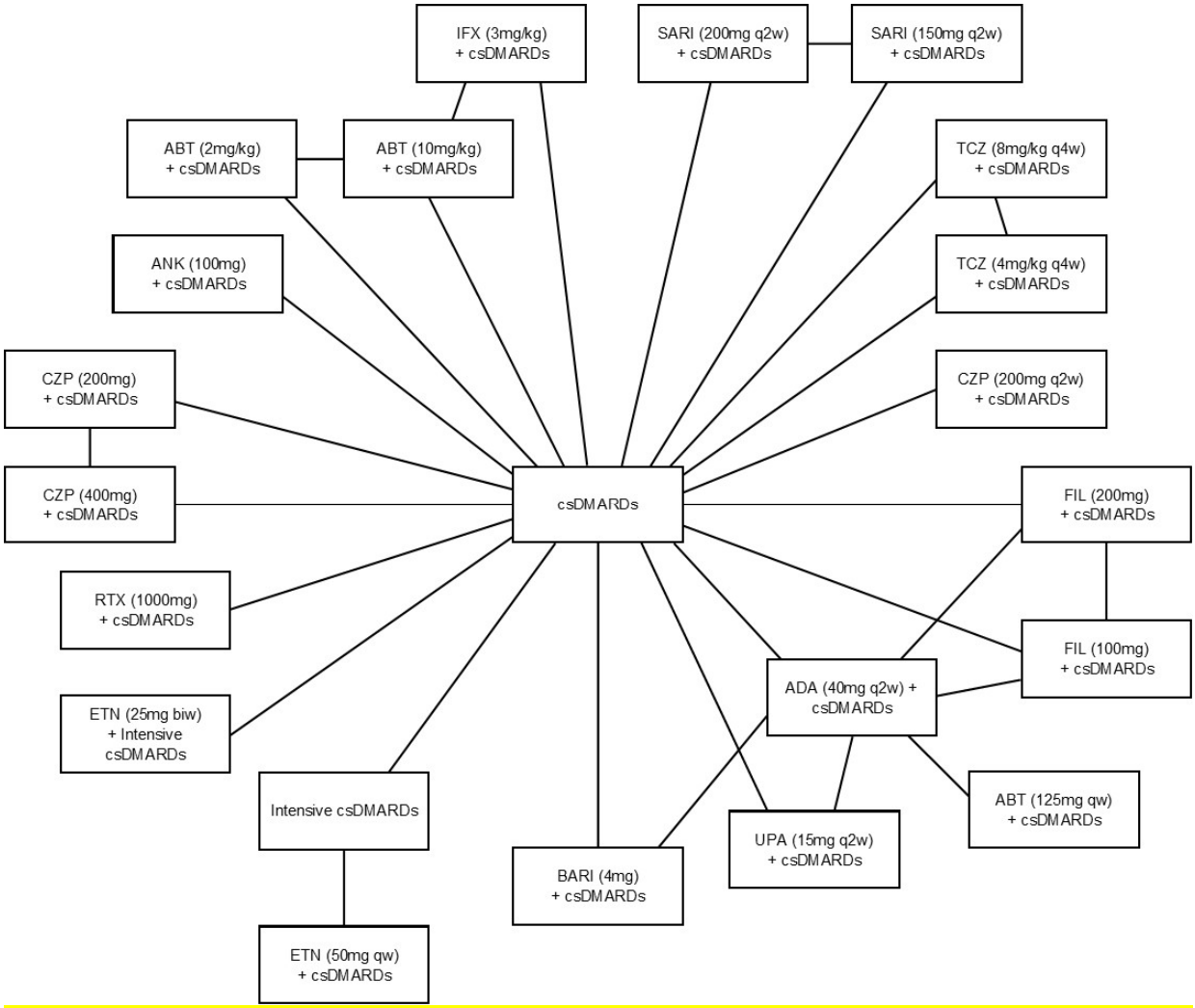
Figure 19. ACR at week 12 network geometry for the cDMARD-IR population



ADA, adalimumab; BARI, baricitinib; bid, twice daily; biw, twice weekly; cDMARD, conventional disease modifying anti-rheumatic drug; CZP, certolizumab pegol; ETN, etanercept; FIL, filgotinib; GLM, golimumab; IFX, infliximab; PFT, peficitinib; qd, every day; qw, once weekly; q2w, once every two weeks; SARI, sarilumab; UPA, upadacitinib;

The analysis network for the ACR at week 24 endpoint consisted of 22 treatments across 30 studies, which were connected via the common comparator of cDMARDs.

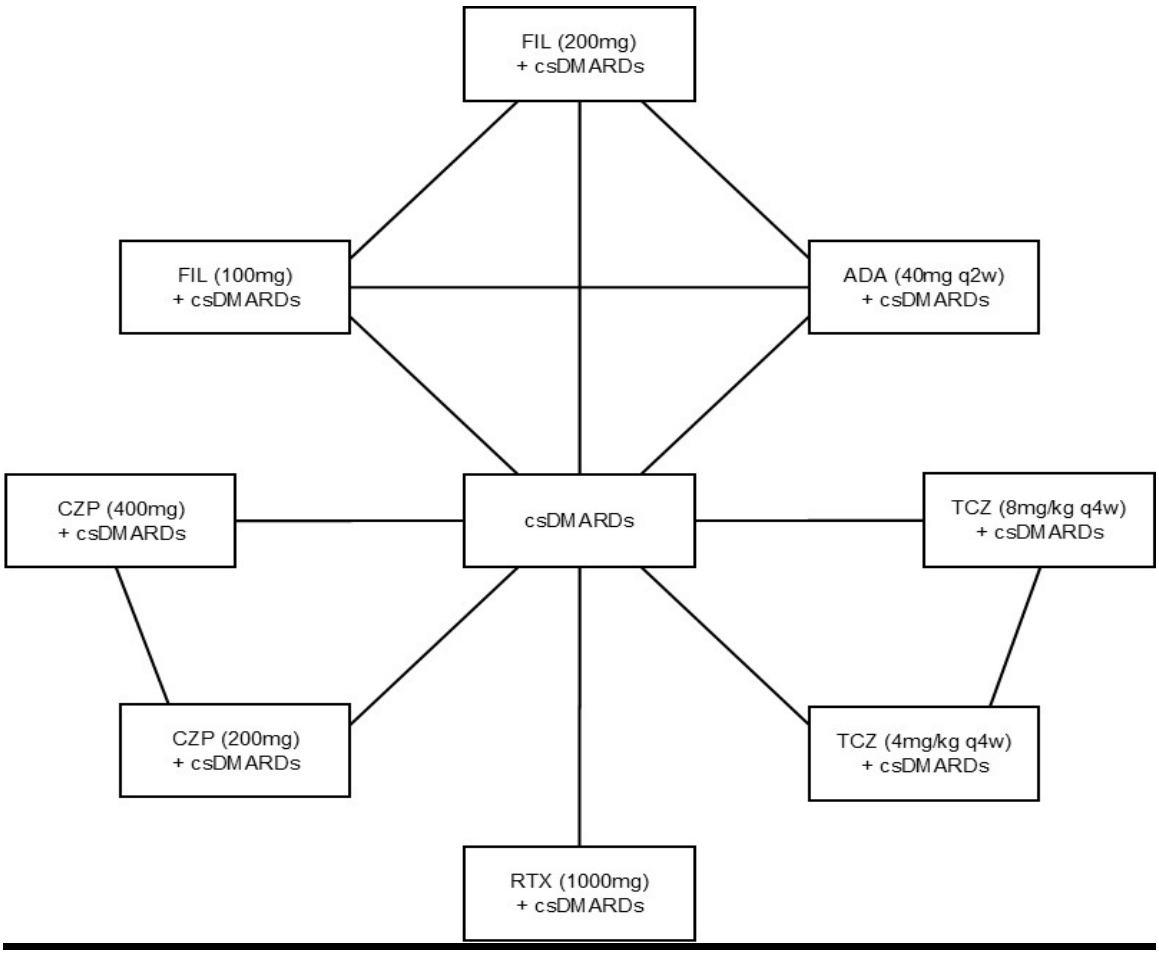
Figure 20. ACR at week 24 network geometry for the cDMARD-IR population



ABT, abatacept; ADA, adalimumab; ANK, anakinra; BARI, baricitinib; biw, twice weekly; cDMARDs, conventional disease modifying anti-rheumatic drug ; CZP, certolizumab pegol; ETN, etanercept; FIL, filgotinib; IFX, infliximab; qw, once weekly; q2w, every two weeks; q4w, every 4 weeks; RTX, rituximab; SARI, sarilumab; TCZ, tocilizumab; UPA, upadacitinib;

The analysis network for EULAR at 24 weeks consisted of nine treatments across nine studies, which were connected via the common comparator of cDMARDs (as shown in Figure 21 below).

Figure 21. EULAR at week 24 Network geometry for the cDMARD-IR population



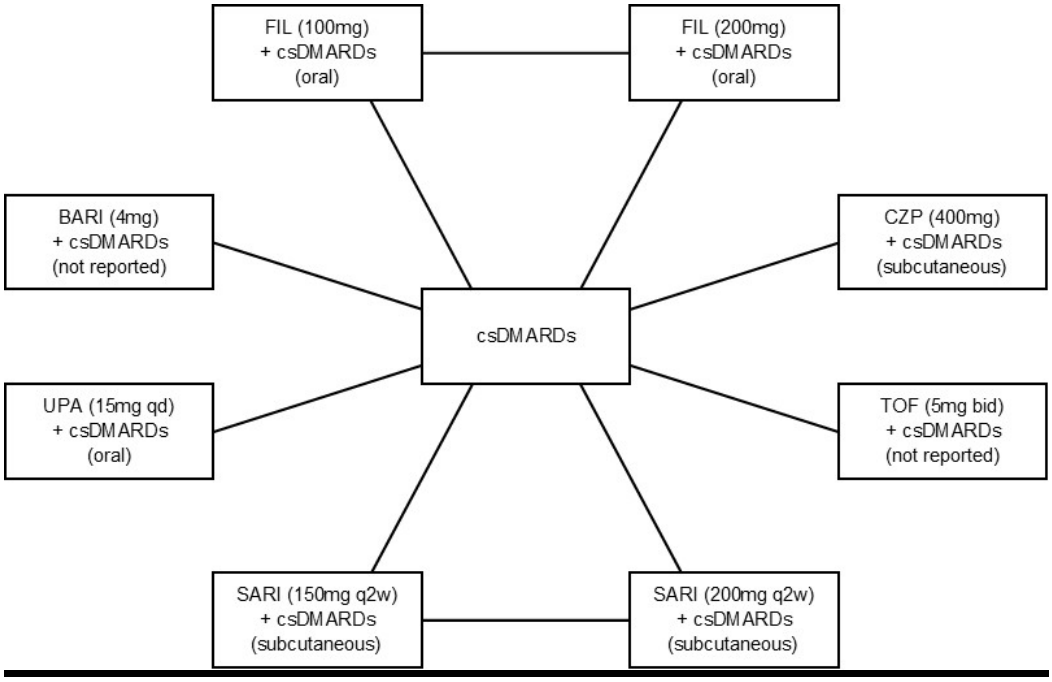
ADA, adalimumab; cDMARD, conventional disease modifying anti-rheumatic drug; CZP, certolizumab pegol; FIL, filgotinib; q2w, every two weeks; q4w, every 4 weeks; RTX, rituximab; TCZ, tocilizumab

bDMARD-IR

The analysis network for ACR at week 12 consisted of nine treatment groups across six studies, which were connected via the common comparator of cDMARDs. The network geometry is shown in Figure 22.

However, treatment with CZP in combination with cDMARDs appeared to be an outlier in the analysis, exhibiting extreme values for the relative effectiveness versus alternative therapies. One study in the network included CZP, and as this study was small (there were only 10 patients in the cDMARDs arm, and 27 patients in the CZP arm). It was therefore excluded from the analysis.

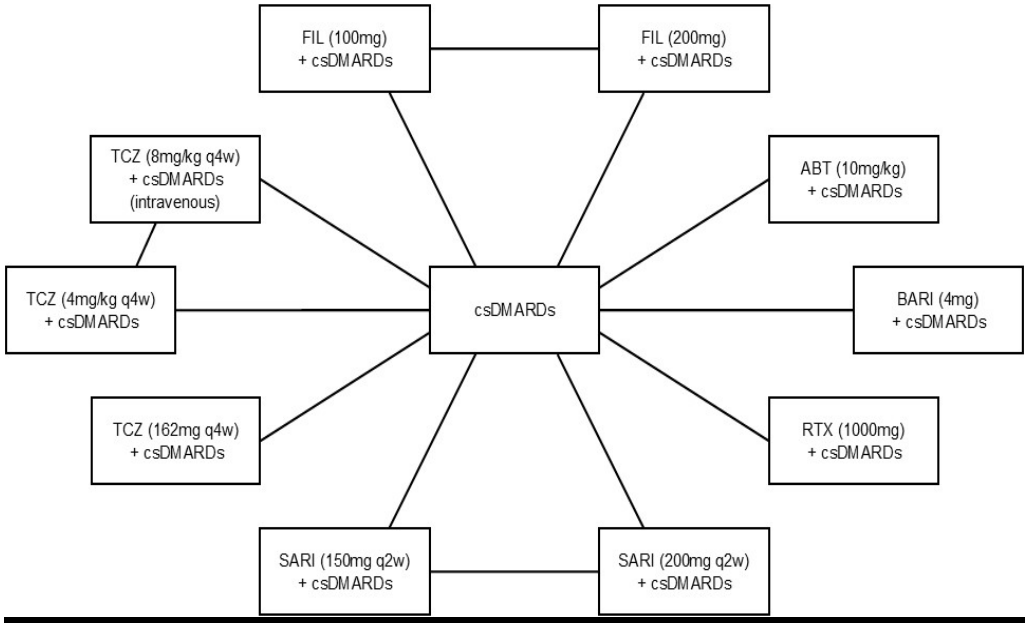
Figure 22. ACR at week 12 network geometry for the bDMARD-IR population



BARI, baricitinib; bid, twice daily; cDMARD, conventional disease modifying anti-rheumatic drug; qd, every day; q2w, every two weeks; SARI, sarilumab; TOF, tofacitinib; UPA, upadacitinib;

The analysis network for ACR at week 24 consisted of 11 treatment groups across seven studies, which were connected via the common comparator of cDMARDs. The geometry of the network is displayed in Figure 23.

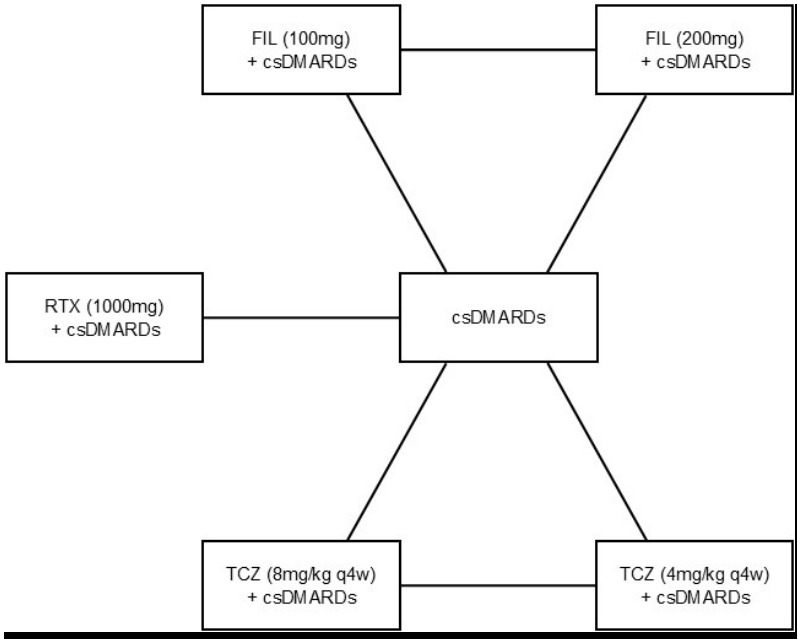
Figure 23. ACR at week 24 network geometry for the bDMARD-IR population



ABT, abatacept; BARI, baricitinib; cDMARD, conventional disease modifying anti-rheumatic drug; q2w, every two weeks; q4w, every 4 weeks; RTX, rituximab; SARI, sarilumab; TCZ, tocilizumab

The analysis network for EULAR at week 24 consisted of six treatment groups across three studies, which were connected via the common comparator of cDMARDs. The geometry of the network is displayed in Figure 24.

Figure 24. EULAR at week 24 bDMARD-IR – network geometry



cDMARD, conventional disease modifying anti-rheumatic drug; FIL, filgotinib; q4w, every 4 weeks; RTX, rituximab; TCZ, tocilizumab

B2.9.6 Studies excluded from the analysis

Trials identified in the clinical SLR that were not included in the NMA are listed in Appendix D, with the reasons for exclusion.

B2.9.7 Methods and outcomes of included studies

Rationale for choice of outcome measure and scale

<u>Primary outcomes</u>

The outcomes included in the indirect comparison, ACR and EULAR response, are among those which are most commonly reported in clinical trials in RA, including the FINCH Phase 3 programme, are directly relevant to patients and were set out in the

NICE scope. In addition, these endpoints have been used in previous HTA submissions in RA, including MTA375 (1).

- ACR scores (2) are the primary endpoints in the FINCH Phase 3 programme and many other clinical trials in RA. ACR requires both an improvement in tender or swollen joint counts, and in at least three of the following: patients global assessment, physician global assessment, pain-visual analogue scale (VAS), disability/functional questionnaire (the HAQ) and erythrocyte sedimentation rate (ESR) or C-reactive protein. ACR is classified as (3):
    - No response (<20% improvement in ACR criteria)
    - 20% or greater improvement in ACR criteria (ACR20)
    - 50% or greater improvement in ACR criteria (ACR50)
    - 70% or greater improvement in ACR criteria (ACR70)
- EULAR response, classifies patients depending on depending on both the change in value from baseline of the disease activity score in 28 joints (DAS28) following treatment and the actual DAS28 score achieved after treatment (4). It consists of the following categorisations:
    - No response
    - Moderate response
    - Good response

For EULAR response, some studies reported the categories of good and moderate response combined. These outcomes were utilised where moderate and good response were not reported separately.

The majority of studies identified in the clinical SLR reported ACR, whilst EULAR was less commonly reported. However, the cost-effectiveness analysis is based on EULAR response, which is more appropriate for use in Europe and aligns with European treatment guidelines as well as previous TA's. Therefore, EULAR was considered as the endpoint for analysis in order to inform cost-effectiveness modelling, either using direct EULAR comparative effectiveness estimates or ACR

estimates converted to EULAR. ACR responses can be mapped to EULAR responses using the established algorithm used in MTA375 derived from US Veterans Affairs Rheumatoid Arthritis Registry (VARA) data.

Comparative ACR response was assessed at 12 weeks and 24 weeks following study drug initiation in line with the primary efficacy endpoints across the FINCH studies and treatment guidelines. Comparative EULAR response was assessed at 24 weeks in line with EULAR 2019 recommendations (5).

B2.9.8 Populations included

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

B2.9.9 Assessment of heterogeneity in trials included in the NMA

There are several published NMAs in RA, including those carried out to inform previous HTA in this area (e.g. TA247, TA485 and TA466), illustrating the feasibility of forming appropriate networks for comparisons in this indication. Therefore, for the purpose of this NMA, a formal feasibility assessment was not conducted, and the homogeneity of the trials was deemed sufficient to conduct the analysis.

B2.9.10 Risk of bias

A quality assessment of each trial in the cDMARD-IR and bDMARD-IR NMA was completed using the Cochrane Collaborations tool for assessing risk of bias (6) and is provided in Appendix D.

B2.9.11 Methods of analysis

Methodology and primary endpoint

NMA was undertaken to evaluate the comparative effectiveness of filgotinib versus alternative treatments for RA in accordance with published NICE Decision Support Unit (DSU) guidance (7, 8). A Bayesian approach to estimation was adopted whereby posterior distributions for treatment effects were estimated using a

generalised linear model framework to synthesise data from trials identified by the clinical SLR and outcomes reported from the FINCH clinical trials.

The primary endpoints considered in this report are ordinal categorical variables (ACR and EULAR response). Each endpoint is made up of ordered values based on response thresholds, as outlined in section B2.9.7. Endpoints of this type may be analysed either by dichotomising the outcomes into binary variables (henceforth referred to as the 'dichotomised approach'; for example, considering ACR20 in a separate analysis to ACR50 and ACR70) or by conducting an analysis of ACR as a single endpoint (henceforth referred to as the 'single model approach'; i.e. including ACR20, ACR50 and ACR70 in one model). The single model approach utilises a conditional binomial likelihood with probit link (allowing for analysis of an ordered categorical variable), where the dichotomised approach utilises a binomial likelihood with a logit link (focussing on an analysis of each component separately).

Figure 25. Top-line comparison of the advantages of the two modelling approaches to the EULAR and ACR outcomes

Advantages of single model approach	Advantages of the dichotomised approach
Considers ACR / EULAR as a single endpoint: Rather than multiple analyses which consider the separate cut-offs within each endpoint, all cut-offs are considered in a single analysis.	**More intuitive interpretation of treatment effects:** In the single model approach, the effect of treatment with bDMARD 2 versus bDMARD 1 (d_{21}) is to change the probit score by d_{21} standard deviations. In the dichotomised approach, standard odds ratios (ORs) are reported.
Takes account of the ordinal nature of the variable: Both ACR and EULAR are based upon categorisation of variables which are on a continuous scale. The dichotomised approach would not account for the natural ordering and correlations between the categories within the outcome measure.	**Proportional odds assumption:** The single model approach assumes that the treatment effect is the same regardless of cut-off. For example; it is assumed that the treatment effect of a bDMARD on achieving ACR20 to be the same as the treatment effect of achieving ACR50. No such assumption is required as per the dichotomised approach.

NICE DSU guidelines have included examples using both single model (7)and dichotomised approaches (8). Specifically, they analyse ACR50 as a binary endpoint (8). However, in previous NICE HTA submissions, the ERG has analysed ACR and EULAR using the single model approach, as the dichotomous approach ignores the natural ordering and correlations between the categories within the outcome measure.

Therefore, analyses considered the single endpoint approach (i.e. all thresholds of ACR and EULAR were included in a single model). Whilst the treatment effect estimates produced by the model are less interpretable than that of a traditional odds ratio, the credible interval for the treatment effects can be interpreted in a similar manner to a log-odds ratio: a credible interval crossing 0 is non-significant. Furthermore, additional model outputs were produced to facilitate interpretation of the results, including calculation of absolute probabilities of achieving the thresholds within the endpoints and relative risks.

Data manipulation was undertaken in R Version 3.4.2 or higher, with WinBUGS version 1.4.3 was utilised for all NMA.

Each analysis consisted of multiple Markov chain Monte Carlo (MCMC) chains, with each chain simulated from different sets of starting values. Vague prior distributions were assumed for all model parameters, in line with NICE DSU guidelines (7). Inferences were made from the posterior distributions of the treatment effects between treatments for outcomes of interest, derived over at least 25,000 iterations following burn in (the iterations to be discarded whilst the chains converge). The number of iterations for burn-in was 25,000 unless additional iterations were required to ensure convergence.

WinBUGS code

WinBUGS version 1.4.3 was used for the NMA with the precise code supplied in Appendix D.

B2.9.12 Choice of model

Both fixed effects and random effects models were considered for each analysis included in the NMA. Absolute model fit was considered through examination of the total residual deviance, in keeping with NICE DSU guidelines (7). The deviance information criterion (DIC) was used to compare the fit of the different models with the same likelihood (e.g. fixed and random effects models, models with and without covariates), with a difference of <5 considered negligible. The DIC considers the absolute fit of the model, whilst adding a penalty for model complexity (i.e. the effective number of parameters). Lower values of the DIC suggest a more parsimonious model, which informed which models should be given most weight when interpreting the results. The goodness of fit diagnostics for the random and fixed effects models for the base-case network in cDMARD-IR and bDMARD-IR populations is shown in the tables below.

cDMARD-IR population

ACR at 12 and 24 weeks

For ACR at 12 weeks, the random effects model was chosen as the model with which to weight the interpretation of results, as the DIC was smaller in this model (388.353 and 330.142 for the fixed and random effects models, respectively) as shown in Table 17.

The random effects model appeared to fit the data better than the fixed effects model, with the total residual deviance, 261.7, relatively close to the number of data points, 190, included in the analysis

Table 17. Fixed and random-effect model fit statistics in cDMARD-IR for ACR at 12 weeks

Analysis	Data points	Total residual deviance Mean	DIC
Fixed effects	190	337.3	388.353
Random effects	**190**	**261.7**	**330.142**

ACR, American College of Rheumatology; cDMARD-IR, conventional disease modifying anti-rheumatic drug insufficient response; DIC, deviance information criterion

Additionally, for ACR at 24 weeks, the random effects model was chosen as the model with which to weight the interpretation of results, as the DIC was smaller in this model (461.316 and 416.795 for the fixed and random effects models, respectively), as shown in Table 18. The random effects model also has a lower total residual deviance, which is closer to the number of data points than the fixed effects model.

Table 18. Fixed and random effect model fit statistics in cDMARD-IR for ACR at 24 weeks

Analysis	Data points	Total residual deviance Mean	DIC
Fixed effects	215	408.3	461.316
Random effects	**215**	**348.8**	**416.795**

ACR, American College of Rheumatology; cDMARD-IR, conventional disease modifying anti-rheumatic drug insufficient response; DIC, deviance information criterion

EULAR at 24 weeks

For EULAR at 24 weeks, the fixed effects model was chosen, as the DIC was similar in both models (93.809 and 92.352 for the fixed and random effects models, respectively), as shown in Table 19. Therefore, as the fixed effects model is simpler, this approach informed the base case analysis.

Additionally, the fixed effects model had lower total residual deviance, which is closer to the number of data points than the random effects model.

Table 19. Fixed and random effect model fit statistics in the cDMARD-IR population for EULAR at 24 weeks

Analysis	Data points	Total residual deviance Mean	DIC
Fixed effects	**39**	**71.08**	**92.352**
Random effects	39	75.72	93.809

cDMARD-IR, conventional disease modifying anti-rheumatic drug insufficient response; DIC, deviance information criterion; EULAR, European League Against Rheumatism

bDMARD-IR population

ACR at 12 and 24 weeks

In the bDMARD-IR population, for ACR at 12 weeks, the fixed effects model was chosen as it is the simpler model and as the DIC was similar in both models (59.473 and 59.854 for the fixed and random effects models, respectively), with differences of < 5 considered negligible (Table 20). For ACR at 24 weeks, the fixed model was also chosen for simplicity in light of similar DIC in both model (85.112 and 85.296 for the fixed and random effects models, respectively) as shown in Table 21. The mean residual deviance is similar for both random and fixed effects models.

Table 20. Fixed and random effect model fit statistics in the bDMARD-IR population for ACR at 12 weeks

Analysis	Data points	Total residual deviance Mean	DIC
Fixed effects	**36**	**45.57**	**59.473**
Random effects	36	45.76	59.854

ACR, American College of Rheumatology; bDMARD-IR, biological disease modifying anti-rheumatic drug insufficient response; DIC, deviance information criterion

Table 21. Fixed and random effect model fit statistics in the bDMARD-IR population for ACR at 24 weeks

Analysis	Data points	Total residual deviance Mean	DIC
Fixed effects	**47**	**66.21**	**85.112**
Random effects	47	66.3	85.296

ACR, American College of Rheumatology; bDMARD-IR, biological disease modifying anti-rheumatic drug insufficient response; DIC, deviance information criterion

EULAR at 24 weeks

For EULAR at 24 weeks, the DIC suggested that there was little difference between the fixed and random effects model in terms of model fit when accounting for model complexity (20.183 for the fixed effects model versus 19.798 for the random effects models). Therefore, the interpretation of point estimates is based upon the simpler, fixed effects model (shown in Table 22). The mean residual deviance is similar for both models.

Table 22. Fixed and random effect model fit statistics in the bDMARD-IR population for EULAR at 24 weeks

Analysis	Data points	Total residual deviance Mean	DIC
Fixed effects	**13**	**11.09**	**20.183**
Random effects	13	10.9	19.798

bDMARD-IR, biological disease modifying anti-rheumatic drug insufficient response; DIC, deviance information criterion; EULAR, European League Against Rheumatism

B2.9.13 Results

Statistics for the posterior distribution of relative effects on the probit scale are reported, including mean, standard deviation (SD), median and 95% credible interval (CrI) for the models (Appendix D), with forest plots for relative effects (chosen model) shown in the sections below.

Similarly, the modelled probabilities of response are reported, as well as relative risks for each level or response, based upon the modelled probabilities (please see Appendix D). The modelled probabilities of response are based on an assumed probability of achieving the first level of response (e.g. ACR20) in the reference treatment group. The assumed probability was based upon conducting a meta-analysis (MA) of responses within the reference treatment arms of included studies, as outlined within NICE DSU guidelines (9).

cDMARD-IR: ACR at 12 weeks

Filgotinib (100mg) showed [redacted] to any treatments other than cDMARDs, were filgotinib 100mg was [redacted]. However, filgotinib 100mg [redacted]

Filgotinib (200mg) also showed [redacted]. Filgotinib (200mg) was [redacted]

For the random effects model, a forest plot of the relative effects to filgotinib (100mg) and filgotinib (200mg) are displayed in Figure 26 and Figure 27. Modelled probabilities of ACR response for all treatments is reported in Table 23.

Figure 26. ACR at week 12 for the cDMARD-IR population - forest plot for relative effects to filgotinib (100mg) on the probit scale

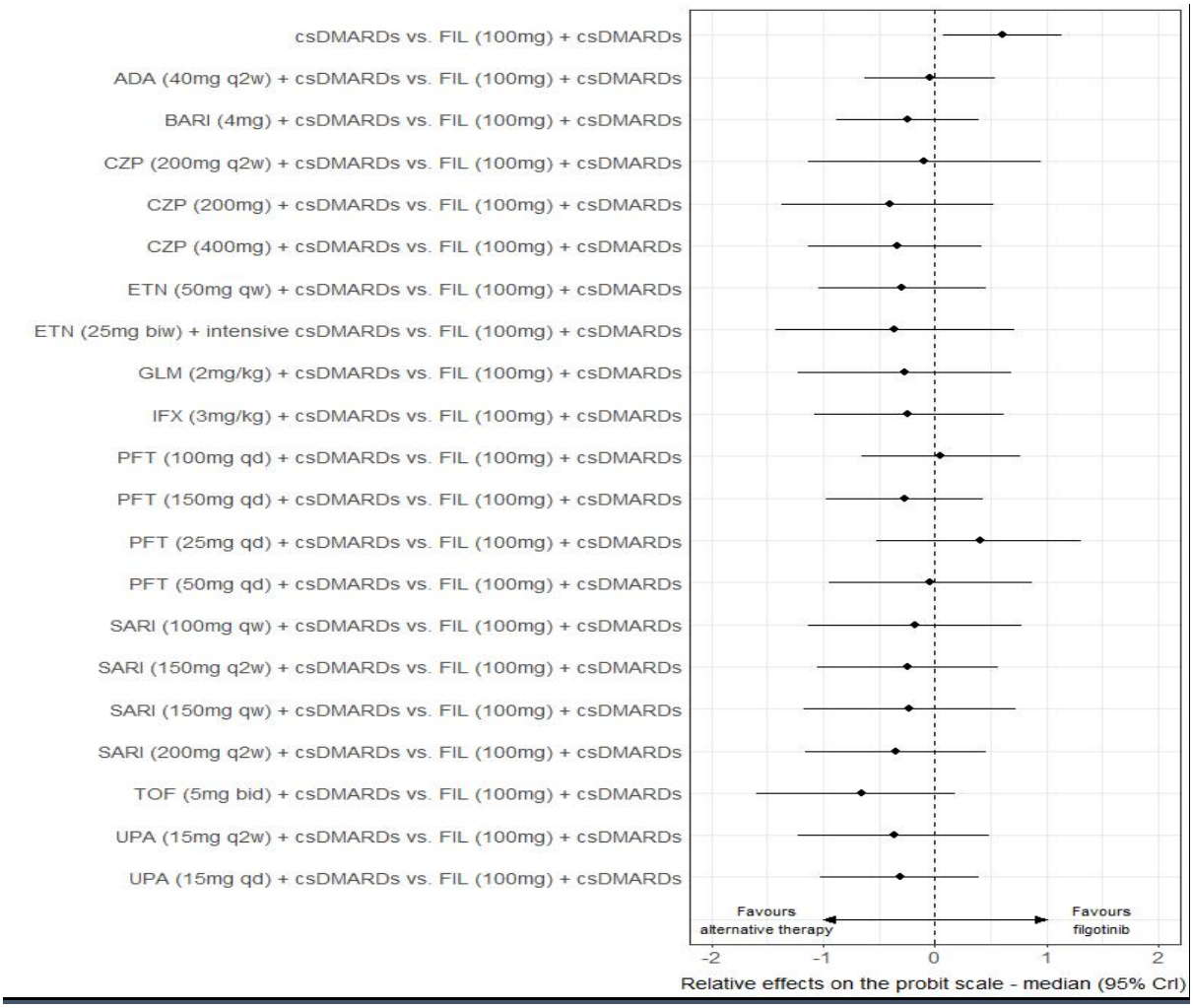


Figure 27. ACR at week 12 for the cDMARD-IR population - forest plot for relative effects to filgotinib (200mg) on the probit scale

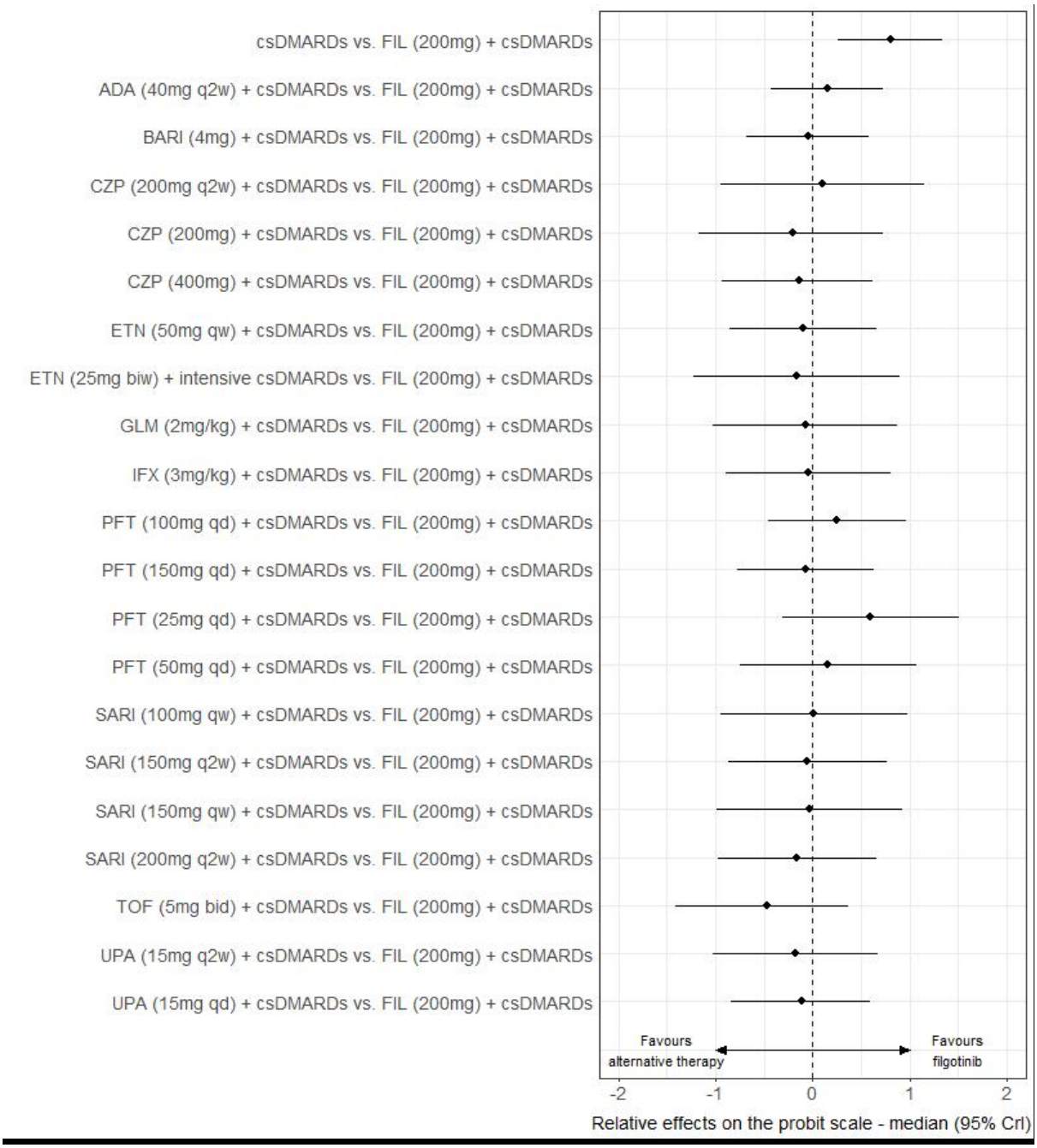


Table 23: ACR at week 12 for the cDMARD-IR population - modelled probability of ACR response

Treatment	Modelled probability of response – posterior median (95% CrI)		
	ACR20	ACR50	ACR70
cDMARDs	[redacted]	[redacted]	[redacted]
FIL (100mg) + cDMARDs	[redacted]	[redacted]	[redacted]
FIL (200mg) + cDMARDs	[redacted]	[redacted]	[redacted]
ADA (40mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
BARI (4mg) + cDMARDs	[redacted]	[redacted]	[redacted]
CZP (200mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
CZP (200mg) + cDMARDs	[redacted]	[redacted]	[redacted]
CZP (400mg) + cDMARDs	[redacted]	[redacted]	[redacted]
ETN (50mg qw) + cDMARDs	[redacted]	[redacted]	[redacted]
ETN (25mg biw) + intensive cDMARDs	[redacted]	[redacted]	[redacted]
GLM (2mg/kg) + cDMARDs	[redacted]	[redacted]	[redacted]
IFX (3mg/kg) + cDMARDs	[redacted]	[redacted]	[redacted]
PFT (100mg qd) + cDMARDs	[redacted]	[redacted]	[redacted]
PFT (150mg qd) + cDMARDs	[redacted]	[redacted]	[redacted]
PFT (25mg qd) + cDMARDs	[redacted]	[redacted]	[redacted]
PFT (50mg qd) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (100mg qw) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (150mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (150mg qw) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (200mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
TOF (5mg bid) + cDMARDs	[redacted]	[redacted]	[redacted]
UPA (15mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]

UPA (15mg qd) + cDMARDs	[redacted]	[redacted]	[redacted]

ACR: American College of Rheumatology; ADA: adalimumab; BARI: baricitinib; bid: twice per day; biw: twice per week; CrI: credible interval; cDMARDs: conventional synthetic disease modifying anti-rheumatic drug; CZP; certolizumab pegol; ETN: etanercept; FIL: filgotinib; GLM: golimumab; IFX: infliximab; PFT: peficitinib; qd: daily; bid: twice per day; q2w: once every two weeks; qw: once every week; SARI: sarilumab; TOF: tofacitinib; UPA: upadacitinib.

Probability of achieving ACR20 in reference treatment (cDMARDs) based on baseline natural history model as detailed in NICE DSU guidelines TSD5 (9)

cDMARD-IR: ACR at 24 weeks

Filgotinib (100mg) showed [redacted]. Filgotinib was also [redacted] to certolizumab pegol (200mg). Filgotinib (100mg) was [redacted] to all other treatments (Figure 28). Modelled probabilities of ACR response for all treatments is reported in Table 24.

Filgotinib (200mg) [redacted] However, [redacted] (Figure 28). However, the modelled probabilities of ACR response were very similar for combination therapy of [redacted] compared with filgotinib (200mg). Full details are shown in Table 24.

Figure 28. ACR at week 24 for the cDMARD-IR population - forest plot for relative effects to filgotinib (100mg) on the probit scale

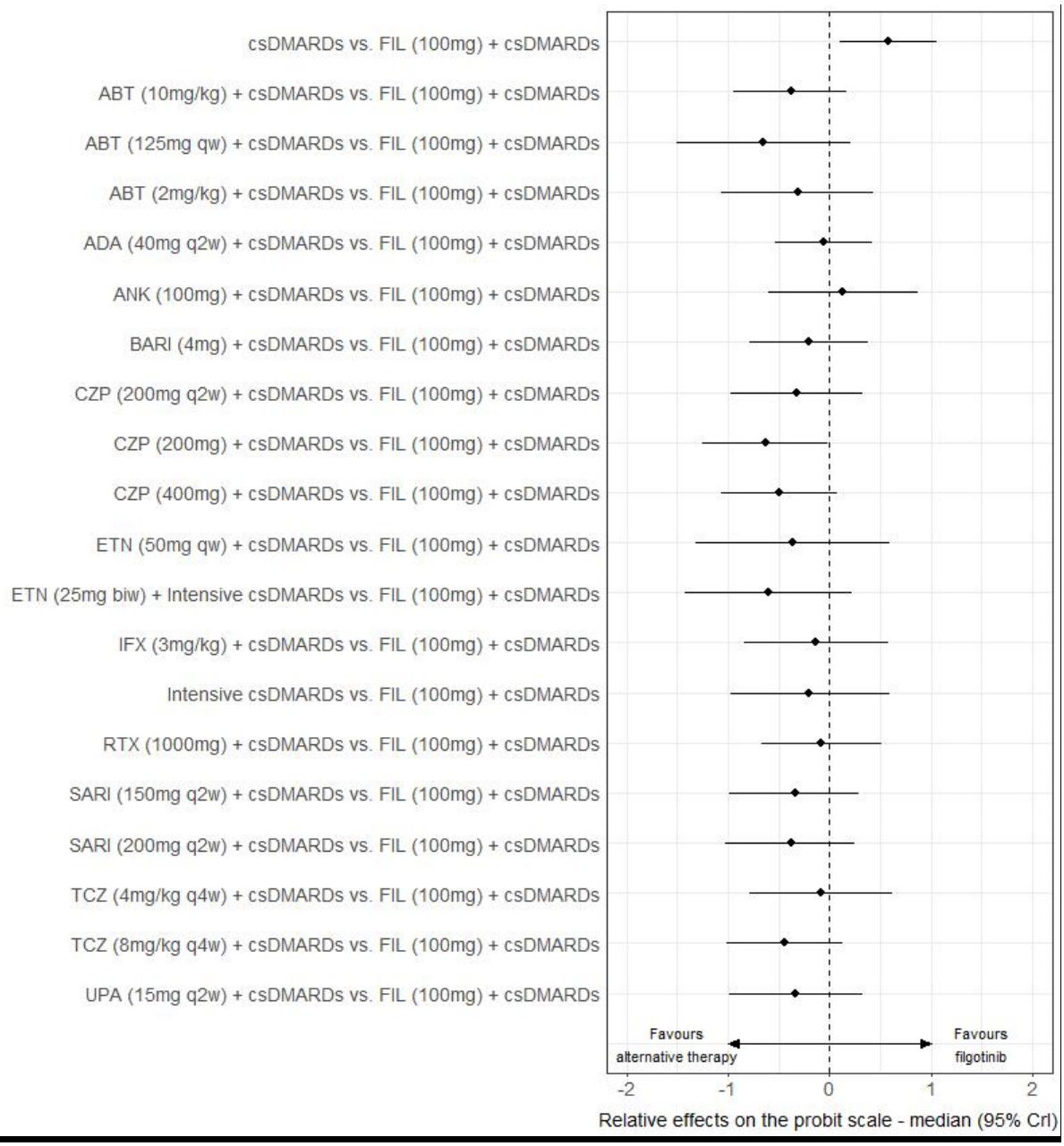


Figure 29. ACR at week 24 cDMARD-IR - forest plot for relative effects to filgotinib (200mg) on the probit scale

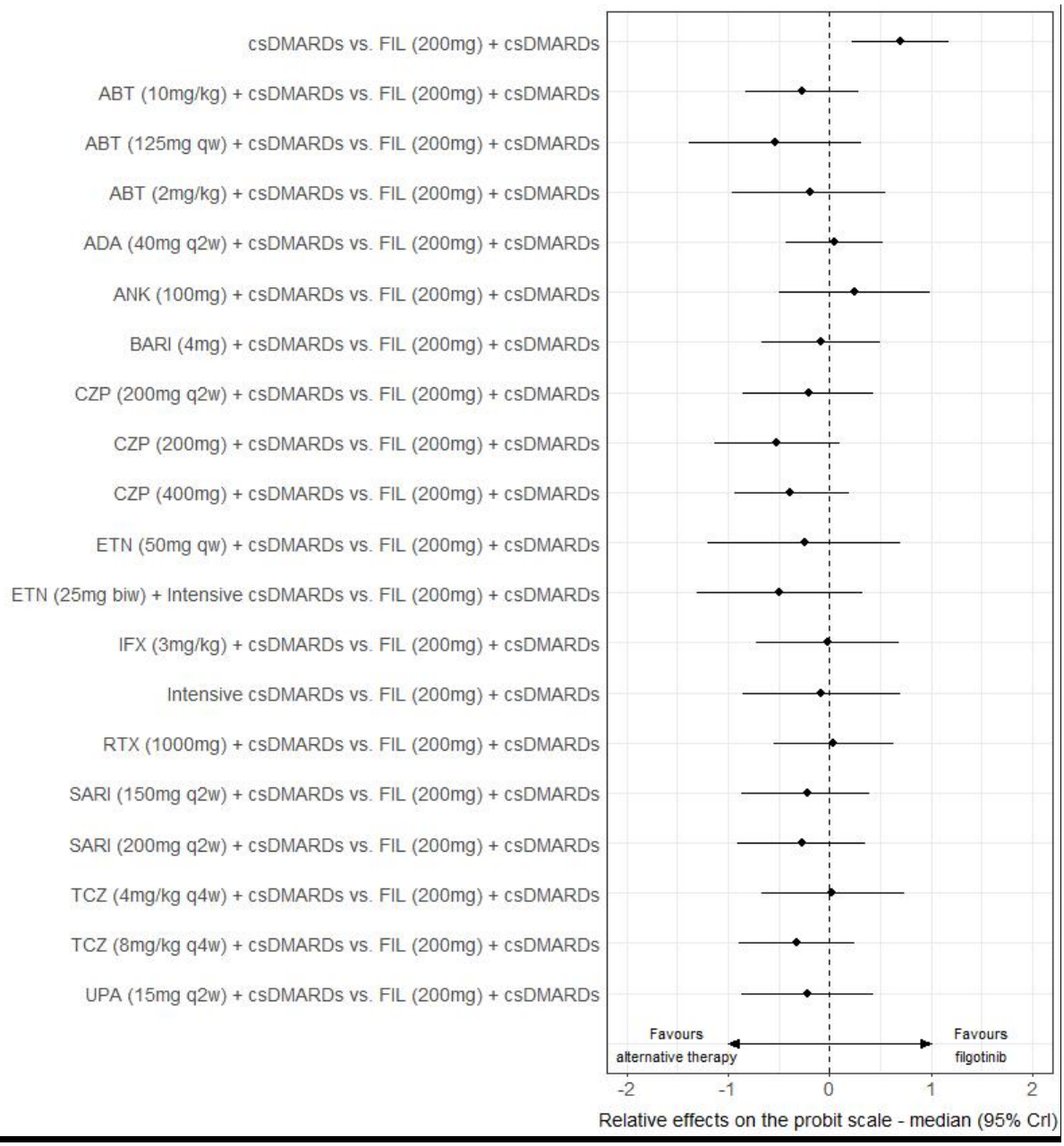


Table 24: ACR at week 24 cDMARD-IR – modelled probability of ACR response

Treatment	Modelled probability of response – posterior median (95% CrI)		
	ACR20	ACR50	ACR70
cDMARDs	[redacted]	[redacted]	[redacted]
FIL (100mg) + cDMARDs	[redacted]	[redacted]	[redacted]
FIL (200mg) + cDMARDs	[redacted]	[redacted]	[redacted]
ABT (10mg/kg) + cDMARDs	[redacted]	[redacted]	[redacted]
ABT (125mg qw) + cDMARDs	[redacted]	[redacted]	[redacted]
ABT (2mg/kg) + cDMARDs	[redacted]	[redacted]	[redacted]
ADA (40mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
ANK (100mg) + cDMARDs	[redacted]	[redacted]	[redacted]
BARI (4mg) + cDMARDs	[redacted]	[redacted]	[redacted]
CZP (200mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
CZP (200mg) + cDMARDs	[redacted]	[redacted]	[redacted]
CZP (400mg) + cDMARDs	[redacted]	[redacted]	[redacted]
ETN (50mg qw) + cDMARDs	[redacted]	[redacted]	[redacted]
ETN (25mg biw) + Intensive cDMARDs	[redacted]	[redacted]	[redacted]
IFX (3mg/kg) + cDMARDs	[redacted]	[redacted]	[redacted]
Intensive cDMARDs	[redacted]	[redacted]	[redacted]
RTX (1000mg) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (150mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (200mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
TCZ (4mg/kg q4w) + cDMARDs	[redacted]	[redacted]	[redacted]
TCZ (8mg/kg q4w) + cDMARDs	[redacted]	[redacted]	[redacted]
UPA (15mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]

ABT: abatacept; ACR: American College of Rheumatology; ADA: adalimumab; ANK: anakinra; BARI: baricitinib; CrI: credible interval; cDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; CZP; certolizumab pegol; ETN: etanercept; FIL: filgotinib; IFX: infliximab; RTX: rituximab; qw: weekly; q2w: once every two weeks; q4w: once every four weeks; SARI: sarilumab; TCZ: tocilizumab; UPA: upadacitinib.

Probability of achieving ACR20 in reference treatment (cDMARDs) based on baseline natural history model as detailed in NICE DSU guidelines TSD5 (9)

cDMARD-IR: EULAR at 24 weeks

Filgotinib (100mg) was [redacted], other than cDMARDs (Figure 30).

Filgotinib (200mg) was [redacted] to adalimumab (40mg q2w) and cDMARDs [redacted] inferior to certolizumab pegol (200mg), certolizumab pegol (400mg) and tocilizumab (8mg/kg) as shown in Figure 30. Filgotinib (200mg) was [redacted] to other combination therapies, [redacted] for rituximab 1000mg and tocilizumab 4mg/kg as shown by the modelled probabilities of response in Table 25.

Patients in the FINCH 1 study exhibited extremely high levels of response when treated with cDMARDs. Therefore, these results should be interpreted with caution, bearing in mind the large differences in included studies in terms of EULAR response in the control arms.

Figure 30. EULAR at week 24 for cDMARD-IR - forest plot for relative effects to filgotinib (100mg and 200mg) based therapies on the probit scale

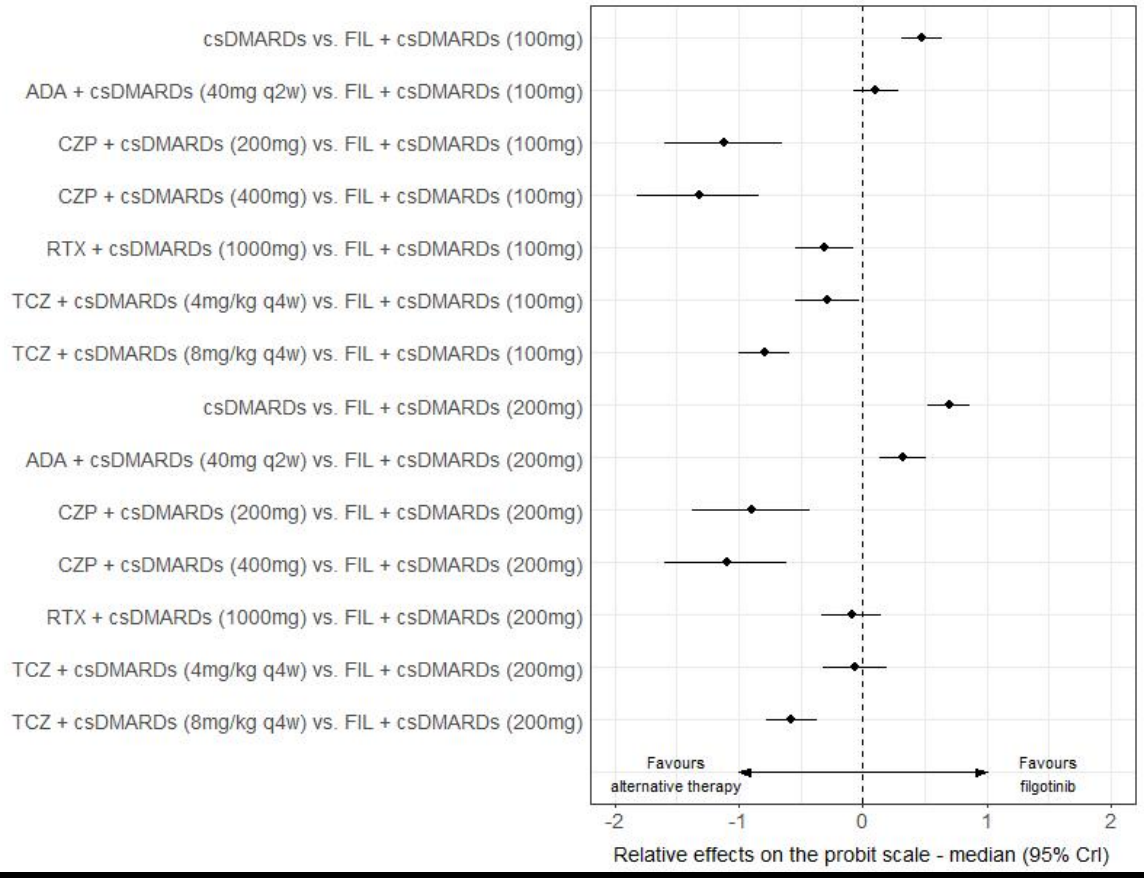


Table 25: EULAR at week 24 cDMARD-IR - modelled probability of EULAR response

Treatment	Modelled probability of response – posterior median (95% CrI)	
	Moderate response	Good response
cDMARDs	[redacted]	[redacted]
FIL + cDMARDs (100mg)	[redacted]	[redacted]
FIL + cDMARDs (200mg)	[redacted]	[redacted]
ADA + cDMARDs (40mg q2w)	[redacted]	[redacted]
CZP + cDMARDs (200mg)	[redacted]	[redacted]
CZP + cDMARDs (400mg)	[redacted]	[redacted]
RTX + cDMARDs (1000mg)	[redacted]	[redacted]
TCZ + cDMARDs (4mg/kg q4w)	[redacted]	[redacted]
TCZ + cDMARDs (8mg/kg q4w)	[redacted]	[redacted]

ADA, adalimumab; cDMARDs, conventional synthetic disease modifying anti-rheumatic drug; CrI, credible interval; EULAR, European League Against Rheumatism; FIL, filgotinib; RTX, rituximab; q2w, once every two weeks; q4w, once every four weeks; TCZ, tocilizumab.

*Probability of achieving at least specified response.

bDMARD-IR: ACR at 12 weeks

Filgotinib (100mg) showed [redacted] (Figure 31). Filgotinib 100mg was [redacted] to sarilumab 150mg and tofacitinib 5mg, but differences were small, as demonstrated in the modelled probabilities of response in Table 26. Filgotinib 100mg was [redacted] to upadacitinib 15mg, baricitinib 4mg, and sarilumab 200mg.

Filgotinib (200mg) was shown to have similar efficacy to other treatment in the network. Filgotinib (200mg) [redacted] to sarilumab (150mg) and cDMARDs and was [redacted] to all other therapies in the network, however, these results were [redacted] (Figure 31). The modelled probabilities of response for ACR are shown in

Table 26.

Figure 31. ACR at week 12 bDMARD-IR - forest plot for relative effects to filgotinib (100mg and 200mg) based therapies on the probit scale

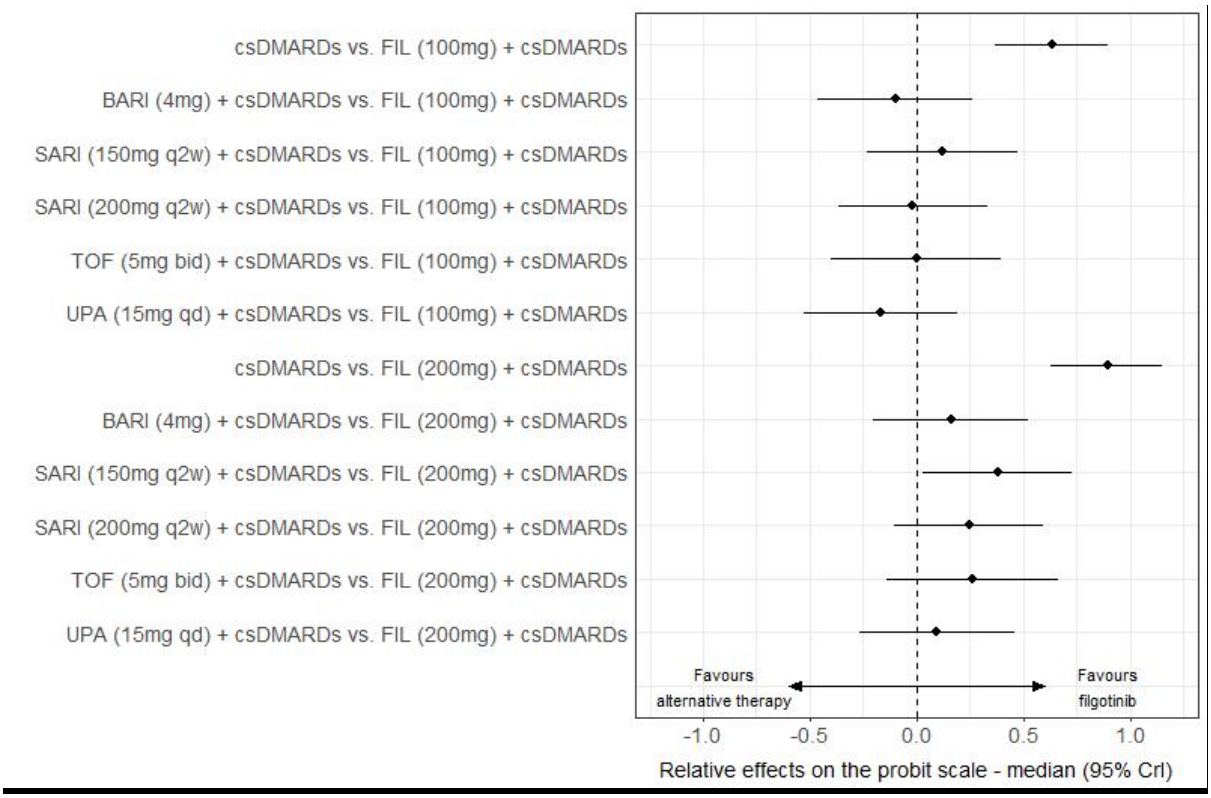


Table 26: ACR at week 12 bDMARD-IR - modelled probability of ACR response

Treatment	Modelled probability of response – posterior median (95% CrI)		
	ACR20	ACR50	ACR70
cDMARDs	[redacted]	[redacted]	[redacted]
FIL (100mg) + cDMARDs	[redacted]	[redacted]	[redacted]
FIL (200mg) + cDMARDs	[redacted]	[redacted]	[redacted]
BARI (4mg) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (150mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (200mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
TOF (5mg bid) + cDMARDs	[redacted]	[redacted]	[redacted]
UPA (15mg qd) + cDMARDs	[redacted]	[redacted]	[redacted]

ACR, American College of Rheumatology; BARI, baricitinib; bid, twice daily; CrI, credible interval; cDMARDs, conventional synthetic disease modifying anti-rheumatic drugs; FIL, filgotinib; qd, daily; q2w; every 2 weeks; SARI, sarilumab; TOF, tofacitinib; UPA, upadacitinib.

Probability of achieving ACR20 in reference treatment (cDMARDs) based off of baseline natural history model as detailed in NICE DSU guidelines TSD5. (9)

bDMARD-IR: ACR at 24 weeks

Filgotinib (100mg) was [redacted] to rituximab (1000mg) and tocilizumab (8mg/kg q4w) (Figure 32). There were [redacted] between filgotinib (100mg) and other therapies ([redacted] Filgotinib (100mg) was [redacted] although [redacted] for baricitinib (4mg) and sarilumab (150mg) as demonstrated in the modelled probabilities of response (Table 27).

Filgotinib (200mg) showed similar efficacy to other treatment in the network and [redacted] to cDMARDs. Filgotinib (200mg) was [redacted] to abatacept (10mg/kg), baricitinib (4mg), sarilumab (150mg q2w), sarilumab (200mg q2w), tocilizumab (162mg q2w), and tocilizumab (4mg/kg), [redacted] (Figure 32). Filgotinib 200mg was [redacted] to tocilizumab (4mg/kg) and rituximab (1000mg), [redacted]

The modelled probabilities of ACR response are shown in

Table 27.

Figure 32. ACR at week 24 bDMARD-IR - forest plot for relative effects to filgotinib (100mg and 200mg) based therapies on the probit scale

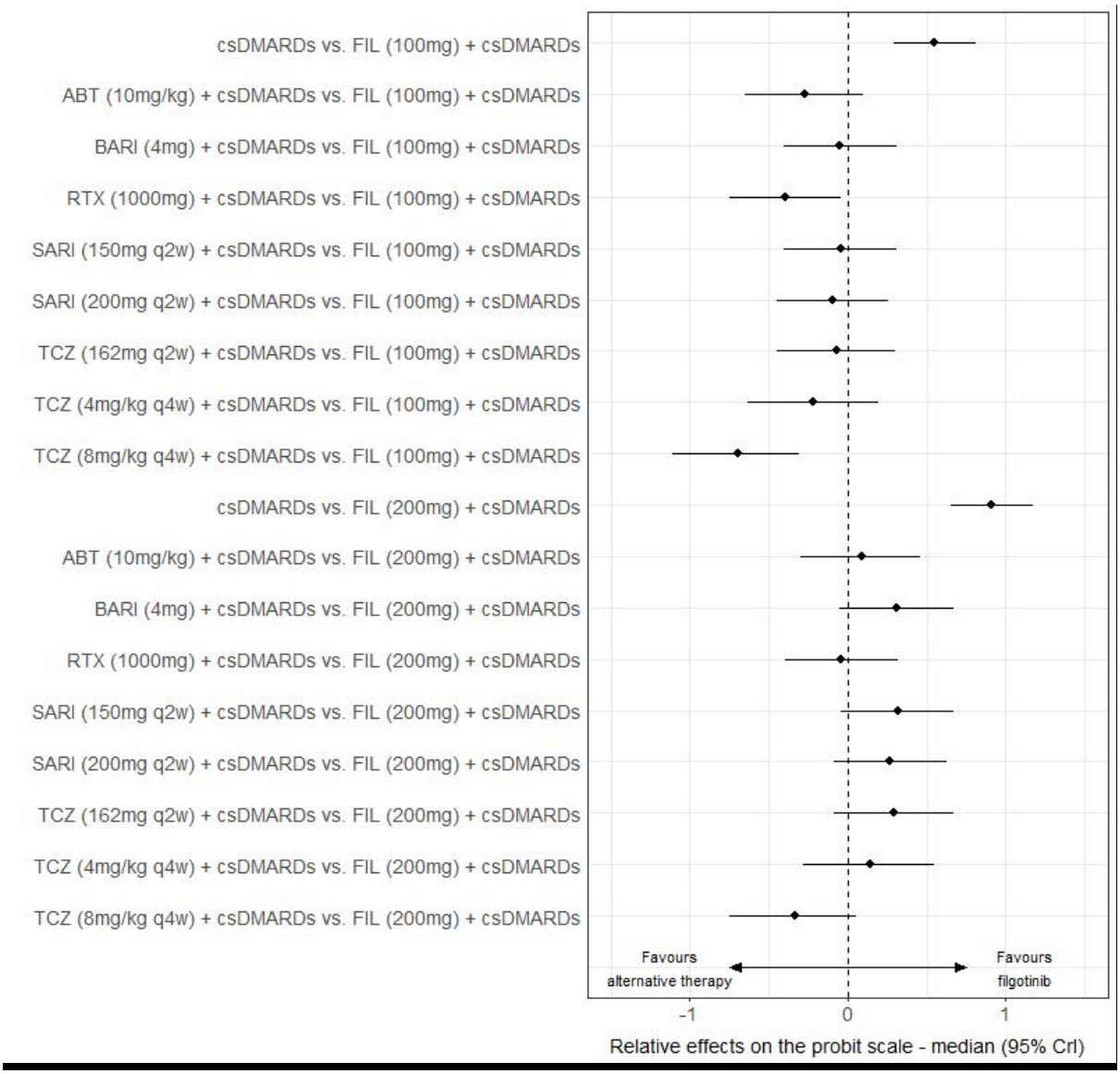


Table 27: ACR at week 24 bDMARD-IR – modelled probability of ACR response

Treatment	Modelled probability of response – posterior median (95% CrI)		
	ACR20	ACR50	ACR70
cDMARDs	[redacted]	[redacted]	[redacted]
FIL (100mg) + cDMARDs	[redacted]	[redacted]	[redacted]
FIL (200mg) + cDMARDs	[redacted]	[redacted]	[redacted]
ABT (10mg/kg) + cDMARDs	[redacted]	[redacted]	[redacted]
BARI (4mg) +	[redacted]	[redacted]	[redacted]

cDMARDs			
RTX (1000mg) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (150mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
SARI (200mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
TCZ (162mg q2w) + cDMARDs	[redacted]	[redacted]	[redacted]
TCZ (4mg/kg q4w) + cDMARDs	[redacted]	[redacted]	[redacted]
TCZ (8mg/kg q4w) + cDMARDs	[redacted]	[redacted]	[redacted]

ABT, abatacept; ACR, American College of Rheumatology; BARI, baricitinib; CrI, credible interval; cDMARDs, conventional synthetic disease modifying anti-rheumatic drugs; FIL, filgotinib; q2w, every 2 weeks, q4w, every 4 weeks; RTX, rituximab; SARI, sarilumab; TCZ, tocilizumab.

Probability of achieving ACR20 in reference treatment (cDMARDs) based off of baseline natural history model as detailed in NICE DSU guidelines TSD5. (9)

bDMARD-IR: EULAR at 24 weeks

The studies included in this network showed a large degree of variability in the control arm (cDMARD) response, for example 86.4% of patients achieved at least a moderate response in the cDMARDs arm in FINCH 2, compared with only 16.5% in the RADIATE and 22% in REFLEX studies. As such, estimates of the modelled probabilities of response were highly uncertain.

The point estimates suggest (Table 28) that rituximab and tocilizumab (both doses) were favourable to filgotinib; but due to the much higher control arm level of response in the FINCH 2 study, results should be interpreted with caution.

Figure 33. EULAR at week 24 bDMARD-IR - forest plot for relative effects to filgotinib based therapies on the probit scale

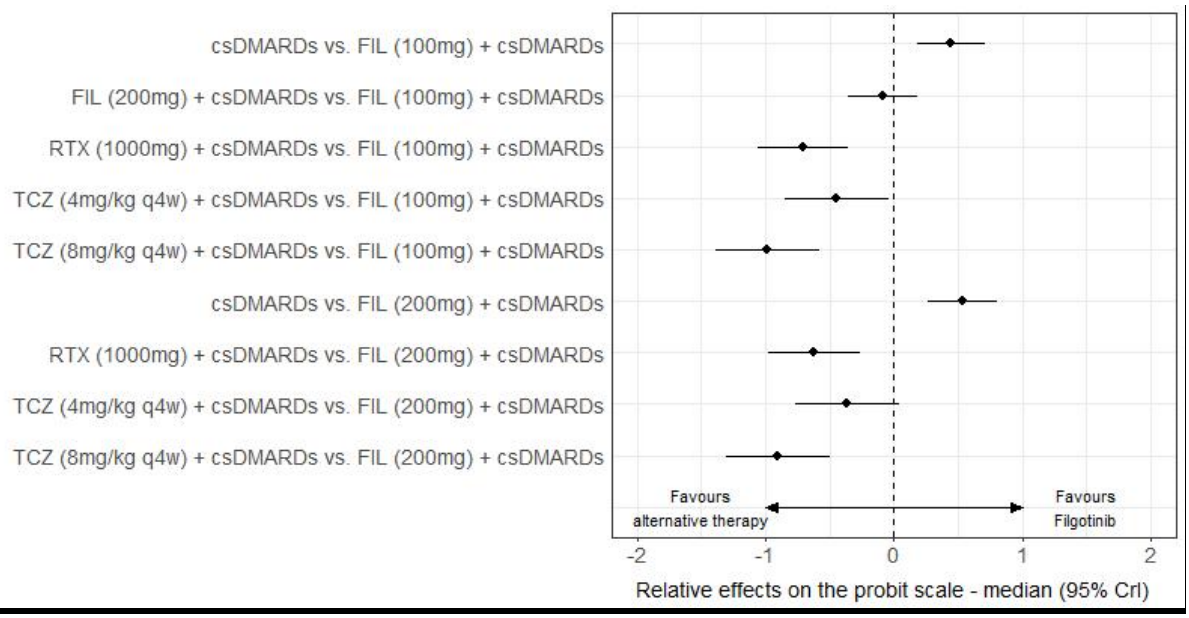


Table 28: EULAR at week 24 bDMARD-IR - modelled probability of EULAR response

Treatment	Modelled probability of response – posterior median (95% CrI)	
	Moderate response	Good response
cDMARDs	[redacted]	[redacted]
FIL (100mg) + cDMARDs	[redacted]	[redacted]
FIL (200mg) + cDMARDs	[redacted]	[redacted]
RTX (1000mg) + cDMARDs	[redacted]	[redacted]
TCZ (4mg/kg q4w) + cDMARDs	[redacted]	[redacted]
TCZ (8mg/kg q4w) + cDMARDs	[redacted]	[redacted]

CrI, credible interval; cDMARDs, conventional synthetic disease modifying anti-rheumatic drugs; EULAR, European League Against Rheumatism; FIL, filgotinib; q4w, every 4 weeks; RTX, rituximab; TCZ, tocilizumab.

Probability of achieving at least a moderate response in reference treatment (cDMARDs) based off of baseline natural history model as detailed in NICE DSU guidelines TSD5 (9)

B.2.10 Adverse reactions

Filgotinib has a manageable and consistent safety and tolerability profile, a summary of adverse events by trial is provided in the sections below.

B.2.10.1 Summary of safety data from FINCH 1

In FINCH 1, at week 24 (placebo-controlled period) a similar proportion of patients experienced serious treatment-emergent adverse events (TEAEs) in each treatment group (4.4% in the filgotinib 200mg arm, 5.0% in the filgotinib 100mg arm, 4.3% in the adalimumab arm and 4.2% in the placebo arm). By week 52 (overall period), these figures were [redacted] in the filgotinib 200mg arm, [redacted] in the filgotinib 100mg arm, and [redacted] in the adalimumab arm.

By week 24, there were two-treatment related deaths in the filgotinib 200mg group (septic shock; septic shock secondary to pneumonia), one treatment-related death in the filgotinib 100mg group in a patient with multiple risk factors (myocardial infarction on day 13), no deaths in the adalimumab group and two deaths in the placebo group (toxic reaction not related to study drug, septic shock non-treatment emergent SAE).

A summary of rates of TEAEs in FINCH 1 up to week 24 and [redacted] is shown in Table 29.

Table 29. TEAEs from baseline to week 24 (placebo-controlled period) and for the overall period up to week 52 (overall period) in FINCH 1 (SAS)

Safety assessment	Week	Filgotinib 200mg + MTX (n=475)	Filgotinib 100mg + MTX (n=480)	Adalimumab + MTX (n=325)	Placebo + MTX (n=475)
TEAE, n (%)	*24*	287 (60.4%)	287 (59.8%)	186 (57.2%)	253 (53.3%)
	52	[redacted]	[redacted]	[redacted]	[redacted]
TEAE related to study drug, n (%)	*24*	103 (21.7%)	104 (21.7%)	70 (21.5%)	87 (18.3%)
	52	[redacted]	[redacted]	[redacted]	[redacted]
TEAE with Grade 3 or higher (%)	*24*	34 (7.2%)	35 (7.3%)	20 (6.2%)	33(6.9%)
	52	[redacted]	[redacted]	[redacted]	[redacted]

Safety assessment	Week	Filgotinib 200mg + MTX (n=475)	Filgotinib 100mg + MTX (n=480)	Adalimumab + MTX (n=325)	Placebo + MTX (n=475)
TEAE leading to premature discontinuation of study drug, n (%)	*24*	15 (3.2%)	9 (1.9%)	13 (4.0%)	15 (3.2%)
	52	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE, n (%)	*24*	21 (4.4%)	24 (5.0%)	14 (4.3%)	20 (4.2%)
	52	[redacted]	[redacted]	[redacted]	[redacted]
Death, n (%)	*24*	2 (0.4%)	1 (0.2%)	0	2 (0.4%)
	52	[redacted]	[redacted]	[redacted]	[redacted]

AE, adverse event; MTX, methotrexate; placebo, placebo; SAS, safety analysis set; TEAE, treatment-emergent adverse event.

*At week 24, all patients assigned to placebo were reassigned 1:1 to either filgotinib 100mg + MTX or filgotinib 200mg + MTX in a blinded fashion and continued in the study per protocol up to week 52. Source: Gilead Data on File. FINCH 1 CSR. 2019. (10)

By week 24, in the filgotinib 200mg arm, the most frequently reported AEs (≥5% of patients), across all grades of severity, were nasopharyngitis (6.5%) and upper respiratory tract infection (5.3%). Nasopharyngitis and upper respiratory tract infection were also reported most frequently across all other study arms with 6.0% and 6.9% in the filgotinib 100mg arm, 4.6% and 5.2% in the adalimumab arm and 5.3% and 2.9% in the placebo arm, respectively. Table 30 presents the most common adverse events, across all grades, as well as the most commonly reported AEs classified as Grade 3 or higher at week 52.

Table 30. FINCH 1 most common TEAEs and most common Grade 3 or higher AEs at week 52, SAS

Safety assessment	Filgotinib 200mg + MTX (n=475)	Filgotinib 100mg + MTX (n=480)	Adalimumab + MTX (n=325)
Most common AEs (≥5% of patients) (%)	[redacted]	[redacted]	[redacted]
Most common Grade 3 or higher (≥1% of patients) (%)	[redacted]	[redacted]	[redacted]

AE, adverse event; MTX, methotrexate; placebo, placebo; SAS, safety analysis set; TEAE, treatment-emergent adverse event. Source: Gilead Data on File. FINCH 1 CSR. 2020. (10)

B.2.10.2 Summary of safety data from FINCH 2

In FINCH 2, at week 24, a similar proportion of patients experienced serious TEAEs in each treatment group (4.1% in the filgotinib 200mg arm, 5.2% in the filgotinib 100mg arm, and 3.4% in the placebo arm). No deaths occurred due to any cause by week 24 (11).

A summary of the main TEAEs in FINCH 2 at week 24 is shown in Table 31.

Table 31. TEAEs from baseline to week 24 in FINCH 2 (SAS)

Safety assessment	Filgotinib QD dose groups		Placebo + cDMARD(s) (n=148)
	200mg + cDMARD(s) (n=147)	100mg + cDMARD(s) (n=153)	
TEAE, n (%)	102 (69.4%)	97 (63.4%)	100 (67.6%)
TEAE related to study drug, n (%)	32 (21.8%)	29 (19.0%)	23 (15.5%)
TEAE leading to premature discontinuation of study drug, n (%)	5 (3.4%)	6 (3.9%)	3 (2.0%)
TEAE with Grade 3 or Higher	8 (5.4%)	13 (8.5%)	9 (6.1%)
Serious TEAE, n (%)	6 (4.1%)	8 (5.2%)	5 (3.4%)
Death, n (%)	0	0	0

AE, adverse event; MTX, methotrexate; placebo, placebo; QD, once per day; SAS, safety analysis set; TEAE, treatment-emergent adverse event. Source: Gilead Data on File. FINCH 2 CSR. 2019. Genovese et al. 2018. (11) (12)

The most frequently reported AEs, across all grades, in the filgotinib 200mg arm were nasopharyngitis (10.2%), upper respiratory tract infection (5.4%), bronchitis (5.4%) and headache (5.4%). Incidence of adverse events was similar in the filgotinib 100mg arm with nasopharyngitis (5.9%), upper respiratory tract infection (5.9%), headache (5.9%) and nausea (5.2%) being the most frequently reported. In the placebo arm, the most commonly reported AEs were rheumatoid arthritis (6.1%), bronchitis (5.4%), nasopharyngitis (4.7%), upper respiratory tract infection (4.1%) and nausea (4.1%) (11).

Grade 3 or above AEs reported for in >1% of patients in any treatment group comprised RA (placebo: three patients, 2.0%) and neutropenia (filgotinib 200mg: two patients, 1.4%) (11).

B.2.10.3 Summary of safety data from FINCH 3

In FINCH 3, at week 24, a similar proportion of patients experienced serious TEAEs in each treatment group (4.1% of patients in the filgotinib 200mg + MTX arm, 2.4% in the filgotinib 100mg + MTX arm, 4.8% in the filgotinib 200mg monotherapy arm and 3.1% of patients in the MTX monotherapy arm).

By week 24, one treatment-related death was reported in the filgotinib 200mg + MTX arm (lupus cardiomyopathy on day 7). A summary of the main TEAEs at week 24 and week 52 in FINCH 3 is shown in Table 32 (13).

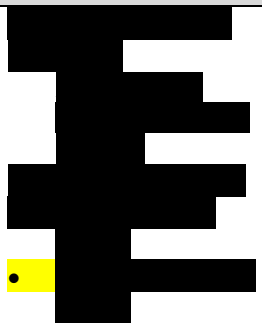
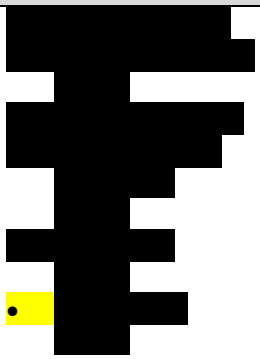
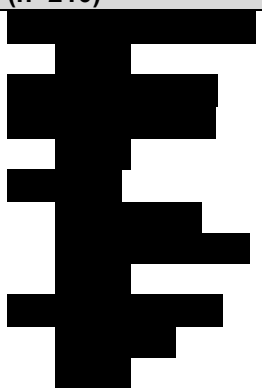
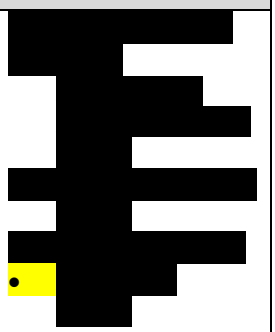
Table 32. TEAEs from baseline to week 24 and for the overall period to week 52 in FINCH 3, SAS

Safety assessment	Week	Filgotinib 200mg + MTX (n=416)	Filgotinib 100mg + MTX (n=207)	Filgotinib 200mg monotherapy (n=210)	MTX monotherapy (n=416)
TEAE, n (%)	*24*	275 (66.1%)	144 (69.6%)	117 (55.7%)	263 (63.2)
	52	[redacted]	[redacted]	[redacted]	[redacted]
TEAE related to study drug, n (%)	*24*	158 (38.0%)	91 (44.0%)	49 (23.0%)	141 (33.9%)
	52	[redacted]	[redacted]	[redacted]	[redacted]
TEAE with Grade 3 or Higher	*24*	33 (7.9%)	17 (8.2%)	10 (4.8%)	22 (5.3%)
	52	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to premature discontinuation of study drug, n (%)	*24*	20 (4.8%)	7 (3.4%)	4 (1.9%)	4 (1.9%)
	52	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE, n (%)	*24*	17 (4.1%)	5 (2.4%)	10 (4.8%)	13 (3.10%)
	52	[redacted]	[redacted]	[redacted]	[redacted]
Death, n (%)	*24*	1 (0.2%)	0	0	0
	52	[redacted]	[redacted]	[redacted]	[redacted]

AE, adverse event; MTX, methotrexate; QD, once per day; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Source: Gilead Data on File. FINCH 3 CSR. 2019. (13)

By week 24, the three most commonly reported AEs, across all grades of severity, in the filgotinib 200mg + MTX arm were nausea (10.3%), upper respiratory tract infection (5.0%), and headache (4.3%). In the filgotinib 100mg + MTX arm these were nausea (15.5%), nasopharyngitis and alopecia (16.3% for both), and diarrhoea (4.8%). In the filgotinib 200mg monotherapy arm nausea (6.2%), nasopharyngitis (15.7%), and upper respiratory tract infection (4.3%) were most frequently reported. Finally, in the MTX monotherapy, nausea (10.8%), diarrhoea (4.8%), and headache (4.6%) were most common. Table 33 presents the most common adverse events, across all grades of severity, as well as the most commonly reported AEs classified as Grade 3 or higher at week 52.

Table 33. FINCH 3 Most common TEAEs and most common Grade 3 or higher AEs at week 52, SAS

Safety assessment	Filgotinib 200mg + MTX (n=416)	Filgotinib 100mg + MTX (n=207)	Filgotinib 200mg monotherapy (n=210)	MTX monotherapy (n=416)
Most common AEs (≥5% of patients) (%)				
Most common Grade 3 or higher (≥1% of patients) (%)				

AE, adverse event; MTX, methotrexate; QD, once per day; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Source: Gilead Data on File. FINCH 3 CSR. 2019 (13).

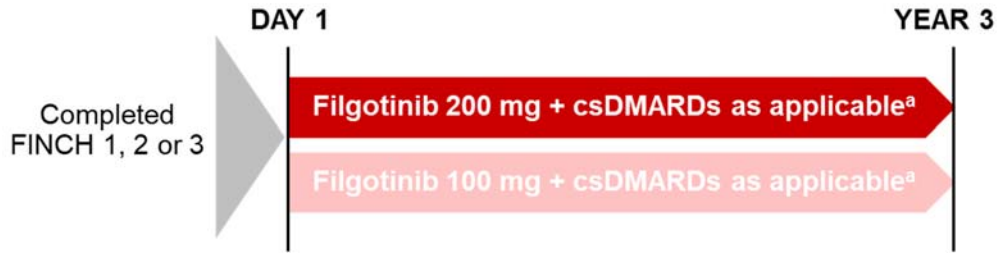
Further details of adverse events can be found in Appendix F.

B.2.11 Ongoing studies

FINCH 4 (14) is an ongoing long-term extension study, to assess the long-term safety and efficacy of filgotinib in patients who have completed one of the other Phase 3 filgotinib studies (FINCH 1, 2 or 3). FINCH 4 is a randomised, double-blind, parallel assignment trial. The two treatment arms comprise of filgotinib 200mg +

cDMARDs, and filgotinib 100mg + cDMARDs, see Figure 34. In this study, patients continue their filgotinib dose, and any concomitant treatments, from the parent study (i.e. filgotinib + MTX if the parent study was FINCH 1; filgotinib ± MTX if the parent study was FINCH 3, or filgotinib + cDMARD(s) if the parent study was FINCH 2).

Figure 34. FINCH 4 trial design



Double-blind continued filgotinib dose from parent study. If not receiving filgotinib in parent study, randomised to 200mg or 100mg of filgotinib. cDMARD=conventional synthetic disease-modifying antirheumatic drug.

Source: Gilead Data on File. FINCH 4 CSR. 2018 (14)

The primary endpoints are the proportion of patients experiencing an AE and the proportion of patients experiencing clinically significant laboratory abnormalities during a follow-up period of up to 3 years. The secondary endpoint is the proportion who achieve ACR-N response. (14)

Exploratory endpoints that will be analysed are:

- Achievement of ACR20/50/70
- EULAR responses (ACR/EULAR remission)
- Evolution of CDAI, SDAI and DAS28-CRP over time
- Evolution of PROs over time

B.2.12 Innovation

Filgotinib is a next generation, potent reversible JAK inhibitor with a selectivity for JAK1. Cytokines associated with JAK1 are involved in the inflammatory signalling pathway that drives RA progression. Targeted inhibition of JAK1 could reduce dominant inflammatory cytokine signalling involved in RA, whilst limiting impact on normal physiological function.

Its oral method of administration, similarly to other JAK inhibitors, means there are no additional costs associated with training for administering the treatment, unlike treatments given by intravenous infusion (IV), or subcutaneously (SC). It also provides more convenient storage for patients compared with regular IV or SC injections that require refrigeration.

In addition to the above, neither filgotinib nor its active metabolite induce or inhibit cytochrome P450 enzymes or inhibit critical drug transporter enzymes, including P-glycoprotein. Therefore, the potential for drug-drug interactions is low, which means filgotinib can be administered with commonly used RA drugs without the need for dose adjustments (15).

B.2.13 Interpretation of clinical effectiveness and safety evidence

Filgotinib is a convenient, once daily, oral, selective and reversible JAK1 inhibitor, with low drug-drug interaction potential (see section B.1.2).

Within the current treatment pathway in England, patients with moderately-to-severely active RA are treated with cDMARDs and are switched to bDMARDs or JAK inhibitors (apart from patients with moderate disease activity, who are currently only treated with cDMARDs in England) if they show inadequate response. Where these patients fail to respond, or are intolerant to, their first advanced treatment, they may be switched to another. JAK inhibitors also represent an important therapeutic option for these non-responder or intolerant patients. The response rates of patients treated with filgotinib underscores its place, and clinical value, in the treatment of patients with moderately -to-severely active RA who have had an inadequate response to, or who are intolerant to, one or more DMARDs.

The efficacy and safety of filgotinib has been investigated in three pivotal Phase 3 trials across the treatment pathway. FINCH 1 (detailed in section B.2.1) compared filgotinib with adalimumab and placebo, all in combination with methotrexate, in patients who had previously experienced an inadequate response to methotrexate monotherapy. FINCH 2 (detailed in section B.2.6.2) compared filgotinib with placebo (both in combination with cDMARDs), in patients with a previous inadequate response or intolerance to at least one bDMARD. Finally, FINCH 3 (detailed in

section B.2.6.3) compared filgotinib (with methotrexate or as monotherapy), with methotrexate monotherapy in patients naïve to methotrexate. Within these three studies, the demographics and other baseline characteristics were well-balanced across the different treatment arms and can be considered to be broadly generalisable to those of patients seen in NHS clinical practise in England.

The primary endpoint of all three trials was ACR20 response (at week 12 or 24), with filgotinib meeting this endpoint in all three trials, demonstrating significantly higher response rates when compared with placebo (FINCH 1 and FINCH 2), or methotrexate monotherapy (FINCH 3). For ACR20/50 and 70, filgotinib demonstrated a rapid onset of action, and demonstrated the maintenance of response with efficacy being generally maintained over the full study period up to 52 weeks. Additionally, clinically relevant results for ACR50 and ACR70 (at 12 and 24 weeks) demonstrated significantly higher response rates across all three studies. Physical function (as measured by HAQ-DI score) and proportion of patients achieving remission (DAS28-CRP <2.6), key secondary efficacy endpoints, demonstrated significant improvement in the change from baseline at week 12 and week 24 across all three trials in filgotinib arms. Filgotinib also showed superiority over placebo for EULAR good response at week 24 across all three trials. Finally, filgotinib 200mg also showed numerical superiority over adalimumab in the secondary endpoint of clinical remission (DAS28-CRP <2.6), as well as ACR50/70 and EULAR efficacy endpoints. Detailed outcomes from the trials are presented in section B.2.6.

Post-hoc subgroup analysis (detailed in section B.2.7) of patients with moderately active RA in FINCH 1 was conducted which compared filgotinib with comparator treatments (i.e. adalimumab and placebo) within the subgroup.

Results of the subgroup analysis for the moderate sub-population demonstrated that for ACR20, [redacted] Additionally, clinically relevant results for ACR50 and ACR70 (at week 24) demonstrated that filgotinib 200mg [redacted] and [redacted] with adalimumab. For the key secondary endpoints,

proportion of patients achieving remission (DAS28-CRP <2.6) and LDA, (DAS28-CRP ≤3.2), filgotinib 200mg [redacted] compared with placebo and a [redacted] versus adalimumab.

When compared with the results of the overall moderately to severely active RA population, filgotinib 200mg [redacted] ACR20, ACR50 and ACR70 response rate at week 24 and a [redacted] of patients achieving clinical remission (defined by a DAS28-CRP <2.6) in the moderate sub-population.

Filgotinib monotherapy showed numerical improvement in primary endpoint, ACR20, compared with MTX monotherapy, and superior improvements to MTX monotherapy in several key secondary endpoints in MTX-naïve populations in FINCH 3, providing supportive evidence for filgotinib as monotherapy. Filgotinib monotherapy also demonstrated numerically comparable response to filgotinib combination therapy for different endpoints such as ACR20, ACR50 and ACR70. Despite the paucity of clinical efficacy data in the filgotinib Phase 3 clinical trial programme for patients receiving monotherapy in DMARD-IR populations, the Phase 2 study DARWIN 2 provides further supportive evidence for filgotinib monotherapy in the MTX-IR population, achieving its primary endpoint of ACR20 response at week 12 for both filgotinib 100mg and filgotinib 200mg, in addition to significant improvements in key secondary endpoints.

It should be also noted that in MTA375, the Committee agreed that the minority of (cDMARD-IR) patients with severe active rheumatoid arthritis who could not tolerate methotrexate should not be treated differently from those with severe disease, as far as possible. The Committee concluded that biologic DMARDs should be recommended as a cost-effective use of NHS resources when used as monotherapy for severely active disease previously treated with DMARDs, where the Marketing Authorisation of the bDMARD allows for this recommendation to be made. It is anticipated that the filgotinib label indication will include use as both monotherapy and combination therapy.

Filgotinib was reported to be generally well tolerated and to have a consistent AE profile; most AEs were mild to moderate and rates were similar across subgroups by geographic region. There are no additional adverse events identified for filgotinib

over and above DMARDs used in current clinical practice. In addition, filgotinib is anticipated to have slightly reduced monitoring requirements to currently available JAK inhibitors. Evidence for adverse events is detailed in section B.2.10.

Finally, in addition to direct clinical evidence, a network meta-analysis, with standard RA treatments not included in the clinical trial programme, was also undertaken to support the efficacy results of filgotinib.

The results of the NMA in the cDMARD-IR population for ACR at 24 weeks indicated that filgotinib 200mg combination therapy [redacted] compared with adalimumab (40mg q2w), rituximab (1000mg), and tocilizumab (4mg/kg q4w) combination therapies. Although filgotinib 200mg was not [redacted] compared with other advanced combination therapies, the differences in modelled probabilities of ACR response were very similar compared with baricitinib (4mg), infliximab (3mg/kg) and intensive cDMARDs. For EULAR at 24 weeks, filgotinib 200mg was [redacted] to adalimumab (40mg q2w) and showed [redacted] to rituximab (1000mg) and tocilizumab (4mg/kg q4w), [redacted]. Filgotinib (200mg) was [redacted] to certolizumab pegol (200mg and 400mg) and tocilizumab (8mg/kg).

In the bDMARD-IR population, ACR at 24 weeks results showed that filgotinib 200mg combination therapy was [redacted] abatacept (10mg/kg), baricitinib (4mg), sarilumab (150mg q2w), sarilumab (200mg q2w), tocilizumab (162mg q2w), and tocilizumab (4mg/kg), [redacted] to rituximab (1000mg). For EULAR at 24 weeks, estimates indicated that filgotinib 200mg was [redacted] tocilizumab (4mg/kg q4w) and [redacted] compared with rituximab (1000mg) and tocilizumab (8mg/kg q4w). However, it should be noted that due to the high degree of variability in the control arm (cDMARDs), response in this network the results should be interpreted with caution. In summary, filgotinib can be considered to be broadly similar to other treatments across both populations. For full details of the NMA, please see section B.2.9.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

B3.1.1 Identification of studies

A systematic literature review was conducted to identify published economic evaluations in moderate to severe RA, which could be used to address the decision problem and inform the economic model structure. Full details of the search are provided in Appendix G, as well as detailed inclusion/exclusion criteria for the review.

B.3.2 Economic analysis

The systematic literature review search of cost-effectiveness studies (detailed in Appendix G) identified 103 unique economic evaluations in RA. No relevant economic evaluations able to provide estimates for the cost-effectiveness of filgotinib in RA were identified. Therefore, a model in line with that presented in MTA375 was developed using Microsoft® Excel® (Office 365, version 1902) with Visual Basic for Applications (VBA) functionality.

As in previous TAs in RA, the economic evaluation conducted by the assessment group (AG) in MTA375 was deemed the most relevant for decision-making in moderate to severe RA in England and Wales (1). Therefore, to the extent feasible, the economic evaluation detailed in this submission was developed to be consistent with that of MTA375, in addition to those presented in subsequent TAs e.g. TA480 and TA466. The comparability between the modelling approaches in MTA375 and this submission is discussed in the proceeding sections, with full details of the model structure discussed in section B3.2.2.

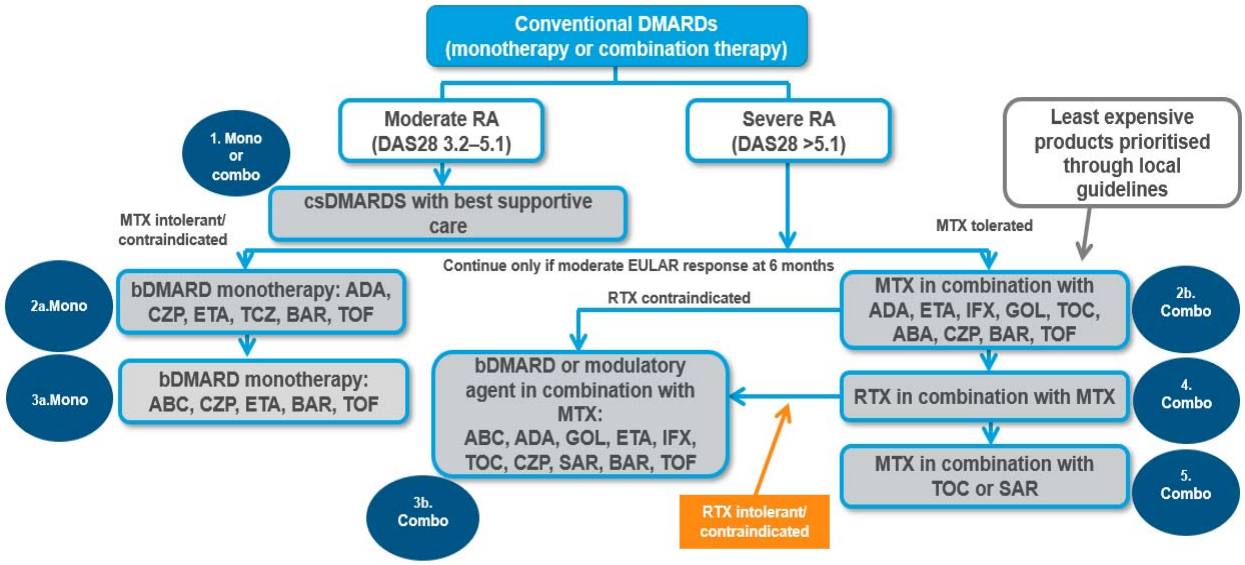
B3.2.1 Patient population

The cost-effectiveness analysis models patients with moderately to severely active RA. Patients are categorised into subpopulations depending on their disease severity, line of treatment and tolerance to guideline-recommended treatments. Broadly, patients encompass three main groups:

1. Adults with moderate RA (DAS28 of 3.2-5.1) who have had inadequate response to or are intolerant to csDMARDs (moderate cDMARD-IR)
2. Adults with severe RA (DAS28 >5.1) who have an inadequate response to csDMARDs only (severe cDMARD-IR)
3. Adults with severe RA (DAS28 >5.1) who have an inadequate response to bDMARDs (severe bDMARD-IR)

In line with NICE treatment guidelines (shown in Figure 35), patients are further sub-categorised providing a total of eight individually analysed populations. Therefore, this cost-effectiveness analysis reflects the use of filgotinib within its anticipated Marketing Authorisation, the populations outlined in the NICE scope, and clinical practice in the UK.

Figure 35. Current NICE treatment guidance on treatment of moderately to severely active RA



ADA=adalimumab; ABC=abatacept; BAR=baricitinib; Combo = combination therapy with methotrexate; CZP=certolizumab pegol; DAS=Disease Activity Score; DMARD=Synthetic disease modifying antirheumatic drugs; ETA=etanercept; GOL=golimumab; IFX=infliximab; Mono = monotherapy; MTX=Methotrexate; RA=Rheumatoid arthritis; RTX=Rituximab; TCZ=tocilizumab; TOF=tofacitinib;

Source: NICE 2009 clinical guideline: 2020 update [NG100] (2)

Two patient populations are modelled for the use of filgotinib in moderate RA:

1a. As monotherapy after two or more cDMARD failures in patients who are MTX ineligible

1b. As combination therapy after two or more cDMARD failures in patients who are MTX eligible

Four patient populations are modelled for the use of filgotinib in combination with MTX in severe RA, for patients who are MTX eligible:

2b. As first line advanced therapy after failure of 2+ csDMARDs

3b. After first line advanced therapy failure in patients who are RTX ineligible

4. After first line advanced therapy failure in patients who are RTX eligible

5. After failure of RTX in combination with MTX

Two patient populations are modelled for the use of filgotinib monotherapy in severe RA, for patients who are MTX ineligible:

2a. As first line advanced therapy after failure of 2+ csDMARDs

3a. After first line advanced therapy failure

B3.2.2 Model perspective

The perspective for this analysis is that of the NHS and Personal and Social services (PSS) in England and Wales (in line with current NICE guidance). This cost-effectiveness analysis therefore excluded patients' out of pocket expenses, carers' costs, and lost productivity costs. All costs are report in pounds sterling (2019/20).

B3.2.3 Model Structure

Model structure and flow

The cost-effectiveness analysis is conducted using a discrete event simulation (DES) model, consistent with MTA375 (1), as well as subsequent submissions in RA. As such, the model generates a cohort of patients, these patients are tracked over time, during which time key events are captured. Each patient's flow through the model is described as follows:

1. Patients are sampled at random from the provided patient population (based on the patient baseline characteristics in the FINCH clinical trial programme)

2. Each patient is simulated through the following process:

    I. Patient time to death is calculated

        i. Upon model initiation a patient's time of death is determined dependent on their age, sex and HAQ-DI.

        ii. If a patient dies within the first six months, this is modelled as an immediate death incurring no costs or QALYs and a new patient is subsequently sampled.

    II. Patients alive at six months progress to the initial treatment phase where they either continue treatment, or discontinue treatment if they do not achieve a good or moderate EULAR response

        i. If a patient remains alive at six months (after the initial treatment phase), then they progress to the six-month initial treatment phase. Thus, all patients who do not die during the initial six months are assumed to complete the initial phase of treatment.

        ii. If a patient experiences an AE during this phase of the model, they complete the initial treatment phase gaining no treatment benefit but incur costs and QALYs based on their baseline HAQ-DI and the respective AE. The patient then re-enters the six-month initial treatment phase on the next treatment line.

        iii. For patients not experiencing an AE by the end of the six-month initial treatment phase, a EULAR treatment response is sampled, based on the efficacy of the specific treatment. If no EULAR response is achieved, then the patient discontinues the current treatment accruing costs and QALYs based on their baseline HAQ-DI and re-enter the model at the six-month initial treatment phase on the next treatment in the sequence.

    III. Patients enter the maintenance treatment phase upon achieving a good or moderate EULAR response

i. Once a patient enters the maintenance treatment phase, time to treatment discontinuation is sampled and compared with time to death. The trajectory of a patient's HAQ-DI score from treatment initiation to the either death or discontinuation (whichever occurs first) is then estimated and relevant utilities, costs, LYs and QALYs are accrued and calculated accordingly.

ii. Note that utility is accrued linearly over each six-month period. For example, if a patient has utility of 0.5 at the start of the period and 1 at the end of the period, the QALYs accrued in the model will be 0.75/2 = 0.375 per six-monthly cycle. This is equivalent to assuming utility increases linearly over, for example, the initial treatment period, or decreases linearly over the last treatment period before discontinuation.

iii. In the event of discontinuation, the patient's HAQ-DI score rebounds to their baseline score, i.e. it is reduced by the same amount as the initial treatment effect, and the patient moves onto the next treatment in the treatment sequence.

iv. If death occurs before treatment discontinuation, the patient's lifetime costs, QALYs and LYs are accrued and the model restarts with the next simulated patient.

v. The model assumes that the final treatment in every treatment sequence is BSC. Therefore, once a patient starts BSC, no discontinuation time is sampled, and the patient remains on this line of treatment until death.

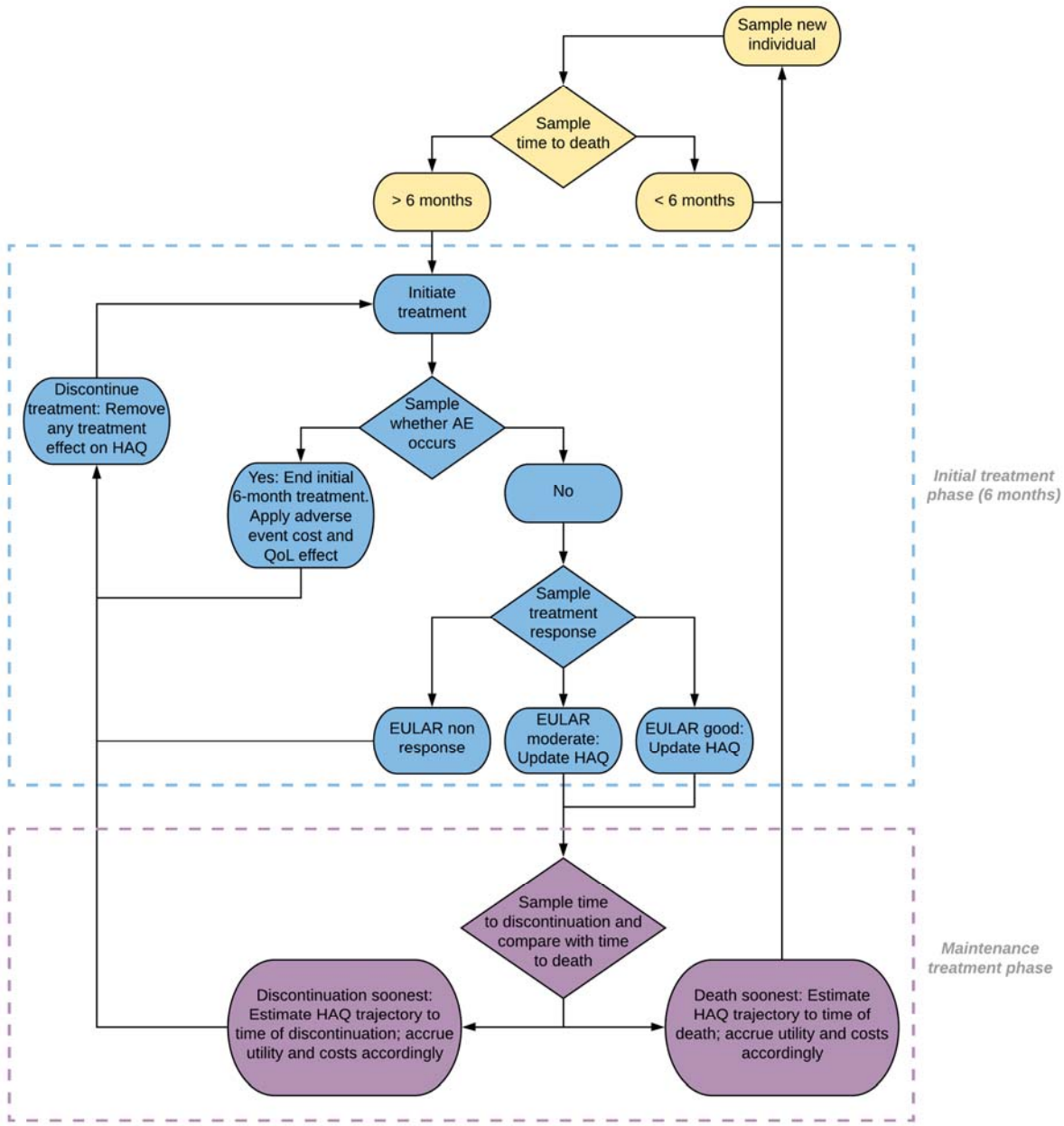
3. Following the death of a simulated patient a new patient is sampled at random with replacement from the provided patient population.

This process is repeated until the sampled population size reaches that specified by the model user, and the base case analysis were conducted using 10,000 patients. Once the full population has been modelled the process is repeated for any

additional treatment arms (strategies) as specified by the user. A set of random numbers is used for sampling events, which is the same for each arm. Therefore, the population in each arm is identical, and the randomly sampled events will occur in the same way, with the only difference being the introduction of different treatments in comparator arms.

A schematic depicting the model pathway is outlined in Figure 36.

Figure 36.Cost-effectiveness model schematic



AE, adverse event; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; QoL, quality of life

The main features of the economic analysis, and other recent NICE submissions in RA, are presented in Table 34.

Table 34. Features of the economic analysis

Factor	Previous appraisals								Current appraisal	
	TA375 (2016) (1)	**TA485 (2017) (2)**	**TA480 (2017) (3)**	**TA466 (2017) (4)**	**TA415 (2016) (5)**	**TA247 (2011) (6)**	**TA225 (2010) (7)**	**TA195 (2010) (8)**	**Chosen values**	**Justification**
Model type	Patient-level CEA model using DES structure				Markov model	Patient-level CEA model using DES structure	Markov model	Patient-level CEA model using DES structure	Patient-level CEA model using DES structure	Consistent with previous models, and MTA375
Were health effect measured in QALYs; if not, what was used?	Yes								Yes	Recommended in the NICE methods guide
Perspective	UK NHS and PSS								UK NHS and PSS	Recommended in the NICE methods guide
Time horizon	Lifetime								Lifetime	Long enough to reflect all important differences in costs or outcomes between the technologies being compared
Discount for utilities and costs	3.5%								3.5%	Recommended in the NICE methods guide
Source of utilities	HAQ-DI values are mapped to EQ-5D utility using algorithm designed by Hernandez-Alva et al. 2013	EQ-5D utility was estimated from patient HAQ-DI using the algorithm developed by Malottki et al. 2011 (9)	HAQ-DI values are mapped to EQ-5D utility using algorithm designed by Hernandez-Alva et al. 2013 (10)	HAQ-DI values are mapped to EQ-5D utility using algorithm designed by Hernandez-Alva et al. 2012	Initial response on first-line treatment was estimated using data from the PREDICT study. HAQ-DI scores were mapped to	The base case analysis uses a quadratic equation to map HAQ-DI to utility, as reported in TA198 (updated and replaced by	EQ-5D values were estimated from HAQ-DI using a regression function from Chen et al. 2006 (11)	The Assessment Group used a non-linear equation to convert HAQ-DI scores to EQ-5D scores	HAQ-DI values are mapped to EQ-5D utility using algorithm designed by Hernandez-Alva et al. 2013	Established approach in RA economical evaluations, and in line with MTA375

					EQ-5D utilities for the following treatments by using the mapping algorithm from Brennan et al.	TA247)				
Source of costs	TA247 NHS reference costs 2011-2012 Malottki et al. 2011	TA375 PSSRU 2016 NHS Reference Costs 2015–16	British National Formulary 2016 NHS Reference Costs 2015–16 and 2010-11 PSSRU 2016 Malottki et al 2011	British National Formulary 2016 TA375 MIMS 2016	British National Formulary 2016 NHS reference costs 2014/15 PSSRU 2015 TA247	British National Formulary 2011 NOAR database	NHS Reference Costs 2008 PSSRU 2009	Chen et al. 2006 (11) PSSRU 2008 British National Formulary 58	TA375 (1) MIMS 2019	Use of latest drug pricing data, as well as inflated costs from the most relevant model, MTA375

Abbreviations: CEA, cost-effectiveness analysis; DES, discrete event simulation; EQ-5D, EuroQol 5 dimension; HAQ-DI, Health Assessment Questionnaire – Disability Index; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NOAR, Norfolk Arthritis Register; PSSRU, Personal Social Services Research Unit; PSS, Personal Social Services; QALY, quality adjusted life year; RA, rheumatoid arthritis; TA, technology appraisal; UK, United Kingdom.

Molecules assessed in TAs: TA485, sarilumab; TA480, tofacitinib; TA466, baricitinib; TA415, certolizumab pegol; TA247, tocilizumab; TA225, golimumab; TA195, adalimumab, etanercept, infliximab, rituximab and abatacept.

B3.2.4 Intervention technology and comparators

The model assessed the first-line comparators and subsequent treatments in sequence, with up to eight treatments considered in a treatment sequence. The efficacy of filgotinib and its comparators were informed by a network meta-analysis (NMA), which informed EULAR response rates in the model.

Intervention

The intervention considered in the model is filgotinib 200mg, administrated once daily orally in combination with methotrexate or as monotherapy. Filgotinib is indicated for the treatment of moderately to severely active RA in adult patients who have responded inadequately to or are intolerant to one or more csDMARDs.

Comparator

Comparators included in the model are consistent with NICE recommendations in the RA treatment pathway and are in line with the final NICE scope for filgotinib, which includes csDMARDs, bDMARDs as well as BSC. BSC was assumed to comprise of 'post-biologic' cDMARD therapies (Leflunomide, gold, cyclophosphamide), in line with MTA375.

Specific molecules were selected based on market share data (Therapy Watch (1)) and clinical validation regarding the most likely sequences utilised in clinical practise. The full treatment sequences modelled are detailed in section B3.2.5.

B3.2.5 Treatment sequences in the model

The model considered treatment sequences of up to eight treatment lines. The specific treatment sequences in each target population are described in Table 35 through Table 43. The treatment sequences used in this submission are in keeping with treatments suggested by NICE guidelines and have been validated using both market share data and clinical expert validation.

Population 1: Moderate RA

Clinical opinion indicated that most patients with moderate disease activity would receive 2 csDMARDs. Failing this, BSC is the only option which includes low dose csDMARDs (which may have been previously trialled) and corticosteroids.

1a. Moderate RA patients after 2 cDMARD failures (MTX ineligible)

Table 35: Treatment sequences considered in moderately active cDMARD-IR patients after two cDMARD failures

Sequence	First-line treatment	Second-line treatment
1	***FIL***	***BSC***
2	PBO/BSC	BSC
Abbreviations: BSC, best supportive care; FIL, filgotinib; MTX, methotrexate; PBO, placebo		

1b. Moderate RA patients after 2 cDMARD failures (MTX eligible)

Table 36: Treatment sequences considered in moderately active cDMARD-IR patients after two cDMARD failures

Sequence	First-line treatment	Second-line treatment
1	***FIL + MTX***	***BSC***
2	PBO/BSC	BSC
Abbreviations: BSC, best supportive care; FIL, filgotinib; MTX, methotrexate; PBO, placebo		

Population 2: cDMARD-IR

2a. Severe RA patients in first line advanced therapy treatment of (MTX ineligible)

Market share data indicates 69% of 1L advanced therapy (not mono- and combination-therapy specific) in the UK comprises of an anti-TNF agent, of which 29.3% and 29.8% is attributable to ADA and ETN (including biosimilars), respectively. BAR is the most commonly used JAK in 1L advanced therapy, contributing 6.1% in the UK compared 2.3% for TOF. Finally, TCZ accounts for 11.2% of all 1L therapies and clinical expert opinion indicated its use in 1L would be mostly in monotherapy. Given 1L and 2L monotherapy options are largely the same,

it was agreed that ABT would be the most likely 2L option and that anti-TNF cycling is not a clinically preferred approach. Throughout analyses, subcutaneous formulations were selected based on clinical preference.

This appropriateness of this selection was validated by clinical experts.

Table 37: Treatment sequences considered in first line advanced therapy treatment of severe RA (MTX ineligible)

Sequence	First-line treatment	Second-line treatment	Third-line treatment
1	***FIL***	***ABC SC***	***BSC***
2	ADA	ABC SC	BSC
3	ETN	ABC SC	BSC
4	BAR	ABC SC	BSC
5	TCZ SC	ABC SC	BSC

Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; MTX, methotrexate; TCZ, tocilizumab

2b. Severe RA patients in first line advanced therapy treatment (MTX eligible)

For patients who are MTX eligible and RTX is tolerated the rationale for the choice of 1L comparators is as per population 2a, with the omission of TCZ based on clinical opinion as described above. At 3L clinical expert opinion indicated that TCZ would be the most utilised option and that SAR should only be modelled if there are significant differences in costs as its usage is expected to be low.

Table 38: Treatment sequences considered in first line advanced therapy treatment of severe RA (MTX eligible, RTX tolerated)

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment
1	***FIL + MTX***	***RTX + MTX***	***TCZ SC + MTX***	***BSC***
2	ADA + MTX	RTX + MTX	TCZ SC + MTX	BSC
3	ETN + MTX	RTX + MTX	TCZ SC + MTX	BSC
4	BAR + MTX	RTX + MTX	TCZ SC + MTX	BSC

Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; MTX, methotrexate; RTX, rituximab; SAR, sarilumab; TCZ, tocilizumab

For patients who are MTX eligible but RTX is contraindicated (or not tolerated) the rationale for 1L treatments is as per Table 38. At 2L, anti-TNF cycling is not considered appropriate (see above) although clinical expert opinion indicated that 2L options could include IL-6 or CD-80 agents. TCZ was preferred to SAR as the 2L option based on clinical opinion and 2L market share data (11.2% vs. 0.5%, respectively).

Table 39: Treatment sequences considered in first line advanced therapy treatment of severe RA (MTX eligible, RTX contraindicated)

Second line IL-6			
Sequence	**First-line treatment**	**Second-line treatment**	**Third-line treatment**
1	***FIL + MTX***	***TCZ SC + MTX***	***BSC***
2	ADA + MTX	TCZ SC + MTX	BSC
3	ETN + MTX	TCZ SC + MTX	BSC
4	BAR + MTX	TCZ SC + MTX	BSC
Second line CD80			
Sequence	**First-line treatment**	**Second-line treatment**	**Third-line treatment**

5	***FIL + MTX***	***ABC SC + MTX***	***BSC***
6	ADA + MTX	ABC SC + MTX	BSC
7	ETN + MTX	ABC SC + MTX	BSC
8	BAR + MTX	ABC SC + MTX	BSC
Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; MTX, methotrexate; RTX, rituximab; SAR, sarilumab; TCZ, tocilizumab			

Population 3: bDMARD-IR

3a. Severe RA patients after failure of first line advanced therapy treatment (MTX ineligible, RTX ineligible)

Comparators were selected in line with the NICE treatment pathway. A limited number of molecules are recommended as 2L advanced treatments. Anti-TNF agents were not included based on clinical expert feedback that anti-TNF cycling is not an optimal treatment approach. All other recommended drug classes are included.

Table 40: Treatment sequences considered after failure of first line advanced therapy treatment of severe RA (MTX ineligible, RTX ineligible)

Sequence	First-line treatment	Second-line treatment
1	***FIL***	***BSC***
2	ABC SC	BSC
3	BAR	BSC
4	TOF	BSC
Abbreviations: ABC, abatacept; BAR, baricitinib; BSC, best supportive care; FIL, filgotinib; MTX, methotrexate; RTX, rituximab; TOF, tofacitinib		

3b. Severe RA patients after failure of first line advanced therapy treatment (MTX eligible, RTX ineligible)

As per clinical advice, the most commonly used agent in each class (at 2L) was selected. Anti-TNFs were excluded as described above.

Table 41: Treatment sequences considered after failure of first line advanced therapy treatment of severe RA (MTX eligible, RTX ineligible)

Sequence	First-line treatment	Second-line treatment
1	***FIL + MTX***	***BSC***
2	ABC SC + MTX	BSC
3	TCZ SC + MTX	BSC
4	SAR + MTX	BSC
5	BAR + MTX	BSC
Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; FIL, filgotinib; MTX, methotrexate; RTX, rituximab; SAR, sarilumab; TCZ, tocilizumab		

Severe RA patients after failure of first line advanced therapy (MTX eligible, RTX eligible)

The only guideline recommended option is RTX. TCZ was preferred to SAR as the appropriate final active therapy based on clinical advice and market share.

Table 42: Treatment sequences considered after failure of first line advanced therapy in MTX eligible patients (RTX eligible)

Sequence	First-line treatment	Second-line treatment	Third-line treatment
1	***FIL + MTX***	***TCZ SC + MTX***	***BSC***
2	RTX + MTX	TCZ SC + MTX	BSC
Abbreviations: BSC, best supportive care; ETN, etanercept; FIL, filgotinib; MTX, methotrexate; RTX, rituximab; SAR, sarilumab; TCZ, tocilizumab			

Severe RA patients after failure of rituximab in combination with methotrexate

After failure of RTX, TCZ and SAR are the only guideline recommend options.

Table 43: Treatment sequences considered in severely active RA, RTX-IR population

Sequence	First-line treatment	Second-line treatment
1	***FIL + MTX***	***BSC***
2	TCZ SC + MTX	BSC
3	SAR + MTX	BSC
Abbreviations: BSC, best supportive care; FIL, filgotinib; MTX, methotrexate; RTX, rituximab; SAR, sarilumab; TCZ, tocilizumab		

B.3.3 Clinical parameters and variables

B3.3.1 Patient population

A patient cohort was generated by random sampling, using characteristics derived from the Phase 3 filgotinib FINCH trials. Where characteristics required for the model were not available from the clinical trials, values have been taken from the Early Rheumatoid Arthritis Study (ERAS) dataset as described by Norton et al (2).

The baseline population characteristics used in the cost-effectiveness model (CEM) are outlined in Table 44. These inputs are taken directly from the FINCH 1 and FINCH 2 trials (3, 4), using data stratified according to disease severity. Using these summary statistics, a cohort of 1,000 patients was sampled randomly, using appropriate probability distributions.

Table 44: Patient baseline characteristics used in the CEM

Characteristics	Moderate cDMARD-IR		Severe cDMARD-IR		Severe bDMARD-IR	
	Mean (SD)	Source	Mean (SD)	Source	Mean (SD)	Source
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion female	[redacted]		[redacted]		[redacted]	
Duration of disease (years)	[redacted]		[redacted]		[redacted]	
Number of prior DMARDs	[redacted]		[redacted]		[redacted]	
Baseline HAQ-DI	[redacted]		[redacted]		[redacted]	
Baseline Pain (VAS)	[redacted]		[redacted]		[redacted]	
Weight (kg)	[redacted]		[redacted]		[redacted]	
DAS28	[redacted]		[redacted]		[redacted]	
RF (positive)	[redacted]		[redacted]		[redacted]	
IMD quartile	2.37	Norton et al. (2)	2.37	Norton et al. (2)	2.37	Norton et al. (2)
ACR (positive)	0.71		0.71		0.71	

Abbreviations: ACR, American College of Rheumatology; bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug; DMARD, disease-modifying anti-rheumatic drug; DAS28, disease activity score 28 joints; HAQ-DI, Health Assessment Questionnaire – Disability index; IMD, index of multiple deprivation; IR, insufficient response; RF, rheumatoid factor; SD, standard deviation; VAS, visual analogue scale

Values were sampled from the following distributions:

- Normal distribution for weight and age
- Variables expected to be positively skewed were sampled using gamma distribution for duration: duration of disease, disease activity score (DAS28), health assessment questionnaire disability index (HAQ-DI) and number of prior DMARDs
- As the pain variable has a limited range (from 0 to 100), a beta distribution was used for sampling baseline pain

Sampled values were bounded by minimum and maximum values, where appropriate. DAS28 was restricted to values ranging from 2 to 10, and patients were assumed to be adults between 18 and 100 years of age.

Additionally, HAQ-DI scores were restricted to values ranging from 0 to 3 by an increment of 0.125, as was done in MTA375. Initially, HAQ-DI scores were assigned to each patient at baseline, by sampling from a gamma distribution. HAQ-DI scores were then rounded up or down to the nearest valid score, using a random variable.

B3.3.2 Efficacy

Clinical response in the model is based on the EULAR response criteria. The probability of achieving a EULAR response (none, moderate or good) at six months (24 weeks) for filgotinib and comparators in the model were estimated from the NMAs evaluating treatment response for RA treatments in both the cDMARD-IR and bDMARD-IR populations. Full details of the NMA are detailed in section 2.9.

Although the ACR response metric is widely used in RA clinical trials, the EULAR response criteria is the preferred measurement of treatment response in UK clinical practice, and is recommended for use in the NICE guidance (5) for RA. The EULAR response is thus the treatment measure used for the economic modelling. ACR responses can be converted to EULAR response based on an approach developed by Stevenson et al., using US Veterans' Affairs Rheumatoid Arthritis Registry (VARA) data where both measures were reported (6). The mapping algorithm as described and used in MTA375, has been applied in this analysis, where applicable.

Efficacy estimates are shown as a proportion of the population achieving response in each outcome: EULAR response (none, moderate or good) in Table 45 and ACR response converted to EULAR response in **Table 27**.

Table 45: Probability of achieving a given response based on 24-week EULAR data.

Treatment	cDMARD-IR population			bDMARD-IR population		
	No response	Moderate response	Good response	No response	Moderate response	Good response
FIL (200mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA (40mg q2w) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX (1000mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
csDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Abbreviations: ADA, adalimumab; bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional synthetic disease-modifying anti-rheumatic drug; EULAR, European League Against Rheumatism; IR, insufficient response; MTX, methotrexate; q2w, once every two weeks; q4w, once every four weeks; RTX, rituximab; TCZ, tocilizumab

*A comparison was not possible in the NMA.

Table 46: Probability of achieving a given response based on 24-week ACR data converted to EULAR.

Treatment	cDMARD-IR population			bDMARD-IR population		
	No response	Moderate response	Good response	No response	Moderate response	Good response
FIL (200mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABC (10mg/kg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABC (125 mg qw) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA (40mg q2w) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BAR (4mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN (50mg qw) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX (1000mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAR (200mg q2w) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ (162mg q2w) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
csDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABC, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; BAR, baricitinib; bDMARD, biologic disease-modifying anti-rheumatic drug; cDMARD, conventional disease-modifying anti-rheumatic drug ; ETN, etanercept; IR, insufficient response; MTX, methotrexate; qw, once a week; q2w, once every two weeks; q4w, once every four weeks; RTX, rituximab; SAR, sarilumab; TCZ, tocilizumab;

* A comparison was not possible in the NMA.

For treatments where the efficacy could not be informed by the NMA, a number of assumptions were made (see Table 47).

BSC is assumed to have no treatment effect (i.e. EULAR non-response), in line with the assumption made in MTA375. Additionally, recent submissions in RA have made the same assumption (TA485, TA480 and TA466 (7-9)).

Efficacy data for filgotinib as monotherapy in the cDMARD-IR and bDMARD-IR populations are not available from the filgotinib clinical trial programme. Therefore, monotherapies were not included in the NMA as no comparison to filgotinib monotherapy can be made for these populations. For the purpose of this economic evaluation, it is assumed that monotherapy will have the same relative effect across all treatments as combination therapy. Data from FINCH 3 demonstrated that the addition of MTX to filgotinib 200mg produced no marked improvement over filgotinib

200mg monotherapy in an MTX-naïve population (percentage of ACR20 responders were 78.1% and 81.0% in the monotherapy and combination therapy arm, respectively at week 24) supporting the assumption of equivalent efficacy for monotherapy versus combination therapy, see B2.6. Furthermore, this approach is in line with that employed in TA466 and is further supported by the committee guidance in MTA375. The guidance indicated that the minority of (cDMARD-IR) patients with severe active rheumatoid arthritis who could not tolerate methotrexate should not be treated differently from other people with severe disease, as far as possible.

Individual studies included in both the cDMARD-IR and bDMARD-IR NMAs mainly reported data for the moderately to severely active RA population, i.e. results stratified by disease severity (for the moderate and severe population separately) are rarely reported. Therefore, due to the lack of available data, NMAs were not conducted separately by disease severity. Therefore, for this economic analysis, it was assumed that the efficacy results from the NMA in the cDMARD-IR population were applicable for both patients in the moderate and severe populations. Similarly, trials included in the bDMARD-IR NMA included patients with moderately to severely active RA but the efficacy results were considered applicable for patients with severely active RA. This is consistent with the approach taken by the Assessment Group in MTA375.

Comparisons of the moderate and severe subgroups efficacy results in the FINCH 1 trial to the whole cohort suggest that the efficacy was similar across the populations considered (see section B2.7). Thus, the use of the same efficacy data is additionally supported by the trial data.

For three treatments, (TCZ SC and ABC SC combination therapies, TOF monotherapy) used in the severe cDMARD-IR and bDMARD-IR populations, additional efficacy assumptions were needed.

A summary of the assumptions relating to treatment efficacy are detailed in Table 47 below.

Table 47: Summary of efficacy assumptions included in the CEM

Patient population	Treatments to which assumption applies	Assumptions	Justification
All populations	All interventions	Due to a paucity of studies reporting results stratified by severity, no NMA was performed separately for the moderate and severe populations. Therefore, efficacy for the moderate and severe subgroups was assumed equivalent to treatment effect in the overall moderately to severely active RA NMAs.	Efficacy results were similar across moderate and severe subpopulations in the FINCH 1 trial
Severe cDMARD-IR	• TCZ SC + MTX	No data available from the cDMARD-IR NMA. Efficacy assumed equivalent to TCZ SC + MTX (in bDMARD-IR NMA)	Relative efficacy not expected to differ significantly through treatment lines
Severe bDMARD-IR	• ABC SC + MTX	No data available from the bDMARD-IR NMA. Efficacy assumed equivalent to ABC IC + MTX (in cDMARD-IR NMA)	Relative efficacy not expected to differ significantly through treatment lines
	• TOF monotherapy	No data available from the bDMARD-IR NMA. Efficacy assumed equivalent to BAR + MTX (in bDMARD-IR NMA)	This approach has previously been applied in TA10389
All populations	• All monotherapy interventions	No NMA for monotherapies was performed, as efficacy data was not available for cDMARD-IR and bDMARD-IR populations for filgotinib as monotherapy. Therefore, all monotherapies are assumed to have the same relative effect as the corresponding combination therapies.	Efficacy results were similar across monotherapy and combination therapy in the FINCH 3 trial

Abbreviations: ABC, abatacept; BAR, baricitinib; bDMARD biologic disease-modifying anti-rheumatic drug; cDMARD conventional disease-modifying anti-rheumatic drug; FIL, filgotinib; IR, insufficient response; IV, intravenous; JAK, Janus kinase; MTX, methotrexate; NMA, network meta-analysis; SC, subcutaneous; TCZ, tocilizumab; TOF, tofacitinib

B3.3.3 HAQ-DI progression

Initial reduction

At the end of the six-month initial treatment phase a patient's HAQ-DI score is assumed to reduce dependent upon the initial treatment effect (i.e. whether achieving a moderate or good EULAR response). Patients with no response do not experience a reduction in HAQ-DI, i.e. their HAQ-DI trajectory is assumed to be constant. The reduction applied was derived by the Assessment Group in MTA375 using data from the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA). Due to limited data availability, this initial HAQ-DI value reduction is independent of treatments received, an approach consistent with that taken in MTA375, and other recent submissions (TA485 (9), TA480 (8), TA466 (7)). The initial reductions in HAQ-DI applied in the model are summarised in Table 48.

Table 48: Initial reduction in HAQ-DI based on the BSRBR-RA database (10)

EULAR response	Mean change in HAQ	SE
Good	-0.672	0.112
Moderate	-0.317	0.048

Abbreviations: BSRBR-RA, British Society of Rheumatology Biologics Register for Rheumatoid Arthritis; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire Disability Index; SE, standard error

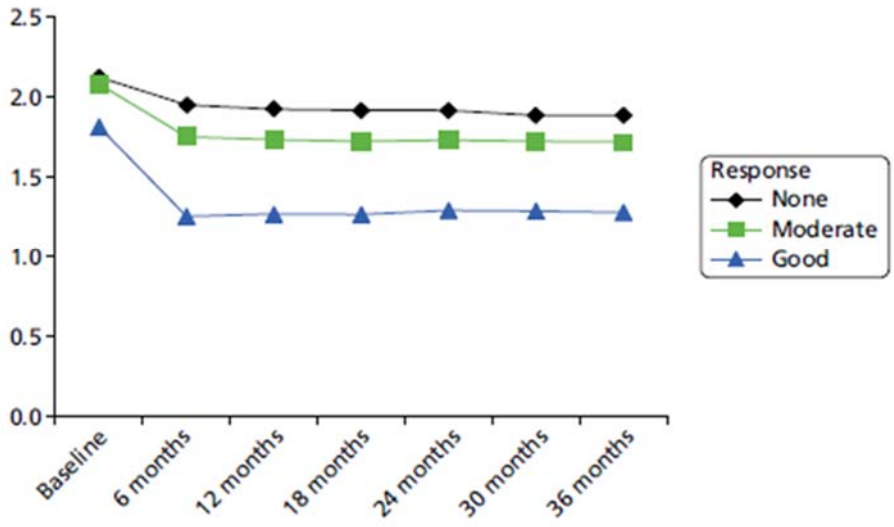
Long-time progression

After the initial six-month treatment phase, as a patient progresses further through the model, the change in HAQ-DI score is dependent on the treatment received. Patients achieving a good or moderate EULAR response at six months continue receiving their current treatment, and experience a treatment-dependent HAQ-DI progression as described below:

- Treatment with a bDMARD results in a HAQ-DI trajectory based on those reported in the 36-month BSRBR dataset analysed by the AG in MTA375 (6). This trajectory is dependent on the initial response of the patient (moderate or good response) and their baseline characteristics including disease duration

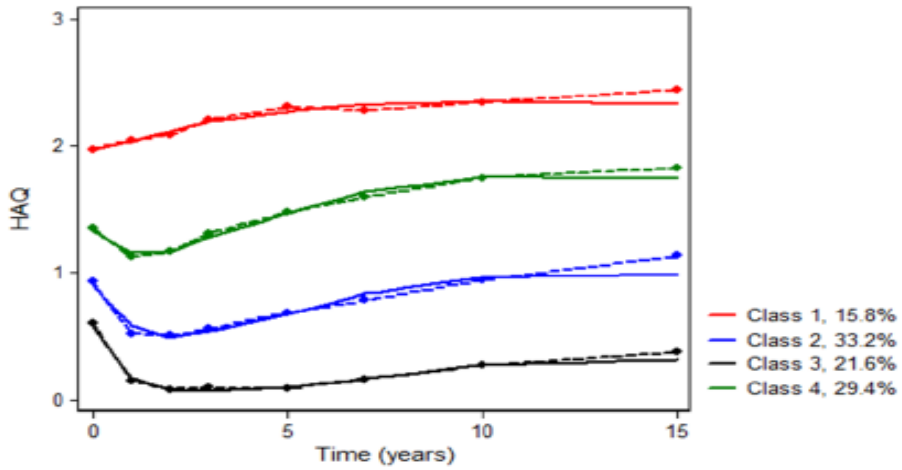
at initiation. The first 36 months of the trajectory are estimated using the autoregressive latent trajectory model in MTA375, after which HAQ-DI is assumed to remain stable. This method is in line with that applied in MTA375. The data used to model the progression is depicted in Figure 37.

Figure 37. Mean HAQ-DI by EULAR response category for those receiving bDMARDs. Figure sourced from MTA375.



- Those patients receiving csDMARDs experience a trajectory in HAQ-DI score based on the 15-year ERAS cohort data described by Norton et al (2). Estimates reported by Norton et al. combined with patient baseline characteristics from the FINCH trials defined the long-term HAQ-DI trajectory for individual patients for 15 years following treatment with a cDMARD, after which HAQ-DI is assumed to remain stable. This assumption is consistent with the approach taken in MTA375. The findings of Norton et al are shown visually in Figure 38; note that the concern of the cost-effectiveness model is to estimate the expected change in HAQ over time, not with the latent classes per se. The latent class analysis provides a more flexible and appropriate method of modelling HAQ change over time

Figure 38. HAQ-DI trajectory for csDMARDs (four latent class) based on Norton et al. (2)



- The patients receiving BSC are assumed to experience the same HAQ-DI trajectory as patients receiving csDMARDs.
- HAQ-DI is assumed to change immediately at the end of each six-month period.

In a scenario analysis, the sensitivity of the model to the chosen HAQ-DI trajectory approach was explored, by assuming patients receiving csDMARDs and BSC experienced a linear HAQ-DI progression based on Malottki et al. (11) (detailed in Table 49) rather than the base case approach by Norton et al.

Table 49: Annual increase in HAQ-DI score for patients on csDMARDs and BSC sourced from Malottki et al.

Treatment	Mean change in HAQ-DI
csDMARDs	0.045
BSC	0.060
Abbreviations: BSC, best supportive care; cDMARD, conventional synthetic disease-modifying anti-rheumatic drug; Health Assessment Questionnaire Disability Index	

B3.3.4 Treatment discontinuation

Treatment discontinuation over time is dependent on a patient's EULAR response (moderate or good response) to treatment and is based on the BSRBR dataset analysis by the AG in MTA375. Patients who achieve a EULAR response (good or

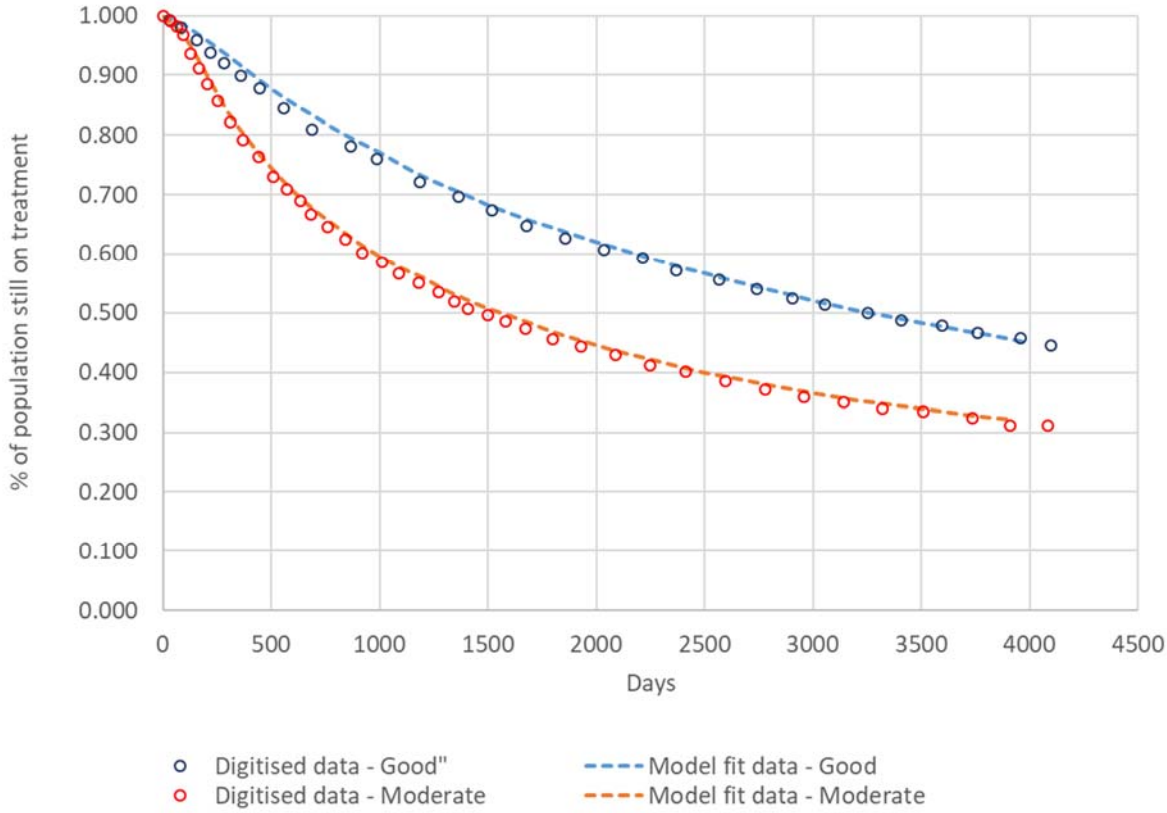
moderate) following the first six-month phase continue their current treatment. Time to treatment discontinuation is sampled for each patient once they enter the maintenance treatment phase.

Model parameters were not published as part of the analysis. Therefore, the published curve was digitised and used to generate individual patient data. This was then used to fit a survival curve (generalised Gamma, in line with the parametric model described in MTA375), the parameters of which have been applied in the model to obtain sampled time to discontinuation for each patient (Table 50). Model fit to digitised data can be seen in Figure 39.

Table 50: Parameters for time to discontinuation for moderate and good EULAR response

Parameters	Moderate EULAR response	Good EULAR response
mu	6.897	8.135
Sigma	1.701	1.612
Q	-0.745	0.067
Abbreviations: EULAR, European League Against Rheumatism		

Figure 39. Parametric survival models estimating time to discontinuation of treatment for patients with moderate and good EULAR response



B3.3.5 Mortality

Age- and sex-specific all-cause survival was derived from UK life-tables 2015-2017(12) . Consistent with the methodology applied in MTA375, Gompertz curves were fitted to the raw data and adjusted within the model dependent on the starting age of the individual patient. Survival was adjusted by relative risk as a function of baseline HAQ-DI. It was assumed that only the baseline HAQ-DI score was important for predicting mortality, in line with the approach taken in MTA375. The hazard ratios (HRs), sourced from MTA375, for survival stratified by HAQ-DI score are outlined in Table 51. As the model considers HAQ-DI score in 0.125 increments, the scores are stratified accordingly. For the reference case, patients with HAQ-DI score of 0, only the all-cause mortality is considered. Other patients experience disease-related mortality calculated using the appropriate HR.

Table 51: Hazard ratio for mortality associated with HAQ-DI category

HAQ-DI score	HR (95% CI)
0.000	1.00 (reference)
0.125 – 0.375	1.40 (1.10, 1.80)
0.500 – 0.875	1.50 (1.20, 1.90)
1.000 – 1.375	1.80 (1.40, 2.20)
1.500 – 1.875	2.70 (2.20, 3.50)
2.000 – 2.375	4.00 (3.10, 5.20)
2.500 – 3.000	5.50 (3.90, 7.70)
Abbreviations: CI, confidence interval; HAQ-DI, health assessment questionnaire disability index; HR, hazard ratio.	

B.3.4 Measurement and valuation of health effects

B3.4.1 Health-related quality-of-life data from clinical trials

The EQ-5D questionnaire was used to collect utility data in the filgotinib Phase 3 trials. EQ-5D scores were collected until the end of each trial, week 52 (FINCH 1) and week 24 (FINCH 2). However, to align the modelling of health related quality of life (HRQoL) with previous submissions (MTA375 and all other submissions identified in Table 34), HRQoL was assumed to be dependent on patient HAQ-DI score progression. This relationship can be used to obtain long-term patient utility based on treatment effects, as opposed to using short-term trial data.

This was done by mapping patients' long-term HAQ-DI score trajectory (detailed in section B3.3.3) to EQ-5D, based on a published mapping algorithm detailed by Hernandez-Alva et al (see section B3.4.2) (13). This approach to RA economic modelling is well established and was applied by the AG in MTA375.

B3.4.2 Mapping

In line with MTA375, and other recent NICE submissions in RA (8, 14), the four latent class model produced by Hernandez-Alva et al (13). is used in the base case to determine utility from current modelled HAQ-DI and pain VAS scores over the entire model horizon. This approach fits with the DES model framework in which HAQ-DI progression is simulated over time and in which there are no defined "health

states" to which specific EQ-5D utility values can be directly attributed. Therefore, this cost-effectiveness analysis utilises the standard approach to mapping EQ-5D to HAQ-DI.

The algorithm presented by Hernandez-Alva et al. (13) uses patients' current age, sex, HAQ-DI and VAS pain scores to determine a utility value at any point in the model.

The mapping algorithm is applied using the following steps:

1. Patients' VAS pain score was estimated using their current HAQ-DI as the input for the mapping algorithm. The polynomial curve, which represents VAS scores as a function of HAQ-DI, published in MTA375, was digitised and fitted with a ninth order polynomial curve in the R software package. The digitised and fitted points are illustrated in Figure 40. The polynomial coefficients obtained are reported in Table 52.

Figure 40. Digitised points and fitted points of the polynomial used to estimate patient pain score in MTA375, and this submission

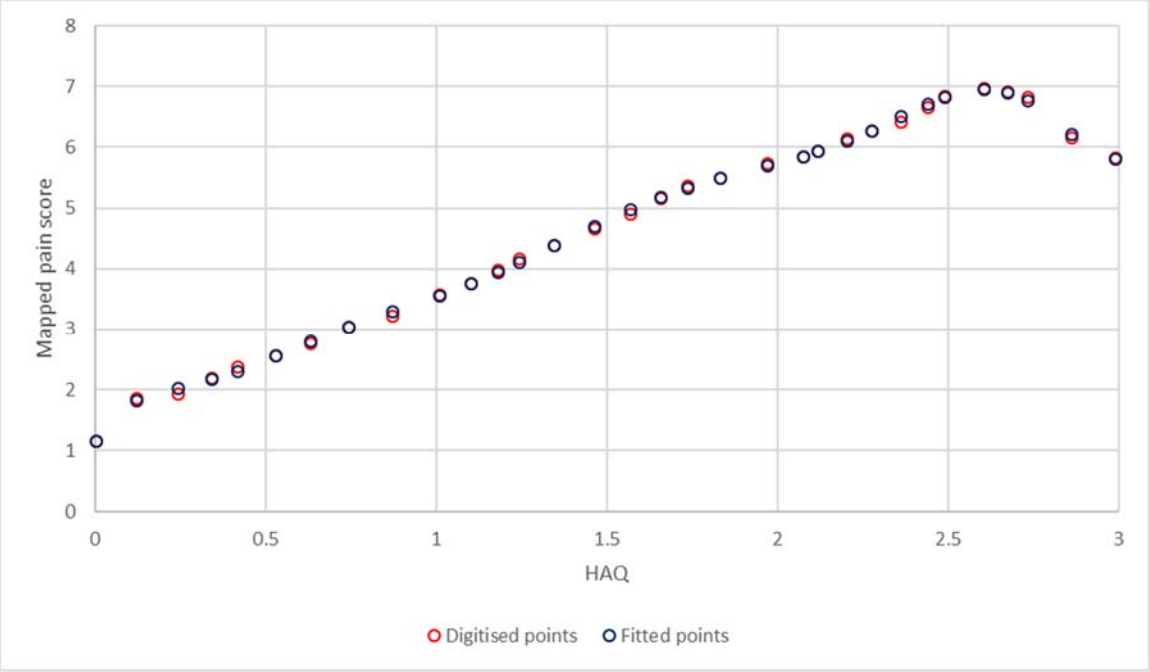


Table 52: Parameters for estimating pain from HAQ-DI

Polynomial term	Coefficient
Intercept	1.13
X	10.15
X^2	-53.78
X^3	163.22
X^4	-268.48
X^5	258.01
X^6	-148.40
X^7	50.15
X^8	-9.16
X^9	0.70

2. The probability of belonging to each of the four latent classes was estimated based each patient's simulated HAQ-DI score and VAS pain score using coefficients reported in Hernandez et al. (13)

3. Utility was estimated based on each patient's HAQ-DI score, pain, age and sex, using coefficients reported in Hernandez et al. (13)

To test the sensitivity of model estimates to this HAQ-DI utility mapping algorithm, an alternative approach was applied in a scenario analysis. A method outlined by Malottki et al. (11) was tested which estimated utility using each patient's current modelled HAQ-DI score using the following equation:

B3.4.3 Health-related quality-of-life studies

A systematic literature review was conducted to identify published literature reporting health state utility values in RA, the details of which are discussed in Appendix H. The identified studies were not used to inform the CEM, as none of the studies were found to present a robust alternative to assessing long-term EQ-5D in RA. As described in Section B.3.4.2, the utility values in the model were found by using the

mapping applied by the AG in MTA375, estimating EQ-5D derived from HAQ-DI scores.

B3.4.4 Adverse events

The only AE considered in the base case analysis was serious infection, which is assumed to occur only during the first six months of any active treatment, an approach which is consistent with MTA375 (6). Rates of AEs (serious infections) were based on those identified as part of the Singh et al. (15) Cochrane review, and were dependent on class of therapy, rather than being treatment-specific. Although the approach represents a simplification of the disease and safety profile of RA therapies, this is considered a conservative approach, as filgotinib is considered to have a favourable safety and tolerability profile in patients with moderately to severely active RA.

The incidence of AEs from Singh et al (15) are reported in Table 53. AEs were assumed not to occur in patients receiving BSC.

Table 53: SAE incidence rate in the CEM

Drug class	Rate of SAE per six-month period
cDMARDs	2.5%
bDMARDs (Inc. JAKs)	3.6%
Abbreviations: bDMARDs, biologic disease-modifying anti-rheumatic drugs; cDMARD, conventional disease-modifying anti-rheumatic drugs	

Additionally, SAE incidence rates reported from the FINCH 1 trial at 24 weeks were applied in a scenario analysis, using data from the filgotinib arm (applied for JAKs), adalimumab arm (applied for other bDMARDs), and the placebo arm (applied for csDMARDs).

Table 54: SAE incidence rate from FINCH 1 applied in scenario analyses

Drug class	Rate of SAE per six-month period
cDMARDs	0.8%
bDMARDs (Excl. JAKs)	2.5%
JAKs	1.7%
Abbreviations: bDMARDs, biologic disease-modifying anti-rheumatic drugs; cDMARD, conventional disease-modifying anti-rheumatic drugs	

For each AE occurrence, a decrement of 0.156 (16) is applied to the patient's overall utility, in line with MTA375. This disutility is applied by assuming that each patient experiences an AE for a total of 28 days of the six-month period.

B3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

HRQoL were unique to each patient and were mapped to the EQ-5D scale from HAQ-DI scores over the model time horizon. Full details of the mapping are presented in section B3.4.2.

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

B3.5.1 Identification of studies

A systematic literature review was conducted to identify cost and resource use data associated with patients with RA from the published literature. Full details of the search are provided in Appendix I. The identified studies were not used to inform the CEM, as no studies identified were found to present a robust alternative to the costing applied by MTA375.Additionally, maintaining consistency with MTA375, to the extent possible, aids the comparability of the outcomes of this analysis with that of MTA375.

B3.5.2 Intervention and comparators' costs and resource use

The model includes separate costs for drug acquisition and administration. Costs are applied six-monthly and are separated for initial treatment (including any loading doses) and maintenance treatment.

Treatment costs provided in the model are based on UK costs and dosing regimens from MIMS 2020 (17). Confidential patient access schemes (PAS) were excluded for Orencia® (abatacept), Olumiant® (baricitinib), Xeljanz® (tofacitinib), Kevzara® (sarilumab), RoActemra® (tocilizumab), and Rixathon® (rituximab). No treatment considered in this analysis has a non-confidential PAS price. Biosimilars, where available, are costed in the same way. The model only considers the lowest priced biosimilars as comparators. Biosimilars for adalimumab and etanercept are included in the model.

For strategies were treatments are used in combination with MTX, the six-monthly cost of MTX was added to the six-monthly cost of the treatments.

The cost of BSC was estimated from MTA375. The costs of BSC are reflective of healthcare costs for patients who are managed without targeted therapy. The costs comprise post-biologic csDMARD therapy (e.g., leflunomide, gold, cyclosporine), and were £360 per 6 months (£60 per month).

For drugs with weight-based dosing (e.g., tocilizumab), doses for patients were computed based on the simulated baseline weight of each patient.

Similarly, the cost of csDMARDs was assumed to equal the cost of MTX, which is considered a more conservative approach than including more expensive csDMARDs, such as sulfasalazine or hydroxychloroquine.

A summary of the pack costs, sizes and dosing regimens for treatments included in the model with the resultant six-monthly medication costs is shown in Table 55 below.

Table 55: Summary of pack cost, sizes and dosing regimens for each treatment

Treatment		Pack cost	Pack size	Dosing regimen (maintenance)	Total monotherapy cost		Total combination therapy cost	
					Initial 6 months	Subsequent 6-monthly	Initial 6 months	Subsequent 6-monthly
ETN	Erelzi™ (biosimilar)	£643.50	50mg x 4	50mg q1w	£4,182.75	£4,182.75	£4,196.27	£4,196.27
ADA	Hulio™ (biosimilar)	£616.25	40mg x 2	40mg q2w	£4,005.63	£4,005.63	£4,019.15	£4,019.15
TCZ	RoActemra® (brand)	£913.12	162mg x 4	162mg q1w	£5,935.28	£5,935.28	£5,948.80	£5,948.80
ABC	Orencia® (brand)	£1,209.60	125mg x 4	125mg q1w	£7,862.40	£7,862.40	£7,875.92	£7,875.92
RTX	Rixathon® (biosimilar)	£1,571.67	500mg x 2	1000mg twice every 6 months	£3,143.34	£3,143.34	£3,156.86	£3,156.86
BAR	Olumiant® (brand)	£2,416.68	4mg x 84	4mg qd	£5,236.14	£5,236.14	£5,249.66	£5,249.66
TOF	Xeljanz® (brand)	£690.03	5mg x 56	5mg bid	£4,485.20	£4,485.20	£4,498.71	£4,498.71
FIL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAR	Kevzara® (brand)	£912.25	200mg x 2	200mg q2w	£5,929.63	£5,929.63	£5,943.15	£5,943.15
MTX (generic)		£52.01	10mg x 100	10mg q1w	£13.52	£13.52	NA	NA

Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; bid, twice a day; ETN, etanercept; IV, intravenous; MTX, methotrexate; PAS, patient access scheme; qd, once daily q1w ,once a week; q2w, once every two weeks; q4w, once every four weeks; qw, once a week; RTX, rituximab; SAR, sarilumab; SC, subcutaneous; TCZ, tocilizumab; TOF, tofacitinib

*model uses cost per kg to calculate cost for each individual patient

Treatment administration costs applied in the model are reflective of route of administration, dosing guidance in MIMS 2020 and the administration costs outlined in MTA375 (1). These administration costs were inflated to 2018/2019 prices using the HCHS and NHSCII indices (2). This amounts to £2.93 per subcutaneous (SC) injection and £173.01 per intravenous (IV) infusion (as shown in Table 56).

Table 56: Drug administration costs

Route of administration	Cost (2019 £)	Source
IV	173.01	MTA375 (1) inflated to 2018/2019 prices using the HCHS and NHSCII indices
SC	2.93	
Oral	0.00	
Abbreviations: IV, intravenous; SC, subcutaneous		

Table 57:Summary of administration costs applied in the model per treatment

Treatments		Mode of Administration	Number of doses		Administration cost (2019 £)	
			Initial 6 months	Subsequent 6-monthly	Initial 6 months	Subsequent 6-monthly
ETN	Erelzi™	SC	26	26	£76.18	£76.18
ADA	Hulio™	SC	13.5	13.5	£38.09	£38.09
		SC	13.5	13.5	£38.09	£38.09
TCZ	RoActemra®	SC	26	26	£76.18	£76.18
ABC	Orencia®	SC	26	26	£76.18	£76.18
RTX	Rixathon®	IV	2	2	£346.02	£346.02
BAR	Olumiant®	Oral	182	182	N/A	N/A
FIL	N/A	Oral	182	182	N/A	N/A
TOF	Xeljanz®	Oral	364	364	N/A	N/A
SAR	Kevzara®	SC	13.5	13.5	£38.09	£38.09
MTX		Oral	26	26	N/A	N/A
Abbreviations: ABC: abatacept; ADA: adalimumab; BAR: baricitinib; ETN: etanercept; Fil, filgotinib, MTX: methotrexate; RTX: rituximab; SAR: sarilumab; TCZ, tocilizumab; TOF, tofacitinib						

B3.5.3 Health-state unit costs and resource use

As discrete event simulation (DES) models do not explicitly have health states, monitoring costs and cost related to hospitalisations are presented in the sections below.

Monitoring costs

Monitoring costs are modelled separately for initial treatment phase and maintenance phase, to allow for more intense monitoring during initiation. Current monitoring costs are sourced from MTA375 (1) and inflated to 2018/2019 prices using the HCHS and NHSCII indices (2). A summary of the six-monthly monitoring costs is shown in Table 58.

Table 58: Monitoring costs

Monitoring cost	Six-monthly cost (2019 £)
Initial treatment phase	£1,870.54
Maintenance phase	£884.66

Hospitalisation costs per HAQ-DI

In line with the approach taken in MTA375, hospital costs are broken down into six categories, according to HAQ-DI level, to reflect the increasing cost burden associated with worsening RA. Current UK costs are taken from MTA375 (1). No resource level breakdown was provided for these costs, as such the overall hospital costs have been inflated to 2018/2019 prices using the HCHS and NHSCII indices (2). A summary of the six-monthly costs applied in the model are shown in Table 59.

Table 59: Hospital costs based on HAQ-DI score

HAQ-DI score	Six-month cost (2019 £)
<0.60	£94.04
0.60-1.10	£57.60
1.10-1.60	£204.85
1.60-2.10	£295.28
2.10-2.60	£700.04
≥2.60	£1,509.87
Abbreviations: HAQ-DI; Health assessment questionnaire disability index	

B3.5.4 Adverse reaction unit costs and resource use

The cost-effectiveness analysis included costs of AEs in the form of serious infections, which were considered the most important treatment related AE (see section B3.4.4 Adverse events The current UK cost of an AE in the model is taken from MTA375 and inflated to 2018/2019 prices using the HCHS and NHSCII indices (2) . The cost per event, as shown in Table 60, is applied to all AEs irrespective of which treatment the patient is receiving.

AEs were assigned a utility decrement of 0.156 (3) per event, which is applied assuming that the event occurs for a duration of 28 days out of the six-month period in which the AE is experienced. The probability of experiencing an AE differed between csDMARDs and bDMARDs, the details of which are described in section B3.4.4.

Table 60: Adverse events costs

Treatment	Cost per event (2019 £)	Source
csDMARDs, bDMARDs & JAK inhibitors	£1,661.55	TA375, HCHS and NHSCII indices (2)
Abbreviation: bDMARD= biologic disease-modifying anti-rheumatic drug; csDMARD= conventional synthetic disease modifying anti-rheumatic drug(s); HCHS= hospital & community health services; JAK= Janus kinase		

B3.5.5 Miscellaneous unit costs and resource use

No additional costs or resource use items were included in the model which are not already included in the preceding sections.

B.3.6 Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

A summary of the base case inputs used in the model is presented in Table 61.

Table 61. Summary of variables applied in the economic model

Variable	Value		Measurement of uncertainty and distribution	Reference to section in submission
Model settings				
Time horizon	Lifetime		NA	Section 3.2
Discounting - costs	3.5%		Low: 0%, high: 6%	Section 3.2
Discounting - utilities	3.5%			Section 3.2
Clinical inputs				
Patient baseline characteristics	Baseline characteristics from the FINCH-I trial (csDMARD-IR population), and FINCH- II trial (bDMARD-IR population)		NA	Section 3.2
Treatment efficacy (EULAR response)	Based on the NMA, Week 24 ACR efficacy data converted to EULAR, **Table 27**		95% CI from the NMA	Section 3.3
HAQ-DI trajectory	As previously reported by MTA375 based on analysis of BSRBR dataset (bDMARDs), and ERAS cohort data described by Norton et al. (4)		NA	Section 3.3
Discontinuation	As previously reported by MTA375 based on BSRBR dataset analysis (generalised gamma distribution applied)		NA	Section 3.3
Pain (VAS score)	Estimated from patients' HAQ-DI score, as previously reported by MTA375 based on NDB data		NA	Section 3.4
AE's (serious infections)	Rates were based on Singh et al,2011 (5)		Varied by +/- 100%	Section 3.4
Treatment costs				
Treatment	Initial 6 months	Subsequent 6 months	NA	Section 3.5
[redacted]	[redacted]	[redacted]		
ABC SC	£7,862.40	£7,862.40		
ADA	£8,011.25	£8,011.25		
BAR	£5,236.14	£5,236.14		
ETN	£4,182.75	£4,182.75		
TCZ SC	£5,948.80	£5,948.80		
TOF	£4,485.20	£4,485.20		
[redacted]	[redacted]	[redacted]		
ABC SC + MTX	£7,875.92	£7,875.92		
ADA + MTX	£4,019.15	£4,019.15		
BAR + MTX	£5,249.66	£5,249.66		
ETN + MTX	£4,196.27	£4,196.27		
RTX + MTX	£3,156.86	£3,156.86		
SAR + MTX	£5,943.15	£5,943.15		
TCZ SC + MTX	£5,948.80	£5,948.80		
MTX	£13.52	£13.52		

Variable	Value		Measurement of uncertainty and distribution	Reference to section in submission
BSC	£360	£360		
Monitoring costs (6-monthly)				
Initial period	£1,870.54		Varied by +/- 20%	Section 3.5
Maintenance period	£884.66			Section 3.5
Administration costs (6-monthly)				
Treatment	Initial 6 months	Subsequent 6 months	Varied by +/- 20%	Section 3.5
ETN (SC)	£76.18	£76.18		
ADA (SC)	£38.09	£38.09		
TCZ (SC)	£76.18	£76.18		
ABC (SC)	£76.18	£76.18		
RTX (IV)	£346.02	£346.02		
SAR (SC)	£38.09	£38.09		
Hospital costs (6-monthly)				
HAQ-DI <0.6	£94.04		Varied by +/- 20%	Section 3.5
HAQ-DI 0.6-<1.1	£57.60			Section 3.5
HAQ-DI 1.1-<1.6	£204.85			Section 3.5
HAQ-DI 1.6-<2.1	£295.28			Section 3.5
HAQ-DI 2.1-<2.6	£700.04			Section 3.5
HAQ-DI ≥2.6	£1,509.87			Section 3.5
Adverse events				
Adverse Event Costs (per event)	£1,661.55		Varied by +/- 20%	Section 3.5
Utility inputs				
HAQ-DI utility mapping	Based on the algorithm reported by Hernandez et al (6)		NA	Section 3.4
AE utility decrement	0.156		Varied by +/- 100%	Section 3.4
Mortality				
Sex-specific background mortality	Gompertz curves fitted on UK 2015-2017 life tables, in line with NICE MTA375		NA	Section 3.4
Mortality stratified by HAQ-DI group				
HAQ-DI 0.000	1.00 (reference)		NA	Section 3.4
HAQ-DI 0.125–0.375	1.40		95% CI: 1.10 - 1.80	Section 3.4
HAQ-DI 0.500–0.875	1.50		95% CI: 1.20 - 1.90	Section 3.4
HAQ-DI 1.000–1.375	1.80		95% CI: 1.40 - 2.20	Section 3.4
HAQ-DI 1.500–1.875	2.70		95% CI: 2.20 - 3.50	Section 3.4
HAQ-DI 2.000–2.375	4.00		95% CI: 3.10 - 5.20	Section 3.4
HAQ-DI 2.500–3.000	5.50		95% CI: 3.90 - 7.70	Section 3.4

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Distributions applied for PSA			
Parameter	Distribution		
Proportion of good/moderate responders by treatment	Dirichlet	N/A	Section 3.8
Initial HAQ-DI reduction	Normal		
Survival hazard ratios	Lognormal		
Hospitalisation costs	Gamma		

Abbreviations: ACR, American College of Rheumatology; AE, adverse event; CI, confidence interval; EULAR, European League Against Rheumatism; FIL, filgotinib; HAQ-DI, Health Assessment Questionnaire – Disability Index; IR, insufficient response; NA, not applicable; NDB, National Databank for Rheumatic Diseases, NMA, network meta-analysis; VAS, visual analogue scale: SC, Subcutaneous injection; IV, intravenous injection.

B3.6.2 Assumptions

A list of assumptions applied in the economic analysis, with the associated rationale, is provided in Table 62.

Table 62. Assumptions applied in the economic model

Base case modelling approach/assumption	Assumption detailed	Aligned with MTA375 model?
Death during initial 6-months	If a patient experiences death during the first six-months of treatment, death is assumed to occur instantly and no QALYs or costs will be accrued.	Yes
Discontinuation due to adverse events	If a patient experiences an AE, they complete the initial treatment phase with no treatment effect, automatically discontinue treatment and re-enter the initial phase on the subsequent treatment line.	Yes
Discontinuation due to loss of effect	Discontinuation due to loss of effect can only occur following at least six months of treatment in either phase. After discontinuation, patients re-enter the model at the initial treatment phase, and move to the next treatment in the sequence.	Yes
Treatment with BSC	Once a patient starts on BSC, the patient remains on this line of treatment until death.	Yes
Treatment effect of BSC	Patients on BSC do not experience a EULAR response	Yes
Efficacy of monotherapy	Relative efficacy between treatments assumed to be the same in monotherapy as estimated for combination therapies with MTX. This approach is consistent with recommendations in MTA375 and previous submissions.	Yes
Efficacy of ABC SC and TCZ SC	ABC SC efficacy for csDMARD-IR patients was assumed equivalent to bDMARD-IR patient efficacy, and TCZ SC efficacy for bDMARD-IR patients was assumed equivalent to csDMARD-IR patient efficacy.	NA
Efficacy in moderate disease activity	Assumed that relative efficacy in moderate disease activity the same as for the moderate to severe population. Sub-group analysis of FINCH 3 confirmed this assumption.	NA
Utility change in the initial treatment phase	During the six-month initial treatment phase, utility is assumed to remain the same. Utility may only change following a successful response after which treatment-related QALYs will begin to accrue.	Yes
AE occurrence	AEs may only occur in the first six months of treatment and are accrued at the end of that six-month period.	Yes
AE occurrence for patients on BSC	AEs do not occur for patients on BSC at any time	Yes
AEs do not affect treatment sequences	The incident of an AE does not change the order of treatments.	Yes

Base case modelling approach/assumption	Assumption detailed	Aligned with MTA375 model?
Cost of AEs	The cost of AEs and associated QALYs are assumed consistent across all treatments i.e. these are not treatment-specific.	Yes
Initial change in HAQ-DI	Patients with no EULAR response at 6 months do not experience a reduction in HAQ-DI. Mean initial change is found for each patient using the average initial effect for other response groups (moderate and good response). This is detailed in section B.3.3.3.	Yes
HAQ-DI trajectory continuation	The HAQ-DI trajectory continues for three years during bDMARD treatment and 15 years for csDMARD treatment. Following this HAQ-DI is assumed to remain constant at its last modelled value until death.	Yes
HAQ-DI trajectory for patients on BSC	The HAQ-DI trajectory of patients receiving BSC is assumed to be the same as those receiving csDMARDs.	Yes

Abbreviations: AE, adverse event; bDMARD, biologic disease-modifying anti-rheumatic drugs ; BSC, best supportive care; csDMARD, conventional disease-modifying anti-rheumatic drugs; HAQ-DI, Health Assessment Questionnaire – Disability Index; QALY, quality adjusted life years;

B.3.7 Base case results

The deterministic base case cost-effectiveness results for the populations outlined in section B3.2.1 are presented below. All base case analyses were conducted by simulating 10,000 patients, using an annual price of [redacted] for filgotinib.

1a. Moderate RA patients after 2 csDMARD failures (MTX ineligible)

The results of the base case analysis for the moderate, MTX ineligible patient population after at least two csDMARD failures are presented in Table 63. Compared to BSC, filgotinib 200mg monotherapy was associated with QALY gains (0.607), and increased costs (£13,183), generating an incremental cost-effectiveness ratio (ICER) of £21,721 per QALY. The model currently applies the conservative assumption that patients with moderately active RA to not progress to a severe state. The incorporation of disease progression in a recent submission indicated that this results in an important reduction in the ICER.

Table 63: Two csDMARD failure, MTX ineligible, moderate RA – versus FIL 200mg monotherapy (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	15.810	[redacted]	-	-	-	21,721.27	-
FIL	[redacted]	15.810	[redacted]	13,182.52	0.000	0.607	-	21,721.27
Abbreviations: BSC, best supportive care; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year								

1b. Moderate RA patients after 2 csDMARD failures (MTX eligible)

The results of the base case analysis for the moderate, MTX eligible patient population after at least two csDMARD failures are presented in Table 64. Compared to BSC, filgotinib 200mg combination therapy was associated with QALY gains (0.607), and increased costs (£13,305), generating an ICER of £21,924 per QALY. The model currently applies the conservative assumption that patients with moderately active RA to not progress to a severe state.

Table 64: Two csDMARD failure, MTX eligible, moderate RA – versus FIL 200mg in combination with MTX (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	15.810	[redacted]	-	-	-	21,923.81	-
FIL + MTX	[redacted]	15.810	[redacted]	13,305.44	0.000	0.607	-	21,923.81
Abbreviations: BSC, best supportive care; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year								

2a. Severe RA patients in first line advanced therapy treatment (MTX ineligible)

The results of the base case analysis for the severe, csDMARD-IR, MTX ineligible patient population are presented in. Filgotinib 200mg monotherapy was associated with lower costs than all comparators and similar QALYs.

Table 65: csDMARD-IR, MTX ineligible, severe RA – versus FIL 200mg monotherapy (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL	[redacted]	14.639	[redacted]	-	-	-	-	-
ADA	[redacted]	14.639	[redacted]	18,513.58	0.000	-0.013	Dominated	Dominated
ETN	[redacted]	14.639	[redacted]	3,250.59	0.000	0.076	342,678.87 SW	42,542.73
BAR	[redacted]	14.639	[redacted]	8,015.03	0.000	-0.039	1,231,213.04 SW	Dominated
TCZ SC	[redacted]	14.639	[redacted]	5,000.95	0.000	-0.048	Dominated	Dominated

Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; TCZ, tocilizumab

2b. Severe RA patients in first line advanced therapy treatment (MTX eligible)

The results of the base case analysis for the severe, csDMARD-IR, MTX eligible, RTX eligible patient population are presented in Table 66. Filgotinib 200mg combination therapy was associated with lower costs than all comparators and similar QALYs.

Table 66: csDMARD-IR, MTX eligible, RTX eligible, severe RA – versus FIL 200mg in combination with MTX (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.639	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.639	[redacted]	18,263.14	0.000	-0.011	Dominated	Dominated
ETN + MTX	[redacted]	14.639	[redacted]	4,100.90	0.000	0.064	418,614.42 SW	63,661.88
BAR + MTX	[redacted]	14.639	[redacted]	7,638.94	0.000	-0.033	1,466,495.03 SW	Dominated

Abbreviations: ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

The results of the base case analysis for the severe, csDMARD-IR, MTX eligible, RTX contraindicated patient population (using second line IL-6) are presented in Table 67. Filgotinib 200mg combination therapy was associated with lower costs than all comparators and similar QALYs.

Table 67: csDMARD-IR, MTX eligible, RTX ineligible, severe RA (using second line IL-6) – versus FIL 200mg in combination with MTX (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.639	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.639	[redacted]	18,275.44	0.000	-0.014	Dominated	Dominated
ETN + MTX	[redacted]	14.639	[redacted]	4,522.59	0.000	0.086	317,815.33 SW	52,874.08
BAR + MTX	[redacted]	14.639	[redacted]	7,348.72	0.000	-0.045	1,110,108.52 SW	Dominated

Abbreviations: ADA, adalimumab; BAR, baricitinib; ETN, etanercept; FIL, filgotinib; IL-6, interleukin 6; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

The results of the base case analysis for the severe, csDMARD-IR, MTX eligible, RTX eligible patient population (using second line CD80) are presented in Table 68. Filgotinib 200mg combination therapy was associated with lower costs than all comparators and similar QALYs.

Table 68: csDMARD-IR, MTX eligible, RTX ineligible severe RA (using second line CD80) – versus FIL 200mg in combination with MTX (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.639	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.639	[redacted]	18,511.67	0.000	-0.013	Dominated	Dominated
ETN + MTX	[redacted]	14.639	[redacted]	3,261.87	0.000	0.076	342,826.47 SW	42,690.46
BAR + MTX	[redacted]	14.639	[redacted]	8,008.97	0.000	-0.039	1,231,350.00 SW	Dominated

Abbreviations: ADA, adalimumab; BAR, baricitinib; CD80, cluster of differentiation 80; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

3a. Severe RA patients after failure of first line advanced therapy treatment (MTX ineligible, RTX ineligible)

The results of the base case analysis for the severe, bDMARD-IR, MTX eligible patient population are presented in Table 69. Filgotinib 200mg monotherapy was associated with lower costs than all comparators and similar QALYs.

Table 69: bDMARD-IR, MTX ineligible, RTX ineligible, severe RA – versus FIL 200mg monotherapy (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL	[redacted]	13.638	[redacted]	-	-	-	-	-
TOF	[redacted]	13.638	[redacted]	18,837.66	0.000	-0.105	Dominated	Dominated
BAR	[redacted]	13.638	[redacted]	5,915.81	0.000	0.000	Dominated	Dominated
ABC	[redacted]	13.638	[redacted]	38,824.93	0.000	0.204	644,289.94 SW	190,639.45
Abbreviations: ABC, abatacept; BAR, baricitinib; FIL, filgotinib; LYG, life year gained; QALY, quality adjusted life year; TOF, tofacitinib								

3b. Severe RA patients after failure of first line advanced therapy treatment (MTX eligible, RTX ineligible)

The results of the base case analysis for the severe, bDMARD-IR, MTX eligible patient population are presented in Table 70. Filgotinib 200mg combination therapy was associated with lower costs than all comparators and similar QALYs.

Table 70: bDMARD-IR, MTX eligible, RTX ineligible, severe RA – versus FIL 200mg in combination with MTX (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.638	[redacted]	-	-	-	-	-
BAR + MTX	[redacted]	13.638	[redacted]	24,736.31	0.000	-0.105	Dominated	Dominated
TCZ + MTX	[redacted]	13.638	[redacted]	6,551.69	0.000	0.008	Dominated	864,430.99
SAR + MTX	[redacted]	13.638	[redacted]	431.84	0.000	0.014	Dominated	30,919.04
ABC + MTX	[redacted]	13.638	[redacted]	31,874.15	0.000	0.182	644,447.82 SW	175,026.45

Abbreviations: ABC, abatacept; BAR, baricitinib; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; SAR, sarilumab; TCZ, tocilizumab

4. Severe RA patients after failure of first line advanced therapy (MTX eligible, RTX eligible)

The results of the base case analysis for the severe, bDMARD-IR, MTX eligible patient population are presented in Table 71. Filgotinib 200mg combination therapy was associated with lower costs than all comparators and similar QALYs.

Table 71: bDMARD-IR, MTX eligible, RTX eligible, severe RA – versus FIL 200mg in combination with MTX (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.638	[redacted]	-	-	-	-	-
RTX + MTX	[redacted]	13.638	[redacted]	14,735.41	0.000	0.009	1,582,703.38 SW	1,582,703.38

Abbreviations: FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; RTX, rituximab;

5. Severe RA patients after failure of rituximab in combination with methotrexate

The results of the base case analysis for the severe, bDMARD-IR, MTX eligible patient population are presented in Table 72. Filgotinib 200mg combination therapy was associated with lower costs than all comparators and similar QALYs.

Table 72: bDMARD-IR, MTX eligible, RTX IR, severe RA – versus FIL 200mg in combination with MTX (deterministic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.638	[redacted]	-	-	-	-	-
TCZ + MTX	[redacted]	13.638	[redacted]	31,288.00	0.000	-0.097	Dominated	Dominated
SAR + MTX	[redacted]	13.638	[redacted]	431.84	0.000	0.014	Dominated	30,919.04

Abbreviations: FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; SAR, sarilumab; TCZ, tocilizumab

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to simultaneously vary multiple parameters, sampled from their assigned distributions, and re-estimate model outputs. In order to reduce computational time, the PSA was conducted using 500 patients. Results are based on 1,000 model runs. Probabilistic sensitivity analyses were conducted for all populations included in the base case analysis.

Table 73: Summary of inputs used for probabilistic sensitivity analyses

Parameter	Section	Distribution	Description
Efficacy			
Proportion of good/moderate responders by treatment	B3.3.2	Dirichlet	Treatment effects in terms of EULAR response (no response, moderate response, good response) were varied by sampling from a multivariate Dirichlet distribution.
Initial HAQ-DI reduction	B3.3.2	Normal	Mean HAQ-DI and standard error reported in MTA375 were used to vary response. Standard error was sampled from a normal distribution.
Hazard ratios			
Survival hazard ratios	*B3.3.5*	Lognormal	HRs were sourced from Michaud et al. (1) with a 95% CI. CIs were used to sample HRs using a lognormal distribution.
Costs			
Hospitalisation costs	*B3.5.3*	Gamma distribution	Hospital costs were taken from MTA375. However, no measure of uncertainty nor breakdown of costs was reported. Therefore, a standard error of 1/10th costs was assumed for each category and costs were sampled from a gamma distribution.

Abbreviations: CI, confidence interval; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire – Disability Index; HR, hazard ratio

Results

1a. Moderate RA patients after 2 csDMARD failures (MTX ineligible)

The results of the PSA are presented in Table 74, with a cost-effectiveness acceptability curve in Figure 41 and a cost-effectiveness plane in Figure 42. Results in PSA are in line with those from the base case results, with an average ICER of £21,745 compared to the base case ICER of £21,721. At a WTP threshold of £20,000, filgotinib had a 9.8% probability of being the optimal treatment. At a WTP of £30,000, this increased to 100%.

Table 74: Two csDMARD failures, MTX ineligible, moderate RA – versus FIL 200mg monotherapy (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	16.081	[redacted]	-	-	-	21,745.28	-
FIL	[redacted]	16.081	[redacted]	14,153.16	0.000	0.651	-	21,745.28
Abbreviations: BSC, best supportive care; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year								

Figure 41. Two csDMARD failures, MTX ineligible, moderate RA – CEAC for PSA

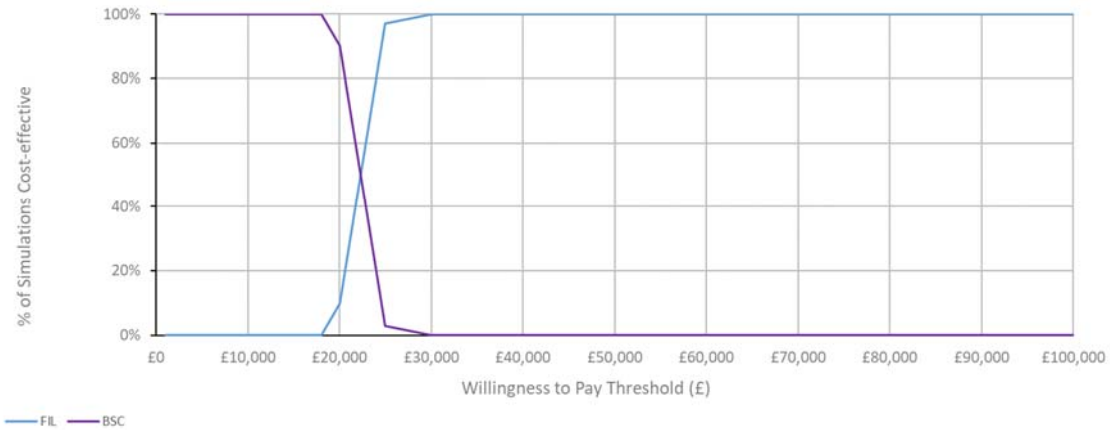
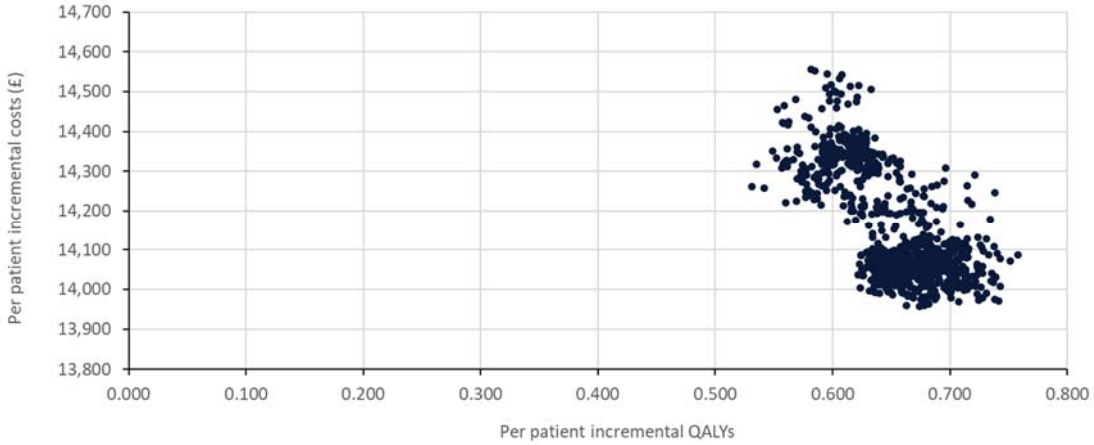


Figure 42. Two csDMARD failures, MTX ineligible, moderate RA – CE plane for PSA: filgotinib vs BSC



1b. Moderate RA patients after 2 csDMARD failures (MTX eligible)

The results of the PSA are presented in Table 75, with a cost-effectiveness acceptability curve in Figure 43 and a cost-effectiveness plane in Figure 44. Results in PSA are in line with those from the base case results, with an average ICER of £21,990 compared to the base case ICER of £21,924. At a WTP threshold of £20,000, filgotinib had a 6.8% probability of being the optimal treatment. At a WTP of £30,000, this increased to 100%.

Table 75: Two csDMARD failures, MTX eligible, moderate RA – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	16.081	[redacted]	-	-	-	21,989.61	-
FIL + MTX	[redacted]	16.081	[redacted]	14,286.15	0.000	0.651	-	21,989.61
Abbreviations: BSC, best supportive care; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year								

Figure 43. Two csDMARD failures, MTX eligible, moderate RA – CEAC for PSA

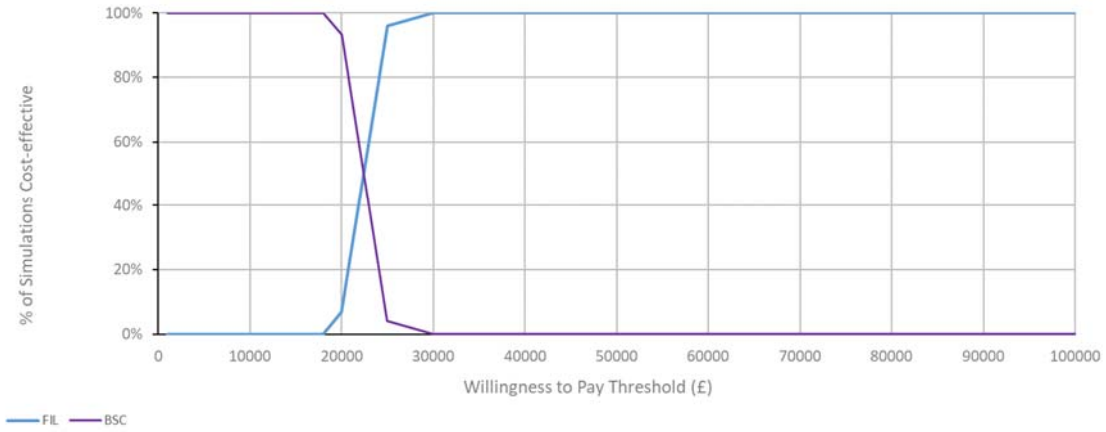
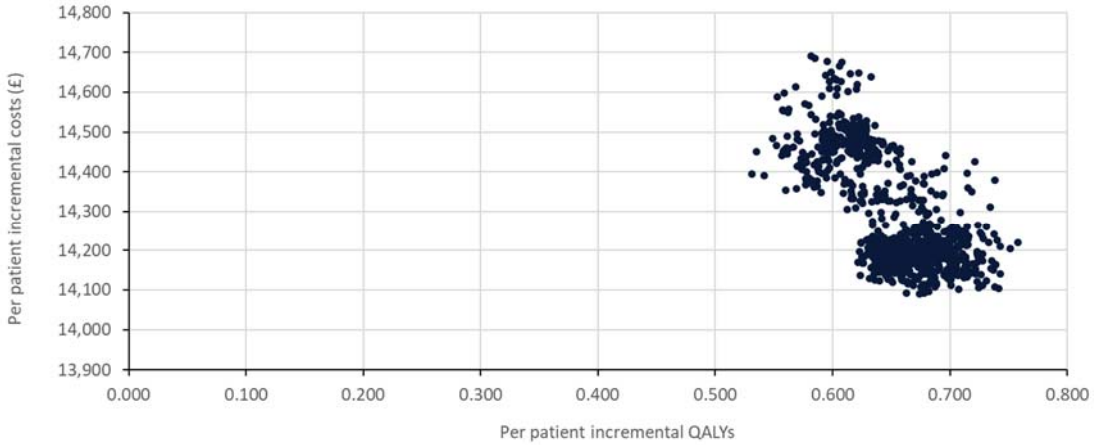


Figure 44. Two csDMARD failures, MTX eligible, moderate RA – CE plane for PSA: filgotinib vs BSC



2a. Severe RA patients in first line advanced therapy treatment of (MTX ineligible)

The results of the PSA are presented in Table 76, with a cost-effectiveness acceptability curve in Figure 45 and a cost-effectiveness plane in

Figure 46. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 76: csDMARD-IR, MTX ineligible, severe RA – versus FIL 200mg monotherapy (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL	[redacted]	14.656	[redacted]	-	-	-	-	-
ADA	[redacted]	14.656	[redacted]	21,450.89	0.000	-0.022	Dominated	Dominated
ETN	[redacted]	14.656	[redacted]	5,307.94	0.000	0.117	244,123.42 SW	37,053.13
BAR	[redacted]	14.656	[redacted]	6,890.12	0.000	-0.058	855,066.54 SW	Dominated
TCZ	[redacted]	14.656	[redacted]	16,014.94	0.000	-0.069	Dominated	Dominated

Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; TCZ, tocilizumab

Figure 45. csDMARD-IR, MTX ineligible, severe RA – CEAC for PSA

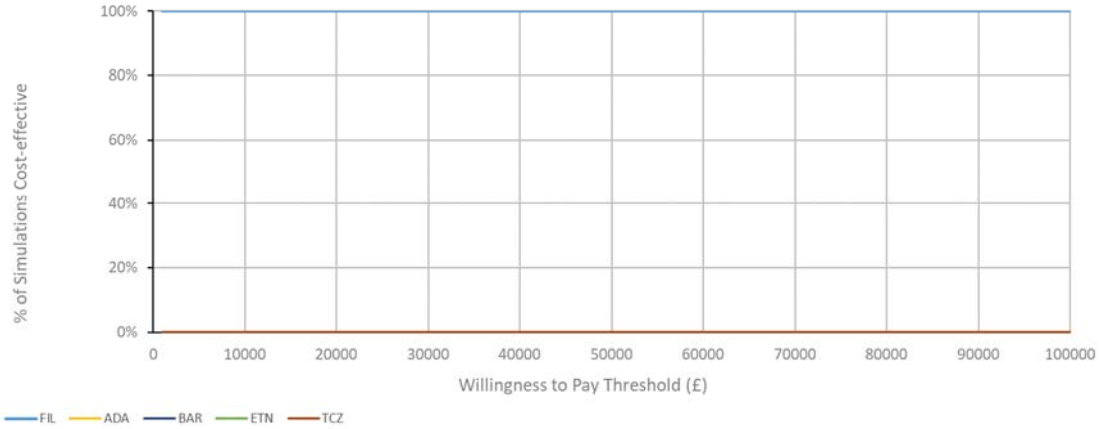
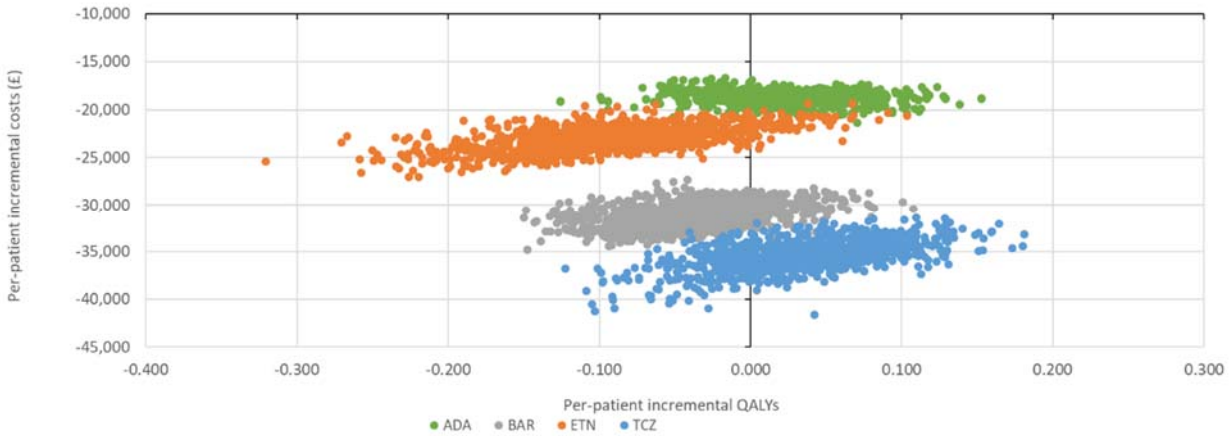


Figure 46. csDMARD-IR, MTX ineligible, severe RA – CE plane for PSA: filgotinib vs comparators



2b. Severe RA patients in first line advanced therapy treatment (MTX eligible)

The results of the PSA for the RTX eligible population are presented in Table 77, with a cost-effectiveness acceptability curve in

Figure 47 and a cost-effectiveness plane in Figure 48. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 77: csDMARD-IR, MTX eligible, RTX eligible, severe RA – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.656	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.656	[redacted]	18,841.28	0.000	-0.013	Dominated	Dominated
ETN + MTX	[redacted]	14.656	[redacted]	4,666.57	0.000	0.080	352,554.74 SW	58,514.09
BAR + MTX	[redacted]	14.656	[redacted]	7,458.41	0.000	-0.045	1,405,757.21 SW	Dominated

Abbreviations: ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Figure 47. csDMARD-IR, MTX eligible, RTX eligible, severe RA – CEAC for PSA

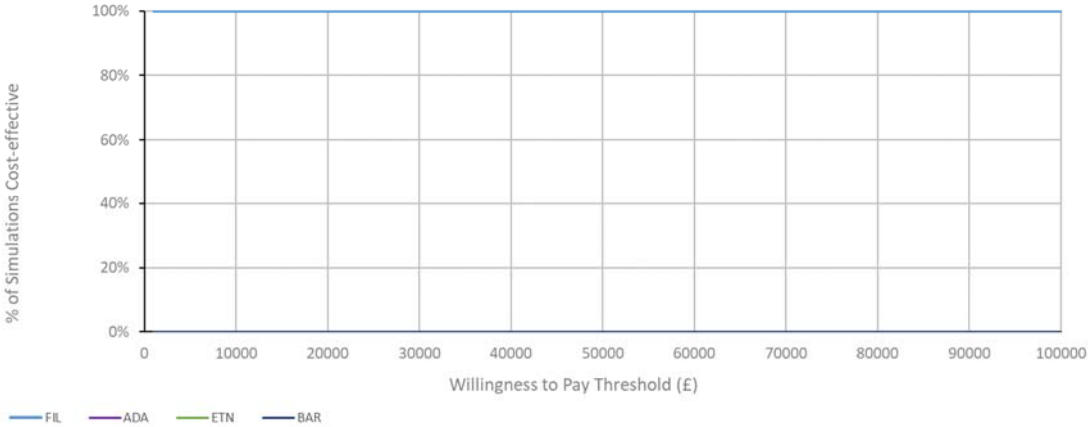
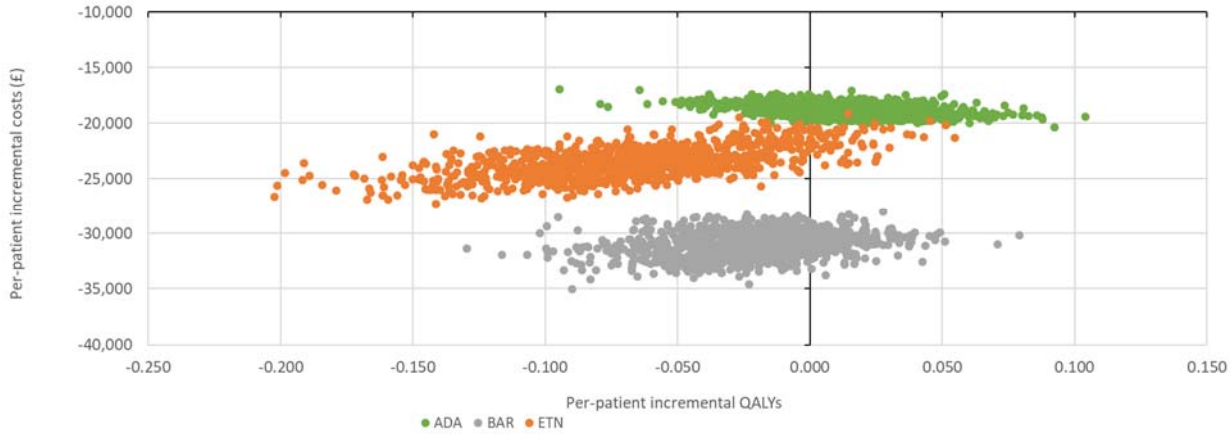


Figure 48. csDMARD-IR, MTX eligible, RTX eligible, severe RA – CE plane for PSA: filgotinib vs comparators



The results of the PSA for the RTX contraindicated population (using second line IL-6) are presented in Table 78, with a cost-effectiveness acceptability curve in Table 78 and Figure 51, and a cost-effectiveness plane in Figure 50. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 78: csDMARD-IR, MTX eligible, RTX contraindicated, severe RA (using second line IL-6) – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.656	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.656	[redacted]	18,451.45	0.000	-0.024	Dominated	Dominated
ETN + MTX	[redacted]	14.656	[redacted]	6,125.72	0.000	0.131	229,792.85 SW	46,830.69
BAR + MTX	[redacted]	14.656	[redacted]	6,902.16	0.000	-0.070	842,696.71SW	Dominated

Abbreviations: ADA, adalimumab; BAR, baricitinib; ETN, etanercept; FIL, filgotinib; IL-6, interleukin 6; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Figure 49. csDMARD-IR, MTX eligible, RTX contraindicated, severe RA, second line IL-6 – CEAC for PSA

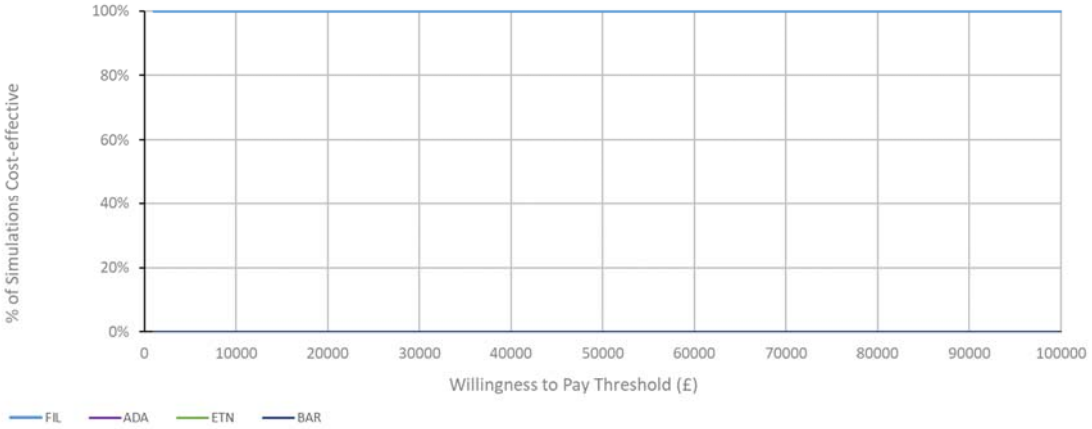
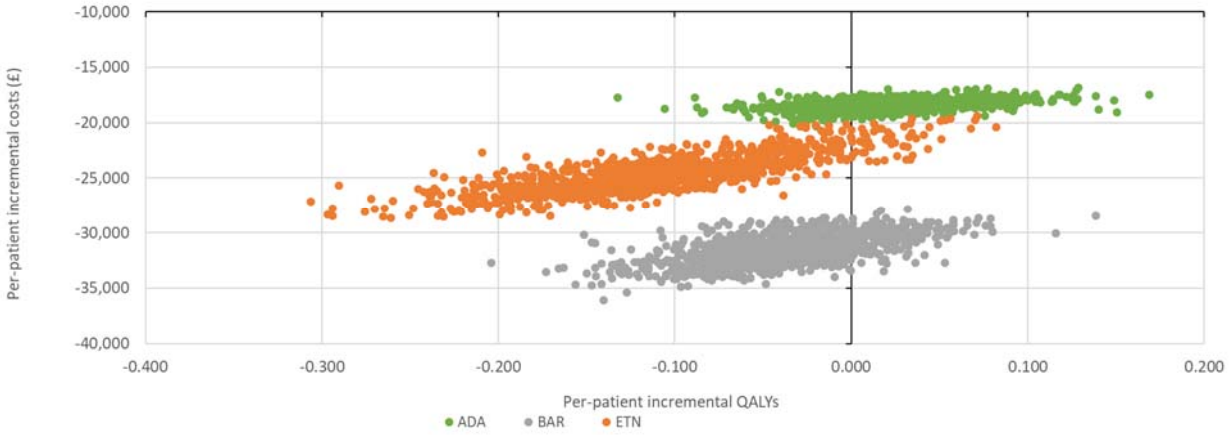


Figure 50. csDMARD-IR, MTX eligible, RTX contraindicated, severe RA, second line IL-6 – CE plane for PSA: filgotinib vs comparators



The results of the PSA for the RTX contraindicated population (using second line CD80) are presented in Table 79, with cost-effectiveness acceptability curve in Figure 51, and cost-effectiveness planes in Figure 52. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 79: csDMARD-IR, MTX eligible, RTX contraindicated, severe RA (using second line CD80) – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.656	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.656	[redacted]	18,699.05	0.000	-0.023	Dominated	Dominated
ETN + MTX	[redacted]	14.656	[redacted]	4,485.31	0.000	0.124	230,139.63 SW	36,160.93
BAR + MTX	[redacted]	14.656	[redacted]	7,940.20	0.000	-0.065	872,987.15 SW	Dominated

Abbreviations: ADA, adalimumab; BAR, baricitinib; CD80, cluster of differentiation 80; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Figure 51. csDMARD-IR, MTX eligible, RTX contraindicated, severe RA, second line CD80 – CEAC for PSA

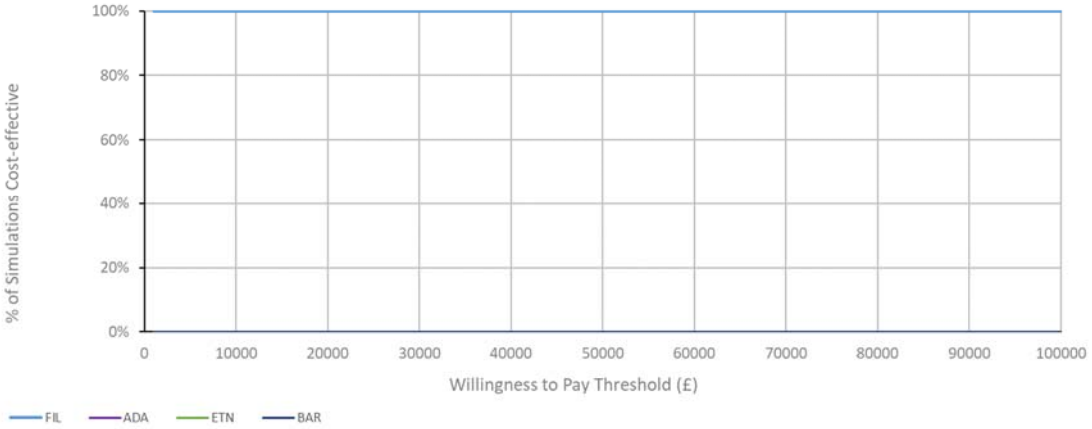
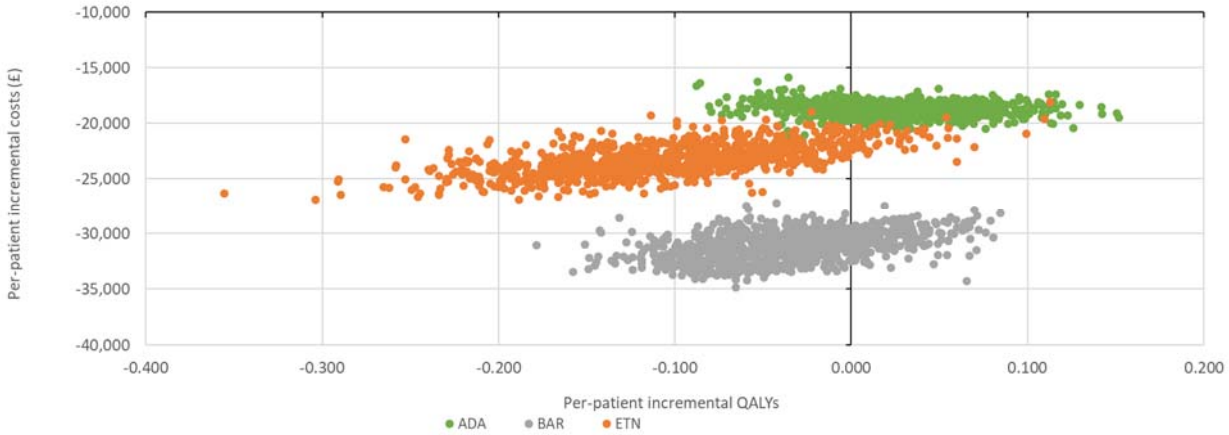


Figure 52. csDMARD-IR, MTX eligible, RTX contraindicated, severe RA, second line CD80 – CE plane for PSA: filgotinib vs comparators



3a. Severe RA patients after failure of first line advanced therapy treatment (MTX ineligible, RTX ineligible)

The results of the PSA are presented in Table 80, with a cost-effectiveness acceptability curve in Figure 53 and a cost-effectiveness plane in Figure 54. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 80: bDMARD-IR, MTX ineligible, RTX ineligible, severe RA – versus FIL 200mg monotherapy (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL	[redacted]	13.675	[redacted]	-	-	-	-	-
TOF	[redacted]	13.675	[redacted]	18,805.00	0.000	-0.150	Dominated	Dominated
BAR	[redacted]	13.675	[redacted]	6,104.92	0.000	0.001	Dominated	4,867,538.53
ABC	[redacted]	13.675	[redacted]	44,099.65	0.000	0.261	615,197.79 SW	169,046.99

Abbreviations: ABC, abatacept; BAR, baricitinib; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; TOF, tofacitinib

Figure 53. bDMARD-IR, MTX ineligible, RTX ineligible, severe RA – CEAC for PSA

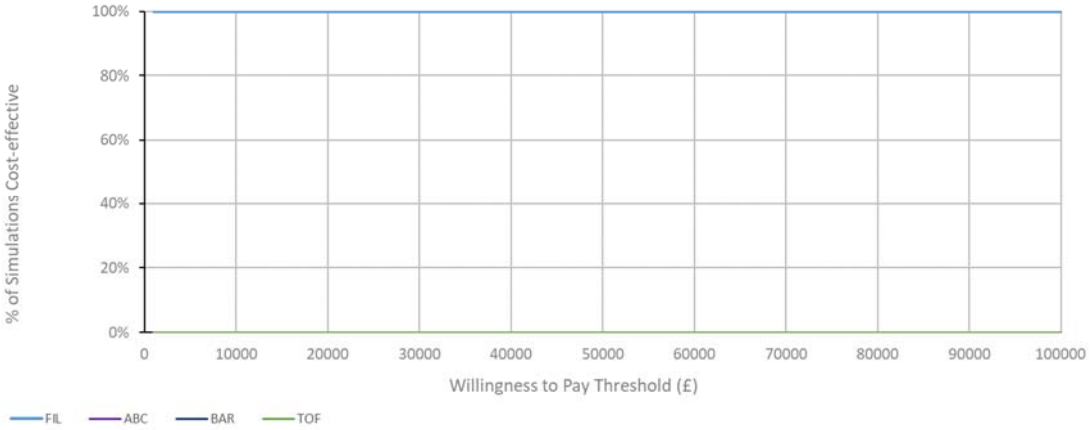
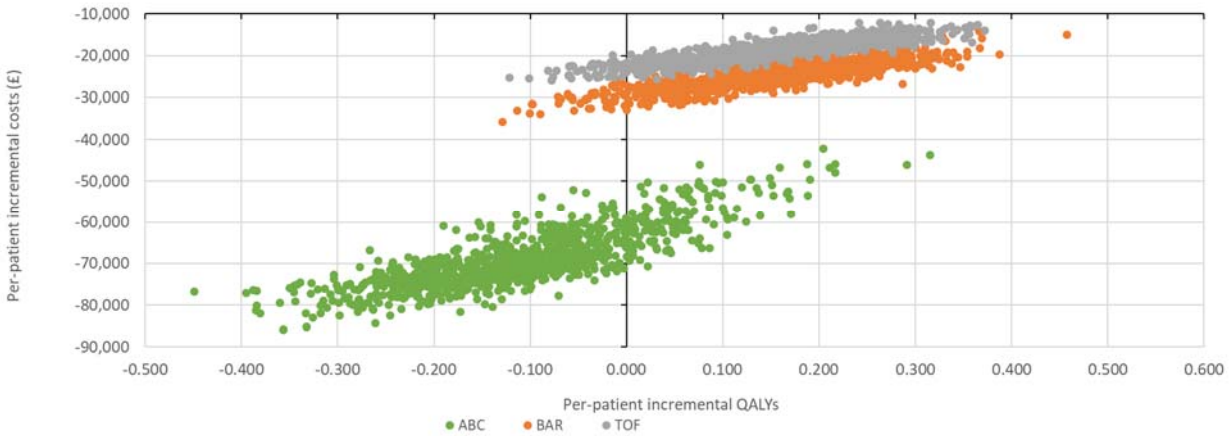


Figure 54. bDMARD-IR, MTX ineligible, RTX ineligible, severe RA – CE plane for PSA: filgotinib vs comparators



3b. Severe RA patients after failure of first line advanced therapy treatment (MTX eligible, RTX ineligible)

The results of the PSA are presented in Table 81, with a cost-effectiveness acceptability curve in Figure 55 and a cost-effectiveness plane in Figure 56. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 81: bDMARD-IR, MTX eligible, RTX ineligible, severe RA – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.675	[redacted]	-	-	-	-	-
BAR + MTX	[redacted]	13.675	[redacted]	24,916.53	0.000	-0.145	Dominated	Dominated
TCZ + MTX	[redacted]	13.675	[redacted]	6,863.21	0.000	0.008	Dominated	869,497.06
SAR + MTX	[redacted]	13.675	[redacted]	568.07	0.000	0.017	Dominated	32,883.63
ABC + MTX	[redacted]	13.675	[redacted]	36,383.58	0.000	0.232	615,737.45 SW	157,038.65

Abbreviations: ABC, abatacept; BAR, baricitinib; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life-year; SAR, sarilumab; TCZ, tocilizumab

Figure 55. bDMARD-IR, MTX eligible, RTX ineligible, severe RA – CEAC for PSA

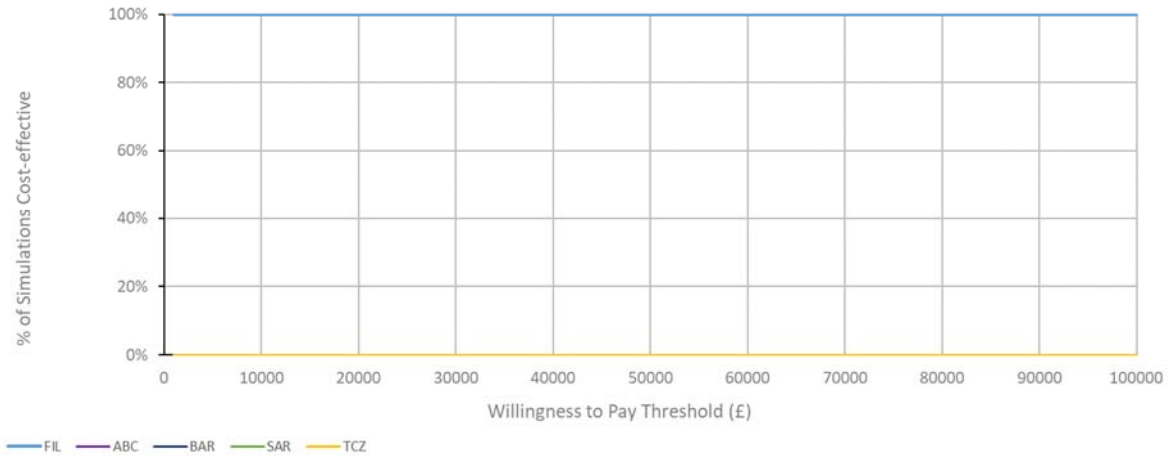
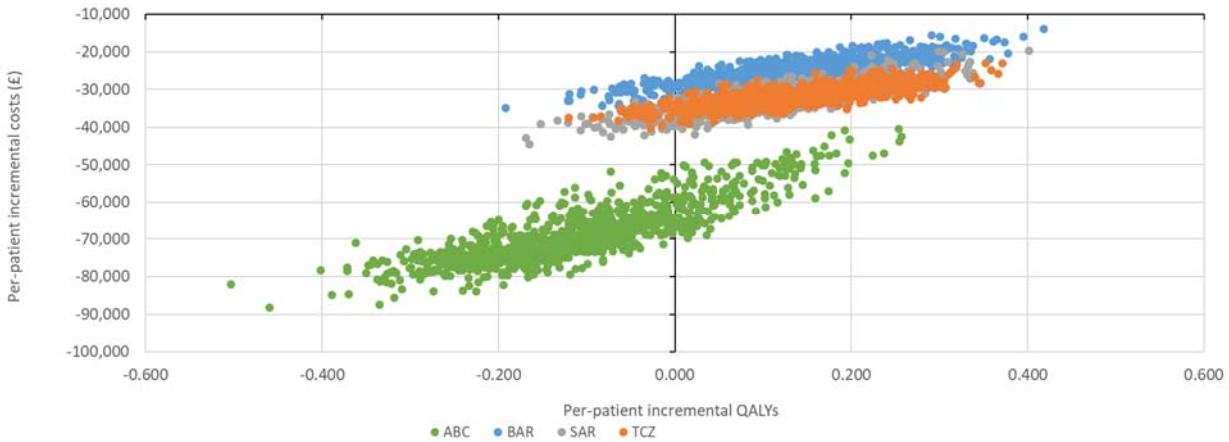


Figure 56. bDMARD-IR, MTX eligible, RTX ineligible, severe RA – CE plane for PSA: filgotinib vs comparators



4. Severe RA patients after failure of first line advanced therapy (MTX eligible, RTX eligible)

The results of the PSA are presented in Table 82, with a cost-effectiveness acceptability curve in Figure 57 and a cost-effectiveness plane in Figure 58. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 82: bDMARD-IR, MTX eligible, RTX eligible, severe RA – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.675	[redacted]	-	-	-	-	-
RTX + MTX	[redacted]	13.675	[redacted]	15,927.37	0.000	0.014	1,108,459 SW	1,108,459
Abbreviations: FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; RTX, rituximab;								

Figure 57. bDMARD-IR, MTX eligible, RTX eligible, severe RA – CEAC for PSA

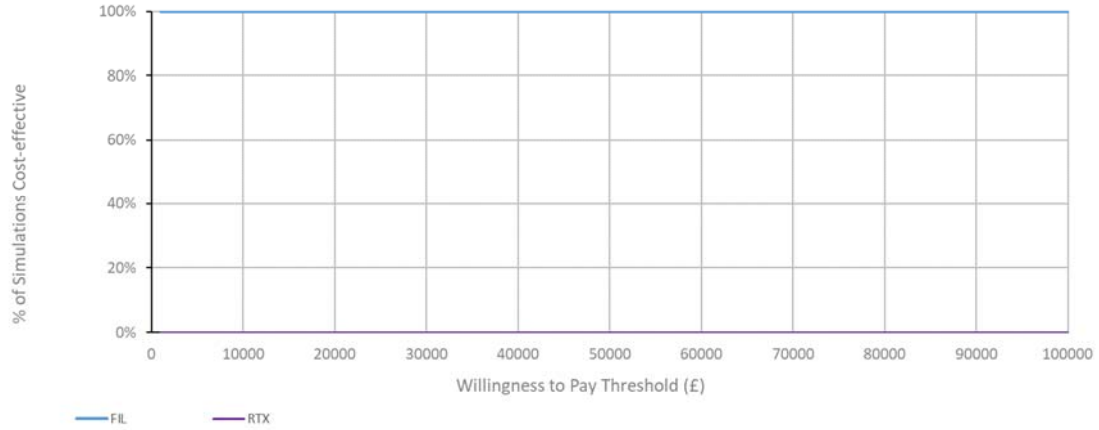


Figure 58. bDMARD-IR, MTX eligible, RTX eligible, severe RA – CE plane for PSA: filgotinib vs RTX

5. Severe RA patients after failure of rituximab in combination with methotrexate

The results of the PSA are presented in Table 83, with a cost-effectiveness acceptability curve in Figure 59 and a cost-effectiveness plane in Figure 60. Results in PSA are in line with those from the base case results. At a WTP threshold of £20,000, and £30,000, filgotinib had a 100% probability of being the optimal treatment.

Table 83: bDMARD-IR, MTX eligible, RTX IR, severe RA – versus FIL 200mg in combination with MTX (probabilistic results)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.675	[redacted]	-	-	-	-	-
TCZ + MTX	[redacted]	13.675	[redacted]	31,912.18	0.000	-0.135	Dominated	Dominated
SAR + MTX	[redacted]	13.675	[redacted]	558.90	0.000	0.017	Dominated	Dominated

Abbreviations: FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year; SAR, sarilumab; TCZ, tocilizumab

Figure 59. bDMARD-IR, MTX eligible, RTX IR, severe RA – CEAC for PSA

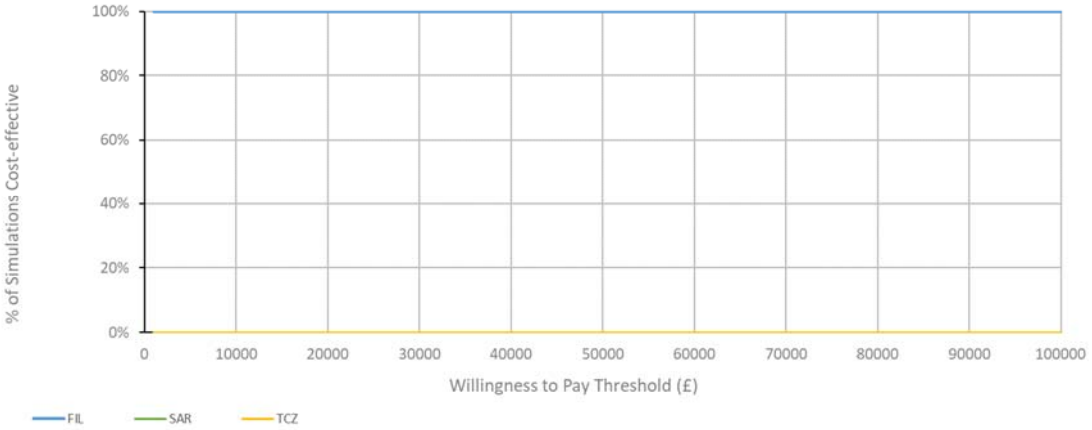
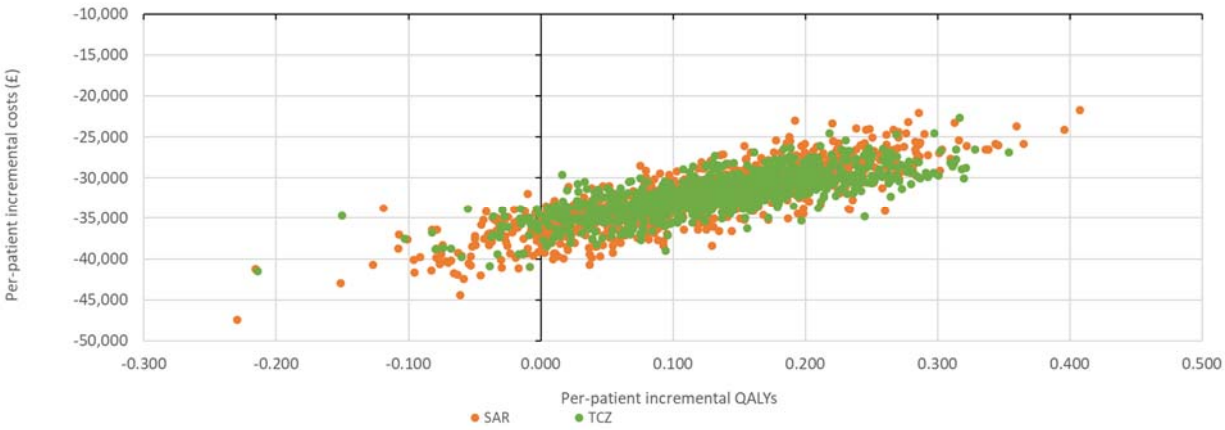


Figure 60. bDMARD-IR, MTX eligible, RTX IR, severe RA – CE plane for PSA: filgotinib vs comparators



B.3.8.2 Deterministic sensitivity analysis

The robustness of the model was tested by a set of deterministic sensitivity analyses (DSAs) and scenario analyses. One parameter or model assumption was varied at a time while the other parameters were kept at base case values. Results are presented in tornado diagrams (Figure 61, Figure 62, and Figure 63). Table 84 summarises the list of parameters and assumptions tested in DSA and scenario analyses. As the ICERs were in many cases in the south-west quadrant, the tornado diagrams are based on net monetary benefit, using a WTP threshold of £20,000.

Three tornado diagrams are presented in this section, for one population from each of the moderate csDMARD-IR, severe csDMARD-IR, and bDMARD-IR populations. Results for other populations are presented in Appendix J.

The tornado diagrams show the results of varying the parameters, as well as the results of the scenario analyses.

Table 84: Parameters and scenarios tested in deterministic sensitivity analysis

Parameters	Base case	DSA input
Discount rate for costs and QALYs	3.5%	0% and 6%
Treatment EULAR response	Median point estimates from the NMA (Section B2.9)	95% CI from the NMA
AE rate	Sourced from Singh et al. Cochrane review (Section	Varied by ±20%

Parameters	Base case	DSA input
	B3.4.4 Adverse events)	
Administration costs	Sourced from MTA375 (Section B3.5.2 Intervention and comparators' costs and resource use)	Varied by ±20%
Monitoring costs	Sourced from MTA375 (Section B3.5.2 Intervention and comparators' costs and resource use)	Varied by ±20%
Hospital costs	Sourced from MTA375 (Section B3.5.2 Intervention and comparators' costs and resource use)	Varied by ±20%
AE costs	Sourced from MTA375 (1) (Section B3.5.2)	Varied by ±20%
AE utility decrement	Sourced from Oppong et al. (Section B3.4.4 Adverse events (2))	Varied by ±20%
Scenario	**Base case**	**DSA input**
Time horizon	Lifetime (patient maximum age 100 years)	20-year time horizon
Using filgotinib EULAR response from the FINCH 1 trial (moderate population only)	Median point estimates from the NMA (Section B2.9)	Subgroup data from FINCH 1
Using AE rates from FINCH 1	Sourced from Singh et al. Cochrane review (Section B3.4.4 Adverse events)	JAKs: 1.7% (rate for filgotinib) bDMARDs: 2.5% (rate for adalimumab) csDMARDs: 0.8% (rate for methotrexate)
Using an alternative HAQ-DI to EQ-5D mapping	Mapping sourced from Hernandez-Alva et al (Section 3.4.2) (3)	Utility mapping algorithm sourced from Malottki et al. (4)
Assuming patients receiving csDMARDs and BSC experienced a linear HAQ-DI progression	HAQ-DI trajectory based on data described by Norton et al. (5)	Linear HAQ-DI progression based on Malottki et al. (4)

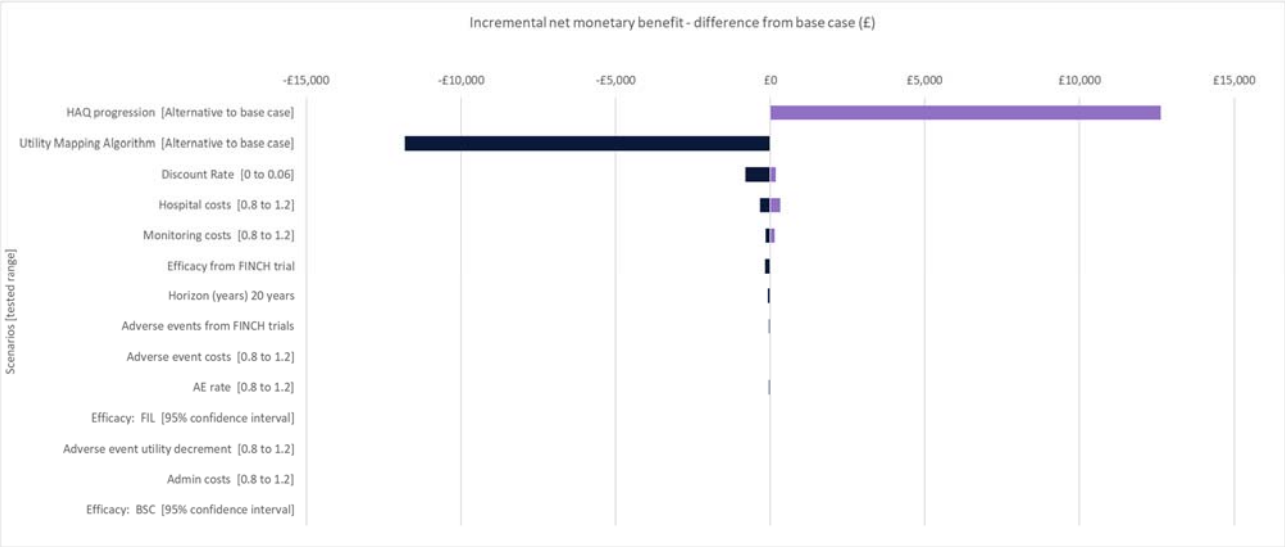
Abbreviations: AE, adverse event; bDMARD, biologic disease-modifying anti-rheumatic drug; CI, confidence interval; csDMARDs, conventional disease-modifying anti-rheumatic drugs; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire – Disability Index; JAK, Janus kinase; NMA, network meta-analysis; QALY, quality adjusted life year;

Moderate population, two csDMARD failures, MTX eligible

The results of the deterministic sensitivity analysis for the moderate, MTX eligible patient population for filgotinib combination therapy versus BSC is presented in

Figure 61. The key model drivers are the HAQ progression, HAQ to EQ-5D mapping algorithm, and discount rate.

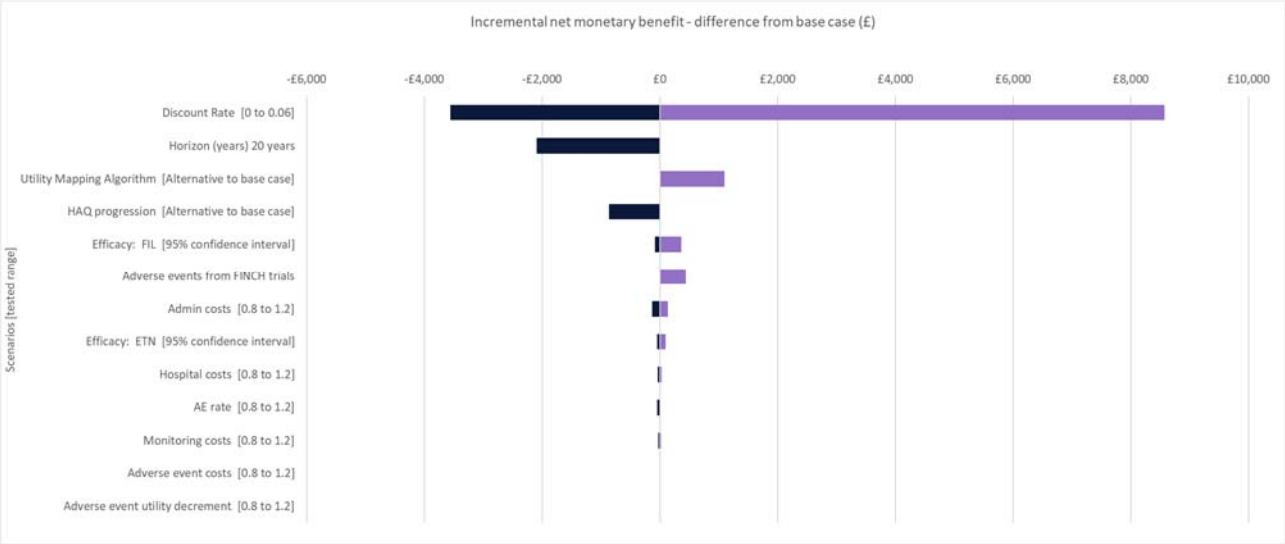
Figure 61. Tornado diagram in csDMARD-IR, MTX eligible, RTX eligible, severe RA (filgotinib combination therapy vs. BSC)



Severe csDMARD-IR, MTX eligible, RTX eligible

The results of the deterministic sensitivity analysis for the severe, csDMARD-IR, MTX eligible, RTX eligible patient population for filgotinib combination therapy presented in Figure 62. The most cost-effective comparator (i.e. with the lowest ICER in the south-west quadrant) was chosen for the analysis, which in this case is etanercept in combination with methotrexate. The key model drivers are the discount rate, annual price of filgotinib, and time horizon.

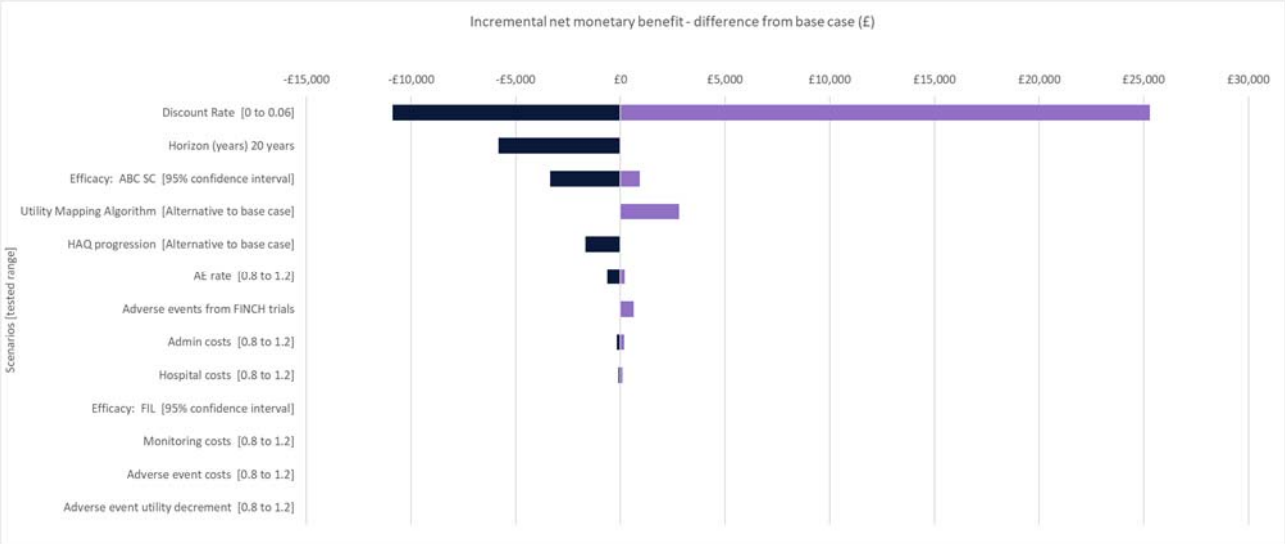
Figure 62. Tornado diagram in csDMARD-IR, MTX eligible, RTX eligible, severe RA (filgotinib combination therapy vs. ETN combination therapy)



Severe bDMARD-IR, MTX eligible, RTX ineligible

The results of the deterministic sensitivity analysis for the severe, bDMARD-IR, MTX eligible, RTX ineligible patient population for filgotinib combination therapy presented in Figure 63. The most cost-effective comparator was chosen for the analysis, which in this case is abatacept in combination with methotrexate. The key model drivers are the discount rate, time horizon, and efficacy of abatacept.

Figure 63. Tornado diagram in bDMARD-IR, MTX eligible, RTX ineligible, severe RA (filgotinib combination therapy vs. ABC combination therapy)



B.3.9 Subgroup analyses

The base case analysis includes separate analyses by disease severity and line of therapy, therefore, no further subgroups analyses are presented here.

B.3.10 Validation

Evaluations were carried out to assess the accuracy of the decision problem, model structure, evidence, treatment sequences, and assumptions in replicating the clinical pathway of interest. These evaluations were performed frequently throughout model development.

Internal validation

Internal quality assurance measures were undertaken. Model outputs were individually validated against their input equations for both survival and treatment discontinuation. Furthermore, a review was carried out to ensure the model operates as expected over the full range of inputs. To ensure consistency, parameter estimations within the model were checked against estimates generated by spreadsheet-based duplicated models. Model programming, calculations and inputs have also been reviewed.

External validation

The model approach has been validated by an independent third-party clinician. The third-party clinician did not identify any shortcomings with the model, and the guidance provided on treatment sequences was incorporated into the model.

Comparison of model output to MTA375 costs and QALYs

The sequences presented in Table 85 were used to validate the cost and QALY outputs of the economic model in this submission with that of the MTA375 model, using the costs and efficacy inputs outlined in sections 3.3 and Table 85, as well as the severe population baseline characteristics from FINCH 1. These sequences are sourced from the ERG report in TA10389 (6).

Table 85: Sequences used to validate the filgotinib model outputs using MTA375 model outputs

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment
1	Int. csDMARDs	IFX + MTX	BSC	-
2	Int. csDMARDs	ADA + MTX	IFX + MTX	BSC
3	ADA + MTX	IFX + MTX	Int. csDMARDs	BSC
4	ADA + MTX	IFX + MTX	BSC	-

Abbreviations: ADA, adalimumab; BSC, best supportive care; csDMARDs, conventional disease modifying anti-rheumatic drug; IFX, infliximab; MTX, methotrexate;

Results compared to the filgotinib model are presented in Table 86. MTA375 model outputs were sourced from a validation conducted by the ERG in TA10389 (6), and were obtained using the inputs presented in TA10389 for upadacitinib, including inputs from the NMA and cost inputs. In all cases, the filgotinib model produces higher costs and QALYs than the MTA375 model, however this variation remained within [redacted]. It should be noted however, that as the results for the two models were found using two different sources of efficacy inputs, these results should be interpreted with caution. This validation exercise suggests that the filgotinib CEM is consistent with the model described in MTA375, as well as other preceding NICE submissions in RA.

Table 86: Results from the filgotinib model compared to the MTA375 model

Sequence	Total discounted costs			Total discounted QALYs		
	FIL model	TA375 model	Ratio	FIL model	TA375 model	Ratio
1	[redacted]	£64,926	[redacted]	[redacted]	7.16	[redacted]
2	[redacted]	£78,306	[redacted]	[redacted]	7.70	[redacted]
3	[redacted]	£92,003	[redacted]	[redacted]	7.77	[redacted]
4	[redacted]	£94,925	[redacted]	[redacted]	7.28	[redacted]

Abbreviations: FIL, filgotinib; QALY, quality adjusted life year

B.3.11 Interpretation and conclusions of economic evidence

B3.11.1 Overall conclusions

The cost-effectiveness of filgotinib has been evaluated across each point in the treatment pathway, in line with the final scope and deemed relevant to all groups likely to benefit from treatment. The results of this analysis demonstrate that filgotinib represents a cost-effective option in moderate and severe disease as both a combination and monotherapy.

Filgotinib has been priced to be cost-effective in both moderate and severe populations. In moderate disease, filgotinib sequences generated a cost-effective incremental cost-effectiveness ratio (ICER) as both combination therapy with MTX (£21,924/QALY) and as monotherapy (£21,721/QALY) compared with BSC. These are likely to be conservative estimates given the model assumption that last-line patients remain on BSC and disease does not progress. This addition to the model could be expected to lower the ICER by approximately £9,000/QALY (7).

A post-hoc subgroup analysis of patients with moderate disease severity in FINCH 1 confirmed the efficacy of filgotinib in this population showing statistically significant efficacy benefit compared with placebo across a range of outcomes including ACR20, ACR50, ACR70 and DAS28 (CRP and LDA) at week 24. Absolute results were also similar to the whole population confirming efficacy across the spectrum of disease activity. Further, similar response to adalimumab was observed across endpoints including ACR at week 52.

In patients with severely active RA, filgotinib sequences were associated with similar QALYs but significantly lower costs than all comparators across all points in the treatment pathway. Although the relative efficacy of monotherapy could not be estimated within the NMA, comparison of the combination and monotherapy arms in FINCH 3 confirmed comparable efficacy across a range of clinically meaningful outcomes including ACR20, ACR50, ACR70 and HAQ-DI.

The robustness of base case results was assessed through deterministic, scenario and probabilistic analyses with results demonstrating the stability of base case results as well as a high level of certainty. This strengthens the conclusions drawn

from the base case analyses. The economic model was found to be most sensitive to scenarios where alternative inputs inform HAQ-DI progression, the algorithm used to map HAQ-DI to EQ-5D, discount factor and time horizon.

The inputs and methodologies employed in developing the economic model are well established in RA modelling and consistent with methods described for the economic model developed by ScHARR in MTA375, as well as subsequent NICE submissions (TA466, TA480 and TA485 (8-10)). Validation work confirmed similar outputs between the manufacturers model and MTA375 allowing for comparability of model outputs (Table 86). Modelled treatment sequences for each population follow NICE guidelines and were validated through clinical expert advice to ensure applicability to clinical practice in England and Wales.

Filgotinib has been shown to be a cost-effective treatment option in moderate and severe disease activity across all points in the treatment pathway. The results have been shown to be both robust and generalisable to a UK population.

B3.11.2 Strengths, limitations and further analysis

Strengths

The model structure, inputs and methodology follow that of MTA375 and other recent NICE submissions to the extent possible and are in line with clinical practise in the UK. In the base case the model applies conservative assumptions, for example, biosimilar costs have been used where available and csDMARDs are costed as per MTX, which is the least costly option. Base case assumptions have been extensively tested by varying model parameters as well as including a range of scenario analyses, for example using trial specific data. Cost-effectiveness conclusions remain largely unchanged across scenario and sensitivity analyses.

Limitations and further analysis

The efficacy of filgotinib monotherapy is assumed to be equivalent to combination therapy. While trial data is not available in the specific populations of interest, this assumption is supported by the similarity of efficacy between filgotinib monotherapy

and combination therapy arms in FINCH 3 (MTX-naïve population). This assumption was also validated through clinical opinion.

A study of UK patients in the Early RA Network (ERAN), a cohort of newly diagnosed RA patients receiving csDMARDs, showed the rate of patients progressing from moderately to severely active disease was 19% over a two-year period (11). The current model does not include the possibility for patients with moderately active RA to progress to severe disease. However, this is likely to be a conservative approach as has been demonstrated in a recent submission where disease progression was incorporated, resulting in significantly improved cost-effectiveness.

The recent TA evaluating upadacitinib in RA included analyses that demonstrated allowing patients to progress from moderate to severe disease resulted in significantly lower ICERs (approximately £9,000/QALY lower) compared with not allowing for disease progression. In addition, the proportion of patients progressing to a severe state was concluded to be an underestimation by the technical team. Including this functionality has been considered appropriate by the ERG and technical team in previous TAs in RA (TA10389, TA485). To better reflect clinical experience, future modelling could include this progression.

The base case analysis estimated ICERs below £22,000/QALY in moderate disease when filgotinib is used as monotherapy or in combination with MTX. Given moderate to severe disease progression was not incorporated in the model, including this progression would be expected to lower the ICER to below the willingness-to-pay threshold of £20,000/QALY.

B.4 References

1. Gilead. Filgotinib Draft Summary of Product Characteristics. 2020.
2. Namour F, Desrivot J, Van der Aa A, Harrison P, Tasset C, van't Klooster G. Clinical Confirmation that the Selective JAK1 Inhibitor Filgotinib (GLPG0634) has a Low Liability for Drug-drug Interactions. Drug Metab Lett. 2016;10(1):38-48.
3. McInnes IB, Schett G. The Pathogenesis of Rheumatoid Arthritis. New England Journal of Medicine. 2011;365(23):2205-19.
4. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis & Rheumatism. 2010;62(9):2569-81.
5. Gibofsky A. Epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis: A Synopsis. Am J Manag Care. 2014;20(7 Suppl):S128-35.
6. Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch MH, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). Annals of the Rheumatic Diseases. 2014;73(1):62-8.
7. van Steenbergen HW, Aletaha D, Beaart-van de Voorde LJJ, Brouwer E, Codreanu C, Combe B, et al. EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis. Annals of the Rheumatic Diseases. 2017;76(3):491-6.
8. Fransen J. Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. Rheumatology. 2004;43(10):1252-5.
9. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part I. Arthritis & Rheumatism. 2008;58(1):15-25.
10. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, et al. The global burden of rheumatoid arthritis: estimates from the Global Burden of Disease 2010 study. Annals of the Rheumatic Diseases. 2014;73(7):1316-22.
11. Symmons D. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. Rheumatology. 2002;41(7):793-800.
12. Office for National Statistics. Population estimates for the UK, England and Wales, Scotland and Northern Ireland.
13. Gilead data on file. Rheumatoid Arthritis Epidemiology. Decision Resources Group Report. 2017.
14. Humphreys JH, Verstappen SMM, Hyrich KL, Chipping JR, Marshall T, Symmons DPM. The incidence of rheumatoid arthritis in the UK: comparisons using the 2010 ACR/EULAR classification criteria and the 1987 ACR classification criteria. Results from the Norfolk Arthritis Register. Annals of the Rheumatic Diseases. 2013;72(8):1315-20.
15. Gilead data on file. Adelphi Market Research. 2020.
16. Kiely P, Walsh D, Williams R, Young A, for the Early Rheumatoid Arthritis N. Outcome in rheumatoid arthritis patients with continued conventional therapy for moderate disease activity--the early RA network (ERAN). Rheumatology. 2011;50(5):926-31.

17. Diffin JG, Lunt M, Marshall T, Chipping JR, Symmons DP, Verstappen SM. Has the severity of rheumatoid arthritis at presentation diminished over time? J Rheumatol. 2014;41(8):1590-9.
18. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. Nature Reviews Disease Primers. 2018;4(1):1-23.
19. Tymms K, Zochling J, Scott J, Bird P, Burnet S, de Jager J, et al. Barriers to Optimal Disease Control for Rheumatoid Arthritis Patients With Moderate and High Disease Activity: Optimal Disease Control Barriers in RA. Arthritis Care & Research. 2014;66(2):190-6.
20. Cole Z, Blanthorn-Hazel S, Mohammed D, Parker B. E044 Healthcare resource utilisation associated with management of patients with moderate rheumatoid arthritis in the UK: initial data from a multi-centre, retrospective, non-interventional study. Rheumatology. 2019;58(Supplement_3):kez110.043.
21. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Annals of the Rheumatic Diseases. 2020:annrheumdis-2019-216655.
22. Scott IC, Mount J, Barry J, Kirkham B. 213 Factors associated with disability in rheumatoid arthritis patients with persistent moderate disease activity. Rheumatology. 2018;57(suppl_3).
23. El Miedany Y. Co-morbidity index in rheumatoid arthritis: time to think. Clin Rheumatol. 2015;34(12):1995-2000.
24. Michaud K, Berglind N, Franzén S, Frisell T, Garwood C, Greenberg JD, et al. Can rheumatoid arthritis (RA) registries provide contextual safety data for modern RA clinical trials? The case for mortality and cardiovascular disease. Annals of the Rheumatic Diseases. 2016;75(10):1797-805.
25. Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther. 2015;17(1).
26. Matcham F, Scott IC, Rayner L, Hotopf M, Kingsley GH, Norton S, et al. The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: A systematic review and meta-analysis. Seminars in Arthritis and Rheumatism. 2014;44(2):123-30.
27. Safiri S, Kolahi AA, Hoy D, Smith E, Bettampadi D, Mansournia MA, et al. Global, regional and national burden of rheumatoid arthritis 1990–2017: a systematic analysis of the Global Burden of Disease study 2017. Annals of the Rheumatic Diseases. 2019;78(11):1463-71.
28. Lundkvist J, Kastäng F, Kobelt G. The burden of rheumatoid arthritis and access to treatment: health burden and costs. Eur J Health Econ. 2008;8(2):49-60.
29. XE Currency Table:s EUR - Euro 2007 [Available from: https://www.xe.com/currencytables/?from=EUR&date=2007-01-01.
30. National Institute for Health and Care Excellence. Rheumatoid arthritis in adults: management. NICE guideline [NG100]. 2018.
31. National Institute for Health and Care Excellence. Overview | Sarilumab for moderate to severe rheumatoid arthritis | Guidance | NICE.
32. Overview | Tofacitinib for moderate to severe rheumatoid arthritis | Guidance | NICE.

33. Overview | Baricitinib for moderate to severe rheumatoid arthritis | Guidance | NICE.
34. Overview | Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor | Guidance | NICE.
35. Overview | Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed | Guidance | NICE.
36. Overview | Tocilizumab for the treatment of rheumatoid arthritis | Guidance | NICE.
37. Overview | Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs | Guidance | NICE.
38. Overview | Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor | Guidance | NICE.
39. National Institute for Health and Care Excellence. Single Technology Appraisal: Upadacitinib for previously treated moderate to severe active rheumatoid arthritis [ID1400]. Committee Papers. 2019.
40. National Institute for Health and Care Excellence. Project information | Sirukumab for previously treated moderate to severe active rheumatoid arthritis (ID1002) | Guidance | NICE [Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10180.
41. National Institute for Health and Care Excellence. Project information | Rheumatoid arthritis (after the failure of conventional DMARDs) -rituximab [ID333] | Guidance | NICE [Available from: https://www.nice.org.uk/guidance/indevelopment/gid-tag418.
42. Kearsley-Fleet L, Davies R, De Cock D, Watson KD, Lunt M, Buch MH, et al. Biologic refractory disease in rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Annals of the Rheumatic Diseases. 2018:annrheumdis-2018-213378.
43. Atzeni F, Masala IF, di Franco M, Sarzi-Puttini P. Infections in rheumatoid arthritis. Current Opinion in Rheumatology. 2017;29(4):323-30.
44. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: A population-based study. Arthritis & Rheumatism. 2002;46(9):2287-93.
45. Winthrop KL, Yamanaka H, Valdez H, Mortensen E, Chew R, Krishnaswami S, et al. Herpes Zoster and Tofacitinib Therapy in Patients With Rheumatoid Arthritis. Arthritis & Rheumatology. 2014;66(10):2675-84.
46. Singh JA, Cameron C, Noorbaloochi S, Cullis T, Tucker M, Christensen R, et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet (London, England). 2015;386(9990):258-65.
47. Woodrick RS, Ruderman EM. Safety of biologic therapy in rheumatoid arthritis. Nature reviews Rheumatology. 2011;7(11):639-52.
48. Vyas D, O'Dell KM, Bandy JL, Boyce EG. Tofacitinib: the first Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis. The Annals of pharmacotherapy. 2013;47(11):1524-31.
49. Genovese MC, Kremer JM, van Vollenhoven RF, Alten R, Scali JJ, Kelman A, et al. Transaminase levels and hepatic events during tocilizumab treatment: pooled

analysis of long-term clinical trial safety data in rheumatoid arthritis. Arthritis Rheumatol. 2017;69(9):1751-61.
50. European Medicines Agency. Tofacitinib (Xeljanz) SPC. Available at: www.ema.europa.eu/documents/product-information/xeljanz-epar-product-information_en.pdf. Accessed February 2019.
51. European Medicines Agency. Baricitinib (Olumiant) SPC. Available at: www.ema.europa.eu/documents/product-information/olumiant-epar-product-information_en.pdf. Accessed February 2019.
52. European Medicines Agency. Methotrexate (Nordimet) SPC. Available at: www.ema.europa.eu/documents/product-information/nordimet-epar-product-information_en.pdf. Accessed January 2019.
53. Dhawan SS, Quyyumi AA. Rheumatoid arthritis and cardiovascular disease. Current atherosclerosis reports. 2008;10(2):128-33.
54. Zhang J, Chen L, Delzell E, Muntner P, Hillegass WB, Safford MM, et al. The association between inflammatory markers, serum lipids and the risk of cardiovascular events in patients with rheumatoid arthritis. Ann Rheum Dis. 2014;73(7):1301-8.
55. Gonzalez-Gay MA, Gonzalez-Juanatey C. Inflammation and lipid profile in rheumatoid arthritis: bridging an apparent paradox. Ann Rheum Dis. 2014;73(7):1281-3.
56. Pfizer Limited. Pfizer Statement on Ongoing Tofacitinib FDA PostMarketing Requirement Study In Patients With Rheumatoid Arthritis 2019 [Available from: https://investors.pfizer.com/investor-news/press-release-details/2019/Pfizer-Announces-Modification-to-Ongoing-Tofacitnib-FDA-Post-Marketing-Requirement-Study-in-Patients-with-Rheumatoid-Arthritis/default.aspx.
57. Li N, Betts KA, Messali AJ, Skup M, Garg V. Real-world Effectiveness of Biologic Disease-modifying Antirheumatic Drugs for the Treatment of Rheumatoid Arthritis After Etanercept Discontinuation in the United Kingdom, France, and Germany. Clinical Therapeutics. 2017;39(8):1618-27.
58. Wei W, Knapp K, Wang L, Chen C-I, Craig GL, Ferguson K, et al. Treatment Persistence and Clinical Outcomes of Tumor Necrosis Factor Inhibitor Cycling or Switching to a New Mechanism of Action Therapy: Real-world Observational Study of Rheumatoid Arthritis Patients in the United States with Prior Tumor Necrosis Factor Inhibitor Therapy. Adv Ther. 2017;34(8):1936-52.
59. Barclay N, Tarallo M, Hendrikx T, Marett S. Patient Preference for Oral Versus Injectable and Intravenous Methods of Treatment for Rheumatoid Arthritis. Value in Health. 2013;16(7):A568.
60. Louder AM, Singh A, Saverno K, Cappelleri JC, Aten AJ, Koenig AS, et al. Patient Preferences Regarding Rheumatoid Arthritis Therapies: A Conjoint Analysis. Am Health Drug Benefits. 2016;9(2):84-93.
61. Bolge SC, Goren A, Tandon N. Reasons for discontinuation of subcutaneous biologic therapy in the treatment of rheumatoid arthritis: a patient perspective. Patient Prefer Adherence. 2015;9:121-31.
62. Svensson B, Andersson ML, Bala SV, Forslind K, Hafstrom I, group Bs. Long-term sustained remission in a cohort study of patients with rheumatoid arthritis: choice of remission criteria. BMJ Open. 2013;3(9):e003554.
63. Nagy G, van Vollenhoven RF. Sustained biologic-free and drug-free remission in rheumatoid arthritis, where are we now? Arthritis Res Ther. 2015;17:181.

64. Conaghan PG, D'Agostino MA, Le Bars M, Baron G, Schmidely N, Wakefield R, et al. Clinical and ultrasonographic predictors of joint replacement for knee osteoarthritis: results from a large, 3-year, prospective EULAR study. Annals of the Rheumatic Diseases. 2010;69(4):644-7.
65. Gwinnutt JM, Symmons DPM, MacGregor AJ, Chipping JR, Marshall T, Lunt M, et al. Twenty-Year Outcome and Association Between Early Treatment and Mortality and Disability in an Inception Cohort of Patients With Rheumatoid Arthritis. Arthritis & Rheumatology. 2017;69(8).
66. Fautrel B, den Broeder AA. De-intensifying treatment in established rheumatoid arthritis (RA): Why, how, when and in whom can DMARDs be tapered? Best Practice & Research Clinical Rheumatology. 2015;29(4):550-65.
67. Gilead. A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 weeks in Combination with Methotrexate to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate (FINCH 1) Clinical Study Report. 2020.
68. Gilead. Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 24 Weeks in Combination with Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug(s) (csDMARDs) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Biologic DMARD(s) Treatment (FINCH 2). Clinical Study Report. 2020.
69. Gilead. A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 Weeks Alone and in Combination with Methotrexate (MTX) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are Naive to MTX Therapy (FINCH 3). Clinical Study Report. 2020.
70. Gilead. Long Term Extension Study to Assess the Safety and Efficacy of Filgotinib in Adults With Rheumatoid Arthritis (FINCH 4). 2018.
71. al Le. Establishing Non-Inferiority of a New Treatment in a Three-Arm Trial: Apply a Step-Down Hierarchical Model in a Papulopustular Acne Study and an Oral Prophylactic Antibiotics Study. International Journal of Statistics in Medical Research. 2014(3):11-20.
72. Abe T. A Multicenter, Double-Blind, Randomized, Placebo Controlled Trial of Infliximab Combined with Low Dose Methotrexate In Japanese Patients With Rheumatoid Arthritis. The Journal of Rheumatology. 2006;33(1).
73. Genant HK, Peterfy CG, Westhovens R, Becker JC, Aranda R, Vratsanos G, et al. Abatacept inhibits progression of structural damage in rheumatoid arthritis: results from the long-term extension of the AIM trial. Ann Rheum Dis. 2008;67(8):1084-9.
74. Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis. 2008;67(8):1096-103.
75. Baek HJ, Lim MJ, Park W, Park SH, Shim SC, Yoo DH, et al. Efficacy and safety of tocilizumab in Korean patients with active rheumatoid arthritis. Korean J Intern Med. 2019;34(4):917-31.

76. Beals C, Baumgartner R, Peterfy C, Balanescu A, Mirea G, Harabagiu A, et al. Magnetic resonance imaging of the hand and wrist in a randomized, double-blind, multicenter, placebo-controlled trial of infliximab for rheumatoid arthritis: Comparison of dynamic contrast enhanced assessments with semi-quantitative scoring. PLoS One. 2017;12(12):e0187397.
77. Chen D-Y. Randomized, Double-blind, Placebo-controlled, Comparative Study of Human Anti-TNF Antibody Adalimumab in Combination with Methotrexate and Methotrexate Alone in Taiwanese Patients with Active Rheumatoid Arthritis. J Formos Med Assoc. 2009;108(4).
78. Cohen S. Interleukin 1 receptor antagonist anakinra improves functional status in patients with rheumatoid arthritis. J Rheumatol. 2003;30(2).
79. Emery P. Treatment of Rheumatoid Arthritis Patients with Abatacept and Methotrexate Significantly Improved Health-Related Quality of Life. The Journal of Rheumatology. 2006.
80. Mease P. Improved health-related quality of life for patients with active rheumatoid arthritis receiving rituximab: Results of the Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) Trial. The Journal of Rheumatology. 2008;35(1).
81. Westhovens R, Taylor PC, Alten R, Pavlova D, Enriquez-Sosa F, Mazur M, et al. Filgotinib (GLPG0634/GS-6034), an oral JAK1 selective inhibitor, is effective in combination with methotrexate (MTX) in patients with active rheumatoid arthritis and insufficient response to MTX: results from a randomised, dose-finding study (DARWIN 1). Ann Rheum Dis. 2017;76(6):998-1008.
82. Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis. 2006;65(10):1357-62.
83. Smolen JS, Burmester G-R, Combe B, Curtis JR, Hall S, Haraoui B, et al. Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. The Lancet. 2016;388(10061):2763-74.
84. Weinblatt M. Intravenous Golimumab Inhibits Radiographic Progression and Maintains Clinical Efficacy and Safety in Patients with Active Rheumatoid Arthritis Despite Methotrexate Therapy: 1-Year Results of a Phase 3 Trial. 2012.
85. Weinblatt ME, Schiff M, Valente R, van der Heijde D, Citera G, Zhao C, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. Arthritis Rheum. 2013;65(1):28-38.
86. Weinblatt ME, Westhovens R, Mendelsohn AM, Kim L, Lo KH, Sheng S, et al. Radiographic benefit and maintenance of clinical benefit with intravenous golimumab therapy in patients with active rheumatoid arthritis despite methotrexate therapy: results up to 1 year of the phase 3, randomised, multicentre, double blind, placebo controlled GO-FURTHER trial. Ann Rheum Dis. 2014;73(12):2152-9.
87. Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. Mod Rheumatol. 2014;24(5):715-24.

88. Tanaka Y. Efficacy and safety of sarilumab plus methotrexate in a phase 3 trial in Japanese patients with active rheumatoid arthritis (KAKEHASI). International journal of rheumatic diseases. 2018.
89. Tanaka Y, Wada K, Takahashi Y, Hagino O, van Hoogstraten H, Graham NMH, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a randomized, placebo-controlled phase III trial in Japan. Arthritis Res Ther. 2019;21(1):79.
90. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004;50(5):1400-11.
91. Ho-Youn K. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR Journal of Rheumatology. 2007(10).
92. Kremer J. Concomitant Leflunomide Therapy in Patients with Active Rheumatoid Arthritis despite Stable Doses of Methotrexate. Annals of Internal Medicine. 2002.
93. Lim MJ. A double-blind, placebo-controlled, multicenter trial of tocilizumab in moderate to severe active RA patients with inadequate response to methotrexate in korean population. 2013.
94. Genovese MC, Fleischmann R, Kivitz AJ, Rell-Bakalarska M, Martincova R, Fiore S, et al. Sarilumab Plus Methotrexate in Patients With Active Rheumatoid Arthritis and Inadequate Response to Methotrexate: Results of a Phase III Study. Arthritis Rheumatol. 2015;67(6):1424-37.
95. Genovese MC, van Adelsberg J, Fan C, Graham NMH, van Hoogstraten H, Parrino J, et al. Two years of sarilumab in patients with rheumatoid arthritis and an inadequate response to MTX: safety, efficacy and radiographic outcomes. Rheumatology (Oxford). 2018;57(8):1423-31.
96. Strand V, Kosinski M, Chen CI, Joseph G, Rendas-Baum R, Graham NM, et al. Sarilumab plus methotrexate improves patient-reported outcomes in patients with active rheumatoid arthritis and inadequate responses to methotrexate: results of a phase III trial. Arthritis Res Ther. 2016;18:198.
97. Takeuchi T, Miyasaka N, Zang C, Alvarez D, Fletcher T, Wajdula J, et al. A phase 3 randomized, double-blind, multicenter comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity, and safety in Japanese subjects with active rheumatoid arthritis. Mod Rheumatol. 2013;23(4):623-33.
98. O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 2013;369(4):307-18.
99. Choy E, McKenna F, Vencovsky J, Valente R, Goel N, Vanlunen B, et al. Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. Rheumatology (Oxford). 2012;51(7):1226-34.
100. Tanaka Y, Suzuki M, Nakamura H, Toyoizumi S, Zwillich SH, Tofacitinib Study I. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in

patients with rheumatoid arthritis and an inadequate response to methotrexate. Arthritis Care Res (Hoboken). 2011;63(8):1150-8.
101. Kang YM, Park YE, Park W, Choe JY, Cho CS, Shim SC, et al. Rapid onset of efficacy predicts response to therapy with certolizumab plus methotrexate in patients with active rheumatoid arthritis. Korean J Intern Med. 2018;33(6):1224-33.
102. Keystone EC, Taylor PC, Drescher E, Schlichting DE, Beattie SD, Berclaz PY, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Ann Rheum Dis. 2015;74(2):333-40.
103. Hobbs K, Deodhar A, Wang B, Bitman B, Nussbaum J, Chung J, et al. Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of etanercept in patients with moderately active rheumatoid arthritis despite DMARD therapy. Springerplus. 2015;4:113.
104. Kivitz A. Peficitinib, a JAK Inhibitor, in the Treatment of Moderate-to-Severe Rheumatoid Arthritis in Patients With an Inadequate Response to Methotrexate. Arthritis & Rheumatology. 2017;69(4):709–19.
105. Taylor PC. Baricitinib Versus Placebo or Adalimumab in Patients with Active Rheumatoid Arthritis (RA) and an Inadequate Response to Background Methotrexate Therapy: Results of a Phase 3 Study. 2015 ACR/ARHP Annual Meeting2015.
106. Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J, et al. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. N Engl J Med. 2017;376(7):652-62.
107. Matsubara T, Inoue H, Nakajima T, Tanimura K, Sagawa A, Sato Y, et al. Abatacept in combination with methotrexate in Japanese biologic-naive patients with active rheumatoid arthritis: a randomised placebo-controlled phase IV study. RMD Open. 2018;4(2):e000813.
108. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. The Lancet. 2008;371(9617):987-97.
109. Dougados M, van der Heijde D, Chen YC, Greenwald M, Drescher E, Liu J, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. Ann Rheum Dis. 2017;76(1):88-95.
110. Kang YM. Efficacy and Safety Of Certolizumab Pegol (Czp) With Concomitant Methotrexate (Mtx) In Korean Rheumatoid Arthritis (Ra) Patients (Pts) With An Inadequate Response To Mtx. Ann Rheum Dis. 2013.
111. Li Z, Hu J, Bao C, Li X, Li X, Xu J, et al. SAT0218 Efficacy and safety of baricitinib in mtx-ir patients with rheumatoid arthritis: 52 week results from a phase 3 study (RA-BALANCE). Saturday, 16 JUNE 20182018. p. 969.2-70.
112. Takeuchi T, Tanaka Y, Tanaka S, Kawakami A, Iwasaki M, Katayama K, et al. Efficacy and safety of peficitinib (ASP015K) in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III randomised, double-blind, placebo-controlled trial (RAJ4) in Japan. Ann Rheum Dis. 2019;78(10):1305-19.
113. Keystone E, Heijde D, Mason D, Jr., Landewe R, Vollenhoven RV, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than

placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 2008;58(11):3319-29.
114. Smolen J, Landewe RB, Mease P, Brzezicki J, Mason D, Luijtens K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009;68(6):797-804.
115. Peterfy C, Emery P, Tak PP, Ostergaard M, DiCarlo J, Otsa K, et al. MRI assessment of suppression of structural damage in patients with rheumatoid arthritis receiving rituximab: results from the randomised, placebo-controlled, double-blind RA-SCORE study. Ann Rheum Dis. 2016;75(1):170-7.
116. Huizinga TW, Fleischmann RM, Jasson M, Radin AR, van Adelsberg J, Fiore S, et al. Sarilumab, a fully human monoclonal antibody against IL-6Ralpha in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. Ann Rheum Dis. 2014;73(9):1626-34.
117. Fleischmann R. Upadacitinib Versus Placebo or Adalimumab in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Results of a Phase III, Double- Blind, Randomized Controlled Trial. Arthritis & Rheumatology. 2019;71(11):788–1800.
118. Burmester GR. A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study of Upadacitinib (ABT-494), a Selective JAK-1 Inhibitor, in Patients with Active Rheumatoid Arthritis with Inadequate Response to Conventional Synthetic Dmards. 2017 ACR/ARHP Annual Meeting2018.
119. Burmester GR, Kremer JM, Van den Bosch F, Kivitz A, Bessette L, Li Y, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. The Lancet. 2018;391(10139):2503-12.
120. Emery P, Deodhar A, Rigby WF, Isaacs JD, Combe B, Racewicz AJ, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). Ann Rheum Dis. 2010;69(9):1629-35.
121. Tanaka Y. 12-week Results of a Phase 2b Dose-Ranging Study of Baricitinib, An Oral JAK1/JAK2 Inhibitor in Japanese Patients with Rheumatoid Arthritis on Background Methotrexate Therapy. 2013.
122. Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. 2008;58(10):2968-80.
123. Weinblatt M. A Trial Of Etanercept, A Recombinant Tumor Necrosis Factor Receptor:Fc Fusion Protein, In Patients With Rheumatoid Arthritis Receiving Methotrexate. The New England Journal of Medicine. 1999;340(4).
124. Genovese M. Abatacept for Rheumatoid Arthritis Refractory to Tumor Necrosis Factor a Inhibition. N Engl J Med. 2005(353).

125. Kivitz A, Olech E, Borofsky MA, Zazueta B, Navarro-Sarabia F, Radominski SC, et al. Two-year Efficacy and Safety of Subcutaneous Tocilizumab in Combination with Disease-modifying Antirheumatic Drugs Including Escalation to Weekly Dosing in Rheumatoid Arthritis. J Rheumatol. 2018;45(4):456-64.
126. Genovese MC, Kalunian K, Gottenberg JE, Mozaffarian N, Bartok B, Matzkies F, et al. Effect of Filgotinib vs Placebo on Clinical Response in Patients With Moderate to Severe Rheumatoid Arthritis Refractory to Disease-Modifying Antirheumatic Drug Therapy: The FINCH 2 Randomized Clinical Trial. JAMA. 2019;322(4):315-25.
127. Schiff MH, von Kempis J, Goldblum R, Tesser JR, Mueller RB. Rheumatoid arthritis secondary non-responders to TNF can attain an efficacious and safe response by switching to certolizumab pegol: a phase IV, randomised, multicentre, double-blind, 12-week study, followed by a 12-week open-label phase. Ann Rheum Dis. 2014;73(12):2174-7.
128. Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, et al. Baricitinib in Patients with Refractory Rheumatoid Arthritis. N Engl J Med. 2016;374(13):1243-52.
129. Smolen JS, Kremer JM, Gaich CL, DeLozier AM, Schlichting DE, Xie L, et al. Patient-reported outcomes from a randomised phase III study of baricitinib in patients with rheumatoid arthritis and an inadequate response to biological agents (RA-BEACON). Annals of the rheumatic diseases (no pagination), 2016. 2016;Date of Publication: October 31.
130. Zamani O. Efficacy and Safety of Baricitinib In Patients With Active Rheumatoid Arthritis And Inadequate Response To Tumour Necrosis Factor Inhibitors: Summary Results From The 24-Week Phase III RA-Beacon Study. 2016.
131. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008;67(11):1516-23.
132. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54(9):2793-806.
133. Keystone E, Burmester GR, Furie R, Loveless JE, Emery P, Kremer J, et al. Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum. 2008;59(6):785-93.
134. Genovese M. Upadacitinib (ABT-494) in Patients with Active Rheumatoid Arthritis and Inadequate Response or Intolerance to Biological Dmards: A Phase 3 Randomized, PlaceboControlled, Double-Blind Study of a Selective JAK-1 Inhibitor. 2017 ACR/ARHP Annual Meeting2017.
135. Fleischmann R. Efficacy and Safety of Sarilumab in Combination with csDMARDs in Patients with Active Rheumatoid Arthritis Who Were Inadequate Responders or Intolerant of Anti-TNF-I Therapy: Results from a Phase 3 Study. 2015 ACR/ARHP Annual Meeting2015.

136. National Institute for Health and Care Excellence. Overview | Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed | Guidance | NICE.
137. Felson. American College of Rheumatology Preliminary Definition of Improvement In Rheumatoid Arthritis. Arthritis & Rheumatism. 1995;Volume 38(Number 6,):727-35.
138. Felson. American College of Rheumatology 20/50/70 criteria (ACR20/50/70) 1999.
139. DAS28. EULAR response criteria 2019
140. Higgins. Cochrane handbook for systematic reviews of interventions. 2008.
141. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making. 2013;33(5):607-17.
142. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. Med Decis Making. 2013;33(5):618-40.
143. Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence Synthesis for Decision Making 5. Medical Decision Making. 2013;33(5):657-70.
144. Gilead. A Multicenter, Double-blind, Long Term Extension Study to Assess the Safety and Efficacy of Filgotinib in Subjects with Rheumatoid Arthritis (FINCH 4). Clinical Study Protocol. 2020.
145. Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J, et al. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. Health Technol Assess. 2016;20(35):1-610.
146. National Institute for Health and Care Excellence. NICE Pathway: Rheumatoid arthritis overview 2020.
147. National Institute for Health and Care Excellence. Overview | Tofacitinib for moderate to severe rheumatoid arthritis | Guidance | NICE.
148. National Institute for Health and Care Excellence. Overview | Baricitinib for moderate to severe rheumatoid arthritis | Guidance | NICE.
149. National Institute for Health and Care Excellence. Overview | Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor | Guidance | NICE.
150. National Institute for Health and Care Excellence. Overview | Tocilizumab for the treatment of rheumatoid arthritis | Guidance | NICE.
151. National Institute for Health and Care Excellence. Overview | Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs | Guidance | NICE.
152. National Institute for Health and Care Excellence. Overview | Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor | Guidance | NICE.
153. Malottki K, Barton P, Tsourapas A, Uthman AO, Liu Z, Routh K, et al. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of

rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. Health Technol Assess. 2011;15(14):1-278.
154. Hernandez Alava M, Wailoo A, Wolfe F, Michaud K. The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis. Rheumatology (Oxford). 2013;52(5):944-50.
155. Chen Y-F. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technology Assessment 2006;10(42).
156. Therapy Watch. 2019.
157. Norton S, Fu B, Scott DL, Deighton C, Symmons DP, Wailoo AJ, et al. Health Assessment Questionnaire disability progression in early rheumatoid arthritis: systematic review and analysis of two inception cohorts. Semin Arthritis Rheum. 2014;44(2):131-44.
158. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford). 2011;50(1):124-31.
159. Office for National Statistics. Statistics OfN. National life tables, UK: 2015 to 2017.
160. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev. 2011(2):CD008794.
161. Oppong R, Kaambwa B, Nuttall J, Hood K, Smith RD, Coast J. The impact of using different tariffs to value EQ-5D health state descriptions: an example from a study of acute cough/lower respiratory tract infections in seven countries. Eur J Health Econ. 2013;14(2):197-209.
162. Monthly Index of Medical Specialities (MIMS) 2020 [Available from: http://www.mims.co.uk/.
163. Curtis LB, Amanda. Unit Costs of Health and Social Care 2018. Project report. University of Kent. 2018.
164. Michaud K, Vera-Llonch M, Oster G. Mortality risk by functional status and health-related quality of life in patients with rheumatoid arthritis. J Rheumatol. 2012;39(1):54-9.

Appendix 2

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Filgotinib for treating moderate to severe rheumatoid arthritis [ID1632]

Appendix E: Subgroup analyses

Company evidence submission

File name	Version	Contains confidential information	Date
ID1632_Filgotinib_STA_Appendix_E_v5.0_AIC	5.0	Yes	September 10th, 2020

1. **Severe subgroup analysis**

1.1 Baseline characteristics

Table 87. Baseline characteristics for the severe RA subgroup in the FINCH 1 trial (SAS) (1)

Parameter	Filgotinib 200mg + MTX (n=369)	Filgotinib 100mg + MTX (n=358)	Adalimumab + MTX (n=251)	Placebo + MTX (n=347)	Total (n=1325)
Age (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of RA (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
hsCRP (mg/L), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RF-positive, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 csDMARD, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥2 csDMARDs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
bDMARD-naïve, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DAS28 (CRP), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SJC66, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TJC68, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SGA (mm), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGA (mm), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain (mm), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Filgotinib 200mg + MTX (n=369)	Filgotinib 100mg + MTX (n=358)	Adalimumab + MTX (n=251)	Placebo + MTX (n=347)	Total (n=1325)
HAQ-DI, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28 (CRP), Disease Activity Score for 28 joints with C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; hsCRP, high sensitivity C-reactive protein; placebo, placebo; PGA, Physician's Global Assessment of Disease Activity; RA, rheumatoid arthritis; RF, rheumatoid factor; SAS, safety analysis set; SD, standard deviation; SGA, Subject's Global Assessment of Disease Activity; SJC66, swollen joint count based on 66 joints; TJC66, tender joint count based on 68 joints.

1.2 Efficacy

ACR20 at week 12

In the severe subgroup, based upon the primary efficacy endpoint of ACR20 response at week 12, filgotinib 200mg was shown to be significantly more effective than placebo ([redacted] versus [redacted], p<0.001) and numerically more effective than adalimumab [redacted] versus [redacted], [redacted]). Filgotinib 100mg was also found to be statistically significantly more effective than placebo [redacted] versus [redacted] and numerically more effective than adalimumab [redacted] versus [redacted]. Full details of the efficacy results including for ACR50 and ACR70 at week 12 are shown in **Error! Reference source not found.** below (1).

When compared with the overall moderate-to-severe population, filgotinib 200mg showed a comparable ACR20 response rate at week 12 in the severe subgroup [redacted] versus [redacted], indicating that filgotinib is similarly effective in both populations (see section B.2.6.1 of Document B)

ACR50 at week 12

At week 12, filgotinib 200mg and 100mg were shown to be statistically significantly more effective than placebo in the severe subgroup [redacted] and [redacted] respectively versus [redacted]. Filgotinib 200mg was also shown to be statistically significantly more effective when compared with adalimumab, with [redacted] versus [redacted] of patients responding, respectively. In the comparison of filgotinib 100mg with adalimumab, filgotinib 100mg was shown to be numerically comparable with a response rate of [redacted] versus [redacted], respectively.

When compared with the overall moderate-to-severe population included in FINCH 1, filgotinib 200mg showed a comparable ACR50 response rate at week 24 in the severe subgroup [redacted] versus [redacted], indicating that filgotinib is similarly effective in both populations (see section B.2.6.1).

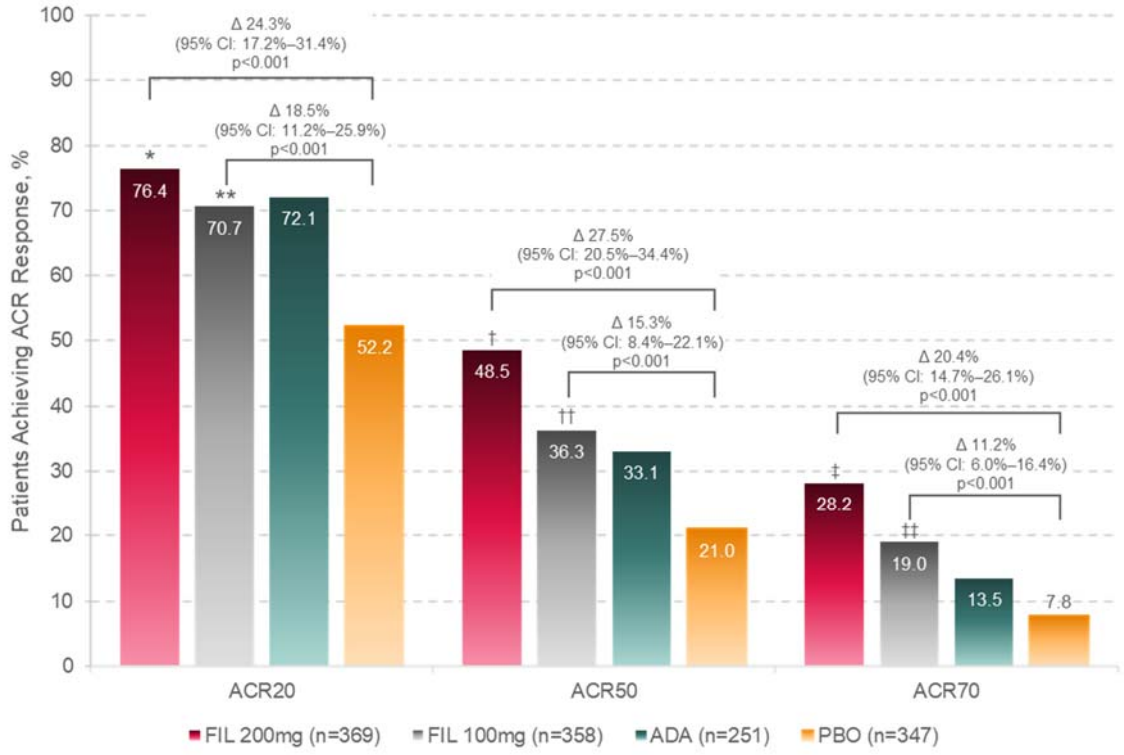
ACR70 at week 12

At week 12, filgotinib 200mg and filgotinib 100mg were shown to be statistically significantly more effective than placebo in the severe subgroup [redacted] and [redacted] respectively versus [redacted]. Filgotinib 200mg was also shown to be statistically significantly more effective when compared with adalimumab, with [redacted] versus [redacted] of patients responding, respectively. In the comparison of filgotinib 100mg with adalimumab, filgotinib 100mg was shown to be numerically comparable with a response rate of [redacted] versus [redacted], respectively.

When compared with the overall moderate-to-severe population included in FINCH 1, filgotinib 200mg showed a comparable ACR20 response rate at week 12 in the

severe subgroup [redacted] versus [redacted], indicating that filgotinib is similarly effective in both populations (see section 2.6.1).

Figure 64 ACR20, ACR50 and ACR70 responses at week 12 – Severe disease activity subgroup



ACR20 at week 24

In the severe subgroup, based upon the primary efficacy endpoint of ACR20 response at week 24, filgotinib 200mg was shown to be significantly more effective than placebo [redacted] versus [redacted] and numerically more effective than adalimumab [redacted], [redacted]. Filgotinib 100mg was also found to be statistically significantly more effective than placebo [redacted] and numerically more effective than adalimumab [redacted] versus [redacted] Full details of the efficacy results including for

ACR50 and ACR70 at week 24 are shown in **Error! Reference source not found.** below (1).

When compared with the overall moderate-to severe population, filgotinib 200mg showed a comparable ACR20 response rate at week 24 in the severe subgroup [redacted] versus [redacted], indicating that filgotinib is similarly effective in both populations (see section B.2.6.1 of Document B)

ACR50 at week 24

At week 24, filgotinib 200mg and 100mg were shown to be statistically significantly more effective than placebo in the severe subgroup [redacted] respectively versus [redacted]. Filgotinib 200mg was also shown to be statistically significantly more effective when compared with adalimumab, with [redacted] versus [redacted] of patients responding, respectively. In the comparison of filgotinib 100mg with adalimumab, filgotinib 100mg was shown to be numerically comparable with a response rate of [redacted] versus [redacted], respectively.

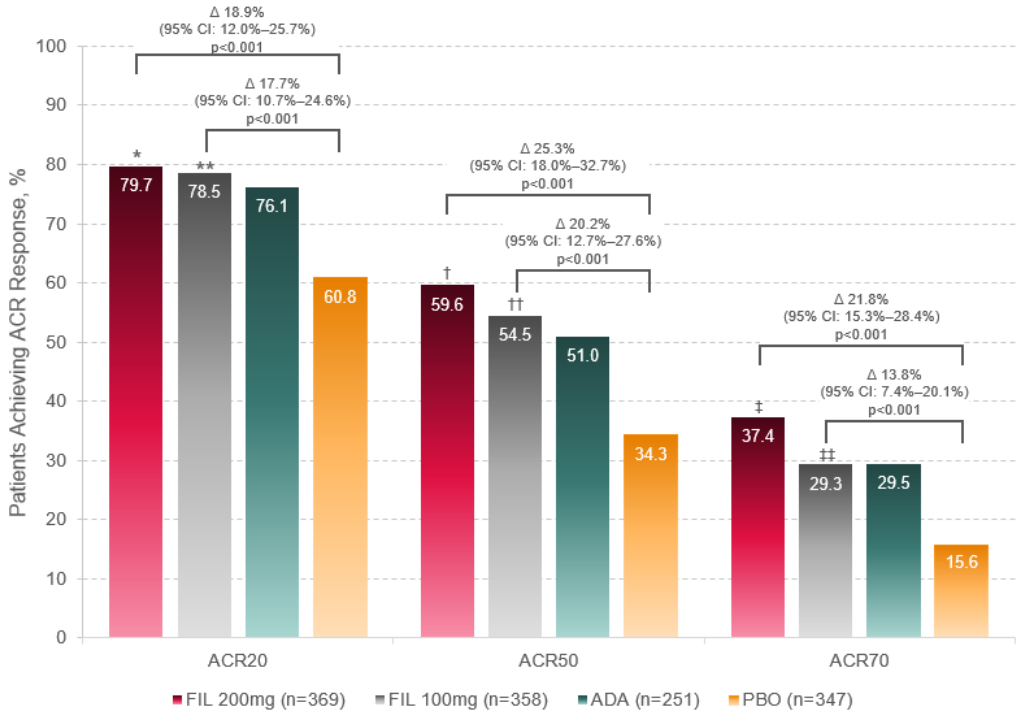
When compared with the overall moderate-to-severe population included in FINCH 1, filgotinib 200mg showed a comparable ACR50 response rate at week 24 in the severe subgroup [redacted] versus [redacted], indicating that filgotinib is similarly effective in both populations (see section B.2.6.1).

ACR70 at week 24

At week 24, filgotinib 200mg and filgotinib 100mg were shown to be statistically significantly more effective than placebo in the severe subgroup [redacted] and [redacted] respectively versus [redacted]. Filgotinib 200mg was also shown to be numerically more effective when compared with adalimumab, with [redacted] versus [redacted] [redacted] of patients responding, respectively. In the comparison of filgotinib 100mg with adalimumab, filgotinib 100mg was shown to be numerically comparable with a response rate of [redacted] versus [redacted], respectively.

When compared with the overall moderate-to-severe population included in FINCH 1, filgotinib 200mg showed a comparable ACR20 response rate at week 24 in the severe subgroup [redacted] versus [redacted], indicating that filgotinib is similarly effective in both populations (see section 2.6.1).

Figure 65. ACR20, ACR50 and ACR70 responses at week 24 – Severe disease activity subgroup



ADA, adalimumab; CI, confidence interval; FIL, filgotinib; PBO, placebo

* p=0.32 vs ADA; ** p=0.49 vs ADA; † p=0.039 vs ADA; †† p=0.41 vs ADA; ‡ p<0.047 vs ADA; ‡‡ p=1.00 vs ADA

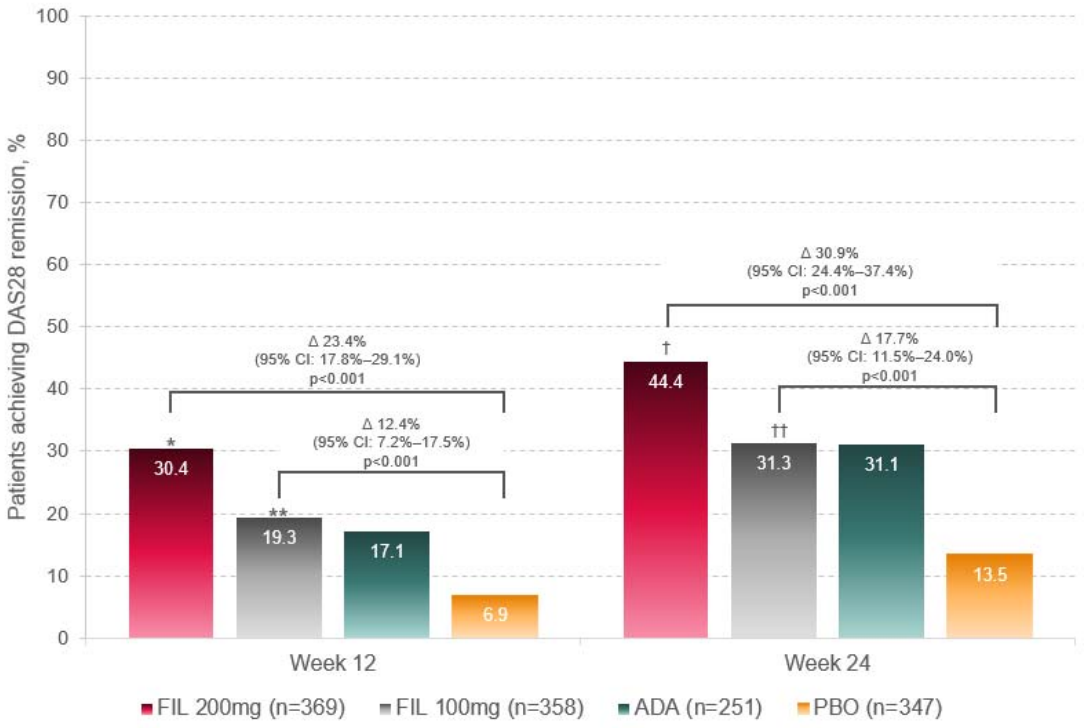
DAS28 (CRP) <2.6 at week 12 and 24

The results of the severe subgroup analysis for clinical remission (defined by a DAS28-CRP <2.6) at week 24, demonstrated superiority for filgotinib 200mg versus placebo in the severe subgroup [redacted] versus [redacted] and significantly greater benefit versus adalimumab (44.4% [39.2%, 49.6%] versus [redacted] at 24 weeks. Filgotinib 100mg also demonstrated superiority versus placebo [redacted] and was shown to be numerically comparable to adalimumab with [redacted] of patients responding, respectively.

When compared with the overall moderate-to-severe population included in FINCH 1, filgotinib 200mg showed a comparable DAS28-CRP <2.6 response rate at week

24 in the severe subgroup [redacted], indicating that filgotinib is similarly effective in both populations (see section B.2.6.1). The results for patients achieving a DAS28-CRP <2.6 at both 12 and 24 weeks are presented in **Error! Reference source not found.**. (1)

Figure 66. DAS28 (CRP) <2.6 at weeks 12 & 24 – severe disease activity subgroup



ADA, adalimumab; CI, confidence interval; DAS28 (CRP), Disease Activity Score for 28 joints with C-reactive protein; FIL, filgotinib; PBO, placebo

* p<0.001 vs ADA; ** p=0.53 vs ADA; † p<0.001 vs ADA; †† p=1.00 vs ADA

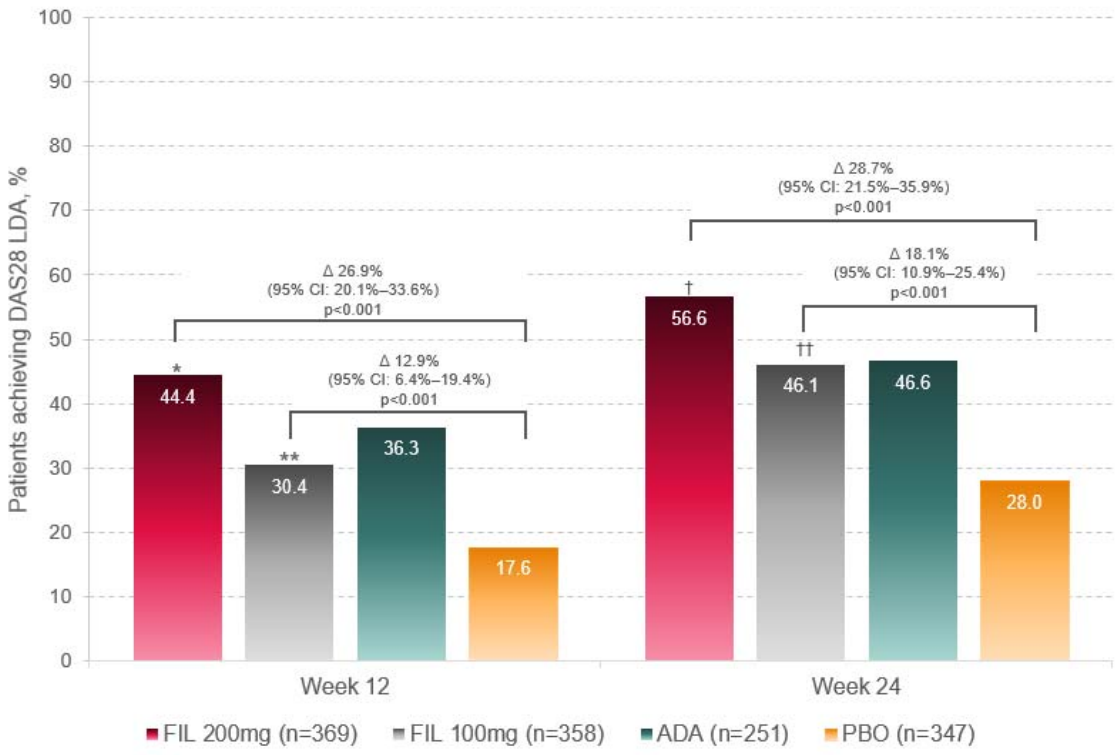
DAS28 (CRP) ≤3.2 at weeks 12 and 24

For the secondary outcome, low disease activity (LDA) as defined by DAS28-CRP ≤3.2, filgotinib 200mg demonstrated a significantly greater treatment effect versus placebo in the severe subgroup [redacted] versus [redacted] and when compared with adalimumab [redacted] at week 24. Filgotinib 100mg also demonstrated superiority versus placebo at week 24 [redacted] versus [redacted] and was shown to

be numerically comparable to adalimumab with [redacted] versus [redacted] of patients responding, respectively.

When compared with the overall moderate-to-severe population included in FINCH 1, filgotinib 200mg showed a comparable DAS28-CRP ≤3.2 response rate at week 24 in the severe subgroup [redacted], indicating that filgotinib is similarly effective in both populations (see section B.2.6.1). Detailed results at week 12 and 24 are shown in **Error! Reference source not found.** below. (1)

Figure 67. DAS28 (CRP) ≤3.2 at weeks 12 & 24 – severe disease activity subgroup



ADA, adalimumab; CI, confidence interval; DAS28 (CRP), Disease Activity Score for 28 joints with C-reactive protein; FIL, filgotinib; LDA, low disease activity; PBO, placebo

* p=0.046 vs ADA; ** p=0.14 vs ADA; † p=0.017 vs ADA; †† p=0.93 vs ADA

EULAR at week 24

For the secondary outcome, EULAR response at week 24, filgotinib 200mg demonstrated a higher percentage of patients achieving a good EULAR response compared with placebo in the severe subgroup [redacted] and when compared with adalimumab [redacted] at week 24. Filgotinib 100mg also demonstrated a higher percentage of patients achieving a good EULAR response compared with placebo [redacted] and was shown to be numerically comparable to adalimumab [redacted]

When compared with the overall moderate-to-severe population, filgotinib 200mg showed a comparable good EULAR response rate at 24 weeks in the severe subgroup [redacted], indicating that filgotinib is similarly effective in both populations (see section 2.6.1). Detailed EULAR response results at 24 weeks are shown in **Error! Reference source not found.** below (1).

Table 88. EULAR responses at week 24 – severe disease activity subgroup (1)

Parameter	Filgotinib 200mg (n=104)	Filgotinib 100mg (n=121)	Adalimumab (n=72)	Placebo (n=128)
Week 24, n	[redacted]	[redacted]	[redacted]	[redacted]
Good response	[redacted]	[redacted]	[redacted]	[redacted]
Moderate response	[redacted]	[redacted]	[redacted]	[redacted]
No response	[redacted]	[redacted]	[redacted]	[redacted]

2. **Pre-planned subgroup analyses**

2.1 ***Baseline characteristics***

Table 89. Pre-planned subgroup analyses (1) (2) (3)

Trial no. (acronym)	NCT02889796 (FINCH 1)	NCT02873936 (FINCH 2)	NCT02886728 (FINCH 3)
Pre-planned subgroups	Subgroup analyses comparing each filgotinib group with the placebo group were performed for the primary endpoint at week 12 for the following subgroups. • Age (on the first dosing date of study drug, <65 or ≥65 years) • Sex at birth (male or female) • Race • Baseline weight (<60 kg, ≥60 kg to <100 kg, or ≥100 kg) • Geographic region (A, B, C, D, or E) • Prior exposure to bDMARDs (Yes or No) • Presence of RF or anti-CCP Antibody (Yes or No) • Duration of RA diagnosis on the first dosing date of study drug (<1 year, ≥1 to<5years, ≥5 to <10 years, or ≥10 years) • Disease activity on the first dosing date of study drug (DAS28[CRP] ≤ 5.1 or DAS28[CRP]>5.1) • Concurrent use of oral corticosteroids on the first dosing date of study drug (Yes or No) • hsCRP at Baseline (≥4 mg/L or <4 mg/L) The proportion of subjects who achieved an ACR20 response was analysed using the Fisher exact test	The primary and key secondary efficacy endpoints were examined using the following subgroups: • Age (on the first dosing date of study drugs, <65 or ≥65) • Sex at birth (male or female) • Race • Baseline weight (<60kg, ≥60kg to <100kg, ≥100kg) • Geographic region (A, B, C, or E) Presence of RF or anti-CCPAb (Yes or No) • Duration of RA diagnosis on the first dosing date of study drugs (< 5 years, ≥5to<10years, ≥ 10 years) • Number of prior bDMARDs exposure (<3 or ≥3; ≤1 or >1; 1, 2, or ≥3) • Disease activity at baseline (DAS28[CRP] ≤5.1 or DAS28[CRP]>5.1) • Concurrent use of MTX on the first dosing date of study drugs (Yes or No) • Number of concurrent csDMARDs use on the first dosing date of study drugs (0-1or≥2) • Concurrent use of oral corticosteroids on the first dosing date of study drugs (Yes or No) hsCRP at	Subgroup analyses comparing each filgotinib group with the MTX monotherapy group were performed for the primary endpoint at week 24 for the following subgroups: • Age (on the first dosing date of study drug, <65or≥65years) • Sex at birth (male or female) • Race • Baseline weight (<60kg, ≥60 to <100 kg, or ≥100kg) • Geographic region (A, B, C, D, or E) • Presence of RF or anti-CCP antibody (Yes or No) • Duration of RA diagnosis on the first dosing date of study drug (<1 year, ≥1to<2years, or ≥2years) • Disease activity on the first dosing date of study drug (DAS28[CRP] ≤5.1or DAS28[CRP]>5.1) • Concurrent use of oral corticosteroids on the first dosing date of study drug (Yes or No) • hsCRPat baseline (≥4mg/L or<4mg/L) The proportion of subjects who achieved an ACR20 response was analysed using the Fisher exact test based on the NRI method for comparison between

Trial no. (acronym)	NCT02889796 (FINCH 1)	NCT02873936 (FINCH 2)	NCT02886728 (FINCH 3)
	based on the NRI method for comparison between treatment groups. The number and percentage of subjects with an ACR20 response was provided for each treatment group within the subgroups.	baseline (≥4mg/L or <4mg/L)	treatment groups. The number and percentage of subjects with an ACR20 response was provided for each treatment group within the subgroups.

bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug DAS28 (CRP), Disease Activity Score for 28 joints with C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; hsCRP, high sensitivity C-reactive protein; placebo, placebo; PGA, Physician's Global Assessment of Disease Activity; RA, rheumatoid arthritis; RF, rheumatoid factor; SAS, safety analysis set; SD, standard deviation; SGA, Subject's Global Assessment of Disease Activity; SJC66, swollen joint count based on 66 joints; TJC66, tender joint count based on 68 joints.

2.2 *Results*

2.1.1. FINCH 1

The primary efficacy endpoint was analysed by subgroup as described above. A summary of the primary endpoint, the ACR20 response rate at week 12, for each subgroup is provided in **Error! Reference source not found.** (1).

Table 90. FINCH 1: ACR20 Response rate at week 12, Subgroup Analysis – NRI (Full Analysis Set)

< 65				
P-value				
≥ 65				
P-value				
Male				
P-value				

Female	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]		
	[redacted]			
American Indian	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]		
Asian	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]		
Black or	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]		
White	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]		
	[redacted]			
< 60 kg	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]		
≥ 60 kg to <	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]		
≥ 100 kg	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]		
	[redacted]			
Group A	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]		
Group B	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]		
Group C	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]		

Group D	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]		
Group E	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]		
[redacted]				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]		
No	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]		
[redacted]				
< 1 year	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]		
≥ 1 year [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]		
≥ 5 years	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]		
≥ 10 years	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]		
[redacted]				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]		
No	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]		
[redacted]				

DAS28(CRP) ≤ 5.1	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]		
DAS28(CRP) > 5.1	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]		
[redacted]				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]		
No	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]		
[redacted]				
≥ 4 mg/L	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]		
< 4 mg/L	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]		

bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28 (CRP), Disease Activity Score for 28 joints with C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; hsCRP, high sensitivity C-reactive protein; placebo, placebo; PGA, Physician's Global Assessment of Disease Activity; RA, rheumatoid arthritis; RF, rheumatoid factor; SAS, safety analysis set; SD, standard deviation; SGA, Subject's Global Assessment of Disease Activity; SJC66, swollen joint count based on 66 joints; TJC66, tender joint count based on 68 joints.

P-value : Pairwise Comparisons versus Placebo

2.2.2. FINCH 2

The primary efficacy endpoint was analysed by subgroup as described above. A summary of the primary endpoint, ACR20 response rate at week 12, for each subgroup is provided in **Error! Reference source not found.** (2).

Table 91. FINCH 2: ACR20 Response rate at week 12 (Subgroup Analysis; Non-responder Imputation; Full Analysis Set)

	[redacted]	[redacted]	[redacted]

[redacted]			
< 65	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	
>= 65	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	
[redacted]			
Male	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	
Female	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	
[redacted]			
American Indian or Alaska	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	
Asian	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	
Black or African American	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	
White	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	
[redacted]			
< 60 kg	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	
>= 60 kg to < 100	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	
>= 100 kg	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	

Group A			
P-value			
Group B			
P-value			
Group C			
P-value			
Group E			
P-value			
Yes			
P-value			
No			
P-value			
< 5 years			
P-value			
>= 5 years to < 10 years			
P-value			
>= 10 years			
P-value			
< 3			
P-value			
>= 3			
P-value			
<=1			

P-value			
> 1			
P-value			
1			
P-value			
2			
P-value			
>= 3			
P-value			
DAS28(CRP) <= 5.1			
P-value			
DAS28(CRP) > 5.1			
P-value			
Yes			
P-value			
No			
P-value			
0 - 1			
P-value			
>= 2			
P-value			
Yes			
P-value			
No			
P-value			

>= 4 mg/L	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	
< 4 mg/L	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	

bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28 (CRP), Disease Activity Score for 28 joints with C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; hsCRP, high sensitivity C-reactive protein; placebo, placebo; PGA, Physician's Global Assessment of Disease Activity; RA, rheumatoid arthritis; RF, rheumatoid factor; SAS, safety analysis set; SD, standard deviation; SGA, Subject's Global Assessment of Disease Activity; SJC66, swollen joint count based on 66 joints; TJC66, tender joint count based on 68 joints.

P-value : Pairwise Comparisons versus Placebo

2.2.3. FINCH 3

The primary efficacy endpoint and key secondary efficacy endpoints were analysed by subgroup as described above. A summary of the primary endpoint, ACR20 response rate at week 24, for each subgroup is provided in **Error! Reference source not found.** (3).

Table 92. FINCH 3: ACR20 Response rate at week 24, Subgroup Analysis, NRI (Full Analysis Set)

	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
Group A	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
Group B	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
Group C	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	

Group D	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
Group E	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
[redacted]				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
No	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
[redacted]				
< 65	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
≥ 65	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
[redacted]				
< 1 year	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
≥ 1 year to < 2	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
≥ 2 years	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
[redacted]				
DAS28 (CRP) ≤ 5.1	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
DAS28 (CRP) > 5.1	[redacted]	[redacted]	[redacted]	[redacted]

P-	[redacted]	[redacted]	[redacted]	
[redacted]				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
No	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
[redacted]				
Male	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
Femal e	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
[redacted]				
< 60 kg	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
≥ 60 kg to < 100 kg	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
≥ 100 kg	[redacted]	[redacted]	[redacted]	[redacted]
P- value compa	[redacted]	[redacted]	[redacted]	
[redacted]				
Americ an Indian	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
Asian	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	

Black or Africa	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
White	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
	[redacted]			
≥ 4 mg/L	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	
< 4 mg/L	[redacted]	[redacted]	[redacted]	[redacted]
P-	[redacted]	[redacted]	[redacted]	

bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28 (CRP), Disease Activity Score for 28 joints with C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; hsCRP, high sensitivity C-reactive protein; placebo, placebo; PGA, Physician's Global Assessment of Disease Activity; RA, rheumatoid arthritis; RF, rheumatoid factor; SAS, safety analysis set; SD, standard deviation; SGA, Subject's Global Assessment of Disease Activity; SJC66, swollen joint count based on 66 joints; TJC66, tender joint count based on 68 joints.

P-value : Pairwise Comparisons versus Placebo

3. **References**

1. Gilead. A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 weeks in Combination with Methotrexate to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate (FINCH 1) Clinical Study Report. 2019.

2. Gilead. Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 24 Weeks in Combination with Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug(s) (csDMARDs) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Biologic DMARD(s) Treatment (FINCH 2). Clinical Study Report. 2019.

3. Gilead. A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 Weeks Alone and in Combination with Methotrexate (MTX) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are Naive to MTX Therapy (FINCH 3). Clinical Study Report. 2019.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Filgotinib for treating moderate to severe rheumatoid arthritis [ID1632]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	National Rheumatoid Arthritis Society - NRAS
3. Job title or position	Volunteer Group Co-ordinator
4a. Brief description of the organisation (including who funds it). How many members does it have?	NRAS is the national organisation representing people with RA and children and young people and their families living with JIA. NRAS also supports the health professionals who treat those with RA and JIA. NRAS has approx 5,500 members including health professional members. They have a wide range of income streams with the majority of their funding coming from grant-giving trusts and foundations, membership, events, legacy income and a maximum cap (self-imposed) of 15% of annual income coming from projects funded by pharmaceutical industry, although to date such funding has never reached as much as 15%.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	Yes –see total pharma income breakdown for 2019 (confidential) **Pharma Income 4003** **Broken down as follows:** **Abbvie** Interview fee Panel participation

	2019	2019
	450	
	450	

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.		Participation in media event	750	
		Travel expenses	268	
		Corporate sponsorship	20,000	
		Elearning contribution	20,000	
		Filming?	3,900	
				45,818
	Chughai			
		Know Your Das APP	4,380	
		Know Your Das APP	4,000	
		Know Your Das APP	14,262	
		Know Your Das APP	1,500	
				24,142
	Eli Lily			
		Q & A session	270	
		Speakers' fee CJ	720	
		BSR sponsorship	1,000	
		Webinar sponsorship	5,000	
		Corporate sponsorship	10,000	
		Patient recruitment	390	
				17,380
	Amgen			
		Support of Rheum4U events in 4000	8,000	
		Contribution to patient survey in 4000	14,976	
				22,976
	Janssen	Core Funding in 4000		8,000
	Nordic			0

	Sanofi				
		Prep of Q & A	3,500		
		Travel to conference	1,116		
		Sundry	250		
		Speaker fee	400		
		Corporate membership	10,000		
		BSR sponsorship	800		
				16,066	
	UCB				
		Corporate membership	8,000		
		BSR sponsorship	350		
				8,350	
	SOBI			0	
	BMS				
		Corporate membership	10,000		
		Spaker fee	400		
				10,400	
	Covance				
	GSK				
	MSD				
	Pfizer				
		Work completed by Clare	1,875		

	Webex presentation - coded to 4000		400	
	Unknown BR		932	
				3,207
Gilead				
	????		825	
	Attendance at summit		1,200	
	Travel expenses		717	
	Honararium		966	
				3,708
Samsung	Filming Rob and Lisa			2,000
Sandoz				
Roche	Corporate membership			10,000
Mylan				
Celltrion				
To check		31-May	260	260
	Total			**172,307**
	Balance in 4003 as at 31/12/2019			172,307

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	NRAS has direct links with its membership and the wider RA community on a daily basis through their helpline, community groups, website interactions, social media channels, email traffic and 3 members of staff live with RA. They regularly run surveys, focus groups, support UK academic and clinical research projects and studies and survey their members annually. I also live with RA and have significant personal experience of living with the disease. I am a community pharmacist and in this role have supported others living with RA.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Being diagnosed with an incurable, painful disease like RA can be extremely distressing as it is life-changing and as you can be diagnosed at any age post 16, it can have a major impact on your future life plans, dreams and aspirations, although being diagnosed today has significantly better potential outcomes than 25+ years ago when treatments and the way the disease was treated were quite different. RA impacts on every area of life and impacts both physical and emotional wellbeing. Health beliefs, how you come to diagnosis (how long it takes to be diagnosed), the network of support you have and how aggressive the disease is will all impact on how you come to terms with your diagnosis and cope day to

	day. It can be very distressing for a partner of someone with RA to witness their loved-one in severe pain and suffering the debilitating effects of fatigue and so this disease does very much impact on the whole family. Seeing the rapid deterioration of the health of a parent with early RA can be very frightening for children of all ages. It can have a massive effect on family dynamic, children perceiving a role reversal feeling the need to look after a parent and that parent fearing becoming a burden. As ¾ of people are diagnosed when of working age, anxiety over job-loss due to their disease is a significant factor and whilst we are making steps towards seeing work as a health outcome, we are far from a situation where rheumatology teams pay enough attention to how worried patients may be about their job. This is particularly the case at time of diagnosis when they may have already had quite a lot of time off work in the process of finding out what is wrong and may already be at risk of losing their job. For young people who are not yet in a permanent relationship, it can be very hard to come to terms with the fact that they have a long term condition and we know from our own research that RA can have a huge impact, making them feel less desirable, much less confident and worried that they will not find a partner. Young adults may fear reduced fertility or the effects of the disease/medication on a pregnancy or relapse and inability to cope after giving birth. Diagnosed in mid-years with young children to care for can also be incredibly challenging. Imagine not being able to pick up your baby and change its nappy. For older people diagnosed as they approach retirement for example, dreams of being able to travel and look after grand-children can suddenly seem unachievable. For whilst much has been done in terms of new and innovative therapies coming into rheumatology and the way in which we now treat the disease, there remains a lot of

	pain and distress at all stages of this disease and unmet need in regard to therapies available that will work for everyone.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	One of the key issues associated with current care is the variability of access to best, evidence-based care and access to all the relevant members of a consultant-led multi-disciplinary team. This has been demonstrated in the past by the Kings Fund and National Audit Office reports into services for people with RA and most recently by the second National Early Inflammatory Arthritis Audit into early RA run by the BSR. People do experience different levels of care and not all, by any means, have access to research studies for example. In the early stages of their disease, people don't know what good looks like or what they should be able to ask for or expect and they are also vulnerable at that time as a consequence. This is where NRAS comes in – their goal is to be there at the start of everyone's journey and whenever they need them along the way. NRAS tries to emphasise the importance of supported self-management early on as the more you know about the disease and the more you can do to help yourself in a positive way, the better your outcomes are likely to be. Unfortunately, whilst there is a lot of rhetoric about self-management for people with LTCs, we still live with a very 'medical management' model where investment in patient education, support and self-management by commissioners is far too low. That's one of the reasons it is essential that health professionals sign-post patients to organisations who can help and support like NRAS. There is no doubt that the increase in access to advanced therapies in the

	last 20 years has revolutionised the ability to treat more effectively than the era prior to the introduction of Ant-TNF. Access to treatment where there are specific eligibility criteria – ref the biologics and biosimilars – is better than pre-NICE, however, with the introduction of biosimilars, the market has changed and there is a lot of confusion at the moment with local procurement deals ensuring that what is available in one area, may not be the same as the next. Even with all the new treatments available, the heterogeneity of this disease syndrome means that there remains unmet need. Even with cheaper drugs available and many people thinking that therefore more people will be able to get the treatment they need, this is not the case unless NICE change the eligibility criteria which currently apply.
8. Is there an unmet need for patients with this condition?	Yes, we are not yet at a stage where stratifying treatment as is done in the field of cancer care, is possible except to a crude degree in RA. Much research is being conducted into being able to identify biomarkers (blood and tissue) so that we can move more to a place when a Dr. will be able to match a patient to a specific drug and we also need to be able to treat patients with bDMARDS and other advanced therapies earlier in the pathway. Approximately 6-8% of patients are resistant to treatment (refractory) and many have to move over time from one therapy to another to maintain disease control. Despite a considerably enlarged arsenal of drugs by comparison to over 20 years ago, there remains unquestionable unmet need.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The key driver of RA is inflammation which can result quite quickly in bone erosion leading ultimately to joint destruction and potential disability. Filgotinib offers a new option in a relatively new class of innovative small molecule therapies (JAK inhibitors) that could potentially be positioned post DMARD failure or post first TNF failure. This represents a real step forward because it adds to the therapeutic

	options available to clinicians and patients. Also, it is an oral therapy which means that there are no costs associated with infusions or manufacture of pens for the sub-cut route. Due to storage requirements, the cost of refrigeration is not an issue as it is with injectables, nor maintaining the cold chain during transportation. Daily dosing is likely to fit easily into current medication regimes and the dose less likely to be forgotten than a weekly or fortnightly dose. **Patients are very likely to prefer an oral (biologic) drug to have a regular infusion or having to inject themselves**
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	It's a daily treatment rather than weekly or monthly however because it is a tablet taken orally I do not think the increased frequency could be considered a disadvantage.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	For people who have significant hand disability and loss of function, taking a tablet is of considerable benefit to having to inject oneself. Some patients are needle-phobic and so might resist or delay starting much needed new self-administered sub-cutaneous medication resulting in further deterioration of joints. Neither I, nor NRAS is aware of anyone who may benefit less.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Not really. There are communities who for one reason or another (cultural/language) may be at a disadvantage in healthcare settings generally, but not specifically related to this treatment.
Other issues	
13. Are there any other issues that you would like the committee to consider?	No
Key messages	

15. In up to 5 bullet points, please summarise the key messages of your submission:

- This is a new option in the small molecule targeted synthetic DMARD class
- Patients are likely to be more prepared to take an oral medicine than inject themselves or be infused
- It has the potential to save a lot of costs due to the fact that it is oral
- It can be potentially used in different places in the current pathway, ie. post dmard failure and post TNF failure

- Provides additional therapeutic options for clinicians and greater choice for patients

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Clinical expert statement

Filgotinib for treating moderate to severe rheumatoid arthritis [ID1632]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	Maya H Buch
2. Name of organisation	University of Manchester

3. Job title or position	Professor of Rheumatology and Honorary Consultant Rheumatologist
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? √ a specialist in the treatment of people with this condition? √ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	√ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The principal aims of treatment are to reduce signs and symptoms of people with rheumatoid arthritis (RA), prevent clinical, functional and structural progression of the disease
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A reduction of disease activity score 28 (or equivalent) of at least 1.2; ability to induce state of low disease activity or ideally remission depending on stage of disease
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – despite the range of therapies and therapeutic classes available in the treatment of RA, it is clear that these fail to confer meaningful improvement in a sizeable proportion of patients. This highlights the need for new molecules. Importantly, it is recognised that molecules within existing classes of therapies may provide benefit where other similar drugs may not, indicating the value for multiple drugs within specific classes.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Currently, RA is initially treated with conventional synthetic (cs) disease modifying anti-rheumatic drugs (DMARDs), with methotrexate (MTX) the ideal first csDMARD. This may be as monotherapy or in combination with other csDMARDs. If persistent disease activity is evident following at least 2 csDMARDs (including MTX), escalation to an advanced therapy (biologic DMARD (bDMARD) or targeted synthetic DMARD (tsDMARD)) is undertaken. However, this is only permitted when disease activity score 28 (DAS28) is in the high category (>5.1). In the event of lack of or later loss of response of a bDMARD (or tsDMARD), patients are cycled to an alternative advanced therapy. Typically, TNFi remains the predominant bDMARD prescribed, following which rituximab is often considered (particularly in antibody-positive RA), and then tocilzumab and abatacept. However, drug selection is tailored to individual patient/disease profile, co-morbidity and route of administration. The currently available bDMARDs and JAKi may be considered following MTX/csDMARD failure. The goal however is to deliver biomarker driven tailoring of treatment.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes – NICE guidelines for the management of RA. European guidelines (EULAR, European League Against Rheumatism) also inform management approach and treatment strategy
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined and NICE technology appraisal attempt to recommend how drugs should be sequenced. However, a 'one size fits all' approach is not appropriate when treating individual patients. The individual drug technology appraisals mean appropriately, different treatment selection may be considered for individual patients. This is important in a heterogeneous population such as RA (with varied RA disease profile and patient features such as age, co-morbidity etc) where different safety and practical considerations come into play. The principal area of unmet need within the pathway is the initial access to advanced therapies that is restricted to only when a patient is in high disease activity state. This contradicts NICE management guidelines of RA that recommend remission or at least low disease activity state should be the target of treatments – and means patients with active disease but in moderate disease activity state have to settle for suboptimal management strategies.

• What impact would the technology have on the current pathway of care?	The technology would provide an important and effective addition to the therapeutic choices for people with RA within the current pathway of care.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, the technology would be adopted for patients with active disease despite csDMARD/MTX and/or bDMARD therapy.
• How does healthcare resource use differ between the technology and current care?	Healthcare resource needed would be no different to current care – as such, the new technology would not present an additional burden on current services
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This is a secondary care technology, prescribing should only be undertaken by rheumatology specialists
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No specific facilities or new resources are needed. This technology would be introduced within the already established multidisciplinary setting for existing cs-, b- and ts DMARDs – doctors and specialist nurses delivering appropriate education and monitoring. Training is typically provided through local, regional and wider educational forums.

12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	I would anticipate the technology will provide meaningful benefit on at least a scale similar to that observed with the currently available JAKi. Real world use will also refine how/whether this technology may be optimally used i.e. certain patient categories. Promisingly, FINCH-2 trial in DMARD-refractory patients (Genovese M, et al. JAMA 2019: 322(4)) comprised multi-biologic DMARD failure patients (with a quarter having previously failed 3 or more) – remarkably, half achieved low disease activity and a quarter achieved remission. These data suggest more meaningful benefits may be observed.
• Do you expect the technology to increase length of life more than current care?	Better treatment of RA is generally associated with improved outcomes including co-morbidity and cardiovascular events (primary driver of excess mortality in RA). The technology would be anticipated to similarly improve patient outcomes. However, absolute length of life is not the appropriate measured disease outcome in RA trials, not relevant for short-term trials, and would be an area to evaluate as part of long-term epidemiological and clinical studies.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes in line with the technology's trial data, health related quality of life would clearly be expected to improve – on a par with current care. Comparative trials are limited to be able to ascribe superiority over all existing standard of care technologies.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology would be appropriate for preference of oral route of administration. Its benefit is observed both following MTX/cDMARD failure but also following bDMARD – as such, its efficacy and the targeting of several key cytokines would be anticipated to benefit patients across the treatment pathway.

The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The technology would be similarly straightforward to use as current standard technologies. No particular challenges are envisaged.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Use of this technology will be in line with standard practice, as is the case for existing technologies. Disease activity score assessment forms the basis for drug initiation and if sufficient improvement is not observed, cessation. No new measurements would be needed to inform use of this technology.

16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Currently, I would not anticipate there would be notable additional benefits over and above that captured in the QALY calculation
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, this technology is innovative, adds to the more recent class of small molecule targeted synthetic assets
• Is the technology a 'step-change' in the management of the condition?	This technology improves what is a relatively modest therapeutic choice in the form of small molecules.

• Does the use of the technology address any particular unmet need of the patient population?	A sizeable proportion of patients across the treatment pathway fail to benefit from existing standard of care. This technology has the potential to fill some of these unmet areas.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The potential adverse effects are largely within the expected profile for a selective JAK1 inhibitor – the integrated data from 7 clinical trials exposure-adjusted incidence rate for serious infections and herpes zoster were generally similar to adalimumab and MTX. The associated monitoring is in line with what is required for immune suppressive therapies generally. As such, this technology does not present any undue or additional burden on RA services or the patient's quality of life.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	The technology has been evaluated as part of a large phase 3 programme that evaluates the key stages of RA treatment pathways where there are unmet needs. The geographical distribution of sites involved and thus the demographics are not necessarily aligned with UK populations.
• If not, how could the results be extrapolated to the UK setting?	Post-marketing surveillance will be an important part of evaluating the effectiveness of this technology in real life and in a UK healthcare and population setting
• What, in your view, are the most important outcomes, and were they measured in the trials?	Response rates, disease activity states achieved, functional and structural outcomes; as well as patient-reported outcome measures – all these have been captured in the phase 3 programme as has safety • Disease activity score states: remission (including more stringent criteria: CDAI/SDAI/Boolean), low disease activity and change in disease activity

	• Response rates: ACR response • Quality of life: HAQ-DI, SF-36 • PROM: Visual analogue score pain, general health, FACIT-fatigue • Radiographic data • Safety including of adverse events of special interest
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No, not that I am aware of – this will need post-marketing /registry surveillance
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator	No, I am not

treatment(s) since the publication of NICE technology appraisal guidance TA485?	
22. How do data on real-world experience compare with the trial data?	Yet to be seen
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	It is important that under-represented populations such as BAME are considered and appropriately evaluated for this technology. Education to provide the necessary reassurance also remains important and significant factor if adherence is to be optimised.
23b. Consider whether these issues are different from issues with current care and why.	These issues are not different to standard of care technologies – but with the introduction of an additional asset, highlights the need to address under-represented populations
Topic-specific questions	
24. At what positions in the treatment pathway would you	Filgotinib would be an attractive choice for patients following MTX/csDMARD failure but also following bDMARD failure, with trial data (in TNFi-failure) particularly impressive.

consider using filgotinib for people with moderate RA and severe RA?	
25. What is the current standard care for people with moderate RA after 2 conventional DMARDs have failed?	In the absence of being able to prescribe advanced therapies in this patient group unless in high disease activity, the current standard of care is suboptimal, and a UK anomaly that sets UK practice as an outlier. A combination of using older csDMARDs and corticosteroids (CS) form the main approach. This adds to the deleterious impact of RA and co-morbidity of this as well as of greater CS usage.
26. What is the current standard care (please list all relevant drugs) used for people with severe RA: • After failure of 2 conventional DMARDs (methotrexate eligible)	Please note, my responses may not exactly align with the TA – rather to what is actually used in the community. The question to some of the scenarios listed suggest a strict approach to which drugs are sequenced. This is not necessarily usual practice – it would not be appropriate/feasible to safely and effectively consider each individual patient's needs. Also, the existing TAs principally cite anti-TNF as the biologic DMARD under consideration, whilst in the scenarios below, appropriately, the term biologic DMARD is used – in line with individual biologic DMARD TAs. Presuming this means failure of x2 csDMARDs including MTX: all currently available therapies may be considered. Whilst anti-TNF biologic DMARDs may still be a predominant choice, this is not exclusively so and will depends on individual patient. Thus all the following may be considered in line with TAs 375, 485,

	480, 466): Biologic DMARDs [Abatacept; Anti-TNF (adalimumab, certolizumab-pegol, etanercept, golimumab, infliximab); IL-6 targeted (Tocilizumab, Sarilumab); Rituximab (B-cell depleting) and Targeted synthetic (tofacitinib and baricitinib).
• After failure of 2 conventional DMARDs (methotrexate ineligible)	Typically, Biologic DMARDs [Anti-TNF (adalimumab, etanercept,) and IL-6 targeted (Tocilizumab, Sarilumab)] are used (TA 375). Also, targeted synthetic DMARDs (tofacitinib and baricitinib) (TA 480 and 466)
• After failure of first-line biologic DMARD (methotrexate eligible, rituximab eligible)	Drug selection depends on the first-line biologic DMARD failed and a prescriptive approach may not necessarily be adopted. TA 195 advises rituximab post anti-TNF failure and this is often used. However, in practice, patient/disease profile (rituximab typically used in seropositive disease only) and prior treatments mean any of the following may be considered more appropriate: Biologic DMARDs [Abatacept; Anti-TNF (adalimumab, certolizumab-pegol, etanercept, golimumab, infliximab); IL-6 targeted (Tocilizumab, Sarilumab); Rituximab (B-cell depleting) and Targeted synthetic (tofacitinib and baricitinib).
• After failure of first-line biologic DMARD	Whilst TA 247 and 485 advocate tocilizumab and sarilumab respectively if rituximab is contraindicated (and presumes prior anti-TNF biologic DMARD), drug selection depends on the first-line biologic DMARD failed and a prescriptive approach may not necessarily be adopted. The following may all be considered: Biologic

(methotrexate eligible, rituximab ineligible) • After failure of first-line biologic DMARD (methotrexate ineligible) • After failure of rituximab in combination with methotrexate	DMARDs [Abatacept; Anti-TNF (adalimumab, certolizumab-pegol, etanercept, golimumab, infliximab); IL-6 targeted (Tocilizumab, Sarilumab). Targeted synthetic DMARDs (tofacitinib and baricitinib) may also be considered Whilst TA 247 and 485 advocate tocilizumab and sarilumab respectively if rituximab is contraindicated (and presumes prior anti-TNF biologic DMARD), anti-TNF may not have been the first-line biologic DMARD failed and thus an alternative approach may be applied. The following are thus typically considered: Anti-TNF (adalimumab, etanercept), IL-6 targeted (tociluzmab, sarilumab). Targeted synthetic DMARDs (tofacitinib and baricitinib) may also be considered TA 247 and 485 advise tocilizumab and sarilumab respectively. However, in practice, depending on patient/disease profile and prior treatments, any of the following may also be considered: Biologic DMARDs [Abatacept; Anti-TNF (adalimumab, certolizumab-pegol, etanercept, golimumab, infliximab); IL-6 targeted (Tocilizumab, Sarilumab); Rituximab (B-cell depleting) and Targeted synthetic (tofacitinib and baricitinib)
27. Would efficacy and safety of filgotinib and other biologics used in RA be expected to be similar if used after failure of 1 or 2 conventional DMARDs?	It is recognised that efficacy of molecules/response rates are virtually always higher when drug is used first-line compared to response to the same drug used later in the treatment pathway. This is reviewed/summarised in the article ‘Smolen JS, Aletaha D. Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. Nat Rev Rheumatol. 2015 Feb 17;11:276–89.

Are you aware of any data to support this?	
28. Would efficacy and safety of filgotinib and other biologics used in RA be expected to be similar when given as monotherapy or combination therapy with methotrexate? Are you aware of any data to support this?	With regards to biologic DMARDs (bDMARDs) trials, combination with MTX has been demonstrated to be superior to bDMARD monotherapy for signs and symptoms. Several systematic reviews including those informing EULAR (European) guidelines demonstrate this. Would refer to most recent EULAR guidelines and associated SLR (Smolen JS, et al. Ann Rheum Dis 2020;79:685–699 and Kerschbaumer A, et al. Ann Rheum Dis 2020;79:744–759). The following caveats: - Approximately a third of real world prescribing is as monotherapy – implying monotherapy is undertaken as a pragmatic choice and is effective on individual level. - IL-6 targeted bDMARDs (tocilizumab, sarilumab) have demonstrated superiority, supporting monotherapy use (Jones GA, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis 2010;69:88–96; Dougados M, et al. Clinical, radiographic and immunogenic effects after 1 year of tocilizumab-based treatment strategies in rheumatoid arthritis: the ACT-RAY study. Ann Rheum Dis 2014;73:803–809), although with suggestion that combination may achieve better high hurdle endpoints (Burmester GR, et al. Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. Ann Rheum Dis 2016;75:1081–91).

	With JAKi, the weight of evidence necessitating combination strategy is not as strong, with trial data demonstrating efficacy as monotherapy (Lee EB, et al. Tofacitinib versus Methotrexate in Rheumatoid Arthritis. New England Journal of Medicine. 2014;370(25):2377-86; Fleischmann R, et al. Baricitinib, Methotrexate, or Combination in Patients With Rheumatoid Arthritis and No or Limited Prior Disease-Modifying Antirheumatic Drug Treatment. Arthritis & Rheumatology. 2017;69(3):506-17).
29. Would efficacy and safety of filgotinib and other biologics used in RA be expected to be similar in people with moderate-severe RA and those with severe RA? Are you aware of any data to support this?	The ability to reduce disease activity to one of remission/equivalent (target of treatment) is implicitly linked to the burden of disease. Effect of a drug in suppressing a given amount of inflammation will mean it can achieve remission/equivalent more easily compared to if starting with higher levels of inflammation as would be the case with severe RA. Safety profile would also likely be better. Since the 1950s, it is well-recognised that RA is associated with increased risk of infection, corticosteroids heighten this risk up to four-fold, anti-TNF for example, up to two-fold (Listing J, et al. Rheumatology (Oxfoed) 2013; 52:53-61). These data emphasise the importance of effective disease control. In this context, high disease activity states further increase risk of infection. Adding an immunosuppressive drug in this context would only enhance the attendant risk (Listing J, et al. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. Rheumatology (Oxford) 2013;52:53–61; Jani M, et al. Curr Opin Rheum 2019; 31(3):285-292.). High disease activity states also increase co-morbidity, known to be a poor predictive factor for treatment response (Conti F, et al. Rheumatology 2018;57:vii11-vii2).

30. What is the estimated proportion of people who progress from moderate to severe RA on an annual basis? Are you aware of any data to support this? Is a spontaneous improvement from severe to moderate RA possible with best supportive care only	The annual rate of progression from moderate to severe disease activity state is tricky to capture. However, the systematic review by Edwards CE, et al. Rheumatology (Oxford) 2019; 00:1-10, identified 3241 patients from 9 studies (from total of 14 studies in moderate disease RA) that had radiographic data and evidenced structural progression in this group. Other studies also suggest similar including Fautrel B, et al. Identifying patients with rheumatoid arthritis with moderate disease activity at risk of significant radiographic progression despite methotrexate treatment. RMD Open 2015;1:e000018'. Spontaneous improvement from severe to moderate disease is highly unlikely in the absence of escalation of intervention. csDMARDs are associated with a low likelihood of improving disease activity state in this context (Kiely P, et al. Rheumatology 2011; 50:926-31). Supportive therapy (allied support of physiotherapy and occupational therapy) cannot alter disease pathogenesis, inflammation suppression and trajectory; medical intervention in this scenario typically unfortunately comprises corticosteroid, which only leads to more complications and burden on patient and NHS.
31. Relative to branded technologies, what is the uptake of biosimilars for new and existing patients? Are you aware of any prescribing data to support this?	Biosimilar uptake for new patients if the treatment is considered the optimal approach would be very high, over 90% unless there was specific reason to consider an originator e.g. anti-TNF in a child-bearing woman for whom certolizumab-pegol would be appropriate (as no placental-foetal transfer). Uptake for existing patients is also high, but more modest, in the 70-90% mark – again, clinical indications to continue existing originator comprise specific scenarios such as complex RA, previous multiple therapies with risk of any change to control too great, history of infusion reactions and immunogenicity.

Key messages
32. In up to 5 bullet points, please summarise the key messages of your statement. • The technology's impressive efficacy profile, including achievement of remission and low disease activity in the more resistant RA disease indicates filgotinib will deliver highly meaningful benefit to the RA population • The technology is can be considered across the treatment pathway • The safety profile is reassuring and can be consolidated with post marketed surveillance • The technology will address an unmet need of persistent disease activity despite the current therapeutic options • The technology in providing JAK1 selective inhibition adds to the introduction of JAKi class

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Patient expert statement

Filgotinib for treating moderate to severe rheumatoid arthritis [ID1632]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Teresa Shakespeare-Smith**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	National Rheumatoid Arthritis Society
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here.	☒ yes (please see below)
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	

10. Is there an unmet need for patients with this condition?	
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	

16. In up to 5 bullet points, please summarise the key messages of your statement:

I have been living with RA for 16 years. It came on suddenly and had a devastating effect on my life as a mother of 2 children and bread-winner (my husband took early retirement due to ill-health). After 3 years of DMARD treatment I was put on to a biologic which truly gave me my life back. I was in remission for a few years before my first biologic started to fail, probably precipitated by the onset of menopause. After a difficult year in which I struggled with RA flare symptoms I was swapped onto a second biologic which again gave me my life back. Not only have I experienced the benefits of treatments that have helped me to achieve remission, I have also experienced the emotional (fear and anxiety) and physical effects when a medication does not work as hoped.
As a community pharmacist I have counselled RA patients on the best use of their medication, helped them prepare to start biologics and witnessed the benefits newer medicines have brought them.

I help to run the Hertfordshire local NRAS group and at our meetings have heard testimonies from other RA patients of living with uncontrolled symptoms and the value of being in remission.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Filgotinib for moderate to severe rheumatoid arthritis

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

Authors
Rob Riemsma, Reviews Manager, Kleijnen Systematic Reviews Ltd, UK
Sabine Grimm, Health Economist, Maastricht UMC, the Netherlands
Ben Wijnen, Health Economist, Maastricht UMC
Debra Fayter, Systematic Reviewer, KSR Ltd
Sue O'Meara, Systematic Reviewer, KSR Ltd
Nigel Armstrong, Health Economist, KSR Ltd
Charlotte Ahmadu, Health Economist, KSR Ltd
Lloyd Brandts, Health Economist, Maastricht UMC
Gill Worthy, Statistician, KSR Ltd
Kate Misso, Information Specialist, KSR Ltd
John Kirwan, Emeritus Professor of Rheumatic Diseases, University of Bristol
Manuela Joore, Health Economist, Maastricht UMC
Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University

Correspondence to Rob Riemsma, Kleijnen Systematic Reviews
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, UK
YO19 6FD

Date completed 28/07/2020

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number STA 13/14/25.

Declared competing interests of the authors

None.

Acknowledgements

None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report

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

This report should be referenced as follows:

Riemsma R, Grimm S, Wijnen B, Fayter D, O'Meara S, Armstrong N, Ahmadu C, Brandts L, Worthy G, Misso K, Kirwan J, Joore MA, Kleijnen J. Filgotinib for moderate to severe rheumatoid arthritis: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2020.

Contributions of authors

Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Sabine Grimm acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Ben Wijnen, Lloyd Brandts, Charlotte Ahmadu and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter and Sue O'Meara acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Kate Misso critiqued the search methods in the submission and contributed to the writing of the report. John Kirwan provided clinical expert advice and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ABA	Abatacept
ACPA	Anti-citrullinated protein antibodies
ACR	American College of Rheumatology
ADA	Adalimumab
AE	Adverse events
AIC	Akaike Information Criterion
AIMS	Arthritis Impact Measurement Scales
ATP	Adenosine triphosphate
BAR	Baricitinib
bDMARD	Biological disease modifying antirheumatic drugs
BSC	Best supportive care
BI	Budget impact
BIC	Bayesian information criterion
CCP	Cyclic citrullinated peptide
CDAI	Clinical disease activity index
cDMARDs	Conventional disease modifying antirheumatic drugs
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSA	Clinically suspect arthralgia
csDMARDs	Conventional synthetic DMARDs (same as cDMARD)
CSR	Clinical study report
CVD	Cardiovascular disease
CZP	Certolizumab pegol
DALY	Disability-adjusted life years
DAS	Disease activity score
DMARD	Disease modifying antirheumatic drugs
DSU	Decision Support Unit
EMA	European Medicines Agency
EMEA	Europe, Middle East and Africa
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
ERAN	Early rheumatoid arthritis network
ERG	Evidence Review Group
ESR	Erythrocyte sedimentation rate
ET	Early termination
ETA	Etanercept
EULAR	European League Against Rheumatism
EUR	Erasmus University Rotterdam
FACIT-F	Functional assessment of chronic illness therapy
FAD	Final appraisal document
FDA	Food and Drug Administration
GOL	Golimumab
HAQ	Health assessment questionnaire
HAQ-DI	Health Assessment Questionnaire Disability Index
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
IC	Indirect comparison

ICER	Incremental cost effectiveness ratio
IC50	Half maximal inhibitory concentration
IFX	Infliximab
IR	Inadequate response
ITC	Indirect treatment comparison
ITT	Intention to treat
JAK	Janus kinase
KSR	Kleijnen Systematic Reviews
LYs	Life years
LYG	Life years gained
MACE	Major adverse cardiovascular events
MCS	Mental component of the SF-36 survey
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MTX	Methotrexate
MTA	Multiple technology appraisal
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported
OS	Overall survival
PAS	Patient access scheme
PCS	Physical component of the SF-36 survey
PDUS	Power Doppler ultrasound
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RF	Rheumatoid factor
RR	Relative risk; risk ratio
RTX	Rituximab
SAE	Serious adverse events
ScHARR	School of Health and Related Research
SD	Standard deviation
SDAI	Simplified disease activity index
SE	Standard error
SF-36	36-item Short Form Survey
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
STA	Single technology appraisal
STATs	Signal transducers and activators of transcription
TA	Technology appraisal
TEAE	Treatment emergent adverse events
TNF	Tumor Necrosis Factor
TOC	Tocilizumab
TOF	Tofacitinib
tsDMARDs	Targeted synthetic DMARDs
TTO	Time trade-off

UK	United Kingdom
ULN	Upper limit of normal
UMC	University Medical Centre
USA	United States of America
WHO	World Health Organization
WTP	Willingness-to-pay

Table of Contents

Table of Tables

Table of Figures

1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The population defined in the scope is: Adults with moderate to severe, active rheumatoid arthritis (RA), whose disease has responded inadequately to, or who are intolerant of conventional or biological disease-modifying anti-rheumatic drugs (DMARD)s. The population in the company submission (CS) is limited to 'Adults with moderately to severely active RA whose disease has responded inadequately to two or more conventional DMARDS (cDMARDs), or who are intolerant to DMARDs, including conventional or biologic DMARDs'. The company states that "in the moderately active RA population the company submission is limited to patients following two or more cDMARD failures, this restriction is applied on the basis of clinical opinion and expected cost-effectiveness" (CS, Table 1, page 15).

The comparators in the CS are not in line with NICE scope (see below).

1.2 Summary of the key issues in the clinical effectiveness evidence

A full summary of the clinical effectiveness evidence can be found in Section 4.6 of this report, the key effectiveness results can be found in Table 4.6 (pages 52-53) and safety results can be found in Tables 4.7 and 4.8 (pages 56-58). Subgroup results for patients with moderately active RA and severely active RA are reported separately in Appendix 2 of this report; and a summary of the Evidence Review Group (ERG) critique on the network meta-analyses (NMAs) can be found in Section 4.4 of this report. The key issues in the clinical effectiveness evidence are as follows:

Decision problem:

- The population in the CS is not in line with National Institute for Health and Care Excellence (NICE) scope in several respects:
  - The NICE scope lists different comparators for people with moderately active RA and for people with severely active RA. The CS does not separate these two populations.
  - Approximately 24% of patients in the FINCH 1 trial had moderate disease and 21% in the FINCH 2 trial. Therefore, results from both trials are more reliable for the severely active RA population, but less reliable for patients with moderately active RA.
  - The CS limits the moderately active RA population to patients who have failed on two or more cDMARDs. The NICE scope mentions failure on one or more DMARDs. In addition, patients in the FINCH 1 trial (the most relevant trial for moderately active disease) includes patients who have failed on one or more cDMARDs.
  - The NICE scope does not mention glucocorticoids (GCs) as a comparator or as a possible previous treatment, even though NICE recommends consideration of them on starting a new cDMARD. According to our clinical expert treatment with cDMARD plus glucocorticoids (GC) is a much more effective treatment than one cDMARD alone because it stops the progression of the underlying joint destruction. Therefore, GC plus cDMARD might be the most effective treatment in newly diagnosed RA; and could be the main comparator in this appraisal. In addition, the therapeutic benefit of treatments may differ for patients who have previously failed on cDMARD+GC (compared to cDMARD alone) before being entered into the FINCH studies, and this would affect both the benefit claimed and the economic evaluation of filgotinib. These data are available in the FINCH 1 trial but are not reported in the CS. A comparison of results between patients who have received previous GCs versus those who have not should be of interest to the committee.
- The comparators in the CS are not in line with NICE scope in several respects:

  - The NICE scope mentions different comparators for moderate disease and for severe disease and differentiates on the basis of response to previous cDMARDs, biologic DMARDs (bDMARDs), Tumor Necrosis Factor (TNF) inhibitors and rituximab. The CS simplifies this by looking at two populations: c-DMARD-inadequate response (IR) and bDMARD-IR; for both populations the CS uses data from all patients with moderate to severe active RA.
  - For moderately active RA, the NICE scope mentions three comparators (combination of two or more cDMARDs, cDMARD with dose escalation and best supportive care (BSC)), while the company included only one: BSC.
  - Several relevant comparators mentioned in the scope were not included in the NMAs because of lack of data. This is partly due to the inclusion criteria used by the company (no monotherapy). As a result, these comparators have also not been included in the economic model.
- The only direct evidence on filgotinib versus an active comparator is for adalimumab in the FINCH 1 trial.

Best supportive care:

- In the economic model BSC is assumed to have no treatment effect. However, in the control arm of the FINCH 1 trial patients received placebo+methotrexate (MTX) and all patients in FINCH 1 had an inadequate response to ongoing stable MTX dose. Nevertheless, "patients in the FINCH-1 study exhibited extremely high levels of response when treated with cDMARDs" according to the company (CS, page 114). Therefore, either the population in the FINCH 1 trial is not in accordance with the NICE scope; or the assumption that BSC has no treatment effect is incorrect for this appraisal.

FINCH trials:

- Both FINCH trials (FINCH 1 and FINCH 2) are good quality international trials. However, FINCH 1 only included 14 UK participants (0.8%) and FINCH 2 included nine UK participants (2%). In addition, follow-up was only 24 weeks for both trials. The FINCH 4 study (not a randomised controlled trial (RCT)) will provide longer term outcomes, but no results are available yet.
- The primary endpoint for both FINCH 1 and FINCH 2 was the proportion of patients achieving a 20% improvement in American College of Rheumatology response (ACR20) at week 12. This is a very weak end point for a life-long condition.
- Comparative evidence from the FINCH 1 and 2 trials is only available for 24-week follow-up. This is very short for a condition that may last 30 years.
- The real long-term benefit of treatment is likely to be related to its ability to stop x-ray progression. This outcome has not been reported for the FINCH trials.

Network meta-analyses:

- The company used different inclusion criteria from the NICE scope:
  - all monotherapy studies were excluded.
  - the search was limited to studies after 1999.

  Therefore, potentially relevant studies were excluded from the NMAs.
- For the decision problem in the moderately active RA population (cDMARD-IR) the company specified patients that had failed on two or more cDMARDs. However, for the intervention, the company included the FINCH 1 study in which patients had failed on one or more DMARDs.

As far as the ERG is aware the company did not adjust the results of the FINCH 1 study for this difference in populations.

- The company based their assumptions of clinical homogeneity on previous technology assessments, but it is not clear whether those contained the same studies. The ERG asked for a justification of clinical homogeneity based on a review of baseline patient data but this was not provided. For both NMA analyses the studies varied in terms of disease duration (from 12 to 174 months in the bDMARD-IR population) so there are potential concerns about clinical heterogeneity if disease duration is an important effect modifier.

1.3 Summary of the key issues in the cost effectiveness evidence

A full summary of the cost effectiveness evidence review conclusions can be found in Section 7.4 of this report. The company's cost effectiveness results are presented in Section, 6, the ERG's summary and detailed critique in Section 5, and the ERG's amendments to the company's model and results are presented in Section 7. Results are reproduced using confidential patient access schemes and biosimilar prices in a confidential appendix. The key issues in the cost effectiveness evidence are as follows:

Population, Intervention, Comparators:

- The company's decision problem is narrower in focus than NICE's scope, focusing on a population of patients who have received at least two prior cDMARDs, rather than at least one prior cDMARD. This potentially affected the appropriateness of the NMA (as described in Section 1.2) and subsequently led to the potential omission of relevant studies informing efficacy and relevant comparators in the economic evaluation.
- The selection of comparators in the model may not have been appropriate: potentially relevant comparators certolizumab pegol, tofacitinib (in most populations), golimumab and infliximab were not included. The ERG considered that market share data and opinion of one expert (for golimumab and infliximab) were likely insufficient justifications. However, infliximab is now rarely used and its exclusion could be appropriate. Golimumab was excluded also because no 24-week assessment data were available. Data for certolizumab pegol were not included in the NMA in the relevant population and those for tofacitinib were not included at the 24-week assessment time point. The ERG considered that these comparators may have been inappropriately excluded, possibly resulting in cost effectiveness results being biased.
- Best supportive care was defined as being comprised of conventional synthetic DMARDs (csDMARDs) administered at lower doses – however, its pricing in the model contradicts this as BSC cost is higher than that of csDMARDs (including palliative care costs, in line with MTA375). With this in mind, BSC as implemented in the model should only be used as the last treatment line – however, the company also used it as the comparator and end-of-sequence treatment after failure with any treatment in the moderate population. This was considered inappropriate by the ERG, as in the moderate population patients do have the option of being treated with further csDMARDs or bDMARDs once they progress to severely active RA. The ERG would have preferred it if the company could enable implementation of separate end-of-sequence treatments for the moderate and severe populations and to change the comparator in the moderate population to csDMARD treatment.
- Treatment sequences in the company's model are a very simplified version of reality, owing to model complexity and run-times. Whilst the ERG acknowledges the difficulty of reflecting treatment sequences accurately in the model, there were concerns over the company's selection. In the moderate population, patients would receive BSC in the comparator arm or after treatment with filgotinib, and if they became severe they would receive adalimumab, the

comparator associated with the smallest quality-adjusted life year (QALY) gain according to the company's cost effectiveness results. The ERG considered it appropriate to use the comparator with the highest QALY gain (etanercept) as first-line bDMARD sequence.

Model structure:

- The model structure is in line with previous submissions to NICE, including MTA 375, and the company added the functionality of moderate RA patients progressing through to a severely active RA state where they can receive bDMARDs (as response to clarification questions raised by ERG). As not all possible treatment sequences could be incorporated in the model (due to model complexity and run-times), uncertainty remains about cost effectiveness in the moderate and severe populations. In addition, the model still does not reflect the possibility of patients transitioning from a severe state to a moderate state. As such, the model simplifies the reality of RA patients, although it is in line with previous submissions.

Treatment effectiveness:

- The model file contained some errors in the VBA underlying the 'Main Settings' sheet that made amendments difficult. In particular, it was unclear how new patient profiles could be generated using differential distributions for each patient population (FINCH 1 moderate only, FINCH 1, severe only, and FINCH 2).
- The company, for the moderate population, used the mid-point Disease Activity Score-28 items (DAS28) score between low and severe disease to inform patients' DAS28 score (i.e. DAS28 score of 4.15). Instead, the ERG prefers the use of the DAS28 score observed in the moderate FINCH population (i.e. DAS28 score of [redacted]).
- The company used the FINCH trial programme to inform effectiveness of filgotinib, which also included patients who had only one prior csDMARD (as opposed to studies included in the NMA), which led to a discrepancy between effectiveness results of filgotinib and comparators.
- The company made assumptions that response rates obtained from the NMA are valid regardless of line-of-treatment and, although observed only at the 24-week assessment, hold throughout life-time; and assumed equivalent treatment effectiveness with or without the addition of methotrexate and also in the moderate and severe populations, which are likely to be implausible according to the ERG.

Health-related quality of life:

- Health-related quality of life was estimated using a mapping function based on Health Assessment Questionnaire Disability Index (HAQ-DI) and pain scores without reliable estimates of pain scores over time being available.

Costs and resource use:

- The company's pricing was unclear as there is differential pricing for patients with moderately to severely active RA and severely active RA and the company only used the former in the model. The ERG changed the price used in the severely active RA model population to that proposed for the severely active RA population.
- Cost of BSC was likely over-estimated, at least in the moderate population.

Model implementation and validation:

- The company's model used an insufficient number of patient profiles (1,000 profiles which are drawn from 10,000 times), which likely under-estimated heterogeneity. The ERG would have

preferred the use of as many patient profiles as patients simulated, which would also make model diagnostics more meaningful. This means that there are concerns about model stability, which could not be fully demonstrated.

- The Probabilistic Sensitivity Analysis (PSA) number of iterations is likely too small and based on too small a number of sampled patients. This limitation is difficult to address given long model run-times.
- The company undertook some efforts to validate their model. Overall, based on its own checks, the ERG is satisfied that the model performs as expected. However, the company could have provided more detail on their validation exercises and could have, in fact, put more effort into model internal, external and cross-validation.

Conclusion:
The ERG considers that there remains substantial uncertainty about the presented cost effectiveness results.

1.4 Summary of the ERG's preferred assumptions and resulting ICER

The ERG corrected errors, violations and adjusted several model assumptions in the ERG base-case.

Moderate population:

1. Use csDMARD (costs and response rates) as comparator instead of BSC
2. Change subsequent BSC costs to csDMARD costs
3. Use DAS28 score from FINCH
4. Alternative treatment sequences in the severe population: replace adalimumab (ADA) (least QALYs) by etanercept (ETA) (most QALYs)
5. Estimate Health-related quality of life (HRQoL) always based on constant pain VAS score from FINCH

Severe population:

1. Filgotinib price not implemented in line with company's Patient Access Scheme (PAS) proposed for the severe population in the CS.
2. Estimate HRQoL always based on constant pain Visual Analogue Scale (VAS) score from FINCH

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG performed the following exploratory scenarios:

1. Alternative filgotinib price for the severely active RA population
2. Include upadacitinib as comparator in populations 2a and 2b (severe RA patients, first-line)
3. Week 12 assessment response rates for all first-line treatments in population 2b (severe RA patients, first-line, MTX eligible) to include tofacitinib

PSA run-times were prohibitive for running the PSA in all populations (approximately 15 hours for a PSA with 1,500 patients – the company's recommended minimum number – and 1,000 PSA runs; approximately four hours for 1,000 patients and 500 PSA runs). Hence, PSA was only performed in population 2b (severe RA patients, first-line, MTX eligible).

Table 1.1: Comparison of cost effectiveness outcomes

Population	Sub-population	Further division	Revised CS base-case	ERG base-case	ERG base-case PSA*	Scenario 1	Scenario 2	Scenario 3
1. Moderate RA patients	a) MTX ineligible	-	FIL cost effective under threshold of £30,000	FIL cost effective under threshold of £30,000	-	-	-	-
1. Moderate RA patients	b) MTX eligible	-	FIL cost effective under threshold of £30,000	FIL cost effective under threshold of £30,000	-	-	-	-
2. Severe RA patients, First line	a) MTX ineligible	-	FIL dominates ADA & TCZ, cheaper & less effective than ETN, BAR	FIL dominates ADA & TCZ, cheaper & less effective than ETN, BAR	-	FIL dominates ADA & TCZ, cheaper & less effective than ETN, BAR	FIL dominates ADA & TCZ, cheaper and less effective than ETN, UPA	FIL dominates TCZ, cheaper and less effective than ETN, BAR, TOF
2. Severe RA patients, First line	b) MTX eligible	1. Second-line RTX	FIL dominates ADA, cheaper & less effective than ETN, BAR	FIL dominates ADA, cheaper & less effective than ETN, BAR	FIL dominates ADA, cheaper & less effective than ETN, BAR	FIL dominates ADA, cheaper & less effective than ETN, BAR	FIL dominates ADA, cheaper and less effective than ETN, BAR, UPA	FIL dominates ADA, cheaper and less effective than ETN, BAR, TOF
2. Severe RA patients, First line	b) MTX eligible	2. Second-line IL-6 (RTX contra-indicated)	FIL dominates ADA, cheaper & less effective than ETN, BAR	FIL dominates ADA, cheaper & less effective than ETN, BAR	-	FIL dominates ADA, cheaper & less effective than ETN, BAR	FIL dominates ADA, cheaper and less effective than ETN, BAR, UPA	FIL dominates ADA, cheaper and less effective than ETN, BAR, TOF

Population	Sub-population	Further division	Revised CS base-case	ERG base-case	ERG base-case PSA*	Scenario 1	Scenario 2	Scenario 3
2. Severe RA patients, First line	b) MTX eligible	3. Second-line CD80 (RTX contra-indicated)	FIL dominates ADA, cheaper & less effective than ETN, BAR	FIL dominates ADA, cheaper & less effective than ETN, BAR	-	FIL dominates ADA, cheaper & less effective than ETN, BAR	FIL dominates ADA, cheaper and less effective than ETN, BAR, UPA	FIL dominates ADA, cheaper and less effective than ETN, BAR, TOF
3. Severe RA patients, Second line, RTX ineligible	a) MTX ineligible	-	FIL dominates TOF and BAR, cheaper & less effective than ABC	FIL dominates TOF and BAR, cheaper & less effective than ABC	-	FIL dominates TOF and BAR, cheaper & less effective than ABC	-	-
3. Severe RA patients, Second line, RTX ineligible	b) MTX eligible	-	FIL dominates BAR, TCZ, SAR, cheaper & less effective than ABC	FIL dominates BAR, TCZ, SAR, cheaper & less effective than ABC	-	FIL dominates BAR, TCZ, SAR, cheaper & less effective than ABC	-	-
4. Severe RA patients, Second line, RTX eligible	MTX eligible	-	FIL cheaper & less effective than RTX	FIL cheaper & less effective than RTX	-	FIL cheaper & less effective than RTX	-	-
5. Severe RA patients, Third line, RTX failure	-	-	FIL dominates TCZ, SAR	FIL dominates TCZ, SAR	-	FIL dominates TCZ, SAR	-	-

2. BACKGROUND

2.1 Introduction

In this report, the ERG provides a review of the evidence submitted by Gilead Sciences in support of filgotinib for patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to, or who are intolerant of one or more DMARDs (one or more DMARDs according to the NICE scope; two or more DMARDs according to the CS), including conventional or biological DMARDs. In this section, the ERG summarises and critiques the company's description of the underlying health problem and the company's overview of the current service provision. The information for this critique is taken from Document B of the Company Submission (CS).[1]

2.2 Critique of company's description of the underlying health problem

The underlying health problem of this appraisal is moderate to severe rheumatoid arthritis, an autoimmune disease. Although the exact cause of RA is unknown, initiation of disease seems to result from an interaction among genetic susceptibility, environmental triggers, and chance.[2] The CS described the swelling and tenderness of joints and subsequent joint damage as key features of RA and highlighted the presence of extra-articular systemic disease manifestations.[1]

Rheumatoid arthritis is a common autoimmune disease. The CS cited a global prevalence of 0.24%. It develops more frequently in women and the CS provided estimates of global prevalence for women (0.35%) and men (0.13%).[1] The company cited a study published in 2002 giving prevalence estimates for the UK of 1.16% in women and 0.44% in men.[3] The company stated, based on current population figures from the Office of National Statistics,[4] that this equated to approximately 400,000 prevalent adult patients in England and Wales.[1] The company also cited data on incidence of RA in the UK. *"The UK-specific incidence rate of RA has been reported to be 40 per 100,000 persons per year in a report published in 2013 (Cs ref 14), with a markedly higher (54 per 100,000 persons, 95% confidence interval [CI]: 44.5 to 64.7) incidence in women than in men (25 per 100,000 persons, 95% CI: 18.1 to 32.4)".*[5] The company used this data to estimate that the number of patients in England and Wales diagnosed with RA each year was approximately 20,000.[1] Diagnosis of rheumatoid arthritis is confirmed using The European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) criteria.[6]

The CS described the DAS28 score (a composite of a count of swelling and tenderness of joints, erythrocyte sedimentation rate (ESR) or C reactive protein (CRP) values and patient global assessment of health). This is used to classify severity of disease. The cut-offs are as follows: DAS28 <2.6: Remission, DAS28 <3.2: Low disease activity (LDA), DAS28 3.2 - 5.1: Moderate disease activity (MDA) and DAS28 >5.1 High disease activity/Severe disease (HDA).[1]

The company conducted market research to ascertain the proportion of patients with moderate disease. "*Out of the total RA patient pool, market research suggests 39% are estimated to have moderately active disease (or around 120,000 in England and Wales), while the proportion of severely active RA patients are estimated to be 29% (approximately 90,000).*"[1]. They also cited a UK study to illustrate the number of patients progressing from moderate to severe disease over time.[7] "*A study of UK patients in the Early RA Network (ERAN), a cohort of newly diagnosed RA patients receiving cDMARDs, showed the rate of patients progressing from moderately to severely active disease was 19% over a two-year period,[7] which translates to approximately 12,000 patients in England and Wales a year who progress to severely active disease*."[1] However, patients in the ERAN-cohort were treated between 2002 and 2008, and it seems they were mostly not treated with what we now know is the most effective

treatment for newly diagnosed RA (a combination of cDMARD and low dose glucocorticoids). Therefore, the outcome at one year and two years might be a pessimistic assessment. There will be fewer patients progressing to severely active disease if the best treatment is used.

The CS described the progressive nature of the disease "*the main symptoms of early RA are pain and fatigue. Without adequate treatment the disease is associated with progressive joint damage and disability, both of which are irreversible".*[1]

The company cited NICE guidance which advises a treat-to-target approach. "*In adults with active RA, measure C-reactive protein (CRP) and disease activity (using a composite score such as DAS28) monthly in specialist care until the target of remission or low disease activity is achieved*."[8] However the company highlighted a UK study where many patients with moderately active RA had received multiple cDMARDS, which suggested a lack of effective treatments for this group of patients.[9] The company further stated that "*These patients also experience reduced quality of life and represent a substantial burden to healthcare systems."*[1] However, this reference is to a meeting abstract describing a retrospective, non-interventional study and included only 24 patients. They were patients who were still moderately active two years after diagnosis, and the study reported they had attended hospital a lot in the previous year.

The company cited evidence of increased comorbidities in patients with RA. "*The 2014 COMORA study (CS ref 6) evaluated the prevalence of comorbidities in RA patients and found that hypertension and dyslipidaemia were most prevalent.*"[1] "*Other potentially serious non-CV related comorbidities prevalent in RA patients include anaemia, psychiatric disorders, malignancies, and diabetes.*"[10]

The CS highlighted the impact of RA on patient quality of life "*A 2014 literature review (26),which included 31 studies (including two from the UK) with a total of 22,335 patients, investigated the effects of RA on HRQoL as measured by the 36-item Short Form survey (SF-36) questionnaire. Results of this study show worse mean scores for the physical component (PCS) of the survey than the mental component (MCS), the mean pooled HRQoL score for PCS was 34.1 (95% CI: 22.0, 46.1) and the mean score for MCS was 45.6 (95% CI: 30.3, 60.8) (100 represents best possible QoL)*"[11]

The company stated that patients with RA are at increased risk of mortality, citing a 2016 study.[12] "*A 2016 study by Michaud et al (CS ref 24) reported age- and sex-standardised mortality incidence rates (per 100 person-years) from RA registries; finding a UK mortality incidence rate of 0.8 per 100 person-years."*[1]

ERG comment:

- The company provided a good overview of the underlying health problem of rheumatoid arthritis illustrating the seriousness of the condition and its impact on patients. The ERG checked the references provided to support the statements in the company submission. In general, these were appropriately referenced. Where citations did not match an alternative source was checked.
- The prevalence and incidence figures were based on relatively old data. For example, the study cited on incidence of RA was based on patients who had symptom onset of joint pain or swelling between January and December 1990.[5] In a more recent study using data from the Global Burden of Diseases, Injuries, and Risk Factors study (GBD) 2017, the following prevalence and incidence rates were provided for the UK. The UK had both the highest age-standardised prevalence rate (471.8 (95% UI 428.9 to 514.9)) per 100,000 and age-standardised incidence rate (27.5 (95% UI 24.7 to 30.0)) in 2017 of the 195 countries investigated.[13]

- The ERG adds to the company's description of the disease that the peak age of incidence in the UK for both men and women is the 50s to 70s, but people of all ages can develop the disease[8] and approximately 75% of patients are of working age.[9]
- The ERG also adds to the company's description of the burden of disease that approximately one-third of people stop work because of the disease within two years of onset, and this increases thereafter.[8]
- The market research conducted by the company on the prevalence of moderate RA was not available to the ERG. In the FINCH trials the proportion with moderate disease was 24% in FINCH 1 and 21% in FINCH 2. Patients with moderate disease are not currently eligible for biological DMARDS under NICE guidance.[8] In a 2013 study performed in Bristol, 50% of 40 new RA patients had DAS<3.2 after 40 weeks, 35% had DAS 3.2 to 5.1, and 15% had DAS>5.1 (Personal communication from John Kirwan, 18 July 2020).[14]
- The ERG adds the following data on comorbidities from the COMORA study.[10] Patients in this study were recruited from 17 countries and 3,920 patients were analysed. Of these 43 patients were from the UK. Average age of the whole sample was 56 years and average disease duration was 10 (SD 9) years. Eighty-two percent were female and average DAS28 was 3.7 (SD 1.6). The most frequently associated diseases (past or current) were: depression, 15%; asthma, 6.6%; cardiovascular events (myocardial infarction, stroke), 6%; solid malignancies (excluding basal cell carcinoma), 4.5%; chronic obstructive pulmonary disease, 3.5%.[10] The study confirmed not only the relatively high prevalence of comorbidities among patients with RA, but also the considerable intercountry variability in the prevalence of these comorbidities.[10]
- The ERG examined the systematic review cited as evidence of reduced quality of life in RA,[11] and noted the lower HRQoL observed for patients with RA when compared to the UK population as a whole.

2.3 Critique of company's overview of current service provision

The main clinical guideline relevant to this submission is CG100 "Rheumatoid arthritis in adults: management" updated in 2018.[8] The NICE guideline outlines the following as initial treatment for newly diagnosed patients.

"For adults with newly diagnosed active rheumatoid arthritis:

Offer first-line treatment with cDMARD monotherapy using oral methotrexate, leflunomide or sulfasalazine as soon as possible and ideally within 3 months of onset of persistent symptoms.

Consider hydroxychloroquine for first-line treatment as an alternative to oral methotrexate, leflunomide or sulfasalazine for mild or palindromic disease.

Escalate dose as tolerated.

Consider short-term bridging treatment with glucocorticoids (oral, intramuscular or intra-articular) when starting a new cDMARD.

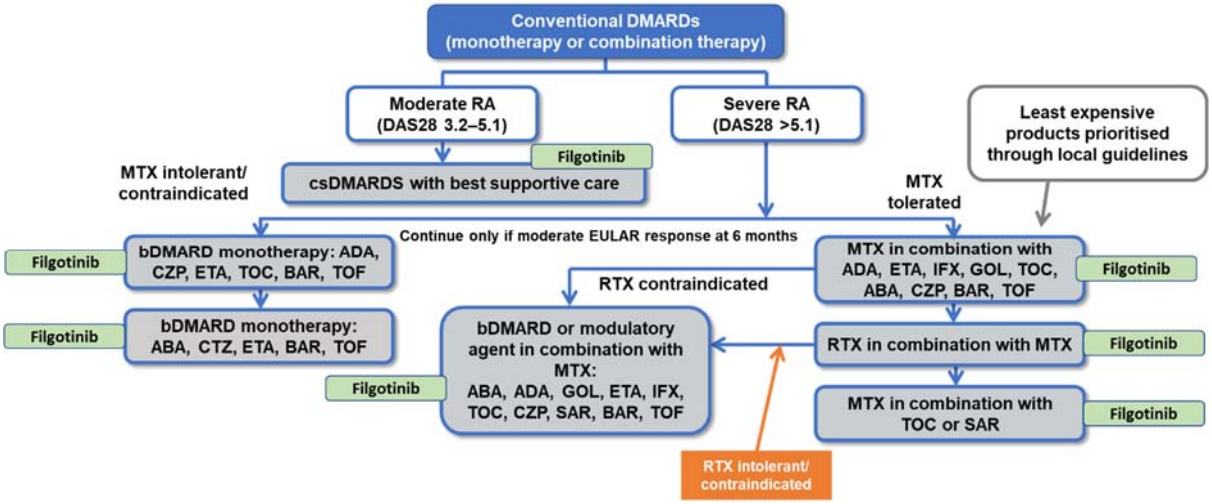
Step-up strategy

Offer additional cDMARDs (oral methotrexate, leflunomide, sulfasalazine or hydroxychloroquine) in combination in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved despite dose escalation."[8]

Further treatment options with biological DMARDS or targeted synthetic DMARDs are offered to patients only with severely active RA (DAS28 score greater than 5.1). The company highlights the lack of further treatment options for patients with moderate disease. They cite the recently updated EULAR guidelines which recommend advanced therapies for moderately or severely active patients, following failure of two cDMARDs, or after one cDMARD in patients with other poor prognostic factors.[15]

Figure 2.1 shows the current treatment pathway with the proposed positioning for filgotinib.

Figure 2.1: Proposed positioning of filgotinib within current NICE treatment pathway



Source: Section 1.1 of the CS[1]
ADA=adalimumab; ABA=abatacept; BAR=baricitinib; CZP=certolizumab pegol; DAS=Disease Activity Score; DMARD=Synthetic disease modifying antirheumatic drugs; ETA=etanercept; GOL=golimumab; IFX=infliximab; MTX=Methotrexate; RA=Rheumatoid arthritis; RTX=Rituximab; TOC=tocilizumab; TOF=tofacitinib.

In Figure 2.1, it can be seen that filgotinib is to be placed at a range of points in the pathway according to whether patients have moderate or severe disease and their previous treatment. At each point in the pathway a range of treatment options are in existence.

For moderate disease filgotinib is to be used:

1a. As monotherapy after two or more cDMARD failures in patients who are MTX ineligible

1b. As combination therapy with MTX after two or more cDMARD failures in patients who are MTX eligible

For severe disease for those who are eligible for MTX filgotinib is to be used:

2b. As combination therapy with MTX as first-line advanced therapy

3b. As combination therapy with MTX, after failure of first-line advanced therapy in patients who are RTX ineligible or intolerant

4. As combination therapy with MTX, after first-line advanced therapy failure in patients who are RTX eligible

5. As combination therapy with MTX, after failure of RTX in combination with MTX

For severe disease for patients who are MTX ineligible filgotinib is to be used:

2a. As monotherapy, used as first-line advanced therapy

3a. As monotherapy, after failure of first-line advanced therapy

The company identified a current unmet need for treatment of patients with RA in terms of improvements in efficacy, safety, patient preference for oral therapy and providing options for patients with moderate disease. As part of the submission we received a statement from the National Rheumatoid Arthritis Society (NRAS) which stated "*Approximately 6-8% of patients are resistant to treatment (refractory) and many have to move over time from one therapy to another to maintain disease control. Despite a considerably enlarged arsenal of drugs by comparison to over 20 years ago, there remains unquestionable unmet need*."[16] Further advantages to patients cited in the NRAS submission included patients being more prepared to take an oral medicine than inject themselves or be infused, use at different places in the clinical pathway and adding further options and choice for clinicians and patients.[16]

ERG comment:

- The company's overview of the current pathway is appropriate. However it should be noted that the NICE scope specified the population as "*adults with moderate to severe, active rheumatoid arthritis whose disease has responded inadequately to, or who are intolerant of conventional or biological DMARDs*."[17] The company stated their population to be adults with moderately to severely active RA whose disease has responded inadequately **to two or more cDMARDs, or who are intolerant to DMARDs, including conventional or biologic DMARDs**. Hence in the proposed pathway, filgotinib is expected to be used as third-line treatment and beyond.
- It should also be noted that glucocorticoids (GCs) have been omitted, even though NICE recommends consideration of them on starting a new cDMARD.[18] According to our clinical expert, it is the combination of GC plus MTX (or any other cDMARD) which has an efficacy similar to bDMARDs in newly diagnosed patients. Treatment with cDMARD plus glucocorticoids might be a much more effective treatment than one cDMARD alone because it stops the progression of the underlying joint destruction. Therefore, GC plus cDMARD might be the most effective treatment in newly diagnosed RA; and could be the main comparator in this appraisal.[19] In addition, the therapeutic benefit of treatments may differ for patients who have previously failed on cDMARD+GC (compared to cDMARD alone) before being entered into the FINCH studies, and this would affect both the benefit claimed and the economic evaluation of filgotinib.
- It is important to note that the direct evidence from the FINCH trial programme does not reflect all of the potential positions in the pathway where filgotinib might be used. Firstly, the main trials are of combination therapy not monotherapy. In FINCH 1 and 2, filgotinib was given as combination therapy (with an ongoing stable dose of MTX in FINCH 1 and with a specified cDMARD continued on a stable dose in FINCH 2 (MTX, hydroxychloroquine, sulfasalazine or leflunomide)).
- Secondly in terms of potential positions in the pathway, moderate and severely affected patients are combined in the FINCH trials although subgroup results were provided for FINCH 1 for moderate and severe groups. Most of the patients in FINCH 1 had severe disease. The network meta-analysis conducted by the company in this submission combined moderate and severe disease as separate NMAs for moderate and severe RA were not feasible.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Population	Adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to, or who are intolerant of one or more DMARDs, including conventional or biological DMARDs	Adults with moderately to severely active, active RA whose disease has responded inadequately to two or more cDMARDs, or who are intolerant to DMARDs, including conventional or biologic DMARDs. The specific populations modelled in the cost-effectiveness analysis are: Filgotinib for moderately active RA: 1a. As monotherapy after two or more cDMARD failures in patients who are MTX ineligible 1b. As combination therapy with MTX after two or more cDMARD failures in patients who are MTX eligible Filgotinib in combination with MTX for severely active RA, for patients who are MTX eligible: 2b. As combination therapy with MTX as first-line advanced therapy[1] 3b. As combination therapy with MTX, after failure of first-line advanced therapy in patients who are RTX ineligible or intolerant 4. As combination therapy with MTX, after first-line advanced therapy failure in patients who are RTX eligible	The populations included within the submission is within the NICE scope. However, in the moderately active RA population the company submission is limited to patients following two or more cDMARD failures, this restriction is applied on the basis of clinical opinion and expected cost-effectiveness.	The population is not in line with NICE scope, see Section 3.1 below.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
		5. As combination therapy with MTX, after failure of RTX in combination with MTX Filgotinib for severely active RA, for patients who are MTX ineligible: 2a. As monotherapy, used as first-line advanced therapy 3a. As monotherapy, after failure of first-line advanced therapy		
Intervention	Filgotinib (as monotherapy or in combination with other cDMARDs, including methotrexate (MTX))	Aligned with NICE scope	NA	The intervention is in line with the NICE scope.
Comparator(s)	For moderately active RA that has not responded adequately to therapy with conventional DMARDs: • Combination of two or more cDMARDs (including MTX and at least one other DMARD, such as sulfasalazine and leflunomide) • cDMARD monotherapy with dose escalation • Best supportive care For severely active RA that has not responded adequately to therapy with cDMARDs: • Biological DMARDs in combination with MTX (adalimumab, etanercept, infliximab, certolizumab	For moderately active RA that has not responded adequately to therapy with cDMARDs: • Best supportive care For severely active RA that has not responded adequately to therapy with cDMARDs: MTX intolerant patients: • Adalimumab, etanercept, tocilizumab or baricitinib (each as monotherapy) MTX tolerant patients: • Biological DMARDs in combination with MTX (adalimumab, etanercept, baricitinib) For severely active RA that has not responded adequately to therapy with	Comparators in the model were applied based on currently reimbursed treatments and availability of evidence to inform comparisons, comparisons are consistent with previous Technology Appraisals. Real-world data and expert opinion, in conjunction with NICE guidance for the treatment of RA, were used to inform treatment sequences, which are reflective of current clinical practice.	The comparators are not in line with the NICE scope, see Section 3.3 below.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	pegol, golimumab, tocilizumab, abatacept or sarilumab) • Adalimumab, etanercept, certolizumab pegol, tocilizumab or sarilumab (each as monotherapy) • Tofacitinib, baricitinib or upadacitinib (each as monotherapy or in combination with MTX) For severely active RA that has not responded adequately to therapy with DMARDs including at least one TNF inhibitor: • Rituximab in combination with MTX When rituximab is contraindicated or withdrawn due to adverse events: • Adalimumab, etanercept, infliximab, abatacept tocilizumab, certolizumab pegol, golimumab or sarilumab (each in combination with MTX) • Tofacitinib, baricitinib, or upadacitinib (each in combination with MTX) When MTX is contraindicated or withdrawn due to adverse events:	bDMARDs including at least one TNF inhibitor: When rituximab is contraindicated or withdrawn due to adverse events, MTX is not tolerated or is contraindicated: • Abatacept, baricitinib or tofacitinib (each as monotherapy) When rituximab is contraindicated or withdrawn due to adverse events, MTX tolerated and is not contraindicated: • Abatacept, baricitinib or tofacitinib in combination with MTX When rituximab is tolerated, MTX is tolerated: • Rituximab in combination with MTX When the disease has not responded adequately to therapy with rituximab in combination with MTX: • Tocilizumab or sarilumab, both in combination with MTX		

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	• Adalimumab, etanercept, certolizumab pegol or sarilumab (each as monotherapy) • Tofacitinib, baricitinib, or upadacitinib (each as monotherapy) When the disease has not responded adequately to therapy with rituximab in combination with MTX: • Tocilizumab, sarilumab (each in combination with MTX) • Upadacitinib (in combination with MTX)			
Outcomes	The outcome measures to be considered include: • disease activity • physical function • joint damage, pain • mortality • fatigue • radiological progression • extra-articular manifestations of disease • adverse effects of treatment • health-related quality of life.	Aligned with final NICE scope (except where noted). Outcome measures considered in the analysis: • disease activity (American College of Rheumatology - ACR20, ACR50, ACR70, European League Against Rheumatism (EULAR) response, Disease Activity Score (DAS28) • physical function (HAQ-DI) • pain, fatigue • mortality • radiological progression	Extra-articular manifestations of disease were not captured in the FINCH trial programme and therefore could not be included within this submission. In line with previous economic models with RA appraised by NICE, including MTA375, fatigue was not modelled in the economic analysis.	Most of these outcomes were captured in the FINCH trials.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
		• adverse effects of treatment • health-related quality of life.		
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. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator technologies and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar	Aligned with NICE scope	NA	The economic analysis is in line with reference case. The company performed a cost effectiveness analysis expressed in terms of incremental cost per quality-adjusted life year (see Table 5.3 of this report).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	products should be taken into account.			
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • moderate disease activity (DAS28 between 3.2 and 5.1) • severe active disease (DAS28 greater than 5.1)	Aligned with NICE scope	NA	In line with NICE scope.

Source: CS, Table 1, page 15-20.
ACR=American College of Rheumatology; DAS=Disease Activity Score; DMARD=Synthetic disease modifying antirheumatic drugs; EULAR=European League Against Rheumatism; FACIT-F=Functional Assessment of Chronic Illness Therapy; HAQ=Health Assessment Questionnaire; HAQ-DI=Health Assessment Questionnaire Disability Index; MTX=Methotrexate; NA=Not applicable; NICE=National Institute for Health and Care Excellence; QALY=Quality-adjusted life years; RA=Rheumatoid Arthritis.
Note 1) Advanced therapy refers to bDMARDs and targeted DMARDs (tsDMARDs) and is used throughout this document to refer to these treatments as one group

3.1 Population

The population defined in the scope is: Adults with moderate to severe, active rheumatoid arthritis (RA), whose disease has responded inadequately to, or who are intolerant of conventional or biological DMARDs.[17] The population in the CS is limited to "Adults with moderately to severely active, active RA whose disease has responded inadequately to two or more cDMARDs, or who are intolerant to DMARDs, including conventional or biologic DMARDs".[1] The company states that *"in the moderately active RA population the company submission is limited to patients following two or more cDMARD failures, this restriction is applied on the basis of clinical opinion and expected cost-effectiveness"* (CS, Table 1, page 15).[1]

Therefore, the population in the CS is not in line with the scope; and also not in line with the population in the trial (FINCH 1). For patients with moderately active RA, the FINCH 1 trial provides the most appropriate data. In the FINCH 1 trial, the following population was included: "Adults with moderately to severely active RA who have inadequate response to ongoing stable MTX dose". This means, clinical effectiveness data from the FINCH 1 trial are based on patients who had an inadequate response to one or more cDMARDs (as in the NICE scope).

The Marketing Authorisation application for filgotinib in the treatment of adults with RA was submitted to the European Medicines Agency in [redacted]. The anticipated date of regulatory approval is[redacted].[1] Therefore, the relevant population for this appraisal is currently unclear.

3.2 Intervention

The intervention (Filgotinib (as monotherapy or in combination with other cDMARDs, including methotrexate (MTX)) is in line with the scope.

According to the company, filgotinib is a potent reversible Janus kinase (JAK) inhibitor with a selectivity for JAK1. Cytokines associated with JAK1 are involved in the inflammatory signalling pathway that drives RA progression. Filgotinib modulates the signalling pathway by preventing the phosphorylation and activation of signal transducers and activators of transcription (STATs) by JAKs, thereby supressing immune cell activity and pro-inflammatory cytokine signalling.[20]

Filgotinib is indicated as monotherapy or in combination with MTX for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to, or who are intolerant to, one or more disease-modifying antirheumatic drugs (DMARDs). Contraindications are hypersensitivity to the active substance or to any of the excipients and pregnancy. The recommended filgotinib dose is one 200 mg tablet once a day. A dose of 100 mg of filgotinib once daily is recommended for patients with severe renal impairment (Creatinine clearance 15 to 30 mL/min).[1]

According to the company no additional investigations outside of routine clinical management of RA are necessary (CS, page 23).[1]

The FINCH 1 and 2 trials do not include a filgotinib monotherapy arm. Therefore, for the purpose of the economic evaluation, the company assumed that monotherapy would have the same relative effect across all treatments as combination therapy (CS, page 153).[1]

3.3 Comparators

The description of the comparators in the NICE scope is as follows:[17]

For moderate active RA that has not responded adequately to therapy with cDMARDs:

- Combination of two or more cDMARDs (including MTX and at least one other DMARD, such as sulfasalazine and leflunomide)
- cDMARD monotherapy with dose escalation
- Best supportive care (BSC)

For severe active RA that has not responded adequately to therapy with cDMARDs:

- Biological DMARDs in combination with MTX (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept or sarilumab)
- Adalimumab, etanercept, certolizumab pegol, tocilizumab or sarilumab (each as monotherapy)
- Tofacitinib, baricitinib or upadacitinib (each as monotherapy or in combination with MTX)

For severe active RA that has not responded adequately to therapy with DMARDs including at least one TNF inhibitor:

- Rituximab in combination with MTX

When rituximab is contraindicated or withdrawn due to adverse events:

- Adalimumab, etanercept, infliximab, abatacept, tocilizumab, certolizumab pegol, golimumab or sarilumab (each in combination with MTX)
- Tofacitinib, baricitinib, or upadacitinib (each in combination with MTX)

When MTX is contraindicated or withdrawn due to adverse events:

- Adalimumab, etanercept, certolizumab pegol or sarilumab (each as monotherapy)
- Tofacitinib, baricitinib, or upadacitinib (each as monotherapy)

When the disease has not responded adequately to therapy with rituximab in combination with MTX:

- Tocilizumab, sarilumab (each in combination with MTX)
- Upadacitinib (in combination with MTX)

The company presented a different set of comparators in Table 1 of the CS. However, the treatments included in the network meta-analyses (NMAs) described in Section B2.9 of the CS are different from those reported in Table 1 of the CS; and the comparators included in the economic model are also different from those reported in Table 1 of the CS. Therefore, the ERG asked the company to clarify which comparators were included for which population in the NMAs and in the economic model (Clarification Letter, Questions A4, A22 and B3).[21] In their response to question B3b, the company stated: *"The comparators included in the final cost-effectiveness model and treatment sequences were deemed most relevant to UK clinical practice based on NICE treatment guidelines, market share data (Therapy Watch, 2019 data) and through validation by UK rheumatologists to guide on both the most likely drug classes at each line and commonly used molecules within each class seen in clinical practice.*[22] *This approach was taken due to the large number of treatment sequences permutations possible given the number of comparators in the NICE treatment pathway, which would be both unfeasible to generate given the model run time and impeded interpretation of results to aid decision making given the volume of analysis."*[21]

ERG comment: As a result of this decision by the company and because of the inclusion criteria used by the company (no monotherapy studies), several interventions were not included in the NMAs and were not included in the economic model (infliximab, certolizumab pegol, upadacitinib, golimumab, and tofacitinib (for cDMARD-IR)). This leaves the potential to cherry-pick comparators.

For moderate active RA, the NICE scope mentions three comparators (combination of two or more cDMARDs, cDMARD with dose escalation and BSC), while the company included only one: BSC. BSC was defined in the CS as "*cDMARDs that patients have already received, administered at lower doses" (CS, page 32); "which is considered to provide little therapeutic benefit to patients"* (CS, page 32).[1] In the economic model "*BSC is assumed to have no treatment effect (i.e. EULAR non-response), in line with the assumption made in MTA375. Additionally, recent submissions in RA have made the same assumption (TA485*[23], *TA480*[24] *and TA466*[25])" (CS, page 150).[1] However, in the control arm of the FINCH 1 trial patients received placebo+MTX and all patients in FINCH-1 had an inadequate response to ongoing stable MTX dose. Nevertheless, *"patients in the FINCH-1 study exhibited extremely high levels of response when treated with cDMARDs"* according to the company (CS, page 114).[1] Therefore, either the population in the FINCH 1 trial is not in accordance with the NICE scope; or the assumption that BSC has no treatment effect is incorrect.

It should also be noted that glucocorticoids (GCs) have not been included as a comparator or mentioned as a possible previous treatment in the NICE scope, even though NICE recommends consideration of them on starting a new cDMARD.[18] According to our clinical expert treatment with cDMARD plus glucocorticoids is a much more effective treatment than one cDMARD alone because it stops the progression of the underlying joint destruction. Therefore, GC plus cDMARD might be the most effective treatment in newly diagnosed RA; and could be the main comparator in this appraisal.[19] In addition, the therapeutic benefit of treatments may differ for patients who have previously failed on cDMARD+GC (compared to cDMARD alone) before being entered into the FINCH studies, and this would affect both the benefit claimed and the economic evaluation of filgotinib.

3.4 Outcomes

The NICE final scope lists the following outcome measures:

- disease activity
- physical function
- joint damage, pain
- mortality
- fatigue
- radiological progression
- extra-articular manifestations of disease
- adverse effects of treatment
- health-related quality of life.

Most of these were captured in the FINCH trials. However, extra-articular manifestations of disease were not assessed in the FINCH trial programme and therefore could not be included within this submission. However, the clinician we consulted for this assessment advised that extra-articular manifestations are extremely unlikely to alter assessments of outcome. In addition, the company stated that "*in line with previous economic models with RA appraised by NICE, including MTA375, fatigue was not modelled in the economic analysis"*.[1]

The real long-term benefit of treatment is likely to be related to its ability to stop x-ray progression. This outcome has not been reported for the FINCH trials.

3.5 Other relevant factors

According to the company, filgotinib is innovative because is a next generation, potent reversible JAK inhibitor with a selectivity for JAK1, it is orally administered and the potential for drug-drug interactions is low (CS, Section B.2.12).[1] However, filgotinib is not the only orally administered DMARD; sulfasalazine, leflunomide, tofacitinib, baricitinib, and upadacitinib are also orally administered.

A PAS is in place between the Department of Health and the company (Gilead) for filgotinib. The actual discount for filgotinib is not specified in the CS. However, based on the model and information in Table 2 of the CS, the discount would be [redacted]%.

End-of-life criteria as specified by NICE are not applicable for this appraisal according to the company (CS, Section A.17).[26]

According to the company, no equality issues were identified in relation to filgotinib (CS, Section B.1.4).[1]

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company conducted two systematic reviews to identify evidence on the efficacy and safety of existing interventions for the treatment of moderately to severely active RA for:

- patients who had intolerance or inadequate response to prior conventional synthetic disease-modifying antirheumatic drugs (cDMARDS) including MTX and
- Patients who had intolerance or inadequate response to previous biologic disease modifying antirheumatic drugs (bDMARD-IR)[1]

Section 4.1 critiques the methods of the systematic reviews including searching, inclusion criteria, data extraction, quality assessment and evidence synthesis.

4.1.1 Searches

Appendix D1 of the CS details two systematic reviews performed to identify studies investigating the clinical efficacy of existing interventions for the treatment of moderately to severely active RA for:

- Patients who had intolerance or inadequate response to prior conventional synthetic disease-modifying antirheumatic drugs (cDMARDs) including MTX.
- Patients who had intolerance or inadequate response to previous biologic disease modifying anti-rheumatic drugs (bDMARD-IR).

Searches were conducted on 8 August 2018 with an update on 18 September 2019. English language limits were applied to the PubMed and Embase searches. All searches were limited by date of publication from 1 January 1999 onwards. A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources for the clinical effectiveness systematic review

Search strategy element	Resource	Host/ source	Reported date range	Date searched
Electronic databases	Embase.com	Elsevier	1.1.99-8.8.18	8.8.18 Updated 18.9.19
	PubMed	NLM	Up to 2018/08/08 Up to 2019/09/08	8.8.18 Updated 18.9.19
	Cochrane Database of Systematic Reviews (CDSR)	Wiley	Search was limited to CENTRAL	8.8.18
	Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley	1999-2018/08/08 2018-2019/09/18	8.8.18 Updated 18.9.19
	Cochrane Methodology Register (CMR)	Wiley**	Search was limited to CENTRAL	8.8.18
	Database of Abstracts of Reviews of Effects (DARE)	Wiley* Update: CRD+	Search was limited to CENTRAL 2018-2019	8.8.18 Updated 18.9.19

Search strategy element	Resource	Host/ source	Reported date range	Date searched
	Health Technology Assessment Database (HTA)	Wiley* Update: CRD+	Search was limited to CENTRAL 2018-2019	8.8.18 Updated 18.9.19
	NHS Economic Evaluation Database (NHS EED)	Wiley* Update: CRD+	Search was limited to CENTRAL 2018-2019	8.8.18 Updated 18.9.19
	Health Economic Evaluations Database (HEED)	Incorrectly reported, this was not searched for the submission	Incorrectly reported, this was not searched for the submission	Not searched.
Trials Registries	NIH Clinialtrials.gov	Web link provided, search terms not reported	Not reported	Not reported.
	International Clinical Trials Register Platform	Web link provided, search terms not reported	Not reported	Not reported.
	European Union's Clinical Trials Register	Web link provided, search terms not reported	Not reported	Not reported.
	Klinische Prufungen PharmNet.Bund	Web link provided, search terms not reported	Not reported	Not reported.
Conference Proceedings	American Congress of Rheumatology (ACR)	Web link provided, search terms not reported	2016-2019/09	Not reported.
	European League Against Rheumatism (EULAR)	Web link provided, search terms not reported	2016-2019/09	Not reported.
	Asia Pacific League of Associations for Rheumatology (APLAR)	Web link provided, search terms not reported	2016-2019/09	Not reported.
	British Society for Rheumatology (BSR)	Web link provided, search terms not reported	2016-2019/09	Not reported.

Search strategy element	Resource	Host/ source	Reported date range	Date searched
	Australian Rheumatology Association (ARA)	Web link provided, search terms not reported	2016-2019/09	Not reported.
HTA Agencies	NICE: MTA & STA documents	Web link provided, search terms not reported	Not reported.	Not reported.
	SMC	Web link & search terms not reported	Not reported.	Not reported.
	United States Food and Drug Administration (FDA) Register	Web link & search terms not reported	Not reported.	Not reported.
	European Public Assessment Reports for Human Medicines (EMA)	Web link & search terms not reported	Not reported.	Not reported.

Source: Appendix D of the Company's submission and the Appendix of the clarification response.[27]
Reference lists of included articles and relevant reviews were scanned for further potentially relevant references.
CRD = Centre for Reviews and Dissemination; EMA = European Medicines Agency; MTA = Multiple technology appraisal; SMC = Scottish Medicines Consortium; STA = Single technology appraisal.
+ The update search of DARE, NHS EED & HTA Database was via the Centre for Reviews and Dissemination website.
* Please note: DARE & NHS EED ceased on 2015/03/31, and no further content was added after that date. The HTA database ceased on 2018/03/31, and no further content was added after that date.
** The Cochrane Methodology Register, DARE, NHS EED and HTA databases were removed from the Cochrane Library in September 2018.

ERG comment:

- A single set of searches was undertaken to identify clinical effectiveness and adverse events data. The CS provided sufficient details for the ERG to appraise the literature searches. A good range of database and conference proceedings were searched, including additional grey literature resources and reference checking. For the most part, searches were well documented, making them transparent and reproducible.
- The CS and Appendix D reported that database searches were limited from 1999 to the search date. The ERG considers this date limit restrictive and as a consequence will have missed potentially relevant studies published before 1999.
- Appendix D reported that the Health Economic Evaluations Database (HEED) was searched as part of the Cochrane Library. As HEED has never been included in the Cochrane Library and ceased publication at the end of 2014, the ERG queried this during clarification. The company responded that they had not searched HEED for this review.
- The ERG was unable to assess how the search of conference proceedings was conducted. The company was unable to provide search terms used or number of records found for the conference proceedings' web searching in the CS and the clarification response.

- Update searches of the DARE, NHS EED and HTA databases were conducted via the Centre for Reviews and Dissemination (CRD) website. Update searches on 18 September 2019 were unnecessary as DARE and NHS EED ceased on 31 March 2015 and the HTA database ceased on 31 March 2018, therefore no new content was added to any of these resources since the company's initial searches on 8 August 2018.
- In parts, the company's searches appeared confused and contained errors. Most importantly the Embase update search (pgs 3-4, Appendix D1.4) was limited to restrict the results to publication date range 1999-2018 (line 53) and then restricted to only show records published 2018-2019. As these date restrictions are contradictory, the ERG queried this. In the clarification response, the company replied that the incorrect limits had been applied which resulted in all 2019 records being excluded from the Embase search. The company confirmed that the 2019 PubMed results were screened and none of the key trials were expected to be missing. The company said they would investigate the impact of this and report back to the ERG on 27 May 2020, however no further communication on this error or its impact was received. Effectively this mistake means that the company's Embase search was up to 8 August 2018 only, which is considerably out of date. As a consequence, the ERG remains concerned that failing to retrieve and screen all 2019 records from Embase could negatively impact on the comprehensiveness of the company's clinical effectiveness reviews.
- The ERG noticed that confused date limits were also applied to the PubMed search, restricting the results to studies published 1999 onwards (line 52, pg 6, Appendix D), and also limiting the results to 8 August 2018 (line 53, pg 6, Appendix D). Therefore, it appeared that the company's Embase search was only up to 8 August 2018 and their PubMed search was only ***from*** 8 August 2018 onwards. The ERG believes the confused and erroneous date limits have impaired searches of both primary bibliographic databases used to underpin the company's two systematic reviews.
- The ERG noted that an RCT filter was applied to the Cochrane library searches. As stated in the MECIR (Methodological Expectations of Cochrane Intervention Reviews) Manual "… do not use filters in pre-filtered databases e.g. do not use a randomized trial filter in CENTRAL or a systematic review filter in DARE."[28] The inclusion of these filters may have resulted in unnecessarily restricting the results retrieved and that potentially relevant references may have been missed. The search was also limited by the Trials tab to CENTRAL results, the RCT filter was unnecessary. The use of this filter means that potentially relevant references could have been missed by the searches.
- The company reported checking recent reviews for relevant studies, however the Embase, PubMed and Cochrane Library searches were all limited to exclude records indexed with the 'review' publication type. When this was queried by the ERG, the company responded that 'reviews' were not considered to be a relevant study design, and that internet searching and desk research was conducted to identify relevant systematic reviews. As none of the documentation for this work was provided to the ERG, it was not possible to assess how successfully this was carried out. The ERG feels that identification of systematic reviews would have been more successful if CDSR results had been included from the Cochrane Library search and the Embase and PubMed searches had not been limited to remove reviews.
- The treatment facet of the Embase and PubMed searches included free-text synonyms and terminology for the intervention and comparator treatments, however these terms were limited to title and abstract only. No Emtree or MeSH indexing, or CAS Registry numbers, were incorporated into the search. When these omissions were queried during the clarification process, the company responded that drug names were expected to appear in the title or abstract.

Best practice for systematic review searching aims to ensure comprehensive recall, by incorporating both indexing and free-text terms for every search facet. The ERG believes that the company's searches should have included appropriate indexing terms for the included treatments, to increase the sensitivity of the search strategies.

- Limiting the Embase and PubMed clinical effectiveness searches to English language only studies may have introduced language bias. Current best practice states that "Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication"[29] and that "research related to language bias supports the inclusion of non-English studies in systematic reviews".[30, 31]

4.1.2 Inclusion criteria

As stated above, the company conducted two systematic reviews to identify evidence on the efficacy and safety of existing interventions for the treatment of moderate to severely active RA for:

- Patients who had intolerance or inadequate response to prior conventional synthetic disease-modifying antirheumatic drugs (cDMARDS) including MTX (cDMARD-IR) and
- Patients who had intolerance or inadequate response to previous biologic disease modifying antirheumatic drugs (bDMARD-IR)[1]

The eligibility criteria used for the systematic reviews is presented in full in Appendix 1 of this report.

Briefly, the company included RCTs (Phase II and above) and open-label follow-up studies of RCTs. Interventions included were: cDMARDS (including MTX and at least one other DMARD), bDMARDS (in combination with MTX or as monotherapy), tsDMARDS (in combination with MTX or as monotherapy) and biosimilars. Comparisons could be made between any of the interventions or to placebo. In addition to the populations outlined above the company included treatment-naïve patients or those intolerant or contraindicated to methotrexate (MTX-naïve). All patients were adults (18 years or over). A range of outcomes were included but only studies in English from 1999 onwards were eligible.

ERG comment:

- It was unclear if two reviewers were involved in the selection of studies which helps to minimise bias.
- It is normally recommended to consider non-randomised evidence in relation to safety. This is particularly relevant as the main trials in the CS provided 12 and 24 week follow up time points so longer term, rarer adverse events might not be identified. The company provided details of FINCH 4, an ongoing long-term extension to FINCH 1, 2 and 3 which has yet to report results.
- The ERG asked if any studies were excluded solely for the reason of being published in a language other than English. The company stated that one study had been excluded but the ERG determined the study was not relevant to the review of clinical effectiveness.
- The ERG asked the company to justify the date limit of 1999 in the systematic review. The company stated that *"Searches were limited to those later than 1999 as a pragmatic way of limiting search results to focus on newer biologic treatments. This was in alignment with the search strategy used in TA466.*[25] *In addition, this date aligns with the first use of biologics for Rheumatoid arthritis*[32]." However, this could have resulted in relevant studies of older drugs being omitted particularly from the network meta-analysis in the cDMARD-IR population.
- The systematic review included treatment-naïve patients, but these are not relevant to the scope and were not included in the NMA.

4.1.3 Critique of data extraction

No information was provided on the number of reviewers who extracted data from included studies.

ERG comment: It is normally recommended that two reviewers are involved in data extraction to avoid bias and error.

4.1.4 Quality assessment

The company assessed the quality of the three main completed trials FINCH 1, 2 and 3 and concluded that the trials were designed and carried out following a robust methodology. Elements assessed were randomisation, allocation concealment, baseline comparability, blinding of participants, care providers and outcome assessors, dropout imbalances, selective outcome reporting and use of intention to treat analysis. All three trials met all quality criteria in the company's assessment.

The company also assessed the quality of the remaining trials in the systematic review for use in the network meta-analysis.

No information was provided on the number of reviewers who assessed the quality of included studies.

ERG comment:

- It is normally recommended that two reviewers are involved in the assessment of study quality to avoid bias and error.
- No supporting statements were provided in the company's quality assessment. In response to the ERG's request, the company supplied these.
- Results of the company's quality assessment and the ERG's assessment are presented in Section 4.2.

4.1.5 Evidence synthesis

A direct meta-analysis of the FINCH trials was not undertaken. The company undertook a network meta-analysis (NMA) to assess the comparative effectiveness of filgotinib versus alternative treatments for RA. Full details and a critique of the NMA can be found in Section 4.3 of this report.

ERG comment: The ERG agrees that a meta-analysis of the FINCH trials was inappropriate given their differing populations. A NMA was an appropriate approach to examine the relative effectiveness of filgotinib compared to other available treatments for RA.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The company stated that the systematic reviews identified 139 trials of relevance to the CS. Of these, the company identified four trials of relevance to filgotinib. Three of these were randomised controlled trials (FINCH 1, 2 and 3) which formed the direct evidence for filgotinib presented in the CS. The fourth, FINCH 4, is a long-term extension study which is ongoing and is as yet to report (see Section 4.2.9 Ongoing studies).

ERG comment:

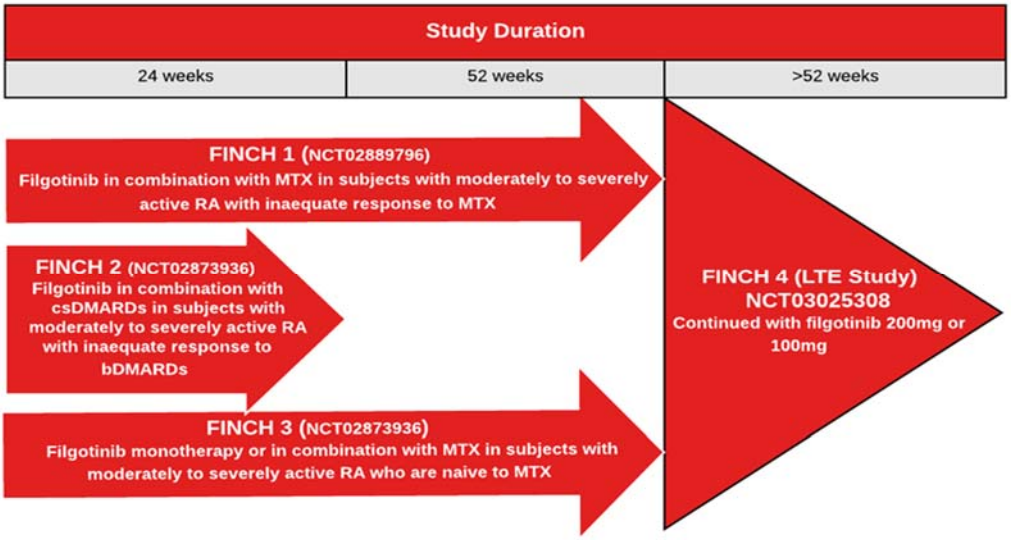
- This section discusses the four trials related to filgotinib (FINCH 1, 2, 3 and 4). Trials included as part of the network meta-analyses are discussed in Section 4.3.
- The ERG noted that two phase 2 trials DARWIN 1 and 2 were mentioned in Appendix D of the CS but were not fully described in the clinical effectiveness section of the CS although they

were included in the network meta-analysis. The ERG asked the company to provide details of the studies and their results in the same format as the FINCH trials and also to provide the CSRs. These trials are discussed in Section 4.2.8 as supporting evidence.

4.2.1 Details of the included filgotinib studies

The company provided a helpful overview of the FINCH trial programme which is displayed in the Figure below.

Figure 4.1: Overview of the filgotinib clinical trial programme



Source: CS, Figure 3, page 39.
DMARDs = disease modifying anti-rheumatic drugs; bDMARDs = biologic DMARDs, csDMARDs = conventional synthetic DMARDS; LTE = long-term extension; MTX = methotrexate; RA = rheumatoid arthritis

All three FINCH trials reporting results (FINCH 1, 2 and 3) were conducted in adults with moderate to severe RA. In FINCH 1 patients had had an inadequate response to MTX. In FINCH 2 patients had received therapy with one or two cDMARDS and had an inadequate response or were intolerant to at least one biologic DMARD. In FINCH 3 patients were MTX-naïve but 18% of patients had received prior cDMARDS. The company noted that the results of FINCH 3 were included in the Marketing Authorisation application for filgotinib to the European Medicine Agency (EMA) but FINCH 3 was not included in the economic model because participants in this trial were naïve to MTX and therefore were not within the scope of this submission. It is not discussed further in this report. FINCH 4 is ongoing and is discussed in Section 4.2.9

In FINCH 1 and 2 filgotinib was given as combination therapy (with an ongoing stable dose of MTX in FINCH 1 and with a specified cDMARD continued on a stable dose in FINCH 2 (MTX, hydroxychloroquine, sulfasalazine or leflunomide)). In FINCH 1 there was an active comparator (adalimumab) and a placebo comparison. FINCH 2 had a placebo comparison.

The primary endpoint for both FINCH 1 and FINCH 2 was the proportion of patients achieving a 20% improvement in American College of Rheumatology response (ACR20) at week 12.

A summary of the populations, interventions, comparators, outcomes and study designs (PICOS) of FINCH 1 and 2 is given in Table 4.2.

Table 4.2: PICOS of the FINCH trials

Study	FINCH 1	FINCH 2
Study design	Randomised, double-blind, placebo- and active-controlled, multicentre, parallel assignment, 52-week Phase 3 trial	Randomised, double-blind, placebo-controlled, multicentre, parallel assignment, 24-week Phase 3 trial
Population	Adults with moderately to severely active RA who have inadequate response to ongoing stable MTX dose	Adults with moderately to severely active RA despite ongoing therapy with 1 or 2 cDMARD(s) and who have had an inadequate response or are intolerant to at least one bDMARD.
Interventions	**Filgotinib 200 mg** • Filgotinib 200 mg once daily • Placebo-to-match (PTM) filgotinib 100 mg once daily • PTM adalimumab -subcutaneous injection every 2 weeks **Filgotinib 100 mg** • Filgotinib 100 mg once daily • PTM filgotinib 200 mg once daily • PTM adalimumab subcutaneous injection every 2 weeks	**Filgotinib 200 mg** • Filgotinib 200mg tablet • PTM filgotinib 100mg tablet administered orally, once daily **Filgotinib 100 mg:** • Filgotinib 100 mg tablet • PTM filgotinib 200 mg tablet, administered orally, once daily
Background treatment	Subjects must have had ongoing treatment with a stable dose of MTX as described below: • Use of oral MTX on a continuous basis for at least 12 weeks prior to Day 1 and on a stable prescribed dose of 7.5 mg to 25 mg/weekly for at least 4 weeks prior to Day 1. • Stable doses of <7.5 mg/week were allowed only in the presence of intolerance or toxicity to higher doses or where higher doses were prohibited by the local label or local clinical practice. • Doses >25 mg weekly were not permitted during the study.	All subjects continued to receive a stable dose of a permitted protocol-specified cDMARD (MTX, hydroxychloroquine, sulfasalazine, or leflunomide).

Study	FINCH 1	FINCH 2
Comparators	**Active comparator** • Adalimumab 40 mg subcutaneous injection every 2 weeks • PTM filgotinib 200 mg once daily • PTM filgotinib 100 mg once daily **Placebo** • PTM filgotinib 200 mg once daily • PTM filgotinib 100 mg once daily • PTM adalimumab subcutaneous injection every 2 weeks	**Placebo** • PTM filgotinib 200 mg tablet • PTM filgotinib 100 mg tablet, administered orally, once daily
Outcomes	**Primary outcome** • The proportion of subjects who achieved an ACR20 response at week 12 **Other outcomes relevant to the decision problem** • Disease activity (American College of Rheumatology - ACR20, ACR50, ACR70, • European League Against Rheumatism (EULAR) response • Disease Activity Score (DAS28) • physical function (HAQ-DI) • pain • mortality • fatigue (FACIT-F) • radiological progression (mTSS) • adverse effects of treatment • health-related quality of life	

Source: Tables 5 and 6 of the CS (abbreviated)
ACR = American College of Rheumatology; CDAI = clinical disease activity index; DAS = disease activity score; DMARDs = disease modifying anti-rheumatic drugs; bDMARDs = biologic DMARDs; cDMARDs = conventional DMARDS; EQ-5D = EuroQol five dimension; ET = early termination; EULAR = European League Against Rheumatism; FACIT-F = functional assessment of chronic illness therapy-fatigue; HAQ-DI = health assessment questionnaire disability index; LDA = low disease activity; mTSS = modified Total Sharp Score; MTX = methotrexate; NA = not applicable; PTM = placebo-to-match; RA = rheumatoid arthritis; SDAI = simplified disease activity index; SF-36 = 36-item short form survey; WPAI = work productivity and activity impairment.

ERG comment:

- The ERG noted that the evidence for filgotinib is based on good quality international RCTs investigating patient-relevant outcomes.
- In both FINCH 1 and 2 filgotinib is compared to placebo. **The only direct evidence on filgotinib versus an active comparator is for adalimumab in FINCH 1.**
- The ERG noted the lack of evidence on filgotinib monotherapy. The company confirmed that, of the FINCH trials, only FINCH 3 provided data on filgotinib as monotherapy but this trial is not relevant to the scope of the submission because participants in this trial were naïve to MTX. The company acknowledged that the Phase 2 DARWIN 2 study also provided data for monotherapy. This study is discussed in Section 4.2.8 as supporting evidence. The clinician we consulted for this appraisal considered that this was not a major issue as although the use of MTX in combination with biological agents is routine it may make little difference to outcome.
- The ERG asked how inadequate response to current therapy was defined to enable patients to be included in the trials. The company stated that "*Patients who had an inadequate response to MTX are defined as patients who have received at least 12 weeks of oral MTX on a continuous basis at a stably prescribed dose of 7.5 to 25mg/week prior to day 1, and met the clinical trial inclusion criteria showing signs & symptoms at study entry of moderately to severely active RA.*"[21]
- The ERG noted that that the proposed dose of filgotinib is 200 mg per day given orally for most patients and that according to the SmPC the 100 mg dose is recommended for patients with severe renal impairment (creatinine clearance 15 to 30 mL/min). However, both doses were included in the FINCH trials, in combination with either MTX (FINCH 1) or cDMARD (FINCH 2). The evidence on 200 mg is likely to be more relevant to practice because the dose of 100 mg of filgotinib once daily is recommended for patients with severe renal impairment (Creatinine clearance 15 to 30 mL/min).[1]
- The ERG noted that the FINCH trials did not assess extra-articular disease. However, the clinician we consulted for this appraisal was not concerned by this omission as he felt that this would be extremely unlikely to alter assessments of outcome.

A more detailed summary of study methodology for FINCH 1 and 2 is presented in Table 4.3.

Table 4.3: Summary of study methodology for included trials

Study	FINCH 1	FINCH 2
Trial design	Patients were randomised in a 3:3:2:3 ratio to receive MTX and: • Filgotinib (200 mg) or • Filgotinib (100 mg) or • Adalimumab (40 mg) or • Placebo Randomisation was stratified by geographic region, prior exposure to bDMARDs and presence of RF or anti-CCP antibodies at screening. At week 14, patients who had not achieved at least 20% improvement from baseline in both SJC and TJC discontinued the investigational drug but continued with study visits and assessments per protocol and received standard of care treatment for RA (as determined by the investigator). At week 24, all patients assigned to placebo were reassigned 1:1 to either filgotinib 100 mg + MTX or filgotinib 200 mg + MTX in a blinded fashion and continued in the study per protocol up to week 52. Subjects previously randomised to filgotinib 100 or 200 mg or adalimumab continued on their original randomisation group. Only patients who maintained a 20% improvement from baseline in TJC and SJC and had not discontinued were eligible for the LTE study.	Patients were randomised in a 1:1:1 ratio to receive a stable dose of cDMARD (MTX, hydroxychloroquine, sulfasalazine, or leflunomide) and: • Filgotinib (200 mg) or • Filgotinib (100 mg) or • Placebo Randomisation was stratified by geographic region, number of bDMARDs previously exposed to (<3 or ≥3), and the presence of RF or anti-CCP antibody at screening and was carried out using a computerised IXRS system. At week 14, patients who had not achieved at least 20% improvement from day 1 in both SJC66 and TJC68 discontinued study drugs, but continued study visits and assessments, and received SoC treatment for RA. All patients who attained responder status at week 14 continued on their assigned study drugs, in a blinded fashion, to week 24. Upon completion of the 24-week dosing period all patients, regardless of response, who had not discontinued the study drug due to toxicity were given the option to screen for enrolment in a separate long-term extension study (FINCH 4).
Eligibility criteria for participants	Age ≥18 years (≥20 years in Japan) Met 2010 ACR/EULAR criteria for RA and were ACR functional class I–III ≥6 swollen joints and ≥6 tender joints at screening and on Day 1 At least one of the following parameters at screening: • ≥1 documented joint erosion on radiographs of the hands, wrists or feet by central reading and a positive result for RF or anti-CCP antibodies	• Aged ≥18 years • Met 2010 ACR/EULAR criteria for RA and were ACR functional class I-III • Had ≥6 swollen joints and ≥6 tender joints at screening and on Day 1 • Undergoing treatment with 1 or 2 cDMARDs at a stable dose

Study	FINCH 1	FINCH 2
	• ≥3 documented joint erosions on radiographs of the hands, wrists or feet by central reading if both RT and anti-CCP antibodies were negative • Serum CRP ≥6 mg/L Underwent treatment with oral MTX for at least 12 weeks prior to Day 1, at a stably prescribed dose	• Prior inadequate response or intolerance to at least one bDMARD
Settings and locations where data were collected	This study was conducted at 303 study centres in: Group A: Australia, Belgium, Germany, Canada, Ireland, Israel, Italy, Netherlands, New Zealand, Republic of Korea, South Africa, Spain, United Kingdom, and the United States Group B: Bulgaria, Czech Republic, Hungary, India, Poland, Romania, Russian Federation, Serbia, Slovakia, Ukraine, Group C: Argentina, Mexico Group D: Hong Kong, Taiwan, Thailand, Group E: Japan	This study was conducted at 114 sites in: Group A: Australia, Belgium, France, Germany, Israel, Italy, Netherlands, South Korea, Spain, Switzerland, United Kingdom, and the United States Group B: Czech Republic, Hungary, Poland Group C: Argentina, Mexico Group D: China (originally planned but no subjects were screened or enrolled from China). Group E: Japan
Trial drugs (number in each group)	**Interventions**: Filgotinib 20 0mg + MTX + placebo (n=477), Filgotinib 100 mg + MTX + placebo (n=480) **Comparators**: Adalimumab + MTX + placebo (n=325), placebo + MTX (n=475).	Interventions: Filgotinib 200 mg + placebo + cDMARD(s) (n=148), Filgotinib 100 mg + placebo +cDMARD(s) (n=153) Comparators: placebo + cDMARD(s) (n=148).
Concomitant medications	Concomitant therapies taken for treatment of pre-existing conditions continued during the study provided they were in accordance with the inclusion and exclusion criteria. It was preferred that these medications were continued without variation of dose or regimen during the study, as much as possible.	

Source: Table 6 of the CS

ACR = American College of Rheumatology; CCP = citric citrullinated peptide; CRP = C-reactive protein; DMARDs = disease modifying anti-rheumatic drugs; bDMARDs = biologic DMARDs; cDMARDs = conventional DMARDS; EULAR = European League Against Rheumatism; LTE = long-term extension; mg = milligrams; MTX = methotrexate; RA = rheumatoid arthritis; RF = Rheumatoid factor; SJC = Swollen joint count; SoC = Standard of care; TJC = Tender joint count

ERG comment:

- FINCH 1 and 2 were large, multinational trials. Across the two trials, 2,203 patients took part. Of these, 622 patients received the 200 mg filgotinib dose which is expected to be used for most patients in practice. A dose of 100 mg of filgotinib once daily is recommended for patients with severe renal impairment (Creatinine clearance 15 to 30 mL/min).[1]
- Although FINCH 1 had just 14 UK participants (0.8%) and FINCH 2 had just nine UK participants (2%) the company provided evidence of generalisability to the UK in response to clarification.[21] The clinician we consulted for this appraisal considered this evidence in addition to the baseline characteristics of the trials to indicate generalisability to UK practice.
- Although FINCH 1 was of 52 weeks' duration, the relevant outcomes are at 12 and 24 weeks as at week 24, all patients assigned to placebo were reassigned to either filgotinib 100 mg + MTX or filgotinib 200 mg + MTX in a blinded fashion and continued in the study per protocol up to week 52.

4.2.2 Statistical analysis of the included filgotinib studies

The primary outcome for FINCH 1 and 2 was the proportion of patients who achieved an American College of Rheumatology 20% improvement (ACR20 response) at week 12. For both trials, the ACR20 response rate at week 12 for filgotinib 200 mg was compared with placebo for a superiority test at the two-sided 0.05-level. A logistic regression analysis adjusted for the randomisation stratification factors was used to compare treatment groups. Patients who did not have sufficient measurements to establish efficacy at week 12 were considered non-responders.

A power calculation to ensure adequate sample size for the primary outcome was reported for both FINCH 1 and 2. In FINCH 1 a sample of 450 patients in each group provided over 95% power to detect an increase in ACR20 response rate of 45% to 65% between the placebo control group and the filgotinib group, respectively, using a two-sided 0.05-level test. The company reported that 1,759 patients were randomised and 1,755 included in the full analysis set. For FINCH 2 a sample size of 141 patients in each of the filgotinib groups and placebo control group provided over 90% power to detect an increase in ACR20 response rate of 25% to 45% between the placebo control group and the filgotinib groups respectively, using a two-sided 0.05-level test. The company reported that 449 patients were randomised and 448 included in the full analysis set.

ERG comment:

- Overall, the statistical analyses appeared to have been conducted appropriately.
- Trials were adequately powered for the primary outcome.
- In FINCH 1 and 2 analyses were conducted using the Full Analysis Set (FAS), comprising all patients who were randomised and received at least one dose of study drug (not strictly intention-to-treat (ITT)). However, this analysis excluded only four patients of 1,755 in FINCH 1 and one of 449 in FINCH 2 who did not receive the study drug. This low number of exclusions from the full analysis are unlikely to bias the results.

4.2.3 Trial participant baseline characteristics

FINCH 1 had a total of 1,755 patients and FINCH 2 had 448. The average age across the trials was 53 in FINCH 1 and 56 in FINCH 2. In FINCH 1 18.9% of patients were 65 or over and in FINCH 2 25.2% were 65 or over. Approximately 82% were female in FINCH 1, and 80% in FINCH 2. Most patients identified as white (68%) although other ethnicities were represented. Fourteen patients (0.8%) in FINCH 1 and nine (2%) in FINCH 2 were from the UK. Most (255, 57%) in FINCH 2 were from the

United States. and Patients had a BMI of approximately 27 in FINCH 1 (indicating overweight) but approximately 30 in FINCH 2 (indicating obese).

Mean duration of RA differed between the FINCH trials. In FINCH 1 mean duration of RA was between 7.3 and 8.5 years across treatment groups. In FINCH 2 mean duration was 12 to 12.6 years across groups. Slightly more participants in FINCH 1 were RF positive (75% vs. 68% in FINCH 2). Slightly more patients were anti-CCP positive in FINCH 1 (79% vs. 71% in FINCH 2). Hence more patients were both RF and anti-CCP positive in FINCH 1 (69% vs. 62% in FINCH 2).

Average Swollen Joint Count 28-joints (SJC-28) was between 11 and 12 across the trials. Average Tender Joint Count 28-joints (TJC-28) was 15 or 16 across the trials. In terms of disability, average HAQ-DI total score was 1.55 to 1.70 across the trials. Full details of patient characteristics are given in Table 4.4.

The company stated that the baseline characteristics were "*broadly generalisable to those of patients seen in clinical practice in England*".[1]

The company noted that the characteristics were well-balanced across the treatment arms (as noted above, randomisation was stratified on key characteristics). However, some differences between arms were identified after randomisation in FINCH 1: 20.2% of patients were male in the filgotinib 200 mg arm versus 16.9% in the filgotinib 100 mg arm. Twenty percent of patients were Asian in the adalimumab arm versus 25.7% in the filgotinib 200 mg arm. Seventy-point five percent were white in the adalimumab arm versus 65.7% in the filgotinib 200 mg arm. Duration of RA since diagnosis was 8.0 years in the adalimumab group and 7.3 years in the filgotinib 200 mg group.

In FINCH 2, 22.2% of patients were male in the filgotinib 100 mg arm and 18.2% were male in the placebo arm. In FINCH 3, 21.0% of patients were male versus 25.0% in the MTX monotherapy arm.

Table 4.4: Baseline characteristics in FINCH 1 and 2

Baseline characteristics	FINCH 1				FINCH 2		
	Filgotinib 200mg (n = 475)	Filgotinib 100mg (n = 480)	Adalimumab (n = 325)	Placebo (n = 475)	Filgotinib 200mg (n = 147)	Filgotinib 100mg (n = 153)	Placebo (n = 148)
Age, mean (SD)	52 (12.8)	53 (12.6)	53 (12.9)	53 (12.8)	56 (12.5)	55 (12.0)	56 (12.1)
Gender, n (%)							
Male	96 (20.2%)	81 (16.9%)	59 (18.2%)	84 (17.7%)	27 (18.4%)	34 (22.2%)	27 (18.2%)
Female	379 (79.8%)	399 (83.1%)	266 (81.8%)	391 (82.3%)	120 (81.6%	119 (77.8%)	121 (81.8%)
Race, n (%)							
American Indian or Alaskan Native	27 (5.7%)	27(5.6%)	20 (6.2%)	29 (6.1%)	7 (4.8%)	9 (5.9%)	10 (6.8%
Asian	122 (25.7%)	115 (24.0%)	65 (20.0%)	109 (22.9%)	15 (10.2%)	20 (13.1%)	15 (10.1%)
Black or African American	6 (1.3%)	7 (1.5%)	10 (3.1%)	12 (2.5%)	14 (9.5%)	12 (7.8%)	21 (14.2%)
Native Hawaiian or Pacific Islander	1 (0.2%)	0	0	2 (0.4%)	NA	NA	NA
White	312 (65.7%)	324 (67.5%)	229 (70.5%)	319 (67.2%)	110 (74.8%)	109 (71.2%)	97 (65.5%)
Other	7 (1.5%)	6 (1.3%)	1 (0.3%)	3 (0.6%)	1 (0.7%)	3 (2.0%)	2 (1.4%)
Not permitted*	0	1 (0.2%)	0	1 (0.2%)	0	0	3 (2.0%)
BMI, mean kg/m2 (SD)	26.7 (5.67)	26.4 (5.80	26.9 (5.97)	27.0 (5.91)	30.5 (7.89)	30.3 (7.66)	29.8 (7.25)
Mean duration of RA from diagnosis, years (SD)	7.3 (7.39)	8.5 (8.22)	8.0 (7.40)	7.3 (7.24)	12.6 (9.48)	12.0 (7.74)	12.6 (10.30)

Baseline characteristics	FINCH 1				FINCH 2		
	Filgotinib 200mg (n = 475)	Filgotinib 100mg (n = 480)	Adalimumab (n = 325)	Placebo (n = 475)	Filgotinib 200mg (n = 147)	Filgotinib 100mg (n = 153)	Placebo (n = 148)
RF positive, n (%)	352 (74.1%)	362 (75.4%)	241 (74.2%)	365 (76.8%)	104 (70.7%)	107 (69.9%)	92 (62.2%)
Anti-CCP positive, n (%)	380 (80.0%)	381 (79.4%)	253 (77.8%)	378 (79.6%)	99 (67.3%)	113 (73.9%)	105 (70.9%)
RF positive + anti-CCP positive, n (%)	331 (69.7%)	332 (69.2%)	219 (67.4%)	333 (70.1%)	91 (61.9%)	102 (66.7%)	84 (56.8%)
SJC 28, mean (SD)	11 (5.2)	11 (5.2)	11 (5.0)	11 (5.0)	12 (6.3)	12 (6.0)	12 (6.0)
TJC 28, mean (SD)	15 (6.4)	15 (6.7)	15 (6.3)	15 (6.4)	16 (7.7)	15 (6.8)	16 (6.9)
HAQ-DI total score, mean (SD)	1.59 (0.611)	1.55 (0.625)	1.59 (0.600)	1.63 (0.613)	1.70 (0.656)	1.64 (0.683)	1.65 (0.633)

Source: Table 7 of the CS
* Not permitted: local regulators did not allow collection of race or ethnicity information
ACR = American College of Rheumatology; BMI = body mass index; CCP = citric citrullinated peptide; CRP = C-reactive protein; cDMARDs = conventional DMARDS; HAQ-DI = health assessment questionnaire disability index; MTX =methotrexate; NA = not applicable; PTM = placebo-to-match; RA = rheumatoid arthritis; RF = Rheumatoid factor; SD = standard deviation; SJC = Swollen joint count; SoC = Standard of care; TJC =Tender joint count.

ERG comment:

- As stated above, although FINCH 1 had just 14 UK participants (0.8%) and FINCH 2 had just nine UK participants (2%) the company provided evidence of generalisability to the UK in response to clarification.[21] The clinician we consulted for this appraisal considered this evidence in addition to the baseline characteristics of the trials to indicate generalisability to UK practice.
- The company provided further details of the moderate and severe subgroups in the FINCH trials at clarification. Approximately 24% had moderate disease in FINCH 1 and 21% in FINCH 2.

4.2.4 Risk of bias assessment for included filgotinib studies

The quality assessment of the key trials, reported in the CS, recorded judgements alone and did not include any supporting information. It was not clear how many reviewers were involved in the quality assessment process. Elements assessed were randomisation, allocation concealment, baseline comparability, blinding of participants, care providers and outcome assessors, dropout imbalances, selective outcome reporting and use of intention to treat analysis. Both FINCH 1 and FINCH 2 met all quality criteria in the company's assessment. See Table 4.5.

Table 4.5: Quality assessment FINCH 1 and FINCH 2

	FINCH 1	FINCH 2
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
Source: Table 9 of the CS		

ERG comment:

- It is normally recommended that two reviewers are involved in the assessment of study quality to avoid bias and error.
- In response to the ERG's request, the company supplied supporting statements for their quality ratings. The ERG re-assessed the quality of the trials. Based on information provided, randomisation and treatment concealment appeared to be appropriate. Treatment groups appeared to be similar in terms of baseline characteristics (any specific imbalances despite randomisation are given in Section 4.2.3). Blinding of patients, care providers and outcome assessors appeared to be appropriate. In FINCH 1 and 2 analyses were conducted using the Full

Analysis Set (FAS), comprising all patients who were randomised and received at least one dose of study drug (not strictly ITT). However, this analysis excluded only four patients of 1,755 in FINCH 1 and one of 449 in FINCH 2 who did not receive the study drug. This low number of exclusions from the full analysis are unlikely to bias the results. Overall, then, the ERG concludes that FINCH 1 and 2 are well-conducted trials.

4.2.5 Efficacy results

In FINCH 1 significantly more patients achieved the primary endpoint of ACR20 response at week 12 with filgotinib 200 mg (76.6% vs. 49.9%, p<0.001) and filgotinib 100 mg (69.8% vs. 49.9%, p<0.001) compared to placebo. Results for ACR50 and ACR70 were also significantly improved with filgotinib 200 mg and 100 mg compared to placebo. More patients also achieved an ACR20, ACR50 or ACR70 response on filgotinib 200 mg and 100 mg compared to adalimumab. EULAR response at week 12 was 51.4% for filgotinib 200 mg, 39.2% for filgotinib 100 mg, 44.8% for adalimumab and 24.6% for placebo patients achieving a good EULAR response. The CS reported no significant differences between treatments in EULAR scores. At week 24 results for ACR20 response favoured filgotinib with 78.1% of filgotinib 200 mg, 77.7% of filgotinib 100 mg and 59.2% of placebo patients achieving an ACR20 response ($p < 0.001$ for each comparison). Full results for outcomes at 12 and 24 weeks are provided in Table 4.6.

In FINCH 2 significantly more patients on filgotinib 200 mg (66% vs. 31.1%, $p < 0.001$) and filgotinib 100 mg (57.5% vs. 31.1%, p<0.001) achieved an ACR20 response at week 12 compared to placebo. Filgotinib 200 mg and 100 mg also showed significantly better efficacy than placebo for ACR50 and ACR70 at week 12 and most other outcomes at week 12 apart from EULAR response. At week 12, 42.6% of filgotinib 200 mg, 40.9% of filgotinib 100 mg and 18.0% of placebo patients achieving a good EULAR response. At week 24 results for ACR20 response also favoured filgotinib with 69.4% of filgotinib 200 mg, 54.9% of filgotinib 100 mg and 34.5% of placebo patients achieving an ACR20 response ($p < 0.001$ for each comparison).

Table 4.6: Efficacy results of FINCH 1 and FINCH 2

Outcomes (mean, (95% CI) or %)	FINCH 1				FINCH 2		
	Filgotinib 200mg + MTX (n=475)	Filgotinib 100mg + MTX (n=480)	Adalimumab + MTX (n=325)	Placebo + MTX (n=475)	Filgotinib 200mg + cDMARDs (n=147)	Filgotinib 100mg + cDMARDs (n=153)	Placebo + cDMARDs (n=148)
12-week results							
ACR20 response	76.6%* [†]	69.8%*	70.5%	49.9%	66.0%*	57.5%*	31.1%
ACR50 response	47.2%* [†]	36.5%*	35.1%	19.8%	42.9%*	32.0%*	14.9%
ACR70 response	26.1%* [†]	18.5%*	14.2%	6.7%	21.8%*	14.4%*	6.8%
EULAR Response	51.4%	39.2%	44.8%	24.6%	42.6	40.9	18.0
% DAS28-CRP <2.6 (remission)	34.1%* [†]	23.8%* [†]	23.7%	9.3%	18.8%*	22.5%*	6.7%
% DAS28-CRP ≤3.2 (LDA)	49.7%* [†]	38.8%*	43.4%	23.4%	40.8%*	37.3%*	15.5%
Change from baseline in HAQ-DI	−0.69 (-0.77 to -0.62) * [†]	−0.56 (-0.65 to -0.50) *	−0.61 (0.68 to -0.52)	−0.42 (-0.48 to -0.33)	-0.55 (-0.61 to -0.40) *	-0.48 (-0.56 to -0.35) *	-0.23 (-0.30 to -0.08)
Change from baseline in SF-36 PCS	9.2 (8.6 to 10.8) * [†]	8.5 (8.0 to 10.2) *	8.4 (7.4 to 9.8)	5.8 (4.8 to 7.1)	[redacted]	[redacted]	[redacted]
Change from baseline in FACIT-Fatigue score	9.2 (-20 to 38) *	9.1 (-24 to 39) *	8.8 (-17 to 33)	6.8 (-20 to 40)	[redacted]	[redacted]	[redacted]
Change from Baseline in patient's pain assessment	-31 (-36 to -31)*	-29 (-34 to -28)*	-27 (-33 to -26)	-21 (-24 to -18)	[redacted]	[redacted]	[redacted]
24-week results							

Outcomes (mean, (95% CI) or %)	FINCH 1				FINCH 2		
	Filgotinib 200mg + MTX (n=475)	Filgotinib 100mg + MTX (n=480)	Adalimumab + MTX (n=325)	Placebo + MTX (n=475)	Filgotinib 200mg + cDMARDs (n=147)	Filgotinib 100mg + cDMARDs (n=153)	Placebo + cDMARDs (n=148)
ACR20 response	78.1%*	77.7%*	74.5%	59.2%	69.4%*	54.9%*	34.5%
ACR50 response	57.9%*	52.7%*	52.3%	33.3%	45.6%*	35.3%*	18.9%
ACR70 response	36.2%* [†]	29.6%*	29.5%	14.9%	32.0%*	20.3%*	8.1%
EULAR Response	68.4%	59.7%	58.0%	41.8%	57.9%	52.3%	35.2%
% DAS28-CRP <2.6 (remission)	48.4%*[†]	35.2%*[†]	35.7%	16.2%	30.6%*	26.1%*	12.2%
% DAS28-CRP ≤3.2 (LDA)	NR	NR	NR	NR	48.3%*	37.9%*	20.9%
Change from baseline in HAQ-DI	-0.82 (-0.90 to -0.75)*	−0.75 (-0.65 to -0.50)*	-0.78 (-0.85 to -0.68)	−0.62 (-0.63 to -0.48)	NR	NR	NR
Change from baseline in mTSS	0.13 (-0.04 to 0.31) *	0.17 (-0.02 to 0.33) *	0.16 (-0.01 to 0.38)	0.37 (0.22 to 0.59)	NR	NR	NR

Source: CS, Sections 2.6.1 and 2.6.2

*P<0.05; versus placebo. †P<0.05; versus adalimumab, results in [].

ADA=adalimumab; cDMARD=conventional synthetic disease-modifying antirheumatic drug; DAS28-CRP=Disease Activity Score based on 28 joints and C reactive protein value; FACIT=Functional Assessment of Chronic Illness Therapy; FIL=filgotinib; HAQ-DI=Health Assessment Questionnaire-Disability Index; LDA=Low disease activity; mTSS=modified total Sharp score; MTX=methotrexate; NR=not reported; QD=once per day; SD=standard deviation; SF-36 PCS=36-item Short Form Health Survey Physical Component Summary.

ERG comments: Both FINCH 1 and FINCH 2 achieved their primary endpoint and demonstrated that significantly more patients receiving filgotinib 200 mg and 100 mg achieved an ACR20 response at week 12. Results for ACR50 and ACR70 at week 12 also favoured filgotinib 200 mg and 100 mg as well as for ACR20, 50 and 70 at week 24. Most other outcomes favoured filgotinib 200 mg and 100 mg: percentage with DAS-CRP <2.6 and <3.2, change from baseline in HAQ-DI, SF-36 physical component score, FACIT fatigue score and the patient's assessment of pain. There were no significant differences reported in the CS in the proportions of patients achieving a good EULAR response at weeks 12 or 24 between filgotinib 200 mg or 100 mg and placebo. Filgotinib 200 mg also significantly improved most outcomes at 12 weeks apart from EULAR response, FACIT fatigue score and patient's assessment of pain compared to the active control, adalimumab. Compared to adalimumab, filgotinib 100 mg only showed improvements in the proportion of patients with DAS-CRP <2.6.

4.2.6 Subgroup analysis of moderate and severe groups

Baseline characteristics and efficacy results for patients with moderately active RA (DAS28 score of 3.2-5.1) and severely active RA (DAS28 score >5.1) are presented in Appendix 2 of this report for the FINCH 1 trial.

As can be seen from Tables A2.1 and A2.2 (Baseline characteristics for patients with moderately active RA and severely active RA, respectively), patients with severe disease had higher scores for CRP, DAS, SJC, TJC, SGA, PGA, pain and HAQ, which was as expected. Age was similar between groups. However, there were relatively [redacted] female patients with severe RA compared to moderate RA ([redacted]% vs. [redacted]%); and contrary to expectation, [redacted] patients with severe disease had used two or more cDMARDS than patients with moderate disease ([redacted]% vs [redacted]%).

The company declined to provide subgroup results from the FINCH 2 study. This is acceptable for the moderate subgroup of FINCH 2 because FINCH 2 is relevant only for those who have had a bDMARD, which implies severely active disease only. In addition, subgroup data for Change from baseline in HAQ-DI, Change from baseline in SF-36 PCS, Change from baseline in FACIT-Fatigue score, Change from Baseline in patient's pain assessment and Change from baseline in mTSS were not provided.

Unfortunately, the company also declined to provide subgroup results from the FINCH 2 study for the severe subgroup of FINCH 2. The company stated in the response to clarification (Questions A13 and A14) that "*FINCH 2 has been deprioritised as agreed with the ERG*". However, the ERG is not aware of any such agreement. During the clarification teleconference between NICE, the company and the ERG, it was agreed that analyses in the moderate subgroup could be omitted from FINCH 2 on the understanding that FINCH 2 is relevant only for those who have had a bDMARD, which implies severely active disease only. Therefore, the company should have provided subgroup data from the FINCH 2 trial for the severe subgroup.

Looking at the results, EULAR scores show the most significant difference between severe RA and moderate RA, with all interventions in the FINCH 1 trial being less effective (~[redacted]% point) in severe disease than in moderate disease.

4.2.7 Safety results

This section considers the information about adverse events provided in the company submission and clinical study reports.

Tables 4.7 and 4.8 present a summary of adverse events from the Phase 3 clinical trials, FINCH 1 and FINCH 2.[33, 34] Table 4.7 presents a summary of treatment-emergent adverse events (TEAEs) for each

treatment group from baseline until week 24, and for the overall period (52 weeks); while Table 4.8 gives an overview of the more frequently observed adverse events for at least 2% of the patients in any treatment group, from the two trials, at week 24. Most frequently observed across the two trials were adverse events of nasopharyngitis, upper respiratory tract infections, headache, nausea, and bronchitis.

In FINCH 1, at week 24 (placebo-controlled period) a similar proportion of patients experienced serious treatment-emergent adverse events (TEAEs) in each treatment group (4.4% in the filgotinib 200 mg arm, 5.0% in the filgotinib 100 mg arm, 4.3% in the adalimumab arm and 4.2% in the placebo arm). By week 52 (overall period), these figures were [redacted] in the filgotinib 200 mg arm, [redacted] in the filgotinib 100 mg arm, and [redacted] in the adalimumab arm. By week 24, there were two-treatment related deaths in the filgotinib 200 mg group (septic shock; septic shock secondary to pneumonia), one treatment-related death in the filgotinib 100 mg group in a patient with multiple risk factors (myocardial infarction on day 13), no deaths in the adalimumab group and two deaths in the placebo group (toxic reaction not related to study drug, septic shock non-treatment emergent SAE).

In FINCH 2, at week 24, a similar proportion of patients experienced serious TEAEs in each treatment group (4.1% in the filgotinib 200 mg arm, 5.2% in the filgotinib 100 mg arm, and 3.4% in the placebo arm). No deaths occurred due to any cause by week 24.

Table 4.7: TEAEs from baseline to week 24 (placebo-controlled period) in FINCH 1 and FINCH 2 (SAS), and for the overall period up to week 52 (overall period) in FINCH 1 (SAS)

Safety assessments	Week	FINCH 1				FINCH 2		
		Filgotinib 200mg + MTX	Filgotinib 100mg + MTX	Adalimumab + MTX	Placebo + MTX	Filgotinib 200mg QD + cDMARD(s)	Filgotinib 100mg QD + cDMARD(s)	Placebo + cDMARD(s)
Number in safety analysis set, n		475	480	325	475	147	153	148
TEAE, n (%)	24	287 (60.4%)	287 (59.8%)	186 (57.2%)	253 (53.3%)	102 (69.4%)	97 (63.4%)	100 (67.6%)
	52	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
TEAE related to study drug, n (%)	24	103 (21.7%)	104 (21.7%)	70 (21.5%)	87 (18.3%)	32 (21.8%)	29 (19.0%)	23 (15.5%)
	52	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
TEAE with Grade 3 or Higher, n (%)	24	34 (7.2%)	35 (7.3%)	20 (6.2%)	33(6.9%)	8 (5.4%)	13 (8.5%)	9 (6.1%)
	52	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
TEAE leading to premature discontinuation of study drug, n (%)	24	15 (3.2%)	9 (1.9%)	13 (4.0%)	15 (3.2%)	5 (3.4%)	6 (3.9%)	3 (2.0%)
	52	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Serious TEAE, n (%)	24	21 (4.4%)	24 (5.0%)	14 (4.3%)	20 (4.2%)	6 (4.1%)	8 (5.2%)	5 (3.4%)
	52	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Death, n (%)	24	2 (0.4%)	1 (0.2%)	0	2 (0.4%)	0	0	0
	52	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR

Source: CS, Tables 29 and 31, pages 124-126.[1]
NA = not available; NR = not reported; MTX = methotrexate; QD = once per day; SAS = safety analysis set; TEAE = treatment-emergent adverse events
*At week 24 all patients assigned to placebo were reassigned 1:1 to either filgotinib 100mg + MTX or filgotinib 200mg + MTX in a blinded fashion and continued in the study per protocol up to week 52.

Table 4.8: Most commonly reported adverse events reported for ≥2% of patients in any treatment group, occurring across all grades of severity, in FINCH 1 and FINCH 2 (SAS*) by preferred term at week 24

Safety assessment	FINCH 1				FINCH 2		
	Filgotinib 200mg + MTX	Filgotinib 100mg + MTX	Adalimumab + MTX	Placebo + MTX	Filgotinib 200mg QD + cDMARD(s)	Filgotinib 100mg QD + cDMARD(s)	Placebo + cDMARD(s)
Number in safety analysis set	475	480	325	475	147	153	148
Number of patients (%) with any TEAE**	287 (60.4%)	287 (59.8%)	186 (57.2%)	252 (53.1%)	102 (69.4%)	97 (63.4%)	100 (67.6%)
Alanine aminotrans-ferase increased, n (%)	13 (2.7%)	15 (3.1%)	14 (4.3%)	11 (2.3%)	NR	NR	NR
Alopecia, n (%)	NR	NR	NR	NR	4 (2.7%)	1 (0.7%)	0
Arthralgia, n (%)	5 (1.1%)	8 (1.7%)	4 (1.2%)	10 (2.1%)	5 (3.4%)	2 (1.3%)	3 (2.0%)
Aspartate aminotrans-ferase increased, n (%)	9 (1.9%)	14 (2.9%)	11 (3.4%)	9 (1.9%)	NR	NR	NR
Back pain, n (%)	NR	NR	NR	NR	2 (1.4%)	2 (1.3%)	5 (3.4%)
Bronchitis, n (%)	12 (2.5%)	10 (2.1%)	8 (2.5%)	14 (2.9%)	8 (5.4%)	3 (2.0%)	8 (5.4%)
Cough, n (%)	3 (0.6%)	9 (1.9%)	5 (1.5%)	11 (2.3%)	1 (0.7%)	3 (2.0%)	4 (2.7%)
Diarrhoea, n (%)	8 (1.7%)	4 (0.8%)	7 (2.2%)	9 (1.9%)	5 (3.4%)	4 (2.6%)	3 (2.0%)
Headache, n (%)	10 (2.1%)	12 (2.5%)	10 (3.1%)	17 (3.6%)	8 (5.4%)	9 (5.9%)	2 (1.4%)
Hypertension, n (%)	16 (3.4%)	7 (1.5%)	9 (2.8%)	5 (1.1%)	6 (4.1%)	5 (3.3%)	2 (1.4%)
Influenza, n (%)	NR	NR	NR	NR	5 (3.4%)	6 (3.9%)	3 (2.0%)
Nasopharyngitis, n (%)	31 (6.5%)	29 (6.0%)	15 (4.6%)	25 (5.3%)	15 (10.2%)	9 (5.9%)	7 (4.7%)
Nausea, n (%)	19 (4.0%)	10 (2.1%)	4 (1.2%)	7 (1.5%)	7 (4.8%)	8 (5.2%)	6 (4.1%)
Rheumatoid arthritis, n (%)	3 (0.6%)	6 (1.3%)	5 (1.5%)	19 (4.0%)	2 (1.4%)	2 (1.3%)	9 (6.1%)
Sinusitis, n (%)	NR	NR	NR	NR	3 (2.0%)	4 (2.6%)	3 (2.0%)

Safety assessment	FINCH 1				FINCH 2		
	Filgotinib 200mg + MTX	Filgotinib 100mg + MTX	Adalimumab + MTX	Placebo + MTX	Filgotinib 200mg QD + cDMARD(s)	Filgotinib 100mg QD + cDMARD(s)	Placebo + cDMARD(s)
Upper respiratory tract Infection, n (%)	25 (5.3%)	33 (6.9%)	17 (5.2%)	14 (2.9%)	8 (5.4%)	9 (5.9%)	6 (4.1%)
Urinary tract infection, n (%)	11 (2.3%)	8 (1.7%)	8 (2.5%)	5 (1.1%)	4 (2.7%)	6 (3.9%)	2 (1.4%)
Vomiting, n (%)	NR	NR	NR	NR	3 (2.0%)	3 (2.0%)	2 (1.4%)

Sources: CSRs Finch 1 and 2.[33, 34]
Adverse events were coded with MedDRA Version 22.0.
NR = not reported; MTX = methotrexate; QD = once per day; SAS = safety analysis set; TEAE = treatment-emergent adverse events.
*) Safety Analysis Set includes patients who received at least 1 dose of study drug.
**) TEAEs began on or after the study drug start date up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation.

4.2.8 Supporting studies

Two Phase 2 trials of filgotinib (DARWIN 1 and 2) were briefly described in an appendix to the CS and the ERG requested more information.[21] Brief details are provided below.

Both trials included adults with moderately to severely active RA who showed inadequate response to MTX. Both were randomised, multicentre trials which aimed to investigate a range of doses. In DARWIN 1 patients were randomised to one of six filgotinib doses/dose regimens (three different dose levels, each administered either once or twice daily) or placebo on top of their stable dose of MTX. In DARWIN 2 patients were randomised to one of three once daily filgotinib dose regimens (50 mg, 100 mg or 200 mg) or to placebo. This trial investigated filgotinib as monotherapy. In both studies the primary outcome was ACR20 at week 12.

Demographic details in the DARWIN trials were similar to those of the FINCH trials. A total of 81% in DARWIN 1 and 82% in DARWIN 2 were female. Most patients identified as white and no patients were from the UK.

ERG comment:

- The DARWIN trials provide supporting evidence only to the main FINCH trials.
- Both DARWIN trials have a placebo comparator only so do not add to the direct evidence in relation to comparator drugs.
- The DARWIN trials are both in populations who showed inadequate response to MTX so do not add to the effectiveness of filgotinib at other points in the pathway. In particular current or previous RA treatment with a biologic DMARD was prohibited.
- DARWIN 2 is the only trial of filgotinib monotherapy (apart from FINCH 3, which is not relevant to the scope). Results, at least for the primary outcome, appear to be comparable to DARWIN 1 and to the FINCH trials. However just 69 patients received the recommended dose of 200 mg and 70 the 100 mg so this is a very small evidence base for monotherapy.

Table 4.9: DARWIN 1 and 2 study details

Study	DARWIN 1	DARWIN 2
Study design	Randomised, placebo-controlled methotrexate add-on study	Randomised, placebo-controlled monotherapy study
Population	Adults with moderate to severely active RA who showed inadequate response to MTX. Current or previous RA treatment with a biologic DMARD was prohibited.	
Interventions	**Filgotinib once daily dosing groups**[$] 50 mg (n=86) 100 mg (n=85) 200 mg (n=86) **Filgotinib twice daily dosing groups**[$] 25 mg (n=86) 50 mg (n=85) 100 mg (n=84)	**Filgotinib once daily dosing groups** 50 mg (n= 72) Responders remain on 50 mg Non-responders assigned to 100 mg 100 mg (n=70) 200 mg (n=69)
Comparators	Placebo (n=72) [$]	Placebo (n=72)
Primary outcome	The proportion of patients who achieved an ACR20 response at week 12	

Source: Appendix D of the CS[1] and Response to letter of clarification[21].
ACR = American College of Rheumatology; DMARDs = disease modifying anti-rheumatic drugs; MTX = methotrexate; RA = rheumatoid arthritis.
$) At Week 12, patients on placebo who had not achieved a 20% improvement in swollen joint count based on 66 joints (SJC66) and tender joint count based on 68 joints (TJC68) were to be re-randomised to treatment with filgotinib 100 mg once daily, or 50 mg twice daily. doses in a blinded fashion; patients on filgotinib 50 mg once daily who had not achieved a 20% improvement in SJC66 and TJC68 were to be assigned to filgotinib 100 mg once daily., and patients on filgotinib 25 mg twice daily who had not achieved a 20% improvement in SJC66 and TJC68 were to be assigned to filgotinib 50 mg twice daily. All re-randomised and re-assigned patients continued their new dose until Week 24.
At Week 12, all patients on placebo and the patients on the 50 mg dose who had not achieved a 20% improvement in swollen joint count 66 (SJC66) and tender joint count 68 (TJC68) were to be assigned to 100 mg once daily in a blinded fashion and were to continue the study until Week 24. Patients in the other groups were to maintain their randomised treatment until Week 24.

Table 4.10: DARWIN 1 Primary outcome results

Outcomes, n (%)	Filgotinib once daily dose groups			Filgotinib twice daily dose groups			Placebo (N = 86)
	Filgotinib 50mg + MTX (N=82)	Filgotinib 100mg + MTX (N=85)	Filgotinib 200mg + MTX (N=86)	Filgotinib 25mg (N=86)	Filgotinib 50mg (N=85)	Filgotinib 100mg (N=84)	
ACR20 response at 12 weeks	46 (56.1)	54 (63.5)*	59 (68.6)**	49 (57.0)	51 (60.0)	66 (78.6)***	38 (44.2)
Source: Response to letter of clarification.[21] ACR = American College of Rheumatology; mg = milligrams. * p< 0.05; ** p< 0.01; *** p< 0.001							

Table 4.11: DARWIN 2 Primary outcome results

Outcomes, n (%)	Filgotinib once daily dose groups			Placebo (N = 72)
	Filgotinib 50mg (N=72)	Filgotinib 100mg (N=70)	Filgotinib 200mg (N=86)	
ACR20 response at 12 weeks	48 (66.7) ***	46 (65.7) ***	50 (72.5) ***	21 (29.2)
Source: Response to letter of clarification.[21] ACR = American College of Rheumatology; mg = milligrams. *** p < 0.001				

4.2.9 Ongoing studies

FINCH 4 is an ongoing extension study to assess the long-term safety and efficacy of filgotinib in patients who have completed one of the filgotinib trials (FINCH 1, 2 or 3). FINCH 4 has treatment arms evaluating filgotinib 200 mg and 100 mg in addition to cDMARDs. Patients continue their filgotinib dose from the parent study alongside MTX (FINCH 1), with/without MTX (FINCH 3) or alongside cDMARDs (FINCH 2). Patients not receiving filgotinib in the parent study, are randomised to 200 mg or 100 mg of filgotinib. Follow up is for three years.

ERG comment:

- The ERG asked when results would be available for the FINCH 4 long-term extension study and if any interim analyses were planned. The company responded that *"An interim clinical study report including safety data has been submitted to regulatory agencies as part of the globally submitted marketing application. An interim clinical study report including both long term safety and efficacy data will be completed and submitted by 4Q 2020. Subsequent interim analyses including both safety and efficacy data may be performed every two years and the final study report will be submitted by Q4 2025."* Should the interim report be available later in 2020 at the time of committee decision making this would provide useful information on long-term Filgotinib use.
- The ERG asked if any other relevant ongoing studies were available, but the company did not indicate any.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company performed two separate network meta-analyses (NMAs), one for the cDMARD-IR population and one for the bDMARD-IR population. The outcomes analysed were ACR at week 12 and 24, and EULAR at 24 weeks. As FINCH 1 and 2 did not include filgotinib monotherapy arms an NMA for monotherapy was not possible according to the company. The company also stated that as most trials did not report results stratified by moderate and severe disease, it was not possible to perform separate NMAs for moderate and severe disease. Therefore, two NMAs were performed: for moderate to severe populations for cDMARD-IR and for bDMARD-IR patients.

The ERG requested that the company performed NMAs in populations comparable to FINCH 1 and 2, in line with the scope. This included: patients with severe disease who were cDMARD-IR using the severe subgroup data from FINCH 1; patients with severe disease who were bDMARD-IR and using the severe subgroup data from FINCH 2. In their response to the clarification letter (CL) the company reported that no other trials were reported in severe RA patients only or provided subgroup results for severe patients and confirmed that it would not be possible for perform an NMA for severe patients only.

Details of the trials included in the cDMARD-IR network are presented in Table 4.12 and details of the trials included in the bDMARD-IR population are presented in Table 4.13. The company did not provide a formal assessment of clinical heterogeneity as they stated that there are other published NMAs in RA (including previous HTAs) therefore *"the homogeneity of the trials was deemed sufficient to conduct the analysis"* according to the company.[1] The ERG requested additional evidence for this statement, but no further information was provided. The risk of bias of the included studies was assessed using the Cochrane Collaboration's tool for RCTs and the results are presented in Figure 4.2 for the cDMARD-IR analysis and Figure 4.3 for the bDMARD-IR analysis.

ERG comment: The company used different inclusion criteria from the NICE scope. Firstly, all monotherapy studies were excluded. This was because the FINCH 1 and 2 trials did not have monotherapy arms. However, the NICE scope mentions several monotherapy comparators which could still have been included. Secondly, the search was limited to studies after 1999. However, many cDMARD studies were performed before 1999. Therefore, potentially relevant studies were excluded from the NMAs. In Appendix 3 of this report, a list is produced with potentially relevant trials for inclusion in the NMAs. Some of these were included in the SLR reported in the CS but excluded from the NMA for not reporting relevant outcomes or being unable to connect to other treatments in the network. However, it is not clear why other studies were excluded.

Separate NMAs for moderate and severe populations were not possible, therefore the company used data from the whole moderate to severe population in both NMAs. For the NMA for the cDMARD-IR population, the company used results from the FINCH 1 study for filgotinib (approximately 24% of patients in the FINCH 1 trial had moderate disease); and for the NMA for the bDMARD-IR population, the company used results from the FINCH 2 study for filgotinib (approximately 21% of patients in the FINCH 2 trial had moderate disease). As the NMA for the cDMARD-IR population is more relevant for patients with moderately active RA, the results from the FINCH 1 study may not be representative for that population.

4.3.1 Trials included in the NMA for cDMARD-IR

A total of 50 trials were included in the NMA for the cDMARD-IR population.

Further details about sample size, comparisons, participants' mean age, gender, disease duration and DAS28 score at baseline are presented in Table 6 in Appendix D of the CS. Data are reported by treatment arm. In summary, the number of patients per treatment arm ranged from 24 to 803. Mean age ranged from 46 years to 58 years (not reported in 11 studies). The percentage of male participants ranged from 4% to 56% (not reported in 10 studies). Mean disease duration ranged from 21 months to 156 months (not reported in 13 studies). Mean DAS28 score at baseline ranged from 5.8 to 7.5 for DAS28-ESR and from 4.1 to 11.6 for DAS28-CRP (not reported in 16 studies).

Table 4.12: Summary of studies included for each NMA outcome - cDMARD-IR

Trial	Treatment	ACR 12-week inclusion	ACR 24-week inclusion	EULAR 24-week inclusion
Abe et al.[35]	IFX (3mg/kg) +cDMARDs	✓	×	×
	cDMARDs	✓	×	×
AIM[36]	ABT (10mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
ATTEST, (NCT00095147)[37]	ABT	×	✓	×
	IFX (3mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
Baek et al.[38]	TCZ (8mg/kg)	×	✓	✓
	cDMARDs	×	✓	✓
Beals et al.[39]	IFX (3mg/kg) +cDMARDs	✓	×	×
	cDMARDs	✓	×	×
Chen et al.[40]	ADA (40mg/kg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×

Trial	Treatment	ACR 12-week inclusion	ACR 24-week inclusion	EULAR 24-week inclusion
Cohen et al.[41]	ANK (100mg) +cDMARDs	×	✓	×
	cDMARDs	×	✓	×
DANCER[42, 43]	RTX (1000mg)	×	✓	✓
	cDMARDs	×	✓	✓
DARWIN 1[44]	FIL (100mg) + cDMARDs	✓	×	×
	FIL (200mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
Etanercept 309[45]	ETN + intensive cDMARDs	×	✓	×
	cDMARDs	×	✓	×
EXXELERATE[46]	CZP + cDMARDs	✓	×	×
	ADA (40mg/kg) + cDMARDs	✓	×	×
FINCH 1	FIL (100mg)/ (200mg) + cDMARDs	✓	✓	✓
	ADA + cDMARDs	✓	✓	✓
	cDMARDs	✓	✓	✓
GOFURTHER[47-49]	GLM (2mg/kg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
J-RAPID (NCT00791999)[50]	CZP (400mg) + cDMARDs	✓	×	✓
	CZP (200mg) + cDMARDs	✓	×	✓
	cDMARDs	✓	×	✓
KAKEHASI[51, 52]	SARI (200mg) +cDMARDs	✓	✓	×
	SARI (150mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×
Keystone et al.[53]	ADA (40mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
Kim et al.[54]	ADA (40mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
Kremer et al.[55]	Intensive cDMARDs	×	✓	×
	cDMARDs	×	✓	×
Lim et al.[56]	TCZ (8mg/kg)	×	✓	✓
	cDMARDs	×	✓	✓
MOBILITY[57-59]	SARI (150mg) + cDMARDs	×	✓	×
	SARI (200mg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
NCT00345748[60]	ABT (10mg/kg) + cDMARDs	×	✓	×
	ABT (2mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
NCT00405275[61]	ETN (50mg) + HCQ (400mg)	×	✓	×
	SSZ (1-2mg) + HCQ (400mg)	×	✓	×
NCT00413660	TOF (5mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
NCT00544154[62]	CZP (400mg) + cDMARDs	×	✓	×

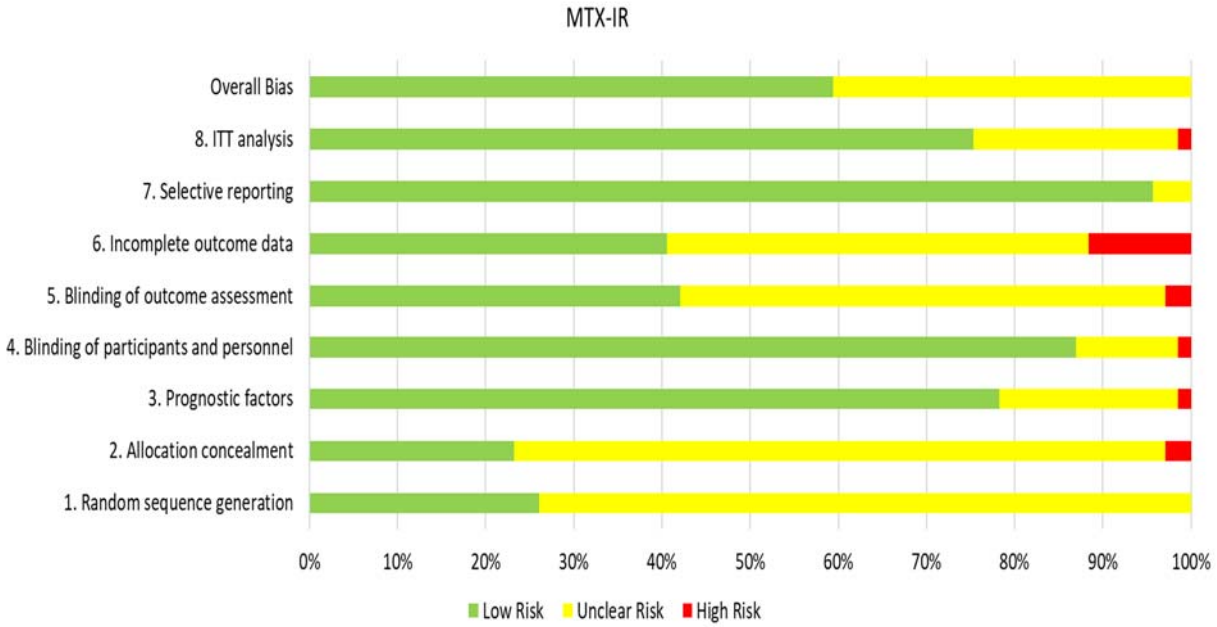
Trial	Treatment	ACR 12-week inclusion	ACR 24-week inclusion	EULAR 24-week inclusion
	cDMARDs	×	✓	×
NCT00603512[63]	TOF (5mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
NCT00993317[64]	CZP (200mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×
I4V-MC-JADA (NCT01185353)[65]	BARI (4mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
NCT01313208[66]	ETN (50mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
NCT01554696[67]	PFT (25, 50, 100, 150mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
NCT01710358[68, 69]	BARI (4mg) + cDMARDs	✓	✓	×
	ADA (40mg/kg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×
NCT01758198[70]	ABT (10mg/kg) +cDMARDs	×	✓	×
	cDMARDs	×	✓	×
NCT02557100	ADA (40mg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
OPTION[71]	TCZ (8mg/kg) + cDMARDs	×	✓	✓
	TCZ (4mg/kg) + cDMARDs	×	✓	✓
	cDMARDs	×	✓	✓
RA-BUILD[72]	BARI (4mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×
RA0025[73]	CZP + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
RA-BALANCE[74]	BARI (4mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
RAJ3[75]	PFT (50mg) + cDMARDs	✓	×	×
	PFT (100mg) + cDMARDs	✓	×	×
	PFT (150mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
RAJ4[75]	PFT (100mg) + cDMARDs	✓	×	×
	PFT (150mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
RAPID 1[76]	CZP (400mg) + cDMARDs	×	✓	×
	CZP + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
RAPID 2, (NCT00175877)[77]	CZP (400mg) + cDMARDs	×	✓	×
	CZP + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
RA-SCORE[78]	RTX (1000mg) + cDMARDs	×	✓	✓

Trial	Treatment	ACR 12-week inclusion	ACR 24-week inclusion	EULAR 24-week inclusion
	cDMARDs	×	✓	✓
SARIL-RA-MOBILITY[79]	SARI (150mg) q2w / qw + cDMARDs	✓	×	×
	SARI (200mg) qw + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
SELECT-COMPARE[80]	UPA (15mg) + cDMARDs	✓	✓	×
	ADA (40mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×
SELECT-NEXT[81, 82]	UPA (15mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
SELECT-SUNRISE	UPA (15mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
SERENE[83]	RTX (1000mg) + cDMARDs	×	✓	✓
	cDMARDs	×	✓	✓
Smolen et al.	UPA (15mg) + cDMARDs	✓	×	×
	UPA (30mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	
Tanaka et al.[84]	BARI (4mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
TOWARD[85]	TCZ (8mg/kg)	×	✓	✓
	cDMARDs	×	✓	✓
Weinblatt et al.[86]	ETN (25mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×

Source: CS, Table 15, pages 90-94.

ABT = abatacept; ACR = American College of Rheumatology; ADA = adalimumab; ANK = anakinra; BARI = baricitinib; CRP = C-reactive protein; cDMARDs = conventional synthetic disease modifying anti-rheumatic drug = CZP = certolizumab pegol; DAS28 = disease activity score; ETN = etanercept; EULAR = European League Against Rheumatism; FIL = filgotinib; GLM = golimumab; IFX = infliximab; PFT = peficitinib; qw = weekly; q2w = biweekly; RTX = rituximab; SAR = sarilumab; TCZ = tocilizumab; TOF = tofacitinib; tsDMARD = targeted synthetic disease modifying anti-rheumatic drug; UPA = upadacitinib.

Figure 4.2: Risk of bias of trials in the cDMARD-IR NMA



Source: CS, Appendix D, Figure 3, page 59.

4.3.2 Trials included in the NMA for bDMARD-IR

Ten trials were eligible for inclusion.

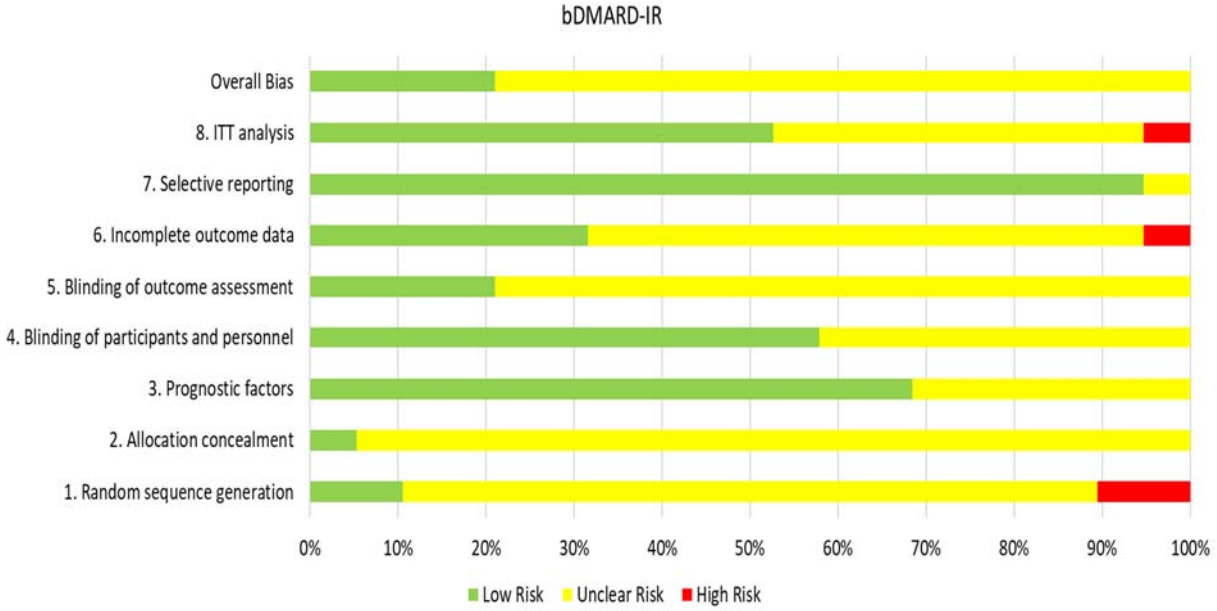
Further details about sample size, comparisons, participants' mean age, gender, disease duration and DAS28 score at baseline are presented in Table 6 in Appendix D of the CS. Data are reported by treatment arm. In summary, the number of patients per treatment arm ranged from 10 to 338. Mean age ranged from 52.1 years to 59 years. The percentage of male participants ranged from 15% to 22% (not reported in one study). Mean disease duration ranged from 12 months to 174 months. Mean DAS28 score at baseline ranged from 5.9 to 6.9 (for ESR or CRP).

Table 4.13: Summary of studies included for each NMA outcome – bDMARD-IR

Trial	Treatment	ACR 12-week inclusion	ACR 24-week inclusion	EULAR 24-week inclusion
ATTAIN[87]	ABT (10mg/kg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
BREVACTA[88]	TCZ (162mg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
FINCH 2[89]	FIL (100mg) + cDMARDs	✓	✓	✓
	FIL (200mg) + cDMARDs	✓	✓	✓
	cDMARDs	✓	✓	✓
NCT01147341[90]	CZP (400mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
ORAL-STEP	TOF (5mg) + cDMARDs	✓	×	×
	cDMARDs	✓	×	×
RA-BEACON[91-93]	BARI (4mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×
RADIATE[94]	TCZ (8mg/kg) + cDMARDs	×	✓	✓

	TCZ (4mg/kg) + cDMARDs	×	✓	✓
	cDMARDs	×	✓	✓
REFLEX[95, 96]	RTX (1000mg) + cDMARDs	×	✓	×
	cDMARDs	×	✓	×
SELECT-BEYOND[97]	UPA (15mg) + cDMARDs	✓	×	×
	UPA (30mg) + cDMARDs	×	×	×
	cDMARDs	✓	×	×
TARGET[98]	SARI (150mg) + cDMARDs	✓	✓	×
	SARI (200mg) + cDMARDs	✓	✓	×
	cDMARDs	✓	✓	×
Source: CS, Table 16, pages 94-95. ADA = adalimumab; BARI = baricitinib; cDMARD = conventional synthetic disease modifying anti-rheumatic drug; CZP = certolizumab pegol; ETN = etanercept; FIL = filgotinib; GLM = golimumab; IFX = infliximab; RTX = rituximab; SARI = sarilumab; TOF = tofacitinib; UPA = upadacitinib.				

Figure 4.3: Risk of bias of trials in the bDMARD-IR NMA



Source: CS, Appendix D, Figure 4, page 59.

4.3.3 NMA statistical analysis methods

The outcomes analysed in the NMA were ACR20, 50 and 70 response at weeks 12 and 24 and EULAR response at week 24. The analysis methods followed those recommended by the NICE DSU and used Bayesian methods. As ACR and EULAR response are ordered categorical outcomes they were analysed using a single endpoint (model) method so rather than performing an analysis of each outcome as a binary variable the different levels are analysed jointly in one model which allows for the ordering and correlation between them. A single model analysis method was used with a conditional binomial likelihood and probit link (for the analysis of an ordered categorical variable). Fixed and random effects models were considered by each analysis and model fit was examined by comparing the total residual deviance, different models were compared using the deviance information criterion (DIC).

Each model was formed from multiple chains with each chain simulated from difference starting values. Inferences were made from posterior distributions after 25,000 iterations following a burn-in period of

25,000 iterations (or more if needed for model convergence). Vague prior distributions were used for baseline and nuisance parameters as well as the between trial variance. Estimates were reported as relative risks (RR) together with 95% credible intervals (CrI). Analyses were performed with WinBUGS version 1.4.3.

ERG comment: The statistical methods used to perform the NMAs were appropriate and followed the methods recommended in NICE DSU TSD report 2 for Bayesian models.[99] The analyses used a multinomial model to jointly model ACR20, 50 and 70 responses which allows for the correlation between them and is more efficient than performing separate analyses modelling each type of response as a binary outcome. Results were provided for both fixed and random effects models.

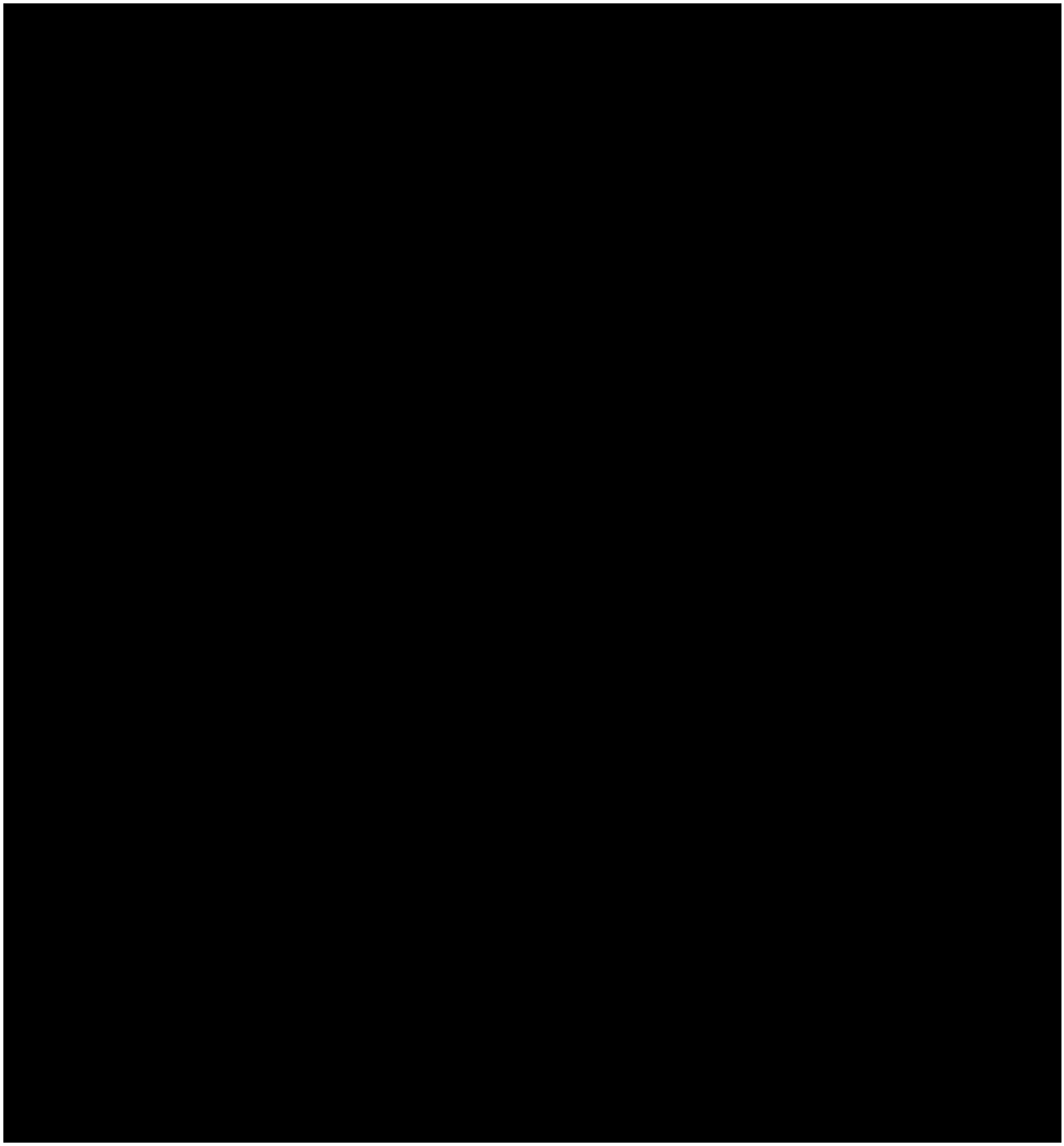
4.3.4 NMA results cDMARD-IR population

4.3.4.1 ACR response at 12 weeks

Results from the NMA of ACR response at 12 weeks for the cDMARD-IR population are shown in forest plots in Figure 4.4 for comparisons with filgotinib 200 mg and Figure 4.5 for comparisons with filgotinib 100 mg. These show the estimate of the median difference between treatments with 95% CrI on a probit scale (the difference in the probability of a response). There was [redacted]. The relative risks (RR) of an ACR response at 12 weeks for [redacted]

Filgotinib 100 mg [redacted] but not compared to any other treatment. Results for an ACR response at 12 weeks for [redacted]

Figure 4.4: Week 12 ACR results for each treatment compared to filgotinib 200 mg



Source: CS, Figure 27, page 110.

Figure 4.5: Week 12 ACR results for each treatment compared to filgotinib 100 mg

Source: CS, Figure 26, page 109.

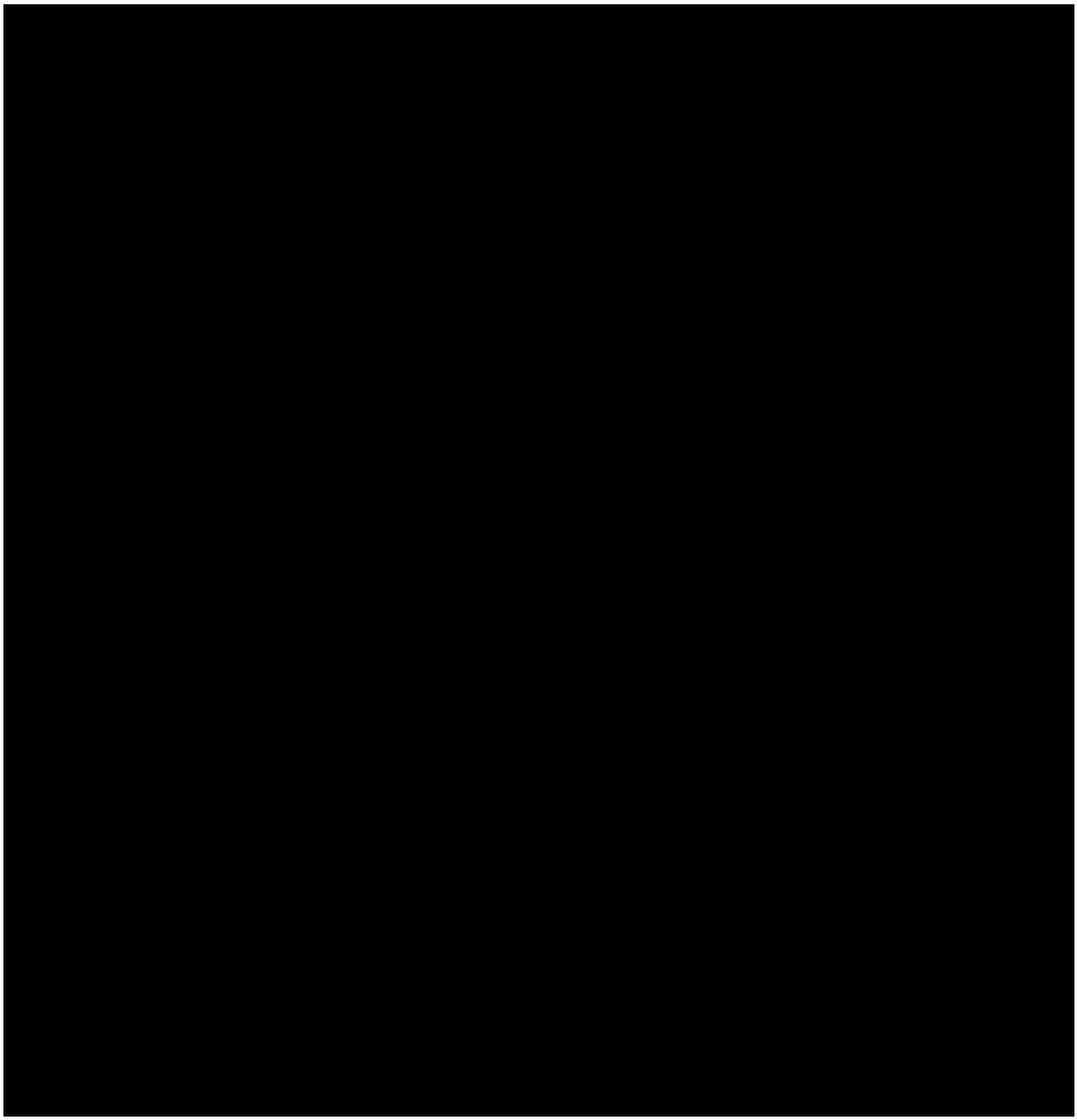
4.3.4.2 ACR response at 24 weeks

Results for ACR response at 24 weeks for the cDMARD-IR population are shown in forest plots in Figure 4.6 for comparisons with filgotinib 200 mg and Figure 4.7 for comparisons with filgotinib 100 mg. These show the estimate of the median difference between treatments with 95% CrI on a probit scale.

. The RR of an ACR response at 24 weeks for .

Filgotinib 100 mg was also . Results for an ACR response at 24 weeks for .

Figure 4.6: Week 24 ACR results for each treatment compared to filgotinib 200 mg



Source: CS, Figure 29, page 114.

Figure 4.7: Week 24 ACR results for each treatment compared to filgotinib 100 mg

Source: CS, Figure 28, page 113.

4.3.4.3 EULAR response at 24 weeks

Results for EULAR response at 24 weeks for the cDMARD-IR population are shown in Figure 4.8. These show the estimate of the median difference between treatments with 95% CrI on a probit scale. At 24 weeks filgotinib 200 mg was [redacted] to adalimumab (40 mg q2w) and cDMARDs [redacted] to certolizumab pegol (200 mg), certolizumab pegol (400 mg) and tocilizumab (8 mg/kg). The RR of achieving at least a moderate EULAR response at 24 weeks for [redacted] For filgotinib 200 mg compared to [redacted].

Filgotinib (100 mg) was [redacted], other than cDMARDs. For filgotinib 100 mg compared to [redacted].

Figure 4.8: Week 24 EULAR results for each treatment compared to filgotinib 100 and 200 mg

Source: CS, Figure 30, page 117.

4.3.5 NMA results bDMARD-IR population

4.3.5.1 ACR response at 12 weeks

Results from the NMA of ACR response at 12 weeks for the bDMARD-IR population are shown in Figure 4.9 for comparisons with filgotinib 200 mg and 100 mg. These show the estimate of the median difference between treatments with 95% CrI on a probit scale. Filgotinib (200 mg) compared to sarilumab (150 mg) and cDMARDs. The RR of an ACR response at 12 weeks for _For the comparison of filgotinib 200 mg with sarilumab 150 mg results

For Filgotinib 100 mg there compared to other treatments apart from cDMARDS for ACR response at week 12. Results for an ACR response at 12 weeks for

Figure 4.9: Week 12 ACR results for each treatment compared to filgotinib 100 and 200 mg

Source: CS, Figure 31, page 119.

4.3.5.2 ACR response at 24 weeks

Results from the NMA of ACR response at 24 weeks for the bDMARD-IR population are shown in Figure 4.10 for comparisons with filgotinib 200 mg and 100 mg. These show the estimate of the median difference between treatments with 95% CrI on a probit scale. Filgotinib (200 mg) [redacted] compared to cDMARDs but not compared to other treatments. The RR of an ACR response at 24 weeks for [redacted]

Filgotinib 100 mg was [redacted] to rituximab (1000 mg) and tocilizumab (8 mg/kg q4w) and [redacted] to cDMARDS for ACR response at week 24. Results for an ACR response at 24 weeks for [redacted]

Figure 4.10: Week 24 ACR results for each treatment compared to filgotinib 100 and 200 mg

Source: CS, Figure 32, page 121.

4.3.5.3 EULAR response at 24 weeks

Results from the NMA of EULAR response at 24 weeks for the bDMARD-IR population are shown in Figure 4.11 for comparisons with filgotinib 200 mg and 100 mg. These show the estimate of the median difference between treatments with 95% CrI on a probit scale.

The CS stated that the NMA results for EULAR response at 24 weeks for the bDMARD-IR population are uncertain as *"The studies included in this network showed a large degree of variability in the control arm (cDMARD) response, for example 86.4% of patients achieved at least a moderate response in the cDMARDs arm in FINCH 2, compared with only 16.5% in the RADIATE and 22% in REFLEX studies. As such, estimates of the modelled probabilities of response were highly uncertain"* (CS, page 122).[1] In addition *"owing to issues surrounding model convergence, the relative risks of achieving EULAR response have not been reported"* (CS, Appendix D, page 95).[27]

Figure 4.11: Week 24 EULAR results for each treatment compared to filgotinib 100 and 200 mg

Source: CS, Figure 33, page 123.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The NMA focussed on two populations, those with an inadequate response to conventional DMARDs (cDMARD-IR) and those with an inadequate response to biologic DMARDs (bDMARD-IR). The analyses were for the moderate to severe population only as although FINCH 1 reported subgroup results for the severe population, other trials were either not in severe patients or did not provide relevant subgroup results. The ERG asked the company to perform NMA in cDMARD-IR patients with severe disease only including severe subgroup data from FINCH 1; and in bDMARD-IR patients with severe disease using severe subgroup data from FINCH 2. However, the company stated that no studies were performed in severe patients only or reported results for severe patients only and it would not be possible to construct networks for severe RA patients only. The NMA results presented are for the moderate to severe population.

The ERG has no concerns with the analysis methods used, which used appropriate Bayesian statistical models and analysed outcomes using a single multinomial model which analysed ACR20, 50 and 70 jointly allowing for ordering and correlation between them. This single model reflects the relationship between different levels of ACR which would be ignored by analysing each as a separate binary outcome. The relative risks for the analysis of EULAR response at 24 weeks for the bDMARD-IR population were not reported due to problems with model convergence which could not be overcome. In the economic model, EULAR responses were used in a scenario; in the company base-case the ACR responses were mapped to EULAR responses.

The ERG's concerns lie with the exclusion of studies, as those published before 1999 were excluded to concentrate on newer biologics, as well as studies of monotherapy treatment and only including studies in which patients had failed on two mor more DMARDs. Potentially relevant studies have been excluded from this submission and it is not clear why. An additional issue is the comparability of the studies included in the networks. The company based their assumptions of clinical homogeneity on previous Technology Assessments, but it is not clear whether those contained the same studies. The ERG asked for a justification of clinical homogeneity based on a review of baseline patient data but this

was not provided. For both NMA analyses the studies varied in terms of disease duration (from 12 to 174 months in the bDMARD-IR population) so there are potential concerns about clinical heterogeneity if disease duration is an important effect modifier.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No further work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The population in the CS differs from the population defined in the NICE scope. The population defined in the scope is: Adults with moderate to severe, active rheumatoid arthritis (RA), whose disease has responded inadequately to, or who are intolerant of conventional or biological disease-modifying anti-rheumatic drugs (DMARD)s. The population in the company submission (CS) is limited to "Adults with moderately to severely active RA whose disease has responded inadequately to two or more conventional DMARDS (cDMARDs), or who are intolerant to DMARDs, including conventional or biologic DMARDs". The company states that *"in the moderately active RA population the company submission is limited to patients following two or more cDMARD failures, this restriction is applied on the basis of clinical opinion and expected cost-effectiveness"* (CS, Table 1, page 15).[1]

Therefore, the population in the CS is not in line with the scope; and also not in line with the population in the trial (FINCH 1). For patients with moderately active RA, the FINCH 1 trial provides the most appropriate data. In the FINCH 1 trial, the following population was included: "Adults with moderately to severely active RA who have inadequate response to ongoing stable MTX dose". This means, clinical effectiveness data from the FINCH 1 trial are based on patients who had an inadequate response to one or more cDMARDs (as in the NICE scope). In addition, it is important to note that most patients in the two main trials had severely active RA (DAS28 score >5.1); approximately 24% of patients in the FINCH 1 trial had moderate disease and 21% in the FINCH 2 trial. Therefore, results from both trials are more reliable for the severely active RA population, but less reliable for patients with moderately active RA.

The intervention (filgotinib (as monotherapy or in combination with other cDMARDs, including methotrexate (MTX)) is in line with the scope. However, the FINCH 1 and 2 trials do not include a filgotinib monotherapy arm. Therefore, for the purpose of the economic evaluation, the company assumed that monotherapy will have the same relative effect across all treatments as combination therapy (CS, page 153).[1] In addition, the ERG noted that that the proposed dose of filgotinib is 200 mg per day given orally for most patients and that according to the Summary of Product Characteristics (SmPC) the 100 mg dose is recommended for patients with severe renal impairment (creatinine clearance 15 to 30 mL/min). Therefore, the evidence on 200 mg is likely to be more relevant to practice.

The comparators in the CS are not in line with NICE scope. Several relevant comparators mentioned in the scope were not included in the NMAs because of lack of data. This is partly due to the inclusion criteria used by the company (no monotherapy). As a result, these comparators have also not been included in the economic model

For moderate active RA, the NICE scope mentions three comparators (Combination of two or more cDMARDs, cDMARD with dose escalation and BSC), while the company included only one: BSC. BSC was defined in the CS as *"cDMARDs that patients have already received, administered at lower doses" (CS, page 32); "which is considered to provide little therapeutic benefit to patients"* (CS, page 32).[1] In the economic model *"BSC is assumed to have no treatment effect (i.e. EULAR non-response), in line with the assumption made in MTA375. Additionally, recent submissions in RA have made the*

same assumption (TA485[23]*, TA480*[24] *and TA466*[25]*)"* (CS, page 150).[1] However, in the control arm of the FINCH 1 trial patients received placebo+MTX and all patients in FINCH 1 had an inadequate response to ongoing stable MTX dose. Nevertheless, "*patients in the FINCH-1 study exhibited extremely high levels of response when treated with cDMARDs"* according to the company (CS, page 114).[1] Therefore, either the population in the FINCH 1 trial is not in accordance with the NICE scope; or the assumption that BSC has no treatment effect is incorrect.

The evidence for filgotinib is based on good quality international RCTs investigating patient-relevant outcomes. In both FINCH 1 and 2, filgotinib is compared to placebo. The only direct evidence on filgotinib versus an active comparator is for adalimumab in FINCH 1. FINCH 1 and 2 were large, multinational trials. Across the two trials, 2,203 patients took part. Of these, 622 patients received the 200 mg filgotinib dose which is expected to be used for most patients in practice. A dose of 100 mg of filgotinib once daily is recommended for patients with severe renal impairment (Creatinine clearance 15 to 30 mL/min).[1]

Although FINCH 1 had just 14 UK participants (0.8%) and FINCH 2 had just nine UK participants (2%) the company provided evidence of generalisability to the UK in response to clarification.[21] The clinician we consulted for this appraisal considered this evidence in addition to the baseline characteristics of the trials to indicate generalisability to UK practice. And, although FINCH 1 was of 52 weeks' duration, the relevant outcomes are at 12 and 24 weeks as at week 24, all patients assigned to placebo were reassigned to either filgotinib 100 mg + MTX or filgotinib 200 mg + MTX in a blinded fashion and continued in the study per protocol up to week 52. Therefore, comparative evidence is only available up to 24 weeks.

In FINCH 1 significantly more patients achieved the primary endpoint of ACR20 response at week 12 with filgotinib 200 mg (76.6% vs. 49.9%, p<0.001) and filgotinib 100 mg (69.8% vs. 49.9%, p<0.001) compared to placebo. Results for ACR50 and ACR70 were also significantly improved with filgotinib 200 mg and 100 mg compared to placebo. More patients also achieved an ACR20, ACR50 or ACR70 response on filgotinib 200 mg and 100 mg compared to adalimumab. EULAR response at week 12 was 51.4% for filgotinib 200 mg, 39.2% for filgotinib 100 mg, 44.8% for adalimumab and 24.6% for placebo patients achieving a good EULAR response. The CS reported no significant differences between treatments in EULAR scores. At week 24 results for ACR20 response favoured filgotinib with 78.1% of filgotinib 200 mg, 77.7% of filgotinib 100 mg and 59.2% of placebo patients achieving an ACR20 response ($p < 0.001$ for each comparison).

In FINCH 2 significantly more patients on filgotinib 200 mg (66% vs. 31.1%, $p < 0.001$) and filgotinib 100 mg (57.5% vs. 31.1%, p<0.001) achieved an ACR20 response at week 12 compared to placebo. Filgotinib 200 mg and 100 mg also showed significantly better efficacy than placebo for ACR50 and ACR70 at week 12 and most other outcomes at week 12 apart from EULAR response. At week 12, 42.6% of filgotinib 200 mg, 40.9% of filgotinib 100 mg and 18.0% of placebo patients achieving a good EULAR response. At week 24 results for ACR20 response also favoured filgotinib with 69.4% of filgotinib 200 mg, 54.9% of filgotinib 100 mg and 34.5% of placebo patients achieving an ACR20 response ($p < 0.001$ for each comparison).

Baseline characteristics and efficacy results for patients with moderately active RA (DAS28 score of 3.2-5.1) and severely active RA (DAS28 score >5.1) are presented in Appendix 2 of this report for the FINCH 1 trial. Looking at the results, EULAR scores show the most significant difference between severe RA and moderate RA, with all interventions in the FINCH 1 trial being less effective (~20% point) in severe disease than in moderate disease.

Adverse events most frequently observed across the two trials were nasopharyngitis, upper respiratory tract infections, headache, nausea, and bronchitis. In FINCH 1, at week 24 (placebo-controlled period) a similar proportion of patients experienced serious treatment-emergent adverse events (TEAEs) in each treatment group (4.4% in the filgotinib 200 mg arm, 5.0% in the filgotinib 100 mg arm, 4.3% in the adalimumab arm and 4.2% in the placebo arm). By week 52 (overall period), these figures were [redacted] in the filgotinib 200 mg arm, [redacted] in the filgotinib 100 mg arm, and [redacted] in the adalimumab arm. By week 24, there were two-treatment related deaths in the filgotinib 200 mg group (septic shock; septic shock secondary to pneumonia), one treatment-related death in the filgotinib 100 mg group in a patient with multiple risk factors (myocardial infarction on day 13), no deaths in the adalimumab group and two deaths in the placebo group (toxic reaction not related to study drug, septic shock non-treatment emergent SAE). In FINCH 2, at week 24, a similar proportion of patients experienced serious TEAEs in each treatment group (4.1% in the filgotinib 200 mg arm, 5.2% in the filgotinib 100 mg arm, and 3.4% in the placebo arm). No deaths occurred due to any cause by week 24.

The company performed two separate network meta-analyses (NMAs), one for the cDMARD-IR population and one for the bDMARD-IR population. The outcomes analysed were ACR at week 12 and 24, and EULAR at 24 weeks. As FINCH 1 and 2 did not include filgotinib monotherapy arms an NMA for monotherapy was not possible according to the company. The company also stated that as most trials did not report results stratified by moderate and severe disease, it was not possible to perform separate NMAs for moderate and severe disease. Therefore, two NMAs were performed: for moderate to severe populations for cDMARD-IR and for bDMARD-IR patients.

The company used different inclusion criteria from the NICE scope. Firstly, all monotherapy studies were excluded. This was because the FINCH 1 and 2 trials did not have monotherapy arms. However, the NICE scope mentions several monotherapy comparators which could still have been included. Secondly, the search was limited to studies after 1999. However, many cDMARD studies were performed before 1999. Therefore, potentially relevant studies were excluded from the NMAs.

Baseline characteristics from the included studies shows that the number of patients per treatment arm ranged from 24 to 803. Mean age ranged from 46 years to 58 years (not reported in 11 studies). The percentage of male participants ranged from 4% to 56% (not reported in 10 studies). Mean disease duration ranged from 21 months to 156 months (not reported in 13 studies). Mean DAS28 score at baseline ranged from 5.8 to 7.5 for DAS28-ESR and from 4.1 to 11.6 for DAS28-CRP (not reported in 16 studies). This shows that there will be large differences between included studies. The company did not provide a detailed summary of clinical heterogeneity but stated that as there are published NMAs in RA including those informing previous HTA therefore *"a formal feasibility assessment was not conducted, and the homogeneity of the trials was deemed sufficient to conduct the analysis"*.[1] The ERG requested additional evidence for this statement, but a response has not been received.[21]

The statistical methods used to perform the NMAs are valid and in line with previous NICE appraisals.

Results from the NMA for the cDMARD-IR population of ACR response at 24 weeks showed that [redacted]. EULAR response at 24 weeks showed that filgotinib 200 mg was [redacted] to adalimumab (40 mg q2w) and cDMARDs [redacted] to certolizumab pegol (200 mg), certolizumab pegol (400 mg) and tocilizumab (8 mg/kg).

Results from the NMA for the bDMARD-IR population of ACR response at 24 weeks showed that filgotinib 200 mg [redacted] compared to cDMARDs but not compared to other

treatments. The CS stated that the NMA results for EULAR response at 24 weeks for the bDMARD-IR population are uncertain as "*The studies included in this network showed a large degree of variability in the control arm (cDMARD) response, for example 86.4% of patients achieved at least a moderate response in the cDMARDs arm in FINCH 2, compared with only 16.5% in the RADIATE and 22% in REFLEX studies. As such, estimates of the modelled probabilities of response were highly uncertain*".[1]

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

5.1.1 Searches performed for cost effectiveness section

Appendix G of the CS details systematic searches of the literature used to identify published economic evaluations in moderate to severe RA, which could be used to address the decision problem and inform the economic model structure.

Searches were conducted from 2000 to 8 August 2018, with two updates carried out on 10 September 2019 and 7 January 2020. Appendix G also reported that an update was conducted on 26 October 2018, however no documentation was provided for that search. English language limits were applied to the PubMed and Embase searches. All searches were limited by publication date from 1 January 2000 onwards. A summary of the sources searched is provided in Table 5.1.

Table 5.1: Data sources for the cost effectiveness systematic review

Search strategy element	Resource	Host/ source	Reported date range	Date searched
Electronic databases	Embase.com	Elsevier	2000-7/01/20	8.8.18 Updated 10.9.19 & 7.1.20
	PubMed	NLM	2000-7/01/20	8.8.18 Updated 10.9.19 & 7.1.20
	Cochrane Database of Systematic Reviews (CDSR)	Wiley	2000-7/01/20	8.8.18 Updated 10.9.19 & 7.1.20
	Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley	2000-7/01/20	8.8.18 Updated 10.9.19 & 7.1.20
	Cochrane Methodology Register (CMR)	Wiley**	2000-2018/09	8.8.18
	Database of Abstracts of Reviews of Effects (DARE)	Wiley*	2000-2015/03/31	8.8.18
	Health Technology Assessment Database (HTA)	Wiley*	2000-2018/03/31	8.8.18
	NHS Economic Evaluation Database (NHS EED)	Wiley*	2000-2015/03/31	8.8.18

Search strategy element	Resource	Host/ source	Reported date range	Date searched
	Health Economic Evaluations Database (HEED)		Incorrectly reported, this was not searched for the submission	Not searched.
	EconLit	Not reported	Up to 2020/01/07	8.8.18 Updated 10.9.19 & 7.1.20
	Econpapers	Not reported	Not reported	Not reported
	CEA Registry (Tufts)	Not reported	Not reported	Not reported
Conference Proceedings	American Congress of Rheumatology (ACR)	Web link & search terms not reported	2000-2020/01	Not reported.
	European League Against Rheumatism (EULAR)	Web link & search terms not reported	2000-2020/01	Not reported.
	Asia Pacific League of Associations for Rheumatology (APLAR)	Web link & search terms not reported	2000-2020/01	Not reported.
	ISPOR	Web link & search terms not reported	2000-2020/01	Not reported.
	British Society for Rheumatology (BSR)	Web link & search terms not reported	2000-2020/01	Not reported.
HTA Agencies	NICE	Web link & search terms not reported	2000-2020/01	Not reported.
	SMC	Web link & search terms not reported	2000-2020/01	Not reported.
	AWSMG	Web link & search terms not reported	2000-2020/01	Not reported.
	PBAC	Web link & search terms not reported	2000-2020/01	Not reported.
	HAS	Web link & search terms not reported	2000-2020/01	Not reported.
	AIFA	Web link & search terms not reported	2000-2020/01	Not reported.

Search strategy element	Resource	Host/ source	Reported date range	Date searched
	IQWIG	Web link & search terms not reported	2000-2020/01	Not reported.
	Instituto de Salud Carlos III-ISCIII	Web link & search terms not reported	2000-2020/01	Not reported.

Source: Appendix G of the Company's submission and the Appendix of the clarification response.[100]
Reference lists of included articles and relevant reviews were scanned for further potentially relevant references.
AIFA= Agenzia Italiana de Farmaco; AWMSG = All Wales Medicines Strategy Medicines Group; CRD = Centre for Reviews and Dissemination; HAS = Haute Autorité de Santé; IQWIG = Institute for Quality and Efficiency in Healthcare; ISPOR = International Society of Pharmacoeconomics and Outcomes Research;; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium.
* Please note: DARE & NHS EED ceased on 2015/03/31, and no further content was added after that date. The HTA database ceased on 2018/03/31, and no further content was added after that date.
** The Cochrane Methodology Register, DARE, NHS EED and HTA databases were removed from the Cochrane Library in September 2018.

ERG comment:

- Searches was undertaken to identify published economics evaluations. The CS provided sufficient details for the ERG to appraise the majority of the literature searches. A good range of databases and conference proceedings were searched, including additional grey literature resources and reference checking. For the most part, searches were well documented, making them transparent and reproducible.
- Appendix G reported that the Health Economic Evaluations Database (HEED) was searched as part of the Cochrane Library. As HEED has never been included in the Cochrane Library and ceased publication at the end of 2014, the ERG queried this during clarification. The company responded that they had not searched HEED for this review.
- Update searches of the DARE, NHS EED, HTA and CMR databases were reported as having been conducted on 10 September 2019 and 7 January 2020 via the Cochrane Library. As these databases were removed from the Cochrane Library in September 2018, update searches would not have been possible. At the time the ERG conducted this appraisal, NHS EED, DARE, HTA and CMR content had been removed from the Cochrane Library; therefore, it was not possible to reproduce the company's Cochrane Library search strategy or results.
- The CS and Appendix G reported that database searches were limited from 2000 to the date of search. The ERG considers this date limit restrictive and as a consequence may have missed potentially relevant studies published before 2000.
- The ERG was unable to assess how the searches of Econpapers, CEA Registry and conference proceedings were conducted, as no information was provided.
- The ERG noted that an economics study design filter was applied in both the Cochrane Library and EconLit searches, which may not have performed as successfully as intended. As stated in the MECIR (Methodological Expectations of Cochrane Intervention Reviews) Manual "… do not use filters in pre-filtered databases e.g. do not use a randomized trial filter in CENTRAL or a systematic review filter in DARE."[28] The inclusion of these filters may have resulted in unnecessarily restricting the results retrieved. A more effective option would have been to omit the economics filter from both searches and to limit the Cochrane Library search to the NHS

EED database only. The use of these filters means that potentially relevant references could have been missed by the searches.

- The company reported checking recent reviews for relevant studies, however as the Cochrane Library search was limited to retrieve cost effectiveness studies, it was unclear how these reviews were identified.
- Only one phrase 'rheumatoid arthritis' was used to search titles, abstracts and indexing for all the reported searches. This could have been extended to include additional synonyms and spelling variants, such as Beauvais disease, chronic polyarthritis, inflammatory arthritis and rheumarthritis, which may have increased the recall of results.

5.1.1.1 Cost and healthcare resource identification, measurement and valuation

Appendix I of the CS details systematic searches of the literature used to identify published literature on cost and resource use data associated with patients with moderate to severe RA. Searches were conducted on 24 October 2019 and updated on 2 December 2019. English language limits were applied to the PubMed and Embase searches. All searches were limited by publication date from 1 January 2000 onwards, and the Embase search was further restricted to published or in-press articles only. A summary of the sources searched is provided in Table 5.2.

Table 5.2: Data sources for the cost and healthcare resource identification, measurement and valuation review

Search strategy element	Resource	Host/ source	Reported date range	Date searched
Electronic databases	Embase.com	Elsevier	2000-2019/12/02	24.10.18 Updated 2.12.19
	PubMed	NLM	2000-2019/12/02	24.10.18 Updated 2.12.19
	Cochrane Database of Systematic Reviews (CDSR)	Wiley	2000-2019/12/02	24.10.18 Updated 2.12.19
	Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley	2000-2019/12/02	24.10.18 Updated 2.12.19
	Cochrane Methodology Register (CMR)	Wiley**	2000-2019/12/02	Reported as 24.10.18
	Database of Abstracts of Reviews of Effects (DARE)	Wiley*	2000-2019/12/02	Reported as 24.10.18
	Health Technology Assessment Database (HTA)	Wiley*	2000-2019/12/02	Reported as 24.10.18
	NHS Economic Evaluation Database (NHS EED)	Wiley*	2000-2019/12/02	Reported as 24.10.18

Search strategy element	Resource	Host/ source	Reported date range	Date searched
	Health Economic Evaluations Database (HEED)	Incorrectly reported, this was not searched for the submission	Incorrectly reported, this was not searched for the submission	Not searched.
	EconLit	Not reported	2000-2019/12/02	24.10.18 Updated 2.12.19
	Econpapers	Not reported	Not reported	Not reported
	CEA Registry (Tufts)	Not reported	Not reported	Not reported
Conference Proceedings	American Congress of Rheumatology (ACR)	Web link & search terms not reported	2000-2019/12/02	Not reported.
	European League Against Rheumatism (EULAR)	Web link & search terms not reported	2000-2019/12/02	Not reported.
	Asia Pacific League of Associations for Rheumatology (APLAR)	Web link & search terms not reported	2000-2019/12/02	Not reported.
	ISPOR	Web link & search terms not reported	2000-2019/12/02	Not reported.
	British Society for Rheumatology (BSR)	Web link & search terms not reported	2000-2019/12/02	Not reported.
HTA Agencies	NICE	Web link & search terms not reported	2000-2019/12/02	Not reported.
	SMC	Web link & search terms not reported	2000-2019/12/02	Not reported.
	AWSMG	Web link & search terms not reported	2000-2019/12/02	Not reported.
	PBAC	Web link & search terms not reported	2000-2019/12/02	Not reported.
	HAS	Web link & search terms not reported	2000-2019/12/02	Not reported.
	AIFA	Web link & search terms not reported	2000-2019/12/02	Not reported.

Search strategy element	Resource	Host/ source	Reported date range	Date searched
	IQWIG	Web link & search terms not reported	2000-2019/12/02	Not reported.
	Instituto de Salud Carlos III-ISCIII	Web link & search terms not reported	2000-2019/12/02	Not reported.

Source: Appendix I of the Company's submission and the Appendix of the clarification response.[101]
Reference lists of included articles and relevant reviews were scanned for further potentially relevant references.
AIFA= Agenzia Italiana de Farmaco; AWMSG = All Wales Medicines Strategy Medicines Group; CRD = Centre for Reviews and Dissemination; HAS = Haute Autorité de Santé; IQWIG = Institute for Quality and Efficiency in Healthcare; ISPOR = International Society of Pharmacoeconomics and Outcomes Research; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium.
* Please note: DARE & NHS EED ceased on 2015/03/31, and no further content was added after that date. The HTA database ceased on 2018/03/31, and no further content was added after that date.
** The Cochrane Methodology Register, DARE, NHS EED and HTA databases were removed from the Cochrane Library in September 2018.

ERG comment:

- Searches was undertaken to identify published costs and healthcare resource use data. The CS provided sufficient details for the ERG to appraise the majority of the literature searches. A good range of databases and conference proceedings were searched, including additional grey literature resources and reference checking. For the most part, searches were well documented, making them transparent and reproducible.
- Appendix I reported that the Health Economic Evaluations Database (HEED) was searched as part of the Cochrane Library. As HEED has never been included in the Cochrane Library and ceased publication at the end of 2014, the ERG queried this during clarification. The company responded that they had not searched HEED for this review.
- All searches of the DARE, NHS EED, HTA and CMR databases were reported as having been conducted on 24 October 2018 and 2 December 2019 via the Cochrane Library. As these databases were removed from the Cochrane Library in September 2018, the searches would not have been possible. At the time the ERG conducted this appraisal, NHS EED, DARE, HTA and CMR content had been removed from the Cochrane Library; therefore, it was not possible to reproduce the company's Cochrane Library strategy or results.
- The CS and Appendix I reported that database searches were limited from 2000 to the search date. The ERG considers this date limit restrictive and as a consequence may have missed potentially relevant studies published before 2000.
- The ERG was unable to assess how the searches of Econpapers and CEA Registry were conducted, as no information was provided.
- The ERG noted that an economics study design filter was applied in both the Cochrane Library and EconLit searches, which may not have performed as successfully as intended. As stated in the MECIR (Methodological Expectations of Cochrane Intervention Reviews) Manual "… do not use filters in pre-filtered databases e.g. do not use a randomized trial filter in CENTRAL or a systematic review filter in DARE."[28] The inclusion of these filters may have resulted in unnecessarily restricting the results retrieved. A more effective option would have been to omit the economics filter from both searches and searching the NHS EED database via the Centre

for Reviews and Dissemination website. The use of these filters means that potentially relevant references could have been missed by the searches.

- Limiting the Embase and PubMed to English language only studies may have introduced language bias. Current best practice states that "Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication"[29] and that "research related to language bias supports the inclusion of non-English studies in systematic reviews".[30, 31]
- The company reported checking recent reviews for relevant studies, however as the Cochrane Library search was limited to retrieve cost effectiveness studies, it was unclear how these reviews were identified.
- Only one phrase 'rheumatoid arthritis' was used to search titles, abstracts and indexing for all the reported searches. This could have been extended to include additional synonyms and spelling variants, such as Beauvais disease, chronic polyarthritis, inflammatory arthritis and rheumarthritis, which may have increased the recall of results.

5.1.2 Inclusion/exclusion criteria used in the study selection

A systematic literature review (SLR) was conducted to identify published economic evaluations in moderate to severe RA to address the decision problem and inform the economic model structure (SC Appendix G[100])).

In- and exclusion criteria for the review on cost effectiveness are presented in Table 5.3.

Table 5.3: Eligibility criteria for the identification of studies describing health economic models for the simulation of patients with moderate-to-severe RA

	Inclusion criteria	Exclusion criteria
Population	Adult (≥ 18 years) patients with moderately to severely active RA (including patients with early and established RA)	Juvenile idiopathic arthritis Studies that include only juveniles Patients with mild RA; if the study population is mixed (i.e., mild to severe), exclude those studies in which data are not reported separately for moderate or severely active RA Patients without RA Non-human studies
Intervention and comparators	Any licensed interventions for the management of moderately to severely active RA	Interventions of interest not reported
Outcomes	Model structure and any health economic outcome, including (but not restricted to) QALYs, ICERs, LYG or costs	Outcomes of interest not reported
Study design	Economic evaluation, pharmacoeconomic evaluation, cost-effectiveness study, cost-utility study, cost-benefit study or cost minimisation study	Randomized clinical trial, non-randomized clinical trial, prospective study, longitudinal study, retrospective study, guideline, cohort study, case reports, letter, editorial, review, retracted
Language restrictions	English language only	Studies published in languages other than English

	Inclusion criteria	Exclusion criteria
Date restriction	2000 to present*	Prior to 2000

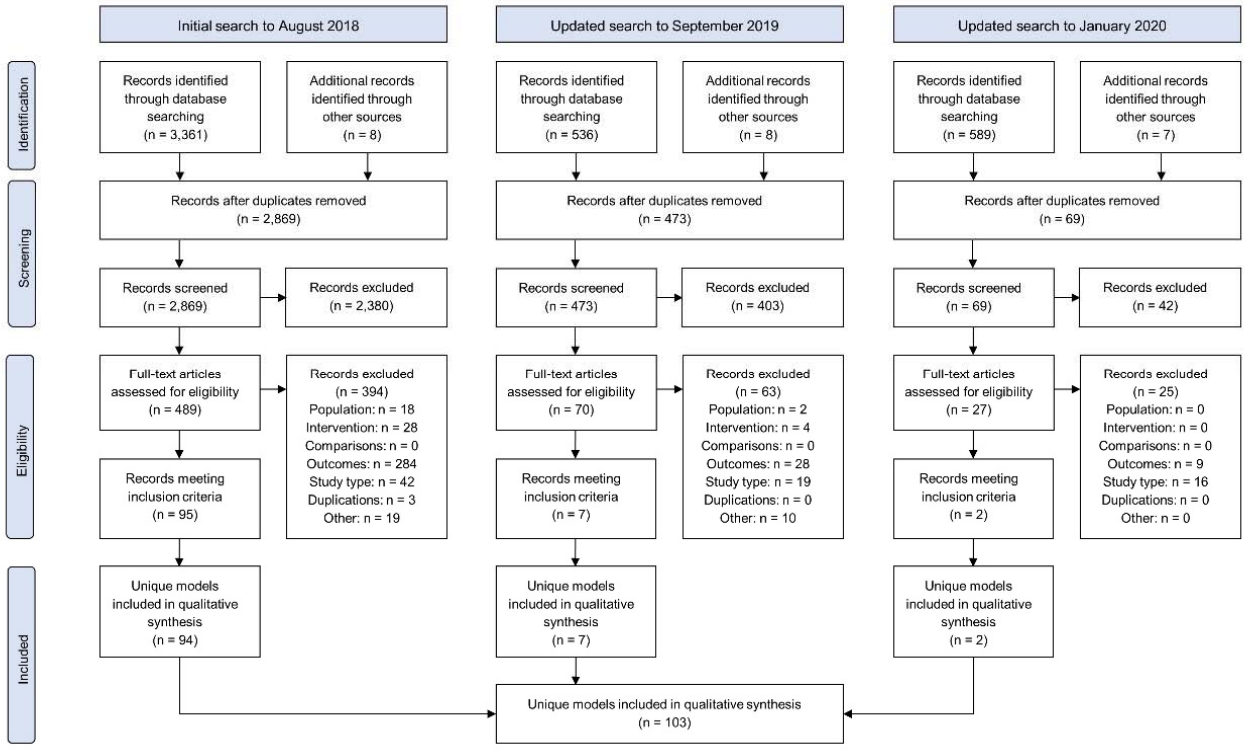
Source: CS appendix G.[100]
ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality adjusted life year; RA = rheumatoid arthritis.
*Date restriction from the year 2000 to present was chosen as the European Commission granted a marketing authorisation throughout the European union for etanercept, the first biologic DMARD licensed for the treatment of adult RA, on 03 February 2000

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies.

5.1.3 Identified studies

In total, 103 models were included in the review (Figure 5.1). However, the company stated that none of the economic evaluations in RA provided relevant effect estimates for the cost effectiveness of filgotinib in RA. The company developed their own model based on the model presented in MTA375 [102], because the economic evaluation conducted by the assessment group (AG) in MTA375 was deemed the most relevant for decision-making in moderate to severe RA in England and Wales [102].

Figure 5.1: PRISMA diagram: Combined Systematic review of cost effectiveness studies from database inception to 7 January 2020



Source: CS appendix G [100]

ERG comment: None of the economic evaluations in RA provided relevant effect estimates for the cost effectiveness of filgotinib in RA. The choice of using a model based on the model presented in MTA375 is reasonable according the ERG.

5.1.4 Interpretation of the review

None of the identified economic evaluations were considered relevant to provide estimates for the cost effectiveness of filgotinib in RA.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.4: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source/Justification	Signpost (location in CS)
Model	Discrete event simulation (DES) model	MTA375 [103]	B.3.2.3
States and events	Patient is simulated through a three-step process: 1) patient time to death is calculated (based on age, gender, HAQ-DI), 2) only patients alive at six months experience the initial treatment phase of six months after which they either continue treatment, or discontinue treatment if they do not achieve a good or moderate EULAR response, and 3) patients enter the maintenance treatment phase upon achieving a good or moderate EULAR response.		B.3.2.3
Comparators	cDMARD-IR population FIL (200 mg) + csDMARDs FIL (200 mg) monotherapy ABC (125 mg qw) + csDMARDs BARI + csDMARDs SARI (200 mg q2w) + csDMARDs ADA (Hulio®) (40 mg q2w) + csDMARDs ETN (Erelzi™) (50 mg qw) + csDMARDs RTX (Rixathon®) (1000 mg) + csDMARDs* IFX (Inflectra®) (3 mg/kg) + csDMARDs TCZ (162 mg q2w) + csDMARDs ADA (Hulio®) (40 mg q2w) monotherapy ETN (Erelzi™) (50 mg qw) monotherapy BARI (4 mg) monotherapy TCZ (162 mg q2w) monotherapy ABC (125 mg qw) monotherapy csDMARDs Intensive csDMARDs BSC bDMARD-IR population FIL (200 mg) + csDMARDs BARI (4 mg) + csDMARDs SARI (200 mg q2w) + csDMARDs TCZ (162 mg q2w) + csDMARDs	Based on NICE treatment guidelines, market share data (Therapy Watch, 2019) and through validation by a UK rheumatologist	Clarification response letter

	Approach	Source/Justification	Signpost (location in CS)
	RTX (Rixathon®) (1000 mg) + csDMARDs ABC (125 mg qw) + csDMARDs ABC (125 mg qw) monotherapy FIL (200 mg) monotherapy BARI (4 mg) monotherapy TOF monotherapy csDMARDs BSC		
Population	Moderate RA: 1a. As monotherapy after two or more cDMARD failures in patients who are MTX ineligible 1b. As combination therapy after two or more cDMARD failures in patients who are MTX eligible Severe RA, for patients who are MTX eligible: 2b. As first line advanced therapy after failure of 2+ csDMARDs, including: 2b1. Severe RA (using second-line RTX), 2b2. Severe RA (using second line IL-6), 2b3. Severe RA (using second line CD80). 3b. After first line advanced therapy failure in patients who are RTX ineligible 4.After first line advanced therapy failure in patients who are RTX eligible 5.After failure of RTX in combination with MTX Severe RA, for patients who are MTX ineligible: 2a. As first line advanced therapy after failure of 2+ csDMARDs 3a. After first line advanced therapy failure	Based on treatment pathway	B.3.2
Treatment effectiveness	Treatment effectiveness in the cost-effectiveness model is mainly informed by the NMA. Long-term HAQ-DI progression was based on those reported in the BSRBR dataset used in MTA375 [103], and on Norton et.al [104], for bDMARD and csDMARD treatment respectively.	NMA MTA375 Norton et.al	B.3.3
Adverse events	Serious infection during the first six months of any active treatment	MTA375	B.3.3

	Approach	Source/Justification	Signpost (location in CS)
Health related QoL	The company used patients' long-term HAQ-DI score trajectory to EQ-5D utilities based on a published mapping algorithm detailed by Hernandez-Alva et al. [105] using the four latent class model based on Norton et al. [104]	MTA375	B.3.4
Resource utilisation and costs	Drug acquisition (MIMS 2020) and administration (MTA 375), hospitalisation costs (MTA 375), and adverse event costs (MTA 375) were applied six-monthly and separated for initial treatment consisting of the first six months of every treatment and maintenance treatment. Costs were inflated to 2018/2019 prices using the HCHS and NHSCII indices.		B.3.5
Discount rates	Discount of 3.5% for utilities and costs.	As per NICE reference case	
Subgroups	No subgroup analyses are reported in CS section 3.9		B.3.9
Sensitivity analysis	Both DSA and PSA were performed as well as scenario analyses.		B.3.8

DES= Discrete event simulation; MTA= Multiple Technology Assessment; HAQ-DI= Health Assessment Questionnaire-Disability Index; EULAR= European League Against Rheumatism; cDMARD = Conventional disease modifying antirheumatic drugs; FIL =Filgotinib; ABC= abatacept ; BARI= baricitinib ; SARI= sarilumab ; ADA= adalimumab ; ETN= etanercept ; RTX= rituximab ; IFX= infliximab ; TCZ= tocilizumab; BSC= best supportive care; bDMARD= Biological disease modifying antirheumatic drugs ; NICE= National Institute for Health and Care Excellence; RA= Rheumatoid Arthritis; MTX= methotrexate ; NMA = network meta-analysis ; BSRBR= British Society of Rheumatology Biologics Register ; EQ-5D = European Quality of Life-5 Dimensions ; HCHS= hospital & community health services ; NHSCII= NHS Cost Inflation Index ; DSA= Deterministic sensitivity analysis; PSA= probabilistic sensitivity analysis.

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.5: NICE reference case checklist

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	As per NICE scope	Partly	The modelled population is narrower compared to the population stated in the final scope as the modelled population is argued to have failed on at least two or more cDMARDs.
Comparator(s)	Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice	Partly	Not all relevant comparators have been included (e.g. certolizumab pegol, tofacitinib).

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Type of economic evaluation	Cost effectiveness analysis	Yes	
Perspective on costs	NHS and Personal Social Services (PSS)	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	
Synthesis of evidence in outcomes	Systematic literature review (SLR)	Yes	
Measure of health effects	Quality adjusted life years (QALYs)	Yes	
Source of data for measurement HRQoL	Described using a standardised and validated instrument	Yes	
Source of preference data for valuation of changes in HRQoL	Time-trade off or standard gamble	Yes	
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic modelling	Partly	The PSA is likely based on an insufficient number of simulations, and patients.

NICE = National Institute for Health and Care Excellence; cDMARD = Conventional disease modifying antirheumatic drugs; NHS = National Health Service; PPS = Personal Social Services; SLR = Systematic literature review; QALY = Quality adjusted life years.

5.2.2 Model structure

The company used a discrete event simulation (DES) model. This is consistent with MTA375 [102], as well as subsequent submissions in RA. Patients are sampled at random from the provided patient population (based on the patient baseline characteristics in the FINCH clinical trial programme).

Each patient is simulated through the following three-step process: 1) patient time to death is calculated, 2) only patients alive at six months experience the initial treatment phase of six months after which they either continue treatment, or discontinue treatment if they do not achieve a good or moderate EULAR response, and 3) patients enter the maintenance treatment phase upon achieving a good or moderate

EULAR response (Figure 5.2). Details of the simulation and main assumptions are described in the CS[1] as follows:

I. *"Patient time to death is calculated*

   i. *Upon model initiation a patient's time of death is determined dependent on their age, sex and HAQ-DI.*

   ii. *If a patient dies within the first six months, this is modelled as an immediate death incurring no costs or QALYs and a new patient is subsequently sampled.*

II. *Patients alive at six months progress to the initial treatment phase where they either continue treatment, or discontinue treatment if they do not achieve a good or moderate EULAR response*

   i. *If a patient remains alive at six months (after the initial treatment phase), then they progress to the six-month initial treatment phase. Thus, all patients who do not die during the initial six months are assumed to complete the initial phase of treatment.*

   ii. *If a patient experiences an AE during this phase of the model, they complete the initial treatment phase gaining no treatment benefit but incur costs and QALYs based on their baseline HAQ-DI and the respective AE. The patient then re-enters the six-month initial treatment phase on the next treatment line.*

   iii. *For patients not experiencing an AE by the end of the six-month initial treatment phase, a EULAR treatment response is sampled, based on the efficacy of the specific treatment. If no EULAR response is achieved, then the patient discontinues the current treatment accruing costs and QALYs based on their baseline HAQ-DI and re-enter the model at the six-month initial treatment phase on the next treatment in the sequence.*

III. *Patients enter the maintenance treatment phase upon achieving a good or moderate EULAR response*

   i. *Once a patient enters the maintenance treatment phase, time to treatment discontinuation is sampled and compared with time to death. The trajectory of a patient's HAQ-DI score from treatment initiation to either death or discontinuation (whichever occurs first) is then estimated and relevant utilities, costs, LYs and QALYs are accrued and calculated accordingly.*

   ii. *Note that utility is accrued linearly over each six-month period. For example, if a patient has utility of 0.5 at the start of the period and 1 at the end of the period, the QALYs accrued in the model will be 0.75/2 = 0.375 per six-monthly cycle. This is equivalent to assuming utility increases linearly over, for example, the initial treatment period, or decreases linearly over the last treatment period before discontinuation.*

   iii. *In the event of discontinuation, the patient's HAQ-DI score rebounds to their baseline score, i.e. it is reduced by the same amount as the initial treatment effect, and the patient moves onto the next treatment in the treatment sequence.*

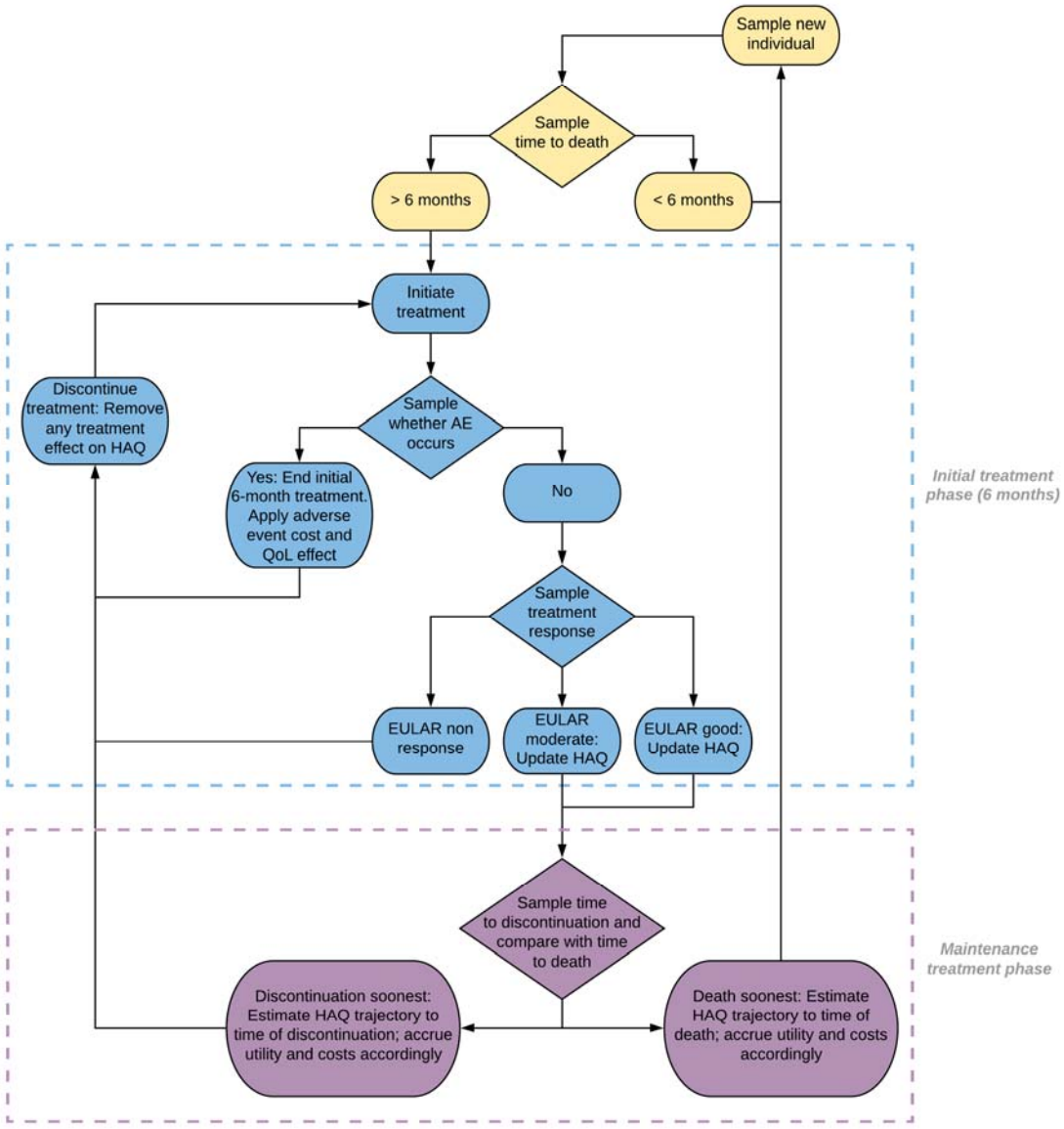
   iv. *If death occurs before treatment discontinuation, the patient's lifetime costs, QALYs and LYs are accrued and the model restarts with the next simulated patient.*

   v. *The model assumes that the final treatment in every treatment sequence is BSC. Therefore, once a patient starts BSC, no discontinuation time is sampled, and the patient remains on this line of treatment until death."*[1]

The base case analyses were conducted using 10,000 samples from 1,000 pre-generated patient profiles per treatment. Once the full population was modelled the process was repeated for any additional

treatment strategies using a set of random numbers for sampling events, which were the same for each strategy. The same model structure was used to model moderate and severe populations, and it was not possible to progress to severe (and receive treatments reserved for this population) for moderate patients.

Figure 5.2: Model structure



Source: Figure 35 CS [1]

5.2.2.1 Model structure in revised base-case

In the original CS, moderate RA patients could become severe over time. However, in the company's original base-case, these patients were not eligible for treatments reserved for severe RA patients. This potentially underestimated health effects and costs for these patients. In response to clarification question B5b[106], the company provided an adapted model structure that enables patients in the moderate cDMARD population (DAS28 >5.1) to receive bDMARD treatment once they progressed to severe RA. To this extent, two steps were undertaken: 1) using patient level trial data to estimate the relationship between change in DAS28 and change in HAQ-DI; and 2) updating simulated patients'

DAS28 scores at every time point in the model based on their modelled HAQ-DI trajectory to determine when progression to the severe state occurs.[1]

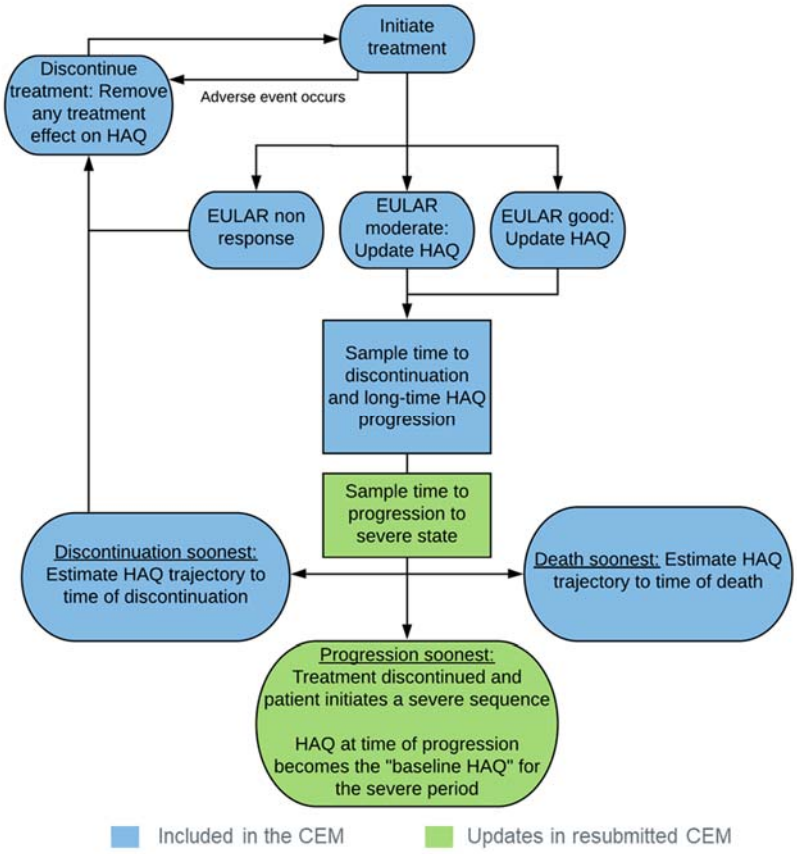
For the first step, in order to estimate the relationship between change in baseline DAS28 over time from HAQ-DI scores, patient level data from the FINCH 1 trial was used to inform a regression analysis. Patients with moderately active RA (DAS28 score at baseline between 3.2 and 5.1), who were in the csDMARD-IR population, on any treatment (filgotinib 200 mg, filgotinib 100 mg, and placebo) were included in the analysis. The regression model estimated change from baseline in DAS28 as a function of change from baseline in HAQ-DI score using the coefficient estimated in the regression:

$$\Delta_{baseline} DAS28 = Coefficient \times \Delta_{baseline} HAQ$$

Furthermore, the company stated that, in response to the ERG critique of TA10389[107] where an estimated constant was not included in the regression, the modification of using a random intercept with mean 0 ensures that no change in HAQ-DI results in no change in DAS28. In addition to the linear mixed model for repeated measures, the inclusion of random effects for the coefficient was explored, providing additional flexibility.

Next, in step two, moderate patients DAS28 score at each six-monthly cycle was calculated by applying the estimated regression coefficient detailed in the first step to the patient's current HAQ-DI, the resulting change in DAS28 score is then applied to the patient's DAS28 score at baseline. Once the DAS28 value exceeds the severe threshold (DAS28 >5.1), the patient discontinues the current treatment in the moderate sequence, and initiates treatment in the subsequent severe sequence. Upon initiating a severe sequence, the HAQ-DI score at the time of transition becomes the updated base HAQ-DI score for the severe period. Following progression to severe disease and initiating advanced treatment, the model does not allow transition from severe RA to moderate RA.[1] Figure 5.3 presents a schematic overview depicting the revised moderate RA patient flow through the model.

Figure 5.3: Revised model structure moderate



Source: Figure 1 of the company's response to clarification [106]

In order to avoid the potential for moderate patients' DAS28 scores at baseline to be sampled as greater than 5.1, the baseline DAS28 scores for the moderate population were sampled using a shifted gamma distribution. When sampling was applied using the mean baseline DAS28 scores for the FINCH 1 moderate subgroup ([redacted]), a sizable proportion of patients had a resulting DAS28 score close to the severe threshold (5.1), and therefore, according to the company, patients progressed rapidly. The company argued that this may not be reflective of the average moderate patient in clinical practice, and hence a more conservative approach was implemented in the base case whereby the midpoint of the moderate DAS28 interval (i.e. a DAS28 score of 4.15, which is the midpoint between the low disease and severe disease activity score thresholds, 3.2 and 5.1) was applied as the mean. Table 5.6 presents the cumulative percentage of BSC patients progressing to a severe state for the different scenarios.

Table 5.6: Cumulative percentage of patients in the CEM progressing to severe RA from moderate RA on BSC

Time	Base case: linear mixed model, gamma using midpoint DAS28 mean	Scenario: linear mixed model with random change coefficient	Scenario: gamma using FINCH 1 DAS28 mean
Year 1	3%	4%	19%
Year 2	5%	7%	26%
Year 3	12%	17%	44%
Year 4	14%	20%	49%
Year 5	24%	33%	59%

Source: Table 13 of the company's response to clarification 21
DAS28 = disease activity score 28-joint count.

The base-case analysis considered the following severe sequences from the CS: patients in population 1a progress to a sequence for population 2a (severe, cDMARD-IR, MTX ineligible), and patients in population 1b progress to a sequence for population 2b (severe, csDMARD-IR, MTX eligible), both using adalimumab as first line advanced therapy (as the most commonly used advanced therapy in first-line) and abatacept in second-line for population 1a, and rituximab and tocilizumab in second- and third-lines for population 1b. The same severe sequence is used for moderate patients in both filgotinib and BSC arms. It was not specified why these specific sequences were chosen in the CQ.

ERG comment: The model structure is in line with previous submissions to NICE, including MTA 375. The main concern of the ERG related to the structural assumption that moderate RA patients could not become severe over time. As a result of this structural assumption, in the model these patients do not become eligible for treatments reserved for severe RA patients. The company agreed that this assumption was expected to have a significant impact on the results of the cost effectiveness analysis and provided an updated version of the model including this functionality at a later stage (as described above). The company's revised analyses lowered the ICERs in both moderate populations, which the company also stated was in line with a scenario analysis presented in TA10389, which suggested that including this functionality lowered the ICER of upadacitinib versus comparators of approximately £9,000 for the moderate population.[107] According to the ERG, this argument should be treated with caution as this appraisal is still ongoing and results do not yet consider all confidential price schemes (and downstream cost effectiveness in the severe population will affect cost effectiveness estimates in the moderate population). In addition, there is a lack of justification regarding the chosen treatment sequences when patients transition to severe RA. Furthermore, the updated model still does not allow for patients transiting from severe to moderate RA. Lastly, the ERG questions whether the use of the not evidence-based mid-point DAS28 score is appropriate and prefers the use of the DAS28 score from the FINCH trials. In conclusion, whilst it is appreciated that the company have implemented the functionality in the model of progressing from moderate to severe disease and therefore making patients eligible for bDMARDs, results from these analyses in the moderate population should be interpreted with caution.

5.2.3 Population

The population defined in the scope is: Adults with moderate to severe, active rheumatoid arthritis, whose disease has responded inadequately to, or who are intolerant of conventional or biological DMARDs. The population in the CS is limited to "Adults with moderately to severely active, active

RA whose disease has responded inadequately to two or more cDMARDs, or who are intolerant to DMARDs, including conventional or biologic DMARDs".[1] The cost effectiveness analysis models patients with moderately to severely active RA, categorised into three subpopulations depending on their disease severity, line of treatment and tolerance to guideline-recommended treatments: moderate RA (DAS28 of 3.2-5.1) who have had inadequate response to or are intolerant to csDMARDs (moderate cDMARD-IR), severe RA (DAS28 >5.1) who have an inadequate response to csDMARDs only (severe cDMARD-IR), severe RA (DAS28 >5.1) who have an inadequate response to bDMARDs (severe bDMARD-IR). Based on NICE treatment guidelines (shown in **Error! Reference source not found.** of the CS [1]), patients are further sub-categorised providing a total of 10 individually analysed populations.

Two patient populations are modelled for the use of filgotinib in moderate RA:

1a. As monotherapy after two or more cDMARD failures in patients who are MTX ineligible

1b. As combination therapy after two or more cDMARD failures in patients who are MTX eligible

Six patient populations are modelled for the use of filgotinib in combination with MTX in severe RA, for patients who are MTX eligible:

2b. As first-line advanced therapy after failure of 2+ csDMARDs. In the economic model (see table 66-68 in the CS [1]) a further distinction was made between three subgroups within this population depending on the nature of second-line treatment, namely: 2b1. Severe RA (using second-line RTX), 2b2. Severe RA (using second-line IL-6), and 2b3. Severe RA (using second-line CD80).

3b. After first-line advanced therapy failure in patients who are RTX ineligible

4. After first-line advanced therapy failure in patients who are RTX eligible

5. After failure of RTX in combination with MTX

Two patient populations are modelled for the use of filgotinib monotherapy in severe RA, for patients who are MTX ineligible:

2a. As first-line advanced therapy after failure of 2+ csDMARDs

3a. After first-line advanced therapy failure

ERG comment: The main concerns of the ERG relate to: a) the additional stratification of the severe RA population (population 2b); b) population of FINCH I and the targeted population in the CS do not align; c) following the revised model structure for the moderate population, clinically implausible adjustments were made to baseline DAS28 scores.

a) In response to question B4 [106] the company explained that patients with severe RA who are MTX eligible may or may not receive second-line RTX depending on whether they are contraindicated to treatment with RTX. Hence this population branches into two stratifications: RTX eligible patients (for who RTX is the NICE recommended second line treatment option) and RTX ineligible patients. For the RTX ineligible population, based on market share data and clinical opinion, IL-6 and CD-80 drugs were recommended by clinical experts as the most suitable options at second-line, hence sequences were built using either options. It may be more informative to present the RTX ineligible population as a weighted average reflecting received IL-6 and CD-80 use in the UK.
b) As detailed in Section 3.1, the population considered in the CS is not in line with (i.e. it is a subset of) the main clinical trials for this appraisal, the FINCH 1 and FINCH 2 trials. In FINCH 1 patients with inadequate response to one or more cDMARDs were included. In the model, inputs (e.g. response rates, utilities, HAQ-DI scores, number of prior treatments) based on FINCH 1 were not

adjusted for patients who failed at least two or more cDMARDs. The ERG is therefore concerned that the model analyses (and efficacy estimates used in them) do not reflect the population that the company are targeting with their submission.

c) Following the updated model structure for patients with moderate RA in response to clarification question B5, the company argued that "*when sampling is applied using the mean baseline DAS28 scores for the FINCH 1 moderate subgroup ([redacted]), a sizable proportion of patients have a resulting DAS28 score close to the severe threshold (5.1), and therefore patients progressed rapidly. Since this may not be reflective of the average moderate patient in clinical practice, a more conservative approach is implemented in the company's base-case whereby the midpoint of the moderate DAS28 interval (i.e. a DAS28 score of 4.15, which is the midpoint between the low disease and severe disease activity score thresholds, 3.2 and 5.1) is applied as the mean*". [21] This raises the question of whether the moderate population considered in FINCH 1 was actually suffering from moderate RA (and not severe RA respectively) and whether a downward adjustment in DAS28 scores at baseline should also be accompanied with a downward adjustment in HAQ-DI scores at baseline given that both are likely to be related in clinical practice. By adjusting DAS28 scores without adjusting HAQ-DI scores, the company may have introduced clinically implausible patient profiles. Consequently, the ERG used DAS28 scores from FINCH in their analysis of the moderate population.

5.2.4 Interventions and comparators

The intervention is filgotinib as monotherapy or in combination with other conventional DMARDs, including methotrexate. This is in line with the scope. The recommended filgotinib dose is one 200 mg tablet once a day. A dose of 100 mg of filgotinib once daily is recommended for patients with severe renal impairment (creatinine clearance 15 to 30 mL/min).[1]

Table 1 of the CS[1] presents an overview of the final scope issued by NICE and how this was addressed in the CS. According to Table 1, several comparators mentioned in the scope, and included in the NMA (infliximab, certolizumab pegol, upadacitinib, golimumab, tofacitinib) were not included in the economic model.

Treatment sequences used in the company's economic model are shown in Tables 35-43 in the CS [1] for the different populations.

ERG comment: The main concerns of the ERG relate to: a) a lack of clarity on why not all the comparators listed in the final scope issued by NICE were included in the economic model, b) the definition of best supportive care (BSC) in the economic model, c) treatment sequences used in the model.

a) In response to clarification question B3a, the company provided a table with an overview of the comparators listed in final scope issued by NICE that were included in the economic model (Table 5.7), however, not all of these are used in the company's base-case analyses.

Table 5.7: Comparators detailed in NICE scope that were included in the economic model

	cDMARD-IR population	bDMARD-IR population
Comparators	FIL (200 mg) + csDMARDs FIL (200 mg) monotherapy ABC (125 mg qw) + csDMARDs BARI + csDMARDs SARI (200 mg q2w) + csDMARDs ADA (Hulio®) (40 mg q2w) + csDMARDs ETN (Erelzi™) (50 mg qw) + csDMARDs RTX (Rixathon®) (1000 mg)+ csDMARDs* IFX (Inflectra®) (3 mg/kg) + csDMARDs TCZ (162mrg q2w) + csDMARDs ADA (Hulio®) (40 mg q2w) monotherapy ETN (Erelzi™) (50 mg qw) monotherapy BARI (4 mg) monotherapy TCZ (162 mg q2w) monotherapy ABC (125 mg qw) monotherapy csDMARDs Intensive csDMARDs** BSC	FIL (200 mg) + csDMARDs BARI (4 mg) + csDMARDs SARI (200 mg q2w) + csDMARDs TCZ (162 mg q2w) + csDMARDs RTX (Rixathon®) (1000 mg) + csDMARDs ABC (125 mg qw) + csDMARDs ABC (125 mg qw) monotherapy FIL (200 mg) monotherapy BARI (4 mg) monotherapy TOF monotherapy csDMARDs BSC
Source: Table 10 of the Clarification response.[21] *included only for the validation against exercise MTA375 **not included in scope		

The company stated that the comparators included in the economic model were the ones deemed most relevant to UK clinical practice based on NICE treatment guidelines, market share data (Therapy Watch, 2019[22]) and through validation by a UK rheumatologist. The market share data is listed in Table 5.8.

Table 5.8: Market share in RA first-line therapy

Molecule	Market share in First Line (2019)
Xeljanz	2.61%
Olumiant	5.40%
RTX biosimilar	2.65%
MabThera	1.03%
Orencia	1.73%
Kevzara	0.49%
RoActemra	9.11%
Simponi	4.14%
Cimzia	9.24%
IFX biosimilar	1.38%
Remicade	0.66%
ADA biosimilar	9.31%
Humira	12.04%

Molecule	Market share in First Line (2019)
ETN biosimilar	34.30%
Enbrel	5.92%
Source: Table 14 of the Clarification response [21]	

Infliximab (Remicade) was not included because based on clinician opinion and market share date it is rarely used (in 2019 2% in first-line). Baricitinib (Olumiant) was included as the most commonly used JAK1 inhibitor, with a market share of 5.4% compared with tofacitinib (Xeljanz) which had 2.6%. Only in population 3a (severe RA patients after failure of first-line advanced therapy, MTX ineligible, RTX ineligible), tofacitinib monotherapy was included but not based on NMA results but an assumption was made on its efficacy. Certolizumab pegol (Cimzia) was not included because it has a lower market share in first-line advanced therapy when compared with the anti-TNFs adalimumab (Humira) and etanercept (Enbrel), including biosimilars, combined (9.2% versus 62%). Golimumab (Simponi) was not included based on a lack of 24-week results, clinician opinion and a market share of 4.1% in first-line use. Although the ERG is aware of the large number of comparators and hence large number of possible treatment sequences in this submission, to the ERG these choices are not fully justified. Market access data is not necessarily a reflection of clinical usefulness, and only one UK rheumatologist's opinion was asked. This holds the risk that potentially effective and cost effective treatment sequences have been ignored. The ERG considers that certolizumab pegol should have been included in populations 3a and 3b (as it is only recommended after at least one anti-TNF and when rituximab is not a treatment option) and tofacitinib in populations 2a, 2b, 3a and 3b. However, no NMA results were available for the ERG to include these in the ERG analyses (see Section 4.3). It may be that cost effectiveness results in these populations are biased in favour of filgotinib due to these omissions. The ERG explored the impact of including tofacitinib in population 2 by using 12-week assessment ACR response data mapped to EULAR responses for all first-line treatments in the comparison. The ERG also explored the inclusion of upadacitinib as a comparator in population 2 in a scenario.

b) In response to question B3b, the company clarified that, based on clinician opinion, BSC comprised of csDMARDs that patients have previously failed on, although at lower doses.[1] It is important to note that the costs of BSC used in the modelling do not reflect this explanation, but include palliative care. This is further discussed in the Resource use and costs section of this report (5.2.9). Furthermore, it is assumed that there is no improvement associated with BSC. This is probably clinically implausible at least in the moderate population in which csDMARDs would be administered even with dose escalation and where extremely high levels of response have been observed in the FINCH 1 trial (see Section 3.3). In the moderate population, the ERG therefore preferred to use csDMARD response rates and costs over BSC zero-response and higher palliative care costs. However, this does not fully address the problem as in the model patients immediately revert to BSC upon treatment failure on their first csDMARD in the moderate population – and they remain on this there for their lifetime unless they progress to severely active RA and receive bDMARDs. The ERG therefore also set the cost of BSC equal to that of csDMARDs – the caveat of this is that this may underestimate costs in the last line of treatment. The ERG would have preferred the company to enable implementation of separate end-of-sequence treatments for the moderate and severe populations.

c) The ERG was concerned that insufficient justification was provided for the company's choice of treatment sequences. In the moderate population, in response to the clarification letter, the company added the functionality of patients becoming eligible for bDMARD treatment upon transitioning to the severe RA state. For populations 1a and 1b, treatment sequences were adapted to include treatment

with bDMARDs in response to the clarification letter[21] Tables 15 and 17: the company selected adalimumab as the first-line bDMARD treatment. This is the comparator associated with the smallest QALY gain (according to the company's cost effectiveness results, see Section 6). The ERG therefore questions whether this is the most appropriate treatment although it should also be mentioned that the company selected adalimumab as being the *"most commonly used advanced therapy in first line"*.[21] The ERG preferred the use of etanercept as the first-line comparator with the largest QALY gain (according to the company's results in populations 2a and 2b1).

In the severe population, the company chose abatacept as the default second-line option for MTX ineligible patients and tocilizumab as third-line option in the MTX eligible population (who receive RTX or alternatives in second-line). These choices were in line with previous STAs (TA10389[107]) and were accepted by the ERG.

5.2.5 Perspective, time horizon and discounting

The perspective for this analysis was that of the NHS and Personal and Social services (PSS) in England and Wales. The analysis had a lifetime horizon and used 3.5% discounting. This is all in line with current NICE guidance.

5.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness in the cost effectiveness model is mainly informed by the NMA, which informed proportions of responders associated with the different treatments. The FINCH clinical trial programme[33, 34, 89] was used to derive patient baseline characteristics. Long-term HAQ-DI progression was based on those reported in the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR) dataset used in MTA375,[103] and on Norton et.al.[104], for bDMARD and csDMARD treatment respectively.

5.2.6.1 Patient population

A patient cohort was generated by random sampling, using characteristics derived from the Phase 3 filgotinib FINCH trials. Where characteristics required for the model were not available from the clinical trials, values were taken from the Early Rheumatoid Arthritis Study (ERAS) dataset as described by Norton et al..[104] The baseline population characteristics used in the cost effectiveness model (CEM) are outlined in Table 5.9.

Table 5.9: Patient baseline characteristics used in the cost effectiveness model

Characteristics	Moderate cDMARD-IR		Severe cDMARD-IR		Severe bDMARD-IR	
	Mean (SD)	Source	Mean (SD)	Source	Mean (SD)	Source
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion female	[redacted]		[redacted]		[redacted]	
Duration of disease (years)	[redacted]		[redacted]		[redacted]	
Number of prior DMARDs	[redacted]		[redacted]		[redacted]	
Baseline HAQ-DI	[redacted]		[redacted]		[redacted]	
Baseline Pain (VAS)	[redacted]		[redacted]		[redacted]	

Characteristics	Moderate cDMARD-IR		Severe cDMARD-IR		Severe bDMARD-IR	
	Mean (SD)	Source	Mean (SD)	Source	Mean (SD)	Source
Weight (kg)	[redacted]		[redacted]		[redacted]	
DAS28	[redacted]		[redacted]		[redacted]	
RF (positive)	[redacted]		[redacted]		[redacted]	
IMD quartile	2.37	Norton et al. [104]	2.37	Norton et al. [104]	2.37	Norton et al.[104]
ACR (positive)	0.71		0.71		0.71	

Source: Table 44 of CS.[1]
* This value has been adjusted in the company's updated analysis for the moderate population
ACR = American College of Rheumatology; bDMARD = biologic disease-modifying anti-rheumatic drug; cDMARD = conventional disease-modifying anti-rheumatic drug; DMARD = disease-modifying anti-rheumatic drug; DAS28 = disease activity score 28 joints; HAQ-DI = Health Assessment Questionnaire – Disability index; IMD = index of multiple deprivation; IR = insufficient response; RF = rheumatoid factor; SD = standard deviation; VAS = visual analogue scale

5.2.6.2 Response rates

Response rates are based on the EULAR response criteria. The CS stated that the EULAR response criteria are the preferred measurement of treatment response in UK clinical practice, and are therefore recommended for use in the NICE guidance.[8] Probabilities of reaching a EULAR response (non, moderate, or good) at six months (24 weeks) for filgotinib and comparators were estimated from the NMAs evaluating treatment response for RA treatment in both the cDMARDS-IR and bDMARD-IR populations. Because in most RA clinical trials the ACR response metric is commonly used, ACR response rates were converted to EULAR response rates based on an approach developed by Stevenson et al., using US Veterans' Affairs Rheumatoid Arthritis Registry (VARA) data where both measures were reported,[102] as described and used earlier in MTA375.[103]

The efficacy estimates are presented as a proportion of the population achieving a) EULAR response (Table 5.10), and b) ACR response converted to EULAR response (Table 5.11).

Table 5.10: Probability of achieving a given response based on 24-week EULAR data

Treatment	cDMARD-IR population			bDMARD-IR population		
	No response	Moderate response	Good response	No response	Moderate response	Good response
FIL (200mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA (40mg q2w) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX (1000mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
csDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS.1
ADA = adalimumab; bDMARD = biologic disease-modifying anti-rheumatic drug; cDMARD = conventional synthetic disease-modifying anti-rheumatic drug; EULAR = European League Against Rheumatism; IR = insufficient response; MTX = methotrexate; q2w = once every two weeks; q4w = once every four weeks; RTX = rituximab; TCZ = tocilizumab
*A comparison was not possible in the NMA.

Table 5.11: Probability of achieving a given response based on 24-week ACR data converted to EULAR

Treatment	cDMARD-IR population			bDMARD-IR population		
	No response	Moderate response	Good response	No response	Moderate response	Good response
FIL (200mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABC (125 mg qw) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA (40mg q2w) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BAR (4mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETN (50mg qw) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RTX (1000mg) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAR (200mg q2w) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCZ (162mg q2w) + MTX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
csDMARDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS.[1, 21]

ABC = abatacept; ACR = American College of Rheumatology; ADA = adalimumab; BAR = baricitinib; bDMARD = biologic disease-modifying anti-rheumatic drug; cDMARD = conventional disease-modifying anti-rheumatic drug; ETN = etanercept; IR = insufficient response; MTX = methotrexate; qw = once a week; q2w = once every two weeks; q4w = once every four weeks; RTX = rituximab; SAR = sarilumab; TCZ = tocilizumab;

* A comparison was not possible in the NMA.

For some treatments, the efficacy could not be informed by the NMA, and a number of assumptions were made in the CS as described below.

1) It was assumed that BSC has no treatment effect (i.e. EULAR non-response). According to the CS this is in line with the assumption made in MTA375, TA485, TA480, and TA466.[23-25, 103]
2) It was assumed that monotherapy will have the same relative effect across all treatments as combination therapy. According to the CS, this approach is in line with the assumption made in TA466[25], and further supported by the committee guidance in MTA375.[103]
3) NMAs were not conducted separately by disease severity, because the company stated that *"results stratified by disease severity (for the moderate and severe population separately) are rarely reported"*.[1] Therefore, it was assumed that the efficacy results from the NMA in the cDMARD-IR population were applicable for both patients in the moderate and severe populations. According to the CS, this approach is in line with the assumption made by the Assessment Group in MTA375.[103] Furthermore, the company stated that the assumption was further supported by the FINCH 1 trial data, which suggested that the efficacy was similar across the populations.[1]
4) For TCZ SC combination therapy in the severe cDMARD-IR population, efficacy was assumed equivalent to TCZ +MTX in the bDMARD-IR NMA.
5) For ABC SC combination therapy in the severe bDMARD-IR population, efficacy was assumed equivalent to ABC +MTX in the cDMARD-IR NMA.

6) For TOF monotherapy in the severe bDMARD-IR population, efficacy was assumed equivalent to BAR+MTX in bDMARD-IR NMA.

5.2.6.3 HAQ-DI progression

Initial reduction

Based on MTA375 using data from the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA), patient's HAQ-DI score was assumed to reduce dependent upon the initial treatment effect (i.e. moderate or good EULAR response) at the end of the six-month initial treatment phase. In patients who showed no response the HAQ-DI trajectory was assumed to be constant. The initial HAQ-DI value reduction was independent of treatments received, in line with MTA375, TA485, TA480, and TA466.[23-25, 103] The initial reductions in HAQ-DI applied in the model are summarised in Table 5.12.

Table 5.12: Initial reduction in HAQ-DI based on the BSRBR-RA database

EULAR response	Mean change in HAQ	SE
Good	-0.672	0.112
Moderate	-0.317	0.048

Source: Table 48 of CS.[1]
BSRBR-RA = British Society of Rheumatology Biologics Register for Rheumatoid Arthritis; EULAR = European League Against Rheumatism; HAQ-DI = Health Assessment Questionnaire Disability Index; SE = standard error

Long-time progression

After the initial six-month treatment phase, the change in HAQ-DI score was based on the treatment received (bDMARD or cDMARD). Treatment with a bDMARD results in a HAQ-DI trajectory based on those reported in the 36-month BSRBR dataset analysed by the AG in MTA375.[103] The first 36 months of the trajectory were estimated using the autoregressive latent class trajectory model in MTA375, after which HAQ-DI was assumed to remain stable.

Those patients receiving csDMARDs experience a trajectory in HAQ-DI score based on the 15-year ERAS cohort data described by Norton et al..[104] The estimates reported by Norton et al. were combined with patient baseline characteristics from the FINCH trials to define the long-term HAQ-DI trajectory for individual patients for 15 years following treatment with a cDMARD, after which HAQ-DI was assumed to remain stable.

5.2.6.4 Time to treatment discontinuation

Time to treatment discontinuation (TTD) is applied in line with the MTA375. A generalised gamma distribution is used to extrapolate TTD, with parameters contingent on response (good or moderate). These parameters could not be directly derived from the MTA, but were obtained through digitisation of printed diagrams to obtain hypothetical individual patient data. Table 50 and Figure 38 of the CS show model parameters and model fit respectively.

5.2.6.5 Mortality

Age- and gender-specific mortality was based on all-cause survival data derived from UK life-tables 2015-2017.[108] Patients disease-related mortality was then based on baseline HAQ-DI score, applying

HAQ-DI stratified hazard ratio's (HRs), which were sourced from MTA375.[103] For the reference case, patients with HAQ-DI score of 0, only all-cause mortality is considered. For other patients, disease-related mortality was calculated using the HRs for survival stratified by HAQ-DI score as presented in Table 5.13.

Table 5.13: Hazard ratio for mortality associated with HAQ-DI category

HAQ-DI score	HR (95% CI)
0.000	1.00 (reference)
0.125 – 0.375	1.40 (1.10, 1.80)
0.500 – 0.875	1.50 (1.20, 1.90)
1.000 – 1.375	1.80 (1.40, 2.20)
1.500 – 1.875	2.70 (2.20, 3.50)
2.000 – 2.375	4.00 (3.10, 5.20)
2.500 – 3.000	5.50 (3.90, 7.70)

Source: Table 50 of CS.[1]
CI = confidence interval; HAQ-DI = health assessment questionnaire disability index; HR = hazard ratio.

ERG comment: The concerns of the ERG include a) patient profiles used in the model; b) implementation of HAQ trajectories; c) efficacy assumptions of TCZ-SC in the severe cDMARD population and ABC SC combination therapy in the severe bDMARD population; d) modelling of mortality; e) an over-simplification of time to treatment discontinuation (TTD); and f) the assumption that EULAR response rates are the same regardless of which line of treatment the therapy is administered and regardless of disease severity for the cDMARD population.

a) Patient profiles used in the model were generated using data from FINCH, assuming that these data could be represented by gamma (duration of disease, DAS28, HAQ-DI and number of prior DMARDs), beta (pain VAS score) and normal (weight and age) distributions and independently sampling from these distributions. Other patient characteristics sampled were presence of rheumatoid factor, the English Index of Multiple Deprivation Index quartile and ACR response. The ERG is concerned about:

   - Independent sampling from distributions about parameters that are likely correlated could generate implausible patient profiles. The company's approach is not in line with the approach taken in MTA 375, where patients who were MTX-experienced were sampled from the BSRBR database allowing for correlation to be maintained between the following characteristics: age; gender; disease duration; DAS; previous DMARDs; HAQ-DI and weight. The authors stated that *"Individual patients were resampled until the patient met the criteria for the population being analysed."* (MTA 375, p360)[103] Furthermore it was mentioned that this method required a considerable amount of re-sampling, due to over-representation of patients with a DAS score of 3.2 to 5.1 in the modelled population compared with the BSRBR. According to the ERG's clinical advisor and his review of real-world data available to him, the potentially correlated parameters include DAS28, pain, and HAQ scores (correlation coefficient of approximately r=0.5) and sampling from these separately may produce some implausible patient profiles, albeit probably only a few. The clinical advisor further highlighted that there are correlations between change in DAS28, HAQ, pain and ACR response, which, if omitted, may make

outcomes appear implausible in a noticeable number of patients. This issue only affects the newly submitted moderate population model where the company used DAS scores that were generated independently of the trial data. This is one of the reasons why the ERG prefers using the DAS scores from the FINCH trial for the generation of patient profiles.

- Only 1,000 patient profiles are generated, which are then sampled from 10,000 times. The ERG considers that it would be preferable to use as many patient profiles as patients simulated.
- The model file contained some errors in the VBA underlying the 'Main Settings' sheet that made amendments difficult. In particular, it was unclear how new patient profiles could be generated using differential distributions for each patient population (FINCH 1 moderate only, FINCH 1, severe only, and FINCH 2).

b) Implementation of HAQ-DI trajectories: the company clarified the use of patient characteristics in the model in response to the point of clarification letter. It was stated that after the initial phase, duration of disease and number of prior DMARDs were used to determine the HAQ trajectory for patients on bDMARDs (using a mapping from MTA375), and duration of disease for patients on csDMARDs/BSC (using a mapping from Norton et al. [104]). This was in line with MTA 375.

c) The assumptions on the efficacy of TCZ-SC in the severe cDMARD population (being equivalent to TCZ+MTX in the bDMARD-IR population) and the efficacy of ABC SC combination therapy in the severe bDMARD population (being equivalent to ABC+MTX in the severe cDMARD-IR population) are weak. The company stated that no data was available from the cDMARD-IR NMA, and additional assumptions were required for inclusion in the CEM. Although a similar assumption was used in an earlier TA [25], comparing SC and IV treatments from the NMA used in the company submission [1] showed a substantial difference between the mean efficacy estimates of TCZ SC and ABC SC compared with TCZ IV and ABC IV respectively in the bDMARD-IR population and cDMARD population (Figures 31 and 28 of the CS respectively), suggesting that assuming equivalence between IV and SC treatments may not be appropriate. As a response to the clarification letter by the *ERG "Gilead acknowledge that EULAR response rates are likely to decline by line of treatment"* [21]. The ERG agrees on the lack of a suitable alternative; however, the ERG wishes to emphasise that results pertaining to the comparisons with TCZ-SC and ABC-SC combination therapy in the severe cDMARD and bDMARD populations should be interpreted with caution.

d) Modelling of mortality was only based on baseline HAQ-DI, gender and age. In clinical practice, this assumption may lack validity as mortality may be correlated with adverse events, response rates or disease progression, however, this assumption is in line with MTA375.

e) Time to treatment discontinuation (TTD) may be an over-simplification and ignore discontinuation caused by adverse events. The company's approach to modelling TTD was based on the analysis described in MTA375 based on data from the BSRBR database. Modelling of differential TTD by treatment was hampered by paucity of data. However, the company did not explore whether this paucity of data persists to date. The ERG considers it potentially valuable to explore data on TTD for different bDMARDs.

f) EULAR response rates obtained from the NMA are the same regardless of which line of treatment the therapy is administered. This is a commonly made assumption in line with for example TA10389, however, response rates are not likely to be the same regardless of treatment positioning in clinical practice. The ERG considers this difficult to solve but wishes to highlight that cost effectiveness results in different treatment positions are to be interpreted with caution. Bias is likely introduced

by using EULAR response rates for all treatments at different treatment positions and this bias is very difficult to quantify.

5.2.7 Adverse events

In the base case analysis, the only AE considered was serious infection during the first six months of any active treatment. The company stated that this approach was consistent with MTA375.[103] Rates of AEs (serious infections) (Table 5.14) were based on those identified as part of the Singh et al.,[109] and were dependent on class of therapy. The company stated that this approach was more conservative compared to using treatment specific rates of AE, because filgotinib is considered to have a favourable safety and tolerability profile in patients with moderately to severely active RA. Additionally, the company provided a scenario analysis in which SAE incidence rates were used based on the FINCH 1 trial at 24 weeks, using data from the filgotinib arm (applied for JAKs), adalimumab arm (applied for other bDMARDs), and the placebo arm (applied for csDMARDs) (Table 5.15). For each AE occurrence, the company applied a decrement of 0.156[110] to the patient's overall utility by assuming that each patient would experience an AE for a total of 28 days of the six-month period, in line with MTA375.[103]

Table 5.14: SAE incidence rate in the CEM

Drug class	Rate of SAE per six-month period
cDMARDs	2.5%
bDMARDs (Inc. JAKs)	3.6%
Source: Table 53 of CS.[1] bDMARDs = biologic disease-modifying anti-rheumatic drugs; cDMARD = conventional disease-modifying anti-rheumatic drugs	

Table 5.15: SAE incidence rate from FINCH 1 applied in scenario analyses

Drug class	Rate of SAE per six-month period
cDMARDs	0.8%
bDMARDs (Excl. JAKs)	2.5%
JAKs	1.7%
Source: Table 54 of CS.[1] bDMARDs = biologic disease-modifying anti-rheumatic drugs; cDMARD = conventional disease-modifying anti-rheumatic drugs	

ERG comment: The main concerns of the ERG relate to a) the assumption AEs depend on class of therapy rather than individual treatments, and b) the claim that filgotinib is considered to have a favourable safety and tolerability profile in patients with moderately to severely active RA compared to other bDMARDs.

a) The ERG questioned whether it was reasonable to assume that AEs depend on class of therapy rather than individual treatments. The company responded that this assumption has been previously accepted by NICE, and was applied in recent technology appraisals in RA (MTA375, TA10389, TA485 and TA466).[23-25, 103] Furthermore, the company provided a scenario analysis [1], which demonstrated that separating JAK AE rates from other bDMARDs,

and varying AE rate, had minimal impact on the results. Given that this simplification is unlikely to affect results, the ERG considers it appropriate in this case.

b) The ERG questioned the claim *that "filgotinib is considered to have a favourable safety and tolerability profile in patients with moderately to severely active RA".*[1] In response to the clarification question the company stated that they have only considered serious infections for the CEM. According to the FINCH 1 trial, rates of serious infection between filgotinib and adalimumab are numerically similar at week 24, and week 52 (both in favour of filgotinib). The incidence of serious adverse events was also numerically comparable between filgotinib and adalimumab (in favour of adalimumab) according to the company. The ERG would state that the safety profile is comparable regarding the occurrence of serious infections, which was considered in the CEM.

5.2.8 Health-related quality of life

The CS stated that a systematic review was conducted to identify published literature reporting health state utility values in RA. However, the identified results were eventually not used in the model as the company argued that none of the studies were found to present a robust alternative to assessing long-term EQ-5D in RA. Furthermore, it was stated in the CS that, although the EQ-5D questionnaire was used to collect utility data in the filgotinib Phase 3 trials, health related quality of life (HRQoL) was assumed to be dependent on patient HAQ-DI score progression to align the modelling of HRQoL with previous submissions (such as MTA375[103]).

To this extent, patients' long-term HAQ-DI score trajectory was mapped to EQ-5D utilities based on a published mapping algorithm detailed by Hernandez-Alva et al.[105] using the four latent class model based on Norton et al.[104], argued to be similar to MTA375.[103] The algorithm presented by Hernandez-Alva et al.[105] uses patients' current age, gender, HAQ-DI and VAS pain scores to determine a utility value at any point in the model. For this purpose, patients' VAS pain score was estimated using their current HAQ-DI as the input for the mapping algorithm based on a polynomial curve, which represents VAS scores as a function of HAQ-DI.[1, 103] This curve was presented in MTA375 and the company digitised it and fitted a ninth order polynomial curve to obtain the polynomial coefficients.[1] Alternatively, the company explored a scenario in which utilities were estimated based on a mapping function outlined by Malottki et al.,[111] which derives utilities values from HAQ-DI scores only.

5.2.8.1 Adverse event related disutilities

In the base case, only serious infection was included in the model as an AE, which was assumed to occur only during the first six months of any active treatment (see Section 5.2.7 of this report). For each AE occurrence, a decrement of 0.156[1] was applied to the patient's overall utility, argued to be in line with MTA375.[103] This disutility was applied by assuming that each patient experienced an AE for a total of 28 days of the six-month period.

ERG comment: The main concerns of the ERG relate to: a) the derivation of VAS pain scores from the HAQ-DI score and the use of both estimates in the mapping function; b) use of pain scores in utility mapping; c) estimated utility values are set to 1 when the utility value exceeds 0.883; d) only adverse events at six months are included (i.e. after each initial treatment phase but not during the maintenance phase); e) after treatment failure, patients' utility remains unchanged (i.e. stable for six months), resulting in a small utility advantage for the filgotinib arm.

a) Utility values in the model are estimated using a mapping algorithm by Hernandez-Alava et al.[1] mapping from HAQ-DI and pain scores to EQ-5D scores, as was done in MTA 375. The VAS pain score used in the mapping algorithm is derived from the HAQ-DI and is also used as a separate

input in the same mapping algorithm. As stated in MTA 375, adding pain as an additional explanatory variable improves model fit, because HAQ-DI and pain are not perfectly correlated. However, it is questionable whether these advantages are also applicable when pain is estimated only based on the HAQ-DI (and not based on actual patient data), as is done in the company's model. The ERG estimated a Pearson's correlation coefficient of 0.735 between estimated VAS pain scores and baseline HAQ-DI, strengthening the idea that the pain VAS-scores do not add much additional information (i.e. given the high correlation between the two measures). Moreover, although the EQ-5D questionnaire was used to collect utility data in the phase three filgotinib trials [1], the company did not use this data in the model and hence opted for the approach described above. In the CS, this is justified as to be in line with MTA 375, however the ERG would have preferred the company to have included utility values based on empirical data as well (e.g. as a scenario). In response to clarification question B18c,[21] the company provided a cross-validation between the algorithms of Hernandez-Alava et al. and Malottki et al. to estimate (average) utilities in the model and the empirical data from the FINCH 1 and FINCH 2 trials. From this comparison, it can be concluded that both mapping algorithms appear to underestimate utility values by 0.075 to 0.112 (compared with the empirical data) using mapping from Hernandez-Alava et al. and by 0.179 to 0.203 using mapping from Malottki et al. The ERG therefore remains concerned that health-related quality of life may not be captured accurately in the model, both because of the mapping algorithm by Hernandez-Alava et al requiring pain VAS scores and because of the discrepancy between mapped and empirical estimates.

b) As mentioned above, the pain score used in the EQ-5D estimation can be based either on the available pain VAS score data from the FINCH trial programme or instead be estimated based on the HAQ-DI, using the mapping from Hernandez-Alava et al (which is used after baseline as well). The company used the former approach at baseline for their base-case of the economic model. The ERG is concerned that the external validity of this mapping algorithm appears to be limited: in response to clarification question B13c,[21] the company provided a cross-validation of derived VAS pain scores in the model and the empirical VAS pain scores in FINCH 1 and FINCH 2 trial which demonstrated that the VAS pain scores in the model were underestimated by 12 to 21 points (on a scale of 0 – 100) depending on the population (larger underestimation in the severe populations) (Table 5.16). This suggests that the mapping algorithm systematically and significantly underestimates the pain VAS score filled in by patients in FINCH for all three cohorts.

Table 5.16: Baseline HAQ-DI scores from the CEM mapped to pain scores, compared to trial baseline pain scores

Cohort	Model mean (SD)	Trial mean (SD)
cDMARD-IR (moderate subgroup) FINCH 1 subgroup data	38 (14.3)	[redacted]
cDMARD-IR (severe subgroup) FINCH 1 subgroup data	49 (12.5)	[redacted]
bDMARD-IR FINCH 2	47 (13.4)	67 (21.0)
Source: Reproduced from Table 15 in the Clarification letter response.[21]		

The model therefore likely over-estimates utility for all treatments. In a scenario analysis performed by the ERG in population 2.b.1, where the baseline pain score was estimated based on mapping from HAQ-DI, QALYs associated with all treatments were higher (by 0.064 points) compared with those in the company's base-case (where the pain score from FINCH was used). However, since the incremental QALY gains remained unchanged, this scenario had no impact on the ICERs. In conclusion, the ERG agrees with the company on using the pain score derived from the FINCH trial programme instead of that derived from HAQ-DI based on mapping at baseline. However, that means that there is inconsistency in the company's base-case as the mapping algorithm is used to obtain a pain score based on HAQ-DI when patients progress through the model, which then is used to inform utility estimates. In response to clarification question B13b, the company also provided a scenario in which VAS pain scores at baseline were used to estimate utility values in population 2b. In this scenario, QALYs increased for each treatment compared to the CS base case while costs remained similar. Although a similar approach has been used in MTA375, the ERG believes that the estimation of VAS pain scores is still a matter of concern and gives slight preference to the use of FINCH baseline VAS pain scores (rather than pain scores mapped from HAQ-DI) to derive utility values throughout the model in the ERG base-case. The ERG acknowledges, however, that assuming a constant pain score over time is likely clinically unrealistic.

c) In the model, estimated utility values were set to 1 when the utility value exceeded 0.883 (the largest plausible EQ-5D-5L score below perfect health). This potentially overestimated the utility values in treated patients. In response to clarification question B13e,[21] the company provided a revised model in which this assumption was dropped, which did not affect the base-case results.

d) In the model, only adverse events that occurred within the first six months were included, and the utility decrement of 0.156 was accrued at six months. In response to clarification question B14,[21] the company argued that "*based on MTA375, it was assumed that patients would not switch to a subsequent treatment within 6 months of initiating a treatment, and that any adverse event would be monitored before changing treatment at 6 months*".[21] While the ERG did request further justification (e.g. supporting data) the company only referred to previous TAs. Whilst this precedence may not mean that the analysis is necessarily correct, the ERG considers that the impact of this is probably minor.

e) In the model, when patients do not respond to treatment, their utility remains similar to the utility at treatment initiation (i.e. stable for six months), whereas patients' health states in the BSC arm

start to worsen from start given that BSC has a 100% non-response rate. This means that when two identical patients are modelled in each arm of the model with identical treatment pathways (apart from having failed at filgotinib), the patient in the filgotinib arm acquires slightly more QALYs due to the six months delay in health state worsening caused by treatment failure. The ERG considers this a minor limitation of the model, which likely does not have a large impact.

5.2.9 Resources and costs

The model included costs for drug acquisition and administration, hospitalisation costs, and adverse event costs. Costs were applied six-monthly and separated for initial treatment consisting of the first six months of every treatment (including any loading doses) and maintenance treatment (after response at six months until time to discontinuation).[1] All costs were inflated to 2018/2019 prices using the HCHS and NHSCII indices.

5.2.9.1 Resource use and costs data identified in the review

According to the CS, the SLR identified several studies reporting relevant resource use and cost information.[1] However, it was argued that none of the identified studies were found to present a robust alternative to the costing applied by MTA375.[103]

5.2.9.2 Drug acquisition and administration costs

The list price of filgotinib is [redacted] per bottle of 30 200 mg tablets, which is equivalent to [redacted] per year. A patient access scheme was provided by the company reducing list prices for moderately to severely active RA to [redacted] per year and for severely active RA only to [redacted] per year. Treatment costs provided in the model were based on UK costs and dosing regimens from MIMS 2020.[112] The company stated that, given that no treatment considered in the model has a non-confidential patient access schemes (PAS) price, PAS were excluded for Orencia® (abatacept), Olumiant® (baricitinib), Xeljanz® (tofacitinib), Kevzara® (sarilumab), and RoActemra® (tocilizumab). Furthermore, it was stated in the CS that biosimilars for adalimumab and etanercept were included in the model and that the model only considered the lowest priced biosimilars as comparators. For strategies where treatments are used in combination with MTX, the six-monthly cost of MTX was added to the six-monthly cost of the treatments. Cost of BSC was estimated from MTA375 and argued to be reflective of healthcare costs for patients who are managed without targeted therapy. Costs of BSC was assumed to be similar to post-biologic csDMARD therapy (£360 per six months). The cost of csDMARDs was assumed to equal the cost of MTX (£13.52 per six months). For drugs with weight-based dosing (e.g., tocilizumab), doses for patients were computed based on the simulated baseline weight of each patient. An overview of pack cost, sizes and dosing regimens for each treatment is shown in Table 5.18 below.

In the CS it is further argued that treatment administration costs applied in the model were reflective of route of administration, dosing guidance in MIMS 2020 and the administration costs outlined in MTA375 (see Table 5.17).[103, 112]

Table 5.17: Summary of administration costs applied in the model per treatment

Treatments		Mode of Administration	Number of doses		Administration cost (2019 £)	
			Initial 6 months	Subsequent 6-monthly	Initial 6 months	Subsequent 6-monthly
ETN	Erelzi™	SC	26	26	£76.18	£76.18
ADA	Hulio™	SC	13.5	13.5	£38.09	£38.09
		SC	13.5	13.5	£38.09	£38.09
TCZ	RoActemra®	SC	26	26	£76.18	£76.18
ABC	Orencia®	SC	26	26	£76.18	£76.18
RTX	Rixathon®	IV	2	2	£346.02	£346.02
BAR	Olumiant®	Oral	182	182	N/A	N/A
FIL	N/A	Oral	182	182	N/A	N/A
TOF	Xeljanz®	Oral	364	364	N/A	N/A
SAR	Kevzara®	SC	13.5	13.5	£38.09	£38.09
MTX		Oral	26	26	N/A	N/A

Source: Based on Table 57 of the CS.1

ABC = abatacept; ADA = adalimumab; BAR = baricitinib; ETN = etanercept; Fil = filgotinib, MTX = methotrexate; RTX = rituximab; SAR = sarilumab; TCZ = tocilizumab; TOF = tofacitinib.

Table 5.18: Summary of pack cost, sizes and dosing regimens for each treatment

Treatment		Pack cost	Pack size	Dosing regimen (maintenance)	Total monotherapy cost		Total combination therapy cost	
					Initial 6 months	Subsequent 6-monthly	Initial 6 months	Subsequent 6-monthly
ETN	Erelzi™ (biosimilar)	£643.50	50mg x 4	50mg q1w	£4,182.75	£4,182.75	£4,196.27	£4,196.27
ADA	Hulio™ (biosimilar)	£616.25	40mg x 2	40mg q2w	£4,005.63	£4,005.63	£4,019.15	£4,019.15
TCZ	RoActemra® (brand)	£913.12	162mg x 4	162mg q1w	£5,935.28	£5,935.28	£5,948.80	£5,948.80
ABC	Orencia® (brand)	£1,209.60	125mg x 4	125mg q1w	£7,862.40	£7,862.40	£7,875.92	£7,875.92
RTX	Rixathon® (biosimilar)	£1,571.67	500mg x 2	1000mg twice every 6 months	£3,143.34	£3,143.34	£3,156.86	£3,156.86
BAR	Olumiant® (brand)	£2,416.68	4mg x 84	4mg qd	£5,236.14	£5,236.14	£5,249.66	£5,249.66
TOF	Xeljanz® (brand)	£690.03	5mg x 56	5mg bid	£4,485.20	£4,485.20	£4,498.71	£4,498.71
FIL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAR	Kevzara® (brand)	£912.25	200mg x 2	200mg q2w	£5,929.63	£5,929.63	£5,943.15	£5,943.15
MTX (generic)		£52.01	10mg x 100	10mg q1w	£13.52	£13.52	NA	NA

Source: Based on Table 55 of the CS.1

ABC = abatacept; ADA = adalimumab; BAR = baricitinib; bid = twice a day; ETN = etanercept; IV = intravenous; MTX = methotrexate; PAS = patient access scheme; qd = once daily; q1w = once a week; q2w = once every two weeks; q4w = once every four weeks; qw = once a week; RTX = rituximab; SAR = sarilumab; SC = subcutaneous; TCZ = tocilizumab; TOF = tofacitinib

*model uses cost per kg to calculate cost for each individual patient

5.2.9.3 Drug Monitoring costs

Monitoring costs were modelled separately for initial treatment phase and maintenance phase and were sourced from MTA375 (see Table 5.19).[103]

Table 5.19: Six-monthly monitoring costs

Monitoring cost	Six-monthly cost (2019 £)
Initial treatment phase	£1,870.54
Maintenance phase	£884.66
Source: Based on Table 58 of the CS.[1]	

5.2.9.4 Hospitalisation costs per HAQ-DI

In the CS it is stated that, in line with MTA375, hospital costs were broken down into six categories, according to HAQ-DI level, to reflect the increasing cost burden associated with worsening RA. Similar to MTA375, no resource level breakdown was provided.

A summary of the six-monthly costs applied in the model is shown in Table 5.20.

Table 5.20: Six-monthly hospital costs based on HAQ-DI score

HAQ-DI score	Six-month cost (2019 £)
<0.60	£94.04
0.60-1.10	£57.60
1.10-1.60	£204.85
1.60-2.10	£295.28
2.10-2.60	£700.04
≥2.60	£1,509.87
Source: Based on Table 59 of the CS 1 HAQ-DI = Health assessment questionnaire disability index	

5.2.9.5 Adverse events costs

In the base case, only serious infection was included in the model, which was assumed to occur only during the first six months of any active treatment.[1] Costs for this were taken from MTA375 and amounted to £1,661.55 per event for csDMARDs, bDMARDs & JAK inhibitors.

ERG comment: The main concerns of the ERG relate to: a) costs were applied six-monthly although the maintenance period could be assumed as a continuous time variable; b) exclusion of PAS for all comparators in the CS; c) same PAS was used for both the moderate as severe population; d) the costs of BSC are likely to be too high for moderate RA patients.

a) In the model, costs are applied six-monthly and are separated for initial treatment (including any loading doses) and maintenance treatment. However, time spent in the maintenance period is based on a time to event function. In response to clarification question B15, the company argued that "*as the HAQ-DI trajectory is calculated on a 6-monthly basis, and used to accrued utilities, the time of discontinuation is rounded to the nearest 6-month cycle. Applying 6-monthly cycles is consistent with the cost-effectiveness analysis in MTA375, and other recent technical appraisals in RA*".[21] As both up- and down-rounding was applied, the ERG believes that this approach is valid.

b) In the CS, all PAS have been excluded from the analyses except for the filgotinib PAS. Although the company did not have access to PAS for other treatments, this does severely hamper the conclusions that can be drawn from the results reported in the CS, as most of the comparators' treatment costs were overestimated in the model. Hence, the ERG has provided a confidential appendix in which all analyses were run using PAS prices made available by NICE. Some comparator treatments are available in the form of biosimilars (adalimumab, etanercept and rituximab). In its base-case, the ERG used the Humira price (the only adalimumab product nationally available) and the lowest biosimilar price for all other biologics. In a scenario, the ERG explored the Humira price and the highest price of other biologics, and in a second scenario, the lowest biosimilar price for all biologics, including adalimumab was used.

c) In the CS, a PAS was provided by the company reducing list prices for moderately to severely active RA to [redacted] per year and for severely active RA only to [redacted] per year. In the model, however, the list prices of [redacted] per year was used for both for moderately to severely active RA and severely active RA only. Hence, the ERG has adjusted this in their base case analyses.

d) In the CS it is stated that the costs of BSC was assumed to be similar to post-biologic csDMARD therapy (£360 per six months) and that these were estimated from MTA375. Furthermore, it was argued that BSC costs should be reflective of healthcare costs for patients who are managed without targeted therapy [1]. However, in MTA375, these costs are labelled as "Palliative Care/Rescue Therapy". As moderate RA patients are still able to receive subsequent treatments (i.e. for severe RA), this does not constitute palliative care. Moreover, as patients with moderate RA commonly do not receive bDMARDs, the use of post-biologic cost prices may also not be applicable. As a result, the ERG is concerned that costs of BSC were too high for moderate RA patients. Hence, for the moderate RA populations, the ERG lowered the costs of BSC to be in line with the cost of csDMARDs (i.e. equal the cost of MTX; £13.52 per six months) in its base case. Given the structure of the model, in moderate RA patients, BSC is provided to patients as comparator from start (in the BSC arm), but also as last resort treatment sequence after all subsequent treatments have failed (for both arms); and the company did not enable differential costing for these two different interpretations of BSC in the model. The ERG acknowledges that lowering BSC costs at the start of the treatment more closely resembles current practice, however lowering BSC costs when used as last resort treatment may be an underestimation of BSC costs. As the CS base case is likely to overestimate costs of BSC in moderate RA patients, and the ERG base case is likely to cause an underestimation of BSC costs, both scenarios are presented in the ERG analyses.

6. COST EFFECTIVENESS RESULTS

6.1 Company's cost effectiveness results

The company presented cost effectiveness results for its 10 populations. The company's deterministic results are shown here for all populations. The company's results use the PAS for filgotinib, which at the time of writing was not yet approved, but not the PAS schemes for comparators.

Table 6.1: Overview of model outcomes in different model populations (CS)

Population	Sub-population	Further division	Health Outcomes FIL vs comparators	Costs	Cost effectiveness
1. Moderate RA patients*	a) MTX ineligible	-	Positive QALY gain vs BSC	More costly than BSC	FIL cost effective under threshold of £30,000*
1. Moderate RA patients*	b) MTX eligible	-	Positive QALY gain vs BSC	More costly than BSC	FIL cost effective under threshold of £30,000*
2. Severe RA patients, First line	a) MTX ineligible	-	Negative QALY gain vs ETN and BAR, positive QALY gain for FIL vs ADA, TCZ	Cheapest	FIL dominates ADA & TCZ, cheaper & less effective than ETN, BAR
2. Severe RA patients, First line	b) MTX eligible	1. Second-line RTX	Negative QALY gain vs ETN and BAR, positive QALY gain vs ADA	Cheapest	FIL dominates ADA, cheaper & less effective than ETN, BAR
2. Severe RA patients, First line	b) MTX eligible	2. Second-line IL-6 (RTX contra-indicated)	Same as above (2.b), but smaller total QALYs	Cheapest	FIL dominates ADA, cheaper & less effective than ETN, BAR
2. Severe RA patients, First line	b) MTX eligible	3. Second-line CD80 (RTX contra-indicated)	Same as above (2.b), QALY gains fall in between second-line RTX and IL-6	Cheapest	FIL dominates ADA, cheaper & less effective than ETN, BAR
3. Severe RA patients, Second line, RTX ineligible	a) MTX ineligible	-	Negative QALY gain vs ABC, positive QALY gain vs TOF and BAR	Cheapest	FIL dominates TOF and BAR, cheaper & less effective than ABC
3. Severe RA patients, Second line, RTX ineligible	b) MTX eligible	-	Negative QALY gain vs ABC, positive QALY gain vs BAR, TCZ, SAR	Cheapest	FIL dominates BAR, TCZ, SAR, cheaper & less effective than ABC

4. Severe RA patients, Second line, RTX eligible	MTX eligible	-	Negative QALY gain vs RTX	Cheapest	FIL cheaper & less effective than RTX
5. Severe RA patients, Third line, RTX failure	-	-	Positive QALY gain vs TCZ, SAR	Cheapest	FIL dominates TCZ, SAR
* Based on both originally submitted model and revision submitted in response to clarification letter. ABC = abatacept; ADA = adalimumab; BAR = baricitinib; BSC = best supportive care; ETN = etanercept; FIL = filgotinib; MTX = methotrexate; QALY = quality adjusted life year; RA = Rheumatoid Arthritis; RTX = rituximab; SAR = sarilumab; TCZ = tocilizumab; TOF = tofacitinib.					

Detailed results of the company's deterministic analyses are presented in the following tables for all 10 populations.

For the moderate RA population, both the original analyses and updated analyses, that is without and with the possibility for patients to receive bDMARDs upon progression to severe RA respectively, are presented.

6.1.1 1a. Moderate RA patients after two csDMARD failures (MTX ineligible)

Table 6.2: Cost effectiveness results population 1a, without bDMARDs upon progression

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	15.810	[redacted]	-	-	-	21,721.27	-
FIL	[redacted]	15.810	[redacted]	13,182.52	0.000	0.607	-	21,721.27

Source: CS Table 63.1
BSC = best supportive care; FIL = filgotinib; LYG = life year gained; MTX = methotrexate; PBO = placebo; QALY = quality adjusted life year

Table 6.3: Cost effectiveness results population 1a, with bDMARDs upon progression

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	15.810	[redacted]	-	-	-	11,843.53	-
FIL	[redacted]	15.810	[redacted]	6,918.39	0.000	0.584	-	11,843.53

Source: Response to Clarification letter Table 23.21
BSC = best supportive care; FIL = filgotinib; LYG = life year gained; MTX = methotrexate; PBO = placebo; QALY = quality adjusted life year

6.1.2 1b. Moderate RA patients after 2 csDMARD failures (MTX eligible)

Table 6.4: Cost effectiveness results population 1b, without bDMARDs upon progression

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	15.810	[redacted]	-	-	-	21,923.81	-
FIL + MTX	[redacted]	15.810	[redacted]	13,305.44	0.000	0.607	-	21,923.81

Source: CS Table 64.1
BSC = best supportive care; FIL = filgotinib; LYG = life year gained; MTX = methotrexate; PBO = placebo; QALY = quality adjusted life year

Table 6.5: Cost effectiveness results population 1b, with bDMARDs upon progression

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	15.810	[redacted]	-	-	-	13,908.64	-
FIL + MTX	[redacted]	15.810	[redacted]	7,855.22	0.000	0.565	-	13,908.64

Source: Response to Clarification letter Table 24.21
BSC = best supportive care; FIL = filgotinib; LYG = life year gained; MTX = methotrexate; PBO = placebo; QALY = quality adjusted life year

6.1.3 2a. Severe RA patients in first line advanced therapy treatment (MTX ineligible)

Table 6.6: Cost effectiveness results population 2a

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL	[redacted]	14.639	[redacted]	-	-	-	-	-
ADA	[redacted]	14.639	[redacted]	18,513.58	0.000	-0.013	Dominated	Dominated
ETN	[redacted]	14.639	[redacted]	3,250.59	0.000	0.076	342,678.87 SW	42,542.73
BAR	[redacted]	14.639	[redacted]	8,015.03	0.000	-0.039	1,231,213.04 SW	Dominated
TCZ SC	[redacted]	14.639	[redacted]	5,000.95	0.000	-0.048	Dominated	Dominated

Source: CS Table 65.1
ABC = abatacept; ADA = adalimumab; BAR = baricitinib; BSC = best supportive care; ETN = etanercept; FIL = filgotinib; LYG = life year gained; MTX = methotrexate; QALY = quality adjusted life year; TCZ = tocilizumab

6.1.4 2b. Severe RA patients in first-line advanced therapy treatment (MTX eligible)

Population 2b is further subdivided into three sub-populations, by type of second-line treatment: RTX for the RTX eligible population, and IL-6 or CD80 treatment for the RTX ineligible population.

Table 6.7: Cost effectiveness results population 2b.1 RTX eligible population (second-line RTX)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.639	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.639	[redacted]	18,263.14	0.000	-0.011	Dominated	Dominated
ETN + MTX	[redacted]	14.639	[redacted]	4,100.90	0.000	0.064	418,614.42 SW	63,661.88
BAR + MTX	[redacted]	14.639	[redacted]	7,638.94	0.000	-0.033	1,466,495.03 SW	Dominated

Source: CS Table 66 .[1]
ADA = adalimumab; BAR = baricitinib; BSC = best supportive care; ETN = etanercept; FIL = filgotinib; LYG = life year gained; MTX = methotrexate; QALY = quality adjusted life year

Table 6.8: Cost effectiveness results population 2b.2 RTX ineligible population (second-line IL-6)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.639	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.639	[redacted]	18,275.44	0.000	-0.014	Dominated	Dominated
ETN + MTX	[redacted]	14.639	[redacted]	4,522.59	0.000	0.086	317,815.33 SW	52,874.08
BAR + MTX	[redacted]	14.639	[redacted]	7,348.72	0.000	-0.045	1,110,108.52 SW	Dominated

Source: CS Table 67.1
ADA = adalimumab; BAR = baricitinib; ETN = etanercept; FIL = filgotinib; IL-6 = interleukin 6; LYG = life year gained; MTX = methotrexate; QALY = quality adjusted life year

Table 6.9: Cost effectiveness results population 2b.3 RTX ineligible population (second-line CD80)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	14.639	[redacted]	-	-	-	-	-
ADA + MTX	[redacted]	14.639	[redacted]	18,511.67	0.000	-0.013	Dominated	Dominated
ETN + MTX	[redacted]	14.639	[redacted]	3,261.87	0.000	0.076	342,826.47 SW	42,690.46
BAR + MTX	[redacted]	14.639	[redacted]	8,008.97	0.000	-0.039	1,231,350.00 SW	Dominated

Source: CS Table 68.1
ADA = adalimumab; BAR = baricitinib; CD80 = cluster of differentiation 80; ETN = etanercept; FIL = filgotinib; LYG = life year gained; MTX = methotrexate; QALY = quality adjusted life year

6.1.5 3a. Severe RA patients after failure of first-line advanced therapy treatment (MTX ineligible, RTX ineligible)

Table 6.10: Cost effectiveness results population 3a

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL	[redacted]	13.638	[redacted]	-	-	-	-	-
TOF	[redacted]	13.638	[redacted]	18,837.66	0.000	-0.105	Dominated	Dominated
BAR	[redacted]	13.638	[redacted]	5,915.81	0.000	0.000	Dominated	Dominated
ABC	[redacted]	13.638	[redacted]	38,824.93	0.000	0.204	644,289.94 SW	190,639.45

Source: CS Table 69.1
ABC = abatacept; BAR = baricitinib; FIL = filgotinib; LYG = life year gained; QALY = quality adjusted life year; TOF = tofacitinib

6.1.6 3b. Severe RA patients after failure of first-line advanced therapy treatment (MTX eligible, RTX ineligible)

Table 6.11: Cost effectiveness results population 3b

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.638	[redacted]	-	-	-	-	-
BAR + MTX	[redacted]	13.638	[redacted]	24,736.31	0.000	-0.105	Dominated	Dominated
TCZ + MTX	[redacted]	13.638	[redacted]	6,551.69	0.000	0.008	Dominated	864,430.99
SAR + MTX	[redacted]	13.638	[redacted]	431.84	0.000	0.014	Dominated	30,919.04
ABC + MTX	[redacted]	13.638	[redacted]	31,874.15	0.000	0.182	644,447.82 SW	175,026.45

Source: CS Table 70.1
ABC = abatacept; BAR = baricitinib; FIL = filgotinib; LYG = life year gained; MTX = methotrexate; QALY = quality adjusted life year; SAR = sarilumab; TCZ = tocilizumab

6.1.7 4. Severe RA patients after failure of first-line advanced therapy (MTX eligible, RTX eligible)

Table 6.12: Cost effectiveness results population 4

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.638	[redacted]	-	-	-	-	-
RTX + MTX	[redacted]	13.638	[redacted]	14,735.41	0.000	0.009	1,582,703.38 SW	1,582,703.38

Source: CS Table 71.1
FIL = filgotinib; LYG = life year gained; MTX = methotrexate; QALY = quality adjusted life year; RTX = rituximab.

6.1.8 5. Severe RA patients after failure of rituximab in combination with MTX

Table 6.13: Cost effectiveness results population 5

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL + MTX	[redacted]	13.638	[redacted]	-	-	-	-	-
TCZ + MTX	[redacted]	13.638	[redacted]	31,288.00	0.000	-0.097	Dominated	Dominated
SAR + MTX	[redacted]	13.638	[redacted]	431.84	0.000	0.014	Dominated	30,919.04

Source: CS Table 72.1
FIL = filgotinib; LYG = life year gained; MTX = methotrexate; QALY = quality adjusted life year; SAR = sarilumab; TCZ = tocilizumab.

6.2 Company's sensitivity analyses

The company undertook several sensitivity and scenario analyses. Deterministic sensitivity analyses were based on the net monetary benefit (NMB) using a threshold of £20,000 per QALY gained and one chosen comparator in each population. Sensitivity and scenario analyses were shown in the same tornado diagrams in Figures 60 to 62 of the CS and Appendix J. Table 84 of the CS shows all the varied parameters and explored scenarios. Of the company's performed analyses, disregarding time horizon and discount rate, company's results were most sensitive to the choice of method for estimating HAQ-DI progression, the choice of method for mapping utilities, hospital cost variations, variations in the efficacy of abatacept (populations 3.a and 3.b), variations in administration costs and source of AE rates (population 4), and variations in the efficacy of sarilumab (population 5).

Furthermore, the company performed probabilistic sensitivity analyses (PSA) in all populations, using only 500 simulated patients (reduced from 10,000 in the deterministic analysis to save up on computational time) and 1,000 PSA runs.

ERG comment: The ERG had concerns over a) the stability of the model given the number of simulated patients used; and b) the reliability of PSA results; and c) the model only allowing for five comparator strategies at a time.

a) The company provided diagnostic plots showing model convergence for costs and QALYs over 30,000 simulated patients to assess model stability at the chosen number of 10,000 simulated patients. These show that some stability is achieved and the company's approach, a compromise between stability and run-times could be deemed reasonable. However, the ERG has the concern that these diagnostic plots may not tell the full story: the company samples 10,000 times from 1,000 patient profiles. Heterogeneity is therefore potentially under-estimated and diagnostic plots are potentially unduly influenced. The ERG would advise the use of a set of as many patient profiles as simulated patients to be able to assess model convergence.

b) Two issues with the PSA related to the low number of simulations run and parameters excluded from the PSA. 1) The company provided convergence plots but also highlighted that the model complexity necessitated a pragmatic approach. The ERG considers that the selected convergence plots do show some convergence at 1,000 simulations, however, together with the low number of modelled patients (500), this is likely insufficient to produce really stable results. Given model run times, the ERG appreciated the difficulty in providing stable PSA results but wishes to highlight that the PSA may be unstable. 2) The PSA included some model parameters (response rates, HAQ-DI reduction, hospitalisation costs) but not all: time to treatment discontinuation and the HAQ-DI trajectory were not included. As for response rates, correlations between these were not taken into account (NMA results were not used directly, but instead means and standard errors were used). In response to the POC letter, the company included all of these in the PSA. The ERG considers this issue as resolved.

c) The model only allows for five comparator strategies to be used at a time in each analysis. For some populations, this means that not all relevant comparators can be included in the analysis. The ERG would appreciate if this could be changed to enable more than five comparator strategies to be evaluated against each other (preferably seven). This would be especially important if the company relaxed their strict inclusion criteria for comparators (in the NMA and the economic analysis).

6.3 Model validation and face validity check

The company stated that it undertook efforts to validate the cost effectiveness model and the cost effectiveness estimates for various inputs and outputs of the model. Internal validation was done by individually validating model outputs against their input equations for both survival and treatment discontinuation. Furthermore, it was stated that *"a review was carried out to ensure the model operates as expected over the full range of inputs"* and that parameter estimations within the model were checked against estimates generated by spreadsheet-based duplicated models.[1]

External validation was done by an independent third-party clinician. Furthermore, the company provided a cross-validation of the cost and QALY outputs of their model to MTA375.[103] In the CS, it is argued that in all cases, the filgotinib model produces higher costs and QALYs than the MTA375 model, however this variation remained within [redacted]. The company further argues that, "as the results for the two models were found using two different sources of efficacy inputs, these results should be interpreted with caution".[1] For this MTA375 model outputs were sourced from a validation conducted by the ERG in TA10389 and were obtained using the inputs presented in TA10389 for upadacitinib, including inputs from the NMA and cost inputs.

Table 6.14: Results from the filgotinib model compared to the MTA375 model

Sequence	Total discounted costs			Total discounted QALYs		
	FIL model	TA375 model	Ratio	FIL model	TA375 model	Ratio
1	[redacted]	£64,926	[redacted]	[redacted]	7.16	[redacted]
2	[redacted]	£78,306	[redacted]	[redacted]	7.70	[redacted]
3	[redacted]	£92,003	[redacted]	[redacted]	7.77	[redacted]
4	[redacted]	£94,925	[redacted]	[redacted]	7.28	[redacted]

Source: CS Table 86.1
FIL = filgotinib; QALY = quality adjusted life year

ERG comment: The ERG had concerns over a) missing information regarding validation of model outputs against input equations; b) lack of information on validation by (clinical) experts; c) minimal cross-validation on input parameters and outcomes of the model; d) transparency issues and faulty interface; e) overall model validity.

a) In the CS, it is mentioned that *"model outputs were individually validated against their input equations for both survival and treatment discontinuation"*.[1] However, this data was not available to the ERG. In response to clarification question B17b, this information was provided and looked satisfying to the ERG. However, it was further stated in the CS that *"a review was carried out to ensure the model operates as expected over the full range of inputs"* and *"to ensure consistency, parameter estimations within the model were checked against estimates generated by spreadsheet-based duplicated models"*.[1] In response to clarification question B17c, the company did not provide results of this review or any other spreadsheet-based duplicated model.

b) In the CS it is stated that model programming, calculations and inputs have also been reviewed and that the model was externally validated by an independent third-party clinician. In response to clarification question B17d & B17e, the company clarified that the reviewer was not involved in creating the model but was an independent assessor. Furthermore, the company stated that the model approach was externally validated by an independent third-party clinician, who has been involved in another recent TA in RA.

c) In the clarification letter, the company was asked to provide cross-validation for all relevant input parameters (e.g. cost inputs, utility inputs, HAQ-DI scores, change in HAQ-DI over time, treatment sequences, and EULAR response rates for relevant comparators, proportions of responders stratified as good, moderate, none, time to treatment discontinuation, excess mortality) and the corresponding inputs with MTA375 and the more recent STAs TA466 and TA480 (clarification question B17f and B17g). In response, the company provided a table in which all approaches were compared. This table lacked, however, direct (quantifiable) comparison of all input parameters and hence was not particularly helpful to the ERG. Furthermore, in clarification question B18b, the company was asked to provide a comparison between modelled outcomes and similar outcomes that can be retrieved from the FINCH 1 & FINCH 2 trials. In response to this question, the company provided a cross-validation between the modelled proportion of simulated EULAR responders at 24 weeks and treatment discontinuation rates at 24 weeks compared to the results of FINCH 1 only (not for FINCH 2). The modelled outcomes closely resembled FINCH 1 data except for treatment discontinuation in sever RA patients in the FIL200 mg + MTX condition (10.9% in FINCH 1 compared to 5.9% in the model). However, this may be due to the difference in population as discontinuation rates in the FINCH 1 were only available for the overall moderate to severely active disease cohort. The ERG would have preferred to have been provided the same cross-validation to the FINCH 2 data and it is unclear to the ERG why this was not provided by the company.

d) The ERG found model adaptation was hampered by a lack of transparency in the model. Hidden sheets, cells and headings induce complexity in reviewing a model. In addition, there were several mistakes made in the model interface: for example, the reset default code would result in patient characteristics being deleted due to an erroneous cell link to an empty array.

e) In conclusion, the ERG is not completely satisfied with the company's efforts of validating the model. In particular, concerns remain about model internal validity (the company should have had other modellers review it). The ERG did undertake additional checks, such as reviewing parts of the VBA code, e.g. utility estimation, survival estimation, patient profile generation, implementation of efficacy and HAQ-DI score calculations, results of which are detailed in the relevant sections. Changes in model inputs did result in model outcome changes in the expected direction, so the ERG is reasonably confident that the company's model is valid. Concerns also remain about the insufficient level of cross-validation and external validation.

7. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

7.1 Exploratory and sensitivity analyses undertaken by the ERG

Table 7.1 summarises the main issues highlighted by the ERG in Section 5.2 of this report, indicates the expected direction of bias introduced by these issues and whether these are examined in ERG analysis either in the base-case or as a scenario conditional on the base case.

Based on all considerations in Section 5.2 (summarised in Table 7.1), the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the ERG form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016)[113]:

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

7.1.1 ERG new base-case

Moderate population:

1. FV: Moderate population: use csDMARD (costs and response rates) as comparator instead of BSC
2. FV: Moderate population: Change subsequent BSC costs to csDMARD costs
3. MJ: Moderate population: use DAS28 score from FINCH
4. MJ: Moderate population: alternative treatment sequences in the severe population: replace ADA (least QALYs) by ETA (most QALYs)
5. MJ: All populations: estimate HRQoL always based on constant pain VAS score from FINCH

Severe population:

1. FE: Severe population: Filgotinib price not implemented in line with company's PAS
2. MJ: All populations: estimate HRQoL always based on constant pain VAS score from FINCH

Results are presented in Table 7.2 – Table 7.11, an overview is provided in Table 7.12.

7.1.2 ERG scenarios

1. Alternative filgotinib price for the severely active RA population
2. Include upadacitinib as comparator in populations 2
3. Week 12 assessment response rates for all first-line treatments in population 2b to include tofacitinib

Table 7.1: Main ERG critique of company's submitted economic evaluation

Issue: numbered if included in ERG base-case (BC)	Likely direction of bias introduced in ICER[a]	ERG analyses (BC or scenario)	Addressed in company analysis?
Model structure (section 5.2.2)			
No progression possible to severe in moderate population	+/-	BC	Yes, in revised base-case
No possibility of moving back to moderate once severe	+/-	-	-
Population, interventions and comparators, perspective and time horizon (sections 5.2.3 to 5.2.5)			
Model includes only >=2csDMARDs, not in line with trial population	+/-	-	-
Potentially relevant comparators excluded (also based on restrictions in NMA)	+/-	Scenarios	Scenarios
Treatment sequences: not all are included	+/-	Scenarios	Scenarios
Best Supportive Care definition not in line with model – should be differential for moderate and severe populations	+/-	BC	-
Treatment effectiveness and extrapolation (section 5.2.6)			
DAS28 score not based on trial data	+/-	BC	-
Patient profiles likely insufficient and underestimating heterogeneity, model stability unclear	+/-	-	-
NMA results likely biased due to inclusion criteria	+/-	-	-
Response rates assumed valid regardless of treatment line and time-point	+/-	BC	Scenarios
Equivalent effectiveness with or without MTX	+/-	-	-
Equivalent effectiveness in moderate and severe csDMARD populations	+/-	-	-
Mortality not based on disease progression / adverse events	+/-	-	-
TTD not differential per treatment	+/-	-	-
Health-related quality of life (section 5.2.8)			
Estimated using mapping function based on HAQ-DI and (unreliable) pain score	+/-	BC	Scenario
Resources and costs (section 5.2.9)			
Filgotinib pricing unclear	+	BC	-

Issue: numbered if included in ERG base-case (BC)	Likely direction of bias introduced in ICER[a]	ERG analyses (BC or scenario)	Addressed in company analysis?
BSC costs likely over-estimated, at least in moderate population	+/-	BC	-
Model implementation (section 6)			
Model stability not demonstrated	+/-	Scenario	-
PSA unstable	+/-	-	-

a Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator.
BC = base-case; BSC = best supportive care; CS = company submission; ERG = Evidence Review Group; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; ITT = intention-to-treat; MJ = matters of judgement; MTX = methotrexate; NMA = network meta-analysis; TTD = time-to-treatment discontinuation.

7.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Table 7.2 – 7.11 show the (deterministic) ERG base-case for all populations, which is summarised in Table 7.12. Results from the PSA in population 2b1 are shown in Table 7.13. PSA run-times were prohibitive for running the PSA in all populations (approximately 15 hours for a PSA with 1,500 patients – the company's recommended minimum number – and 1,000 PSA runs; approximately four hours for 1,000 patients and 500 PSA runs). The impact of each ERG change on the ICERs is illustrated in population 1b for the moderate population changes, and in population 2b1 for the severe population in Tables 7.14 and 7.20 respectively. The exploratory scenario analyses are presented in Tables 7.21 onwards. These are all conditional on the ERG base-case. A summary table comparing the cost effectiveness results in CS base-case, ERG base-case and scenarios is provided in Table 7.40. The submitted model file contains technical details on the analyses performed by the ERG (the "ERG" sheets provide an overview of the cells that were altered for each adjustment).

Table 7.2: ERG base-case Population 1a

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) vs BSC	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
BSC	[redacted]	[redacted]					7.831	9.309
FIL (200mg) monotherapy	[redacted]	[redacted]	0.288	£7,855	£27,251	NA	7.727	9.335

Table 7.3: ERG base-case Population 1b

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) vs BSC	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
BSC	[redacted]	[redacted]					7.831	9.309
FIL (200mg) + csDMARDs	[redacted]	[redacted]	0.288	£7,977	£27,676	NA	7.721	9.331

Table 7.4: ERG base-case Population 2a

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
FIL (200mg) monotherapy	[redacted]	[redacted]			£0		4.559	6.610

ADA (Hulio®) (40mg q2w) monotherapy	[redacted]	[redacted]	-0.010	£16,775	FIL dominating	Dominated	3.710	6.041
ETN (Erelzi™) (50mg qw) monotherapy	[redacted]	[redacted]	0.055	£3,251	FIL less costly and less effective	£59,110	3.602	5.988
BARI monotherapy	[redacted]	[redacted]	-0.028	£8,015	FIL less costly and less effective	Dominated	3.174	5.693
TCZ (162mg q2w) monotherapy	[redacted]	[redacted]	-0.034	£5,001	FIL dominating	Dominated	2.890	5.492

Table 7.5: ERG base-case Population 2b1

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		5.451	7.254
ADA (Hulio®) (40mg q2w) + csDMARDs	[redacted]	[redacted]	-0.008	£16,525	FIL dominating	Dominated	4.615	6.694
ETN (Erelzi™) (50mg qw) + csDMARDs	[redacted]	[redacted]	0.047	£4,101	FIL less costly and less effective	£87,322	4.457	6.604
BARI + csDMARDs	[redacted]	[redacted]	-0.024	£7,639	FIL less costly and less effective	Dominated	4.052	6.327

Table 7.6: ERG base-case Population 2b2

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		5.584	7.259
ADA (Hulio®) (40mg q2w) + csDMARDs	[redacted]	[redacted]	-0.011	£16,537	FIL dominating	Dominated	4.746	6.697

ETN (Erelzi™) (50mg qw) + csDMARDs	[redacted]	[redacted]	0.061	£4,523	FIL less costly and less effective	£74,005	4.581	6.607
BARI + csDMARDs	[redacted]	[redacted]	-0.032	£7,349	FIL less costly and less effective	Dominated	4.182	6.331

Table 7.7: ERG base-case Population 2b3

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		4.548	6.603
ADA (Hulio®) (40mg q2w) + csDMARDs	[redacted]	[redacted]	-0.010	£16,773	FIL dominating	Dominated	3.699	6.034
ETN (Erelzi™) (50mg qw) + csDMARDs	[redacted]	[redacted]	0.055	£3,262	FIL less costly and less effective	£59,316	3.591	5.980
BARI + csDMARDs	[redacted]	[redacted]	-0.028	£8,009	FIL less costly and less effective	Dominated	3.163	5.685

Table 7.8: ERG base-case Population 3a

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
FIL (200mg) monotherapy	[redacted]	[redacted]			£0		6.555	7.628
TOF monotherapy	[redacted]	[redacted]	-0.078	£17,008	FIL dominating	Dominated	5.627	6.984
BARI (4mg) monotherapy	[redacted]	[redacted]	0.000	£5,916	FIL dominating	Dominated	5.331	6.786

ABC (125mg qw) monotherapy	[redacted]	[redacted]	0.149	£38,825	FIL less costly and less effective	£261,273	3.539	5.641

Table 7.9: ERG base-case Population 3b

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		6.549	7.624
BARI (4mg) + csDMARDs	[redacted]	[redacted]	-0.078	£22,907	FIL dominating	Dominated	5.326	6.783
TCZ (162mg q2w) + csDMARDs	[redacted]	[redacted]	0.006	£6,552	FIL dominating	£1,096,378	5.004	6.570
SARI (200mg q2w) + csDMARDs	[redacted]	[redacted]	0.010	£432	FIL dominating	£44,483	4.992	6.566
ABC (125mg qw) + csDMARDs	[redacted]	[redacted]	0.133	£31,874	FIL less costly and less effective	£239,808	3.532	5.637

Table 7.10: ERG base-case Population 4

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)

FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		5.382	6.948
RTX (Rixathon®) (1000mg) + csDMARDs	[redacted]	[redacted]	0.007	£12,906	FIL less costly and less effective	£1,960,015	4.744	6.524

Table 7.11: ERG base-case Population 5

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		6.549	7.624
TCZ (162mg q2w) + csDMARDs	[redacted]	[redacted]	-0.072	£29,459	FIL dominating	Dominated	5.004	6.570
SARI (200mg q2w) + csDMARDs	[redacted]	[redacted]	0.010	£432	FIL dominating	£44,483	4.992	6.566

Table 7.12: Overview of model outcomes in different model populations (ERG base-case)

Population	Sub-population	Further division	Health Outcomes FIL vs comparators	Costs	Cost effectiveness
1. Moderate RA patients	a) MTX ineligible	-	Positive QALY gain vs BSC	More costly than BSC	FIL cost effective under threshold of £30,000
1. Moderate RA patients	b) MTX eligible	-	Positive QALY gain vs BSC	More costly than BSC	FIL cost effective under threshold of £30,000

Population	Sub-population	Further division	Health Outcomes FIL vs comparators	Costs	Cost effectiveness
2. Severe RA patients, First line	a) MTX ineligible	-	Negative QALY gain vs ETN and BAR, positive QALY gain for FIL vs ADA, TCZ	Cheapest	FIL dominates ADA & TCZ, cheaper & less effective than ETN, BAR
2. Severe RA patients, First line	b) MTX eligible	1. Second-line RTX	Negative QALY gain vs ETN and BAR, positive QALY gain vs ADA	Cheapest	FIL dominates ADA, cheaper & less effective than ETN, BAR
2. Severe RA patients, First line	b) MTX eligible	2. Second-line IL-6 (RTX contra-indicated)	Same as above (2.b), but smaller total QALYs	Cheapest	FIL dominates ADA, cheaper & less effective than ETN, BAR
2. Severe RA patients, First line	b) MTX eligible	3. Second-line CD80 (RTX contra-indicated)	Same as above (2.b), QALY gains fall in between second-line RTX and IL-6	Cheapest	FIL dominates ADA, cheaper & less effective than ETN, BAR
3. Severe RA patients, Second line, RTX ineligible	a) MTX ineligible	-	Negative QALY gain vs ABC, positive QALY gain vs TOF and BAR	Cheapest	FIL dominates TOF and BAR, cheaper & less effective than ABC
3. Severe RA patients, Second line, RTX ineligible	b) MTX eligible	-	Negative QALY gain vs ABC, positive QALY gain vs BAR, TCZ, SAR	Cheapest	FIL dominates BAR, TCZ, SAR, cheaper & less effective than ABC
4. Severe RA patients, Second line, RTX eligible	MTX eligible	-	Negative QALY gain vs RTX	Cheapest	FIL cheaper & less effective than RTX
5. Severe RA patients, Third line, RTX failure	-	-	Positive QALY gain vs TCZ, SAR	Cheapest	FIL dominates TCZ, SAR

ABC = abatacept; ADA = adalimumab; BAR = baricitinib; BSC = best supportive care; ETN = etanercept; FIL = filgotinib; MTX = methotrexate; QALY = quality adjusted life year; RA = Rheumatoid Arthritis; RTX = rituximab; SAR = sarilumab; TCZ = tocilizumab; TOF = tofacitinib.

Table 7.13: Probabilistic results (1,000 patients, 500 PSA runs) ERG base-case population 2b1

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0	
ADA (Hulio®) (40mg q2w) + csDMARDs	[redacted]	[redacted]	-0.007	£16,307	FIL dominating	Dominated
ETN (Erelzi™) (50mg qw) + csDMARDs	[redacted]	[redacted]	0.036	£3,462	FIL less costly and less effective	£97,434
BARI (4mg) + csDMARDs	[redacted]	[redacted]	-0.018	£7,843	FIL less costly and less effective	Dominated

Table 7.14: ERG base-case adjustment 1 (csDMARD (costs and response rates) as comparator instead of BSC) in population 1b

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) vs BSC	ICER (£/QALY) incremental
csDMARDS / BSC	[redacted]	[redacted]				
FIL (200mg) + csDMARDs	[redacted]	[redacted]	0.419	£10,145	£24,198	NA

Table 7.15: ERG base-case adjustment 2 (Change subsequent BSC costs to csDMARD costs) in population 1b

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) vs BSC	ICER (£/QALY) incremental
BSC	[redacted]	[redacted]				
FIL (200mg) + csDMARDs	[redacted]	[redacted]	0.565	£10,584	£18,741	NA

Table 7.16: ERG base-case adjustment 3 (use DAS28 score from FINCH) in population 1b

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) vs BSC	ICER (£/QALY) incremental
BSC	[redacted]	[redacted]				
FIL (200mg) + csDMARDs	[redacted]	[redacted]	0.479	£924	£1,932	NA

Table 7.17: ERG base-case adjustment 4 (alternative treatment sequences in the severe population) in population 1b

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) vs BSC	ICER (£/QALY) incremental
BSC	[redacted]	[redacted]				
FIL (200mg) + csDMARDs	[redacted]	[redacted]	0.560	£7,636	£13,635	NA

Table 7.18: ERG base-case adjustment 5 (estimate HRQoL always based on constant pain VAS score from FINCH) in population 1b

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) vs BSC	ICER (£/QALY) incremental
BSC	[redacted]	[redacted]				
FIL (200mg) + csDMARDs	[redacted]	[redacted]	0.440	£7,895	£17,960	NA

Table 7.19: ERG base-case adjustment 6 (Filgotinib price not implemented in line with company's PAS) in population 2b1

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0	
ADA (Hulio®) (40mg q2w) + csDMARDs	[redacted]	[redacted]	-0.011	£16,524	FIL dominating	Dominated
ETN (Erelzi™) (50mg qw) + csDMARDs	[redacted]	[redacted]	0.064	£4,109	FIL less costly and less effective	£63,783
BARI + csDMARDs	[redacted]	[redacted]	-0.033	£7,635	FIL less costly and less effective	Dominated

Table 7.20: ERG base-case adjustment 7 (estimate HRQoL always based on constant pain VAS score from FINCH) in population 2b1

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0	
ADA (Hulio®) (40mg q2w) + csDMARDs	[redacted]	[redacted]	-0.008	£18,262	FIL dominating	Dominated
ETN (Erelzi™) (50mg qw) + csDMARDs	[redacted]	[redacted]	0.047	£4,109	FIL less costly and less effective	£87,488
BARI + csDMARDs	[redacted]	[redacted]	-0.024	£7,635	FIL less costly and less effective	Dominated

7.3 ERG scenarios

7.3.1 Cost effectiveness results for Scenario 1

Table 7.21: ERG scenario 1 Population 2a

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k)	NHB (30k)
FIL (200mg) monotherapy	[redacted]	[redacted]			£0		4.649	6.671
ADA (Hulio®) (40mg q2w) monotherapy	[redacted]	[redacted]	-0.010	£18,587	FIL dominating	Dominated	3.710	6.041
ETN (Erelzi™) (50mg qw) monotherapy	[redacted]	[redacted]	0.055	£3,251	FIL less costly and less effective	£59,110	3.602	5.988
BARI monotherapy	[redacted]	[redacted]	-0.028	£8,015	FIL less costly and less effective	Dominated	3.173	5.693
TCZ (162mg q2w) monotherapy	[redacted]	[redacted]	-0.034	£5,001	FIL dominating	Dominated	2.889	5.492

Table 7.22: ERG scenario 1 Population 2b1

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k)	NHB (30k)

FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		5.541	7.314
ADA (Hulio®) (40mg q2w) + csDMARDs	[redacted]	[redacted]	-0.008	£18,337	FIL dominating	Dominated	4.616	6.694
ETN (Erelzi™) (50mg qw) + csDMARDs	[redacted]	[redacted]	0.047	£4,101	FIL less costly and less effective	£87,322	4.457	6.605
BARI + csDMARDs	[redacted]	[redacted]	-0.024	£7,639	FIL less costly and less effective	Dominated	4.052	6.326

Table 7.23: ERG scenario 1 Population 2b2

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k)	NHB (30k)
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		5.674	7.319
ADA (Hulio®) (40mg q2w) + csDMARDs	[redacted]	[redacted]	-0.011	£18,349	FIL dominating	Dominated	4.746	6.697
ETN (Erelzi™) (50mg qw) + csDMARDs	[redacted]	[redacted]	0.061	£4,523	FIL less costly and less effective	£74,005	4.581	6.607
BARI + csDMARDs	[redacted]	[redacted]	-0.032	£7,349	FIL less costly and less effective	Dominated	4.182	6.331

Table 7.24: ERG scenario 1 Population 2b3

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k)	NHB (30k)
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		4.638	6.663
ADA (Hulio®) (40mg q2w) + csDMARDs	[redacted]	[redacted]	-0.010	£18,586	FIL dominating	Dominated	3.699	6.034
ETN (Erelzi™) (50mg qw) + csDMARDs	[redacted]	[redacted]	0.055	£3,262	FIL less costly and less effective	£59,316	3.591	5.980
BARI + csDMARDs	[redacted]	[redacted]	-0.028	£8,009	FIL less costly and less effective	Dominated	3.162	5.685

Table 7.25: ERG scenario 1 Population 3a

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k)	NHB (30k)
FIL (200mg) monotherapy	[redacted]	[redacted]			£0		6.651	7.692
TOF monotherapy	[redacted]	[redacted]	-0.078	£18,915	FIL dominating	Dominated	5.627	6.984

BARI (4mg) monotherapy	[redacted]	[redacted]	0.000	£5,916	FIL dominating	Dominated	5.331	6.787
ABC (125mg qw) monotherapy	[redacted]	[redacted]	0.149	£38,825	FIL less costly and less effective	£261,273	3.539	5.641

Table 7.26: ERG scenario 1 Population 3b

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k)	NHB (30k)
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		6.644	7.688
BARI (4mg) + csDMARDs	[redacted]	[redacted]	-0.078	£24,814	FIL dominating	Dominated	5.326	6.783
TCZ (162mg q2w) + csDMARDs	[redacted]	[redacted]	0.006	£6,552	FIL dominating	£1,096,378	5.004	6.571
SARI (200mg q2w) + csDMARDs	[redacted]	[redacted]	0.010	£432	FIL dominating	£44,483	4.992	6.566
ABC (125mg qw) + csDMARDs	[redacted]	[redacted]	0.133	£31,874	FIL less costly and less effective	£239,808	3.532	5.636

Table 7.27: ERG scenario 1 Population 4

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k)	NHB (30k)
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		5.477	7.011

RTX (Rixathon®) (1000mg) + csDMARDs	[redacted]	[redacted]	0.007	£14,813	FIL less costly and less effective	£2,249,652	4.743	6.524

Table 7.28: ERG scenario 1 Population 5

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k)	NHB (30k)
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		6.644	7.688
TCZ (162mg q2w) + csDMARDs	[redacted]	[redacted]	-0.072	£31,366	FIL dominating	Dominated	5.004	6.571
SARI (200mg q2w) + csDMARDs	[redacted]	[redacted]	0.010	£432	FIL dominating	£44,483	4.992	6.566

7.3.2 Cost effectiveness results for Scenario 2

Table 7.29: ERG scenario 2 Population 2a

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
FIL (200mg) monotherapy	[redacted]	[redacted]			£0		4.558	6.610

ADA (Hulio®) (40mg q2w) monotherapy	[redacted]	[redacted]	-0.010	£16,761	FIL dominating	Dominated	3.740	6.061
ETN (Erelzi™) (50mg qw) monotherapy	[redacted]	[redacted]	0.055	£3,260	FIL less costly and less effective	£59,278	3.632	6.008
TCZ (162mg q2w) monotherapy	[redacted]	[redacted]	-0.062	£13,006	FIL dominating	Dominated	2.919	5.512
UPA (15mg q2w)	[redacted]	[redacted]	0.056	£46,849	FIL less costly and less effective	£833,781	0.633	4.006

Table 7.30: ERG scenario 2 Population 2b1

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		5.450	7.254
ADA (Hulio®) (40mg q2w) + csDMARDs	[redacted]	[redacted]	-0.008	£16,511	FIL dominating	Dominated	4.644	6.713
ETN (Erelzi™) (50mg qw) + csDMARDs	[redacted]	[redacted]	0.047	£4,109	FIL less costly and less effective	£87,488	4.485	6.623
BARI (4mg) + csDMARDs	[redacted]	[redacted]	-0.024	£7,635	FIL less costly and less effective	Dominated	4.081	6.346
UPA (15mg q2w) + cDMARDs	[redacted]	[redacted]	0.019	£52,125	FIL less costly and less effective	£2,758,071	1.492	4.626

Table 7.31: ERG scenario 2 Population 2b2

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		5.584	7.259

ADA (Hulio®) (40mg q2w) + csDMARDs	[redacted]	[redacted]	-0.011	£16,523	FIL dominating	Dominated	4.777	6.717
ETN (Erelzi™) (50mg qw) + csDMARDs	[redacted]	[redacted]	0.061	£4,533	FIL less costly and less effective	£74,176	4.611	6.627
BARI + csDMARDs	[redacted]	[redacted]	-0.032	£7,343	FIL less costly and less effective	Dominated	4.213	6.352
UPA (15mg q2w) + cDMARDs	[redacted]	[redacted]	0.025	£52,342	FIL less costly and less effective	£2,114,769	1.620	4.631

Table 7.32: ERG scenario 2 Population 2b3

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		4.548	6.603
ADA (Hulio®) (40mg q2w) + csDMARDs	[redacted]	[redacted]	-0.010	£16,759	FIL dominating	Dominated	3.729	6.054
ETN (Erelzi™) (50mg qw) + csDMARDs	[redacted]	[redacted]	0.055	£3,271	FIL less costly and less effective	£59,484	3.620	6.000

BARI + csDMARDs	[redacted]	[redacted]	-0.028	£8,004	FIL less costly and less effective	Dominated	3.192	5.705
UPA (15mg q2w) + cDMARDs	[redacted]	[redacted]	0.022	£51,849	FIL less costly and less effective	£2,333,725	0.622	3.999

7.3.3 Cost effectiveness results for Scenario 3

Table 7.33: ERG scenario 3 Population 2a

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
FIL (200mg) monotherapy	[redacted]	[redacted]			£0		4.558	6.610
ETN (Erelzi™) (50mg qw) monotherapy	[redacted]	[redacted]	0.045	£20,013	FIL less costly and less effective	£441,025	3.602	5.988
TOF mono	[redacted]	[redacted]	-0.067	£246	FIL dominating	Dominated	3.523	5.913
BARI monotherapy	[redacted]	[redacted]	0.038	£7,769	FIL less costly and less effective	£202,197	3.173	5.693
TCZ (162mg q2w) monotherapy	[redacted]	[redacted]	-0.034	£5,001	FIL dominating	Dominated	2.889	5.492

Table 7.34: ERG scenario 3 Population 2b1

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		5.513	7.310
ADA (Hulio®) (40mg q2w) + csDMARDs	[redacted]	[redacted]	-0.020	£18,290	FIL dominating	Dominated	4.578	6.680
ETN (Erelzi™) (50mg qw) + csDMARDs	[redacted]	[redacted]	0.032	£3,542	FIL less costly and less effective	£111,978	4.433	6.593
BARI (4mg) + csDMARDs	[redacted]	[redacted]	-0.007	£9,419	FIL less costly and less effective	Dominated	3.955	6.272
TOF (5mg bid) + cDMARDs	[redacted]	[redacted]	0.051	£34,433	FIL less costly and less effective	£671,967	2.284	5.176

Table 7.35: ERG scenario 3 Population 2b2

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		5.637	7.313

ADA (Hulio®) (40mg q2w) + csDMARDs	[redacted]	[redacted]	-0.027	£18,029	FIL dominating	Dominated	4.709	6.685
ETN (Erelzi™) (50mg qw) + csDMARDs	[redacted]	[redacted]	0.045	£4,028	FIL less costly and less effective	£90,306	4.551	6.595
BARI (4mg) + csDMARDs	[redacted]	[redacted]	-0.010	£9,299	FIL less costly and less effective	Dominated	4.076	6.275
TOF (5mg bid) + cDMARDs	[redacted]	[redacted]	0.068	£34,937	FIL less costly and less effective	£511,376	2.397	5.178

Table 7.36: ERG scenario 3 Population 2b3

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) FIL vs X	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
FIL (200mg) + csDMARDs	[redacted]	[redacted]			£0		4.653	6.690
ADA (Hulio®) (40mg q2w) + csDMARDs	[redacted]	[redacted]	-0.026	£18,515	FIL dominating	Dominated	3.701	6.047
ETN (Erelzi™) (50mg qw) + csDMARDs	[redacted]	[redacted]	0.041	£3,093	FIL less costly and less effective	£75,171	3.587	5.984

BARI (4mg) + csDMARDs	[redacted]	[redacted]	-0.010	£9,546	FIL less costly and less effective	Dominated	3.101	5.657
TOF (5mg bid) + cDMARDs	[redacted]	[redacted]	0.061	£33,272	FIL less costly and less effective	£547,297	1.498	4.609

Table 7.37: Comparison of cost effectiveness outcomes

Population	Sub-population	Further division	Revised CS base-case	ERG base-case	ERG base-case PSA*	Scenario 1	Scenario 2	Scenario 3
1. Moderate RA patients	a) MTX ineligible	-	FIL cost effective under threshold of £30,000	FIL cost effective under threshold of £30,000	-		-	-
1. Moderate RA patients	b) MTX eligible	-	FIL cost effective under threshold of £30,000	FIL cost effective under threshold of £30,000	-		-	-
2. Severe RA patients, First line	a) MTX ineligible	-	FIL dominates ADA & TCZ, cheaper & less effective than ETN, BAR	FIL dominates ADA & TCZ, cheaper & less effective than ETN, BAR	-	FIL dominates ADA & TCZ, cheaper & less effective than ETN, BAR	FIL dominates ADA & TCZ, cheaper and less effective than ETN, UPA	*FIL dominates TCZ, cheaper and less effective than ETN, BAR, TOF*
2. Severe RA patients, First line	b) MTX eligible	1. Second-line RTX	FIL dominates ADA, cheaper & less effective than ETN, BAR	FIL dominates ADA, cheaper & less effective than ETN, BAR	FIL dominates ADA, cheaper & less effective than ETN, BAR	FIL dominates ADA, cheaper & less effective than ETN, BAR	FIL dominates ADA, cheaper and less effective than ETN, BAR, UPA	FIL dominates ADA, cheaper and less effective than ETN, BAR, TOF

Population	Sub-population	Further division	Revised CS base-case	ERG base-case	ERG base-case PSA*	Scenario 1	Scenario 2	Scenario 3
2. Severe RA patients, First line	b) MTX eligible	2. Second-line IL-6 (RTX contra-indicated)	FIL dominates ADA, cheaper & less effective than ETN, BAR	FIL dominates ADA, cheaper & less effective than ETN, BAR	-	FIL dominates ADA, cheaper & less effective than ETN, BAR	FIL dominates ADA, cheaper and less effective than ETN, BAR, UPA	FIL dominates ADA, cheaper and less effective than ETN, BAR, TOF
2. Severe RA patients, First line	b) MTX eligible	3. Second-line CD80 (RTX contra-indicated)	FIL dominates ADA, cheaper & less effective than ETN, BAR	FIL dominates ADA, cheaper & less effective than ETN, BAR	-	FIL dominates ADA, cheaper & less effective than ETN, BAR	FIL dominates ADA, cheaper and less effective than ETN, BAR, UPA	FIL dominates ADA, cheaper and less effective than ETN, BAR, TOF
3. Severe RA patients, Second line, RTX ineligible	a) MTX ineligible	-	FIL dominates TOF and BAR, cheaper & less effective than ABC	FIL dominates TOF and BAR, cheaper & less effective than ABC	-	FIL dominates TOF and BAR, cheaper & less effective than ABC	-	-
3. Severe RA patients, Second line, RTX ineligible	b) MTX eligible	-	FIL dominates BAR, TCZ, SAR, cheaper & less effective than ABC	FIL dominates BAR, TCZ, SAR, cheaper & less effective than ABC	-	FIL dominates BAR, TCZ, SAR, cheaper & less effective than ABC	-	-
4. Severe RA patients, Second line, RTX eligible	MTX eligible	-	FIL cheaper & less effective than RTX	FIL cheaper & less effective than RTX	-	FIL cheaper & less effective than RTX	-	-
5. Severe RA patients,	-	-	FIL dominates TCZ, SAR	FIL dominates TCZ, SAR	-	FIL dominates TCZ, SAR	-	-

Population	Sub-population	Further division	Revised CS base-case	ERG base-case	ERG base-case PSA*	Scenario 1	Scenario 2	Scenario 3
Third line, RTX failure								

7.4 Conclusions of the cost effectiveness section

The company identified no economic evaluations addressing the decision problem it aimed to target: the cost-effectiveness of filgotinib in moderately to severely active RA. In the absence of economic evaluations for this decision problem, the company developed a *de novo* economic evaluation, which was heavily based on MTA375. The company's economic evaluation met most of the NICE reference case criteria, with the exception of probabilistic modelling: a sufficient number of simulations (and patients) was hampered by the model's long run-times (a common problem with discrete event simulations). It is worth highlighting that the company's decision problem is narrower in focus than NICE's scope, focusing on a population of patients who have received at least two prior csDMARDs, rather than at least one prior csDMARD. This potentially affected the appropriateness of the NMA (as described in Section 1.3 of this report) and subsequently led to the potential omission of relevant comparators and relevant studies informing efficacy. The company used the FINCH trial programme to inform effectiveness of filgotinib, which also included patients who had only one prior csDMARD, which led to a discrepancy between effectiveness results. Further limitations include the company's assumptions that response rates obtained from the NMA are valid regardless of line-of-treatment and although observed only at the 24-weeks assessment hold throughout life-time; equivalent treatment effectiveness with or without the addition of methotrexate and also in the moderate and severe populations. The ERG considers that there remains substantial uncertainty about the presented cost effectiveness results for these reasons.

As mentioned above, the selection of comparators in the model may not have been appropriate: potentially relevant comparators certolizumab pegol, tofacitinib (in most populations), golimumab and infliximab were not included. The ERG considered that market share data and opinion of one expert (for golimumab and infliximab) were likely insufficient justifications. However, infliximab is now rarely used and its exclusion could be appropriate. Golimumab was excluded also because no 24-week assessment data were available. Data for certolizumab pegol in the correct population and tofacitinib at 24 weeks were not included in the NMA. The ERG considered that these comparators may have been inappropriately excluded, possibly resulting in cost effectiveness results being biased. The ERG was furthermore concerned about the implementation of Best Supportive Care in the model. It was defined as being comprised of csDMARDs administered at lower doses – however, its pricing in the model contradicts this (including palliative care costs, in line with MTA375). With this in mind, BSC as implemented in the model should only be used as the last treatment line – however, the company used it also as the comparator and end-of-sequence treatment after failure with any treatment in the moderate population. This was considered inappropriate by the ERG, as in the moderate population patients do have the option of being treated with further csDMARDs or bDMARDs once they progress to severely active RA. The ERG considers that it would be preferred if the company could enable implementation of separate end-of-sequence treatments for the moderate and severe populations and the ERG also changed the comparator in the moderate population to csDMARD treatment.

The model structure was in line with previous submissions to NICE, including MTA375, and after a request from the ERG the company added the functionality of moderate RA patients progressing through to a severely active RA state where they can receive bDMARDs. As not all possible treatment sequences could be incorporated in the model (due to model complexity and run-times), uncertainty remains about cost effectiveness in the moderate and severe populations. In addition, the model still does not reflect the possibility of patients transitioning from a severe state to a moderate state. As such, the model simplifies the reality of RA patients, although it is in line with previous submissions.

Treatment sequences in the company's model are a very simplified version of reality, owing to model complexity and run-times. Whilst the ERG acknowledges the difficulty of reflecting treatment sequences

accurately in the model, there were concerns over the company's selection. In the moderate population, patients would receive BSC in the comparator arm or after treatment with filgotinib, and if they became severe they would receive adalimumab, the comparator associated with the smallest QALY gain according to the company's cost effectiveness results. The ERG considered it appropriate to explore the comparator with the highest QALY gain (etanercept) as first-line bDMARD sequence.

The company's model likely used an insufficient number of patient profiles (1,000 profiles which are drawn from 10,000 times), which likely under-estimated heterogeneity. The ERG would have preferred the use of as many patient profiles as patients simulated (which would also make model diagnostics more meaningful). This means that there are concerns about model stability, which could not be fully demonstrated.. Likewise, the PSA number of iterations is likely small and based on a small number of sampled patients. This limitation is difficult to address given long model run-times.

Common issues in RA models also observed in this model include mortality being based only on baseline HAQ-DI, gender, and age, rather than also taking changes in HAQ-DI and adverse events into account; time to treatment discontinuation being assumed the same for all treatments (i.e. not taking discontinuation based on adverse events into account), and health-related quality of life being estimated using a mapping function based on HAQ-DI and pain scores without reliable estimates of pain scores being available. The impact of these assumptions is difficult to quantify.

The company's pricing was unclear as there is differential pricing for patients with moderately to severely active RA and severely active RA and the company only used the former in the model. The ERG changed the price used in the severely active RA model population to that proposed for the severely active RA population.

The company undertook some effort to validate their model. Overall, based on its own checks, the ERG is satisfied that the model performs as expected. However, the company could have provided more detail on their validation exercises and could have, in fact, put more effort into model internal, external and cross-validation.

Based on these considerations, the ERG made multiple changes to the model, including fixing errors, fixing violations and matters of judgement. It is important to bear in mind that both the company's and ERG's ICERs suffered from some uncertainty relating to the population, comparators and effectiveness estimates that could not be resolved. The main concern was that of insufficient patient profiles casting doubt over the stability of model results. The lack of stability means that different sets of patient profiles could result in different results. The ERG is therefore not confident about the company's and the ERG's cost-effectiveness results. However, it should be noted that differences in QALYs between comparators were relatively small in all analyses, except in the moderate population where the ERG considers uncertainty to be larger.

8. REFERENCES

[1] Gilead Sciences. *Filgotinib for treating moderate-to-severe rheumatoid arthritis [ID1632]. Document B: company evidence submission to National Institute of Health and Care Excellence. Single technology appraisal (STA) [Word document provided by the company]*: Gilead Sciences, 16th April 2020 [accessed 21.4.20]. 228p.

[2] Gibofsky A. Epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis: A synopsis. *Am J Manag Care* 2014;20(7 Suppl):S128-135.

[3] Symmons D. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. *Rheumatology* 2002;41(7):793-800.

[4] Office for National Statistics. Population estimates for the UK, England and Wales, Scotland and Northern Ireland.

[5] Humphreys JH, Verstappen SMM, Hyrich KL, Chipping JR, Marshall T, Symmons DPM. The incidence of rheumatoid arthritis in the UK: comparisons using the 2010 ACR/EULAR classification criteria and the 1987 ACR classification criteria. Results from the Norfolk Arthritis Register. *Ann Rheum Dis* 2013;72(8):1315-1320.

[6] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;62(9):2569-2581.

[7] Kiely P, Walsh D, Williams R, Young A, for the Early Rheumatoid Arthritis Network. Outcome in rheumatoid arthritis patients with continued conventional therapy for moderate disease activity: the early RA network (ERAN). *Rheumatology* 2011;50(5):926-931.

[8] National Institute for Health and Care Excellence. NICE Pathway: Rheumatoid arthritis overview 2020.

[9] Cole Z, Blanthorn-Hazel S, Mohammed D, Parker B. E044 Healthcare resource utilisation associated with management of patients with moderate rheumatoid arthritis in the UK: initial data from a multi-centre, retrospective, non-interventional study. *Rheumatology* 2019;58(Suppl 3):kez110.043.

[10] Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch MH, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). *Ann Rheum Dis* 2014;73(1):62-68.

[11] Matcham F, Scott IC, Rayner L, Hotopf M, Kingsley GH, Norton S, et al. The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis. *Semin Arthritis Rheum* 2014;44(2):123-130.

[12] Michaud K, Berglind N, Franzén S, Frisell T, Garwood C, Greenberg JD, et al. Can rheumatoid arthritis (RA) registries provide contextual safety data for modern RA clinical trials? The case for mortality and cardiovascular disease. *Ann Rheum Dis* 2016;75(10):1797-1805.

[13] Safiri S, Kolahi AA, Hoy D, Smith E, Bettampadi D, Mansournia MA, et al. Global, regional and national burden of rheumatoid arthritis 1990–2017: a systematic analysis of the Global Burden of Disease study 2017. *Ann Rheum Dis* 2019;78(11):1463-1471.

[14] Ahmed M. *A re-audit of the rheumatoid arthritis care pathway: comparing clinical practice with best practice. Year 3 External SSC 2011-12 [Unpublished]*, n.d. [accessed 21.7.20]

[15] Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020:annrheumdis-2019-216655.

[16] Shakespeare-Smith T. *Filgotinib for treating moderate to severe rheumatoid arthritis. Patient organisation submission [ID1632] [Word document supplied with the company submission]*: National Rheumatoid Arthritis Society (NRAS), [accessed 7.7.20]

[17] National Institute for Health and Care Excellence. *Filgotinib for treating moderate to severe rheumatoid arthritis: final scope*. London: NICE, 2020 [accessed 7.7.20]. 6p.

[18] National Institute for Health and Care Excellence. *Rheumatoid arthritis in adults: management. NICE guideline [NG100] [Internet]*. London: NICE, 11.7.18 [accessed 7.7.20] Available from: https://www.nice.org.uk/guidance/ng100

[19] Gunasekera W, Kirwan J. Rheumatoid arthritis: previously untreated early disease. *Clin Evid* 2014;Clinical Evidence(8):1124.

[20] Gilead. Filgotinib: draft summary of product characteristics. 2020.

[21] National Institute for Health and Care Excellence. *Filgotinib for treating moderate to severe rheumatoid arthritis [ID1632]: Clarification response (part 1, V1.0)*. London: NICE, 27.5.2020 [accessed 4.6.20]. 76p.

[22] Therapy Watch. 2019.

[23] National Institute for Health and Care Excellence. *Sarilumab for moderate to severe rheumatoid arthritis. Technology appraisal guidance [TA485] [Internet]*. London: NICE, 2017 [accessed 7.7.20] Available from: https://www.nice.org.uk/guidance/ta485

[24] National Institute for Health and Care Excellence. *Tofacitinib for moderate to severe rheumatoid arthritis. Technology appraisal guidance [TA480] [Internet]*. London: NICE, 2017 [accessed 7.7.20] Available from: https://www.nice.org.uk/guidance/ta480

[25] National Institute for Health and Care Excellence. *Baricitinib for moderate to severe rheumatoid arthritis. Technology appraisal guidance [TA466] [Internet]*. London: NICE, 2017 [accessed 7.7.20] Available from: https://www.nice.org.uk/guidance/ta466

[26] Gilead Sciences. *Filgotinib for treating moderate-to-severe rheumatoid arthritis [ID1632]. Document A: Company evidence submission summary for committee. Single technology appraisal (STA) [Word document provided by the company]*: Gilead Sciences, 16th April 2020 [accessed 21.4.20]. 50p.

[27] Gilead Sciences. *Filgotinib for treating moderate-to-severe rheumatoid arthritis [ID1632]. Appendix D: Identification, selection and synthesis of clinical evidence [Word document provided by the company]*: Gilead Sciences, 16th April 2020 [accessed 21.4.20]. 43p.

[28] Higgins J, Lasserson T, Chandler J, Tovey D, Churchill R. *Methodological Expectations of Cochrane Intervention Reviews (MECIR): standards for the conduct and reporting of new Cochrane Intervention Reviews, reporting of protocols and the planning, conduct and reporting of updates. Version 1.04 [Internet]*, 2017 [accessed 12.12.17] Available from: http://community.cochrane.org/mecir-manual

[29] Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *Int J Technol Assess Health Care* 2012;28(2):138-44.

[30] Egger M, Zellweger-Zähner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. *Lancet* 1997;350(9074):326-9.

[31] Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M, et al. Chapter 4: Searching for and selecting studies. 4.4.5 Language, date and document format restrictions. In: Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. *Cochrane handbook for systematic reviews of interventions version 6.0 (updated July 2019) [Internet]*: Cochrane, 2019 [accessed 21.7.20]. Available from: https://training.cochrane.org/handbook/current/chapter-04

[32] Curtis JR, Singh JA. Use of biologics in rheumatoid arthritis: current and emerging paradigms of care. *Clin Ther* 2011;33(6):679-707.

[33] Gilead. *A randomized, double-blind, placebo- and active-controlled, multicenter, phase 3 study to assess the efficacy and safety of filgotinib administered for 52 weeks in combination with methotrexate to subjects with moderately to severely active rheumatoid arthritis who have an inadequate response to methotrexate (FINCH 1) clinical study report*: Gilead, 2020

[34] Gilead. *Randomized, double-blind, placebo-controlled, multicenter, phase 3 study to assess the efficacy and safety of filgotinib administered for 24 weeks in combination with conventional synthetic disease-modifying anti-rheumatic drug(s) (csDMARDs) to subjects with moderately to severely active rheumatoid arthritis who have an inadequate response to biologic DMARD(s) Treatment (FINCH 2). Clinical study report*: Gilead, 2020

[35] Abe T. A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. *J Rheumatol* 2006;33(1):37-44.

[36] Genant HK, Peterfy CG, Westhovens R, Becker JC, Aranda R, Vratsanos G, et al. Abatacept inhibits progression of structural damage in rheumatoid arthritis: results from the long-term extension of the AIM trial. *Ann Rheum Dis* 2008;67(8):1084-9.

[37] Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis* 2008;67(8):1096-103.

[38] Baek HJ, Lim MJ, Park W, Park SH, Shim SC, Yoo DH, et al. Efficacy and safety of tocilizumab in Korean patients with active rheumatoid arthritis. *Korean J Intern Med* 2019;34(4):917-931.

[39] Beals C, Baumgartner R, Peterfy C, Balanescu A, Mirea G, Harabagiu A, et al. Magnetic resonance imaging of the hand and wrist in a randomized, double-blind, multicenter, placebo-controlled trial of infliximab for rheumatoid arthritis: Comparison of dynamic contrast enhanced assessments with semi-quantitative scoring. *PLoS One* 2017;12(12):e0187397.

[40] Chen D-Y. Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. *J Formos Med Assoc* 2009;108(4).

[41] Cohen S. Interleukin 1 receptor antagonist anakinra improves functional status in patients with rheumatoid arthritis. *J Rheumatol* 2003;30(2).

[42] Emery P. Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. *J Rheumatol* 2006;33(4):33(4):681-9.

[43] Mease P. Improved health-related quality of life for patients with active rheumatoid arthritis receiving rituximab: results of the dose-ranging assessment: International clinical evaluation of rituximab in rheumatoid arthritis (DANCER) trial. *J Rheumatol* 2008;35(1).

[44] Westhovens R, Taylor PC, Alten R, Pavlova D, Enriquez-Sosa F, Mazur M, et al. Filgotinib (GLPG0634/GS-6034), an oral JAK1 selective inhibitor, is effective in combination with methotrexate (MTX) in patients with active rheumatoid arthritis and insufficient response to MTX: results from a randomised, dose-finding study (DARWIN 1). *Ann Rheum Dis* 2017;76(6):998-1008.

[45] Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. *Ann Rheum Dis* 2006;65(10):1357-62.

[46] Smolen JS, Burmester G-R, Combe B, Curtis JR, Hall S, Haraoui B, et al. Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. *Lancet* 2016;388(10061):2763-2774.

[47] Weinblatt M. Intravenous golimumab inhibits radiographic progression and maintains clinical efficacy and safety in patients with active rheumatoid arthritis despite methotrexate therapy: 1-year results of a phase 3 trial., 2012.

[48] Weinblatt ME, Schiff M, Valente R, van der Heijde D, Citera G, Zhao C, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. *Arthritis Rheum* 2013;65(1):28-38.

[49] Weinblatt ME, Westhovens R, Mendelsohn AM, Kim L, Lo KH, Sheng S, et al. Radiographic benefit and maintenance of clinical benefit with intravenous golimumab therapy in patients with active rheumatoid arthritis despite methotrexate therapy: results up to 1 year of the phase 3, randomised, multicentre, double blind, placebo controlled GO-FURTHER trial. *Ann Rheum Dis* 2014;73(12):2152-9.

[50] Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. *Mod Rheumatol* 2014;24(5):715-24.

[51] Tanaka Y. Efficacy and safety of sarilumab plus methotrexate in a phase 3 trial in Japanese patients with active rheumatoid arthritis (KAKEHASI). *Int J Rheum Dis* 2018.

[52] Tanaka Y, Wada K, Takahashi Y, Hagino O, van Hoogstraten H, Graham NMH, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a randomized, placebo-controlled phase III trial in Japan. *Arthritis Res Ther* 2019;21(1):79.

[53] Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004;50(5):1400-11.

[54] Kim H, Lee S, Song Y, Yoo H, Koh E, Ypp B, et al. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. *APLAR J Rheumatology* 2007;10(1):9-16.

[55] Kremer J. Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate. *Ann Intern Med* 2002.

[56] Lim MJ. A double-blind, placebo-controlled, multicenter trial of tocilizumab in moderate to severe active RA patients with inadequate response to methotrexate in Korean population. 2013.

[57] Genovese MC, Fleischmann R, Kivitz AJ, Rell-Bakalarska M, Martincova R, Fiore S, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a phase III study. *Arthritis Rheumatol* 2015;67(6):1424-37.

[58] Genovese MC, van Adelsberg J, Fan C, Graham NMH, van Hoogstraten H, Parrino J, et al. Two years of sarilumab in patients with rheumatoid arthritis and an inadequate response to MTX: safety, efficacy and radiographic outcomes. *Rheumatology (Oxford)* 2018;57(8):1423-1431.

[59] Strand V, Kosinski M, Chen CI, Joseph G, Rendas-Baum R, Graham NM, et al. Sarilumab plus methotrexate improves patient-reported outcomes in patients with active rheumatoid arthritis and inadequate responses to methotrexate: results of a phase III trial. *Arthritis Res Ther* 2016;18:198.

[60] Takeuchi T, Miyasaka N, Zang C, Alvarez D, Fletcher T, Wajdula J, et al. A phase 3 randomized, double-blind, multicenter comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity, and safety in Japanese subjects with active rheumatoid arthritis. *Mod Rheumatol* 2013;23(4):623-33.

[61] O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, et al. Therapies for active rheumatoid arthritis after methotrexate failure. *N Engl J Med* 2013;369(4):307-18.

[62] Choy E, McKenna F, Vencovsky J, Valente R, Goel N, Vanlunen B, et al. Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. *Rheumatology (Oxford)* 2012;51(7):1226-34.

[63] Tanaka Y, Suzuki M, Nakamura H, Toyoizumi S, Zwillich SH, Tofacitinib Study I. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Care Res (Hoboken)* 2011;63(8):1150-8.

[64] Kang YM, Park YE, Park W, Choe JY, Cho CS, Shim SC, et al. Rapid onset of efficacy predicts response to therapy with certolizumab plus methotrexate in patients with active rheumatoid arthritis. *Korean J Intern Med* 2018;33(6):1224-1233.

[65] Keystone EC, Taylor PC, Drescher E, Schlichting DE, Beattie SD, Berclaz PY, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. *Ann Rheum Dis* 2015;74(2):333-40.

[66] Hobbs K, Deodhar A, Wang B, Bitman B, Nussbaum J, Chung J, et al. Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of etanercept in patients with moderately active rheumatoid arthritis despite DMARD therapy. *Springerplus* 2015;4:113.

[67] Kivitz A. Peficitinib, a JAK inhibitor, in the treatment of moderate-to-severe rheumatoid arthritis in patients with an inadequate response to methotrexate. *Arthritis Rheumatol* 2017;69(4):709–719.

[68] Taylor PC. Baricitinib versus placebo or adalimumab in patients with active rheumatoid arthritis (RA) and an inadequate response to background methotrexate therapy: results of a phase 3 study. *2015 ACR/ARHP Annual Meeting*, 2015.

[69] Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med* 2017;376(7):652-662.

[70] Matsubara T, Inoue H, Nakajima T, Tanimura K, Sagawa A, Sato Y, et al. Abatacept in combination with methotrexate in Japanese biologic-naive patients with active rheumatoid arthritis: a randomised placebo-controlled phase IV study. *RMD Open* 2018;4(2):e000813.

[71] Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008;371(9617):987-997.

[72] Dougados M, van der Heijde D, Chen YC, Greenwald M, Drescher E, Liu J, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis* 2017;76(1):88-95.

[73] Kang YM. Efficacy and safety of certolizumab pegol (czp) with concomitant methotrexate (mtx) in Korean rheumatoid arthritis (ra) patients (pts) with an inadequate response to mtx. *Ann Rheum Dis* 2013.

[74] Hu J, Bao C, Li X, Spindler A, Zhang X, Xu J, et al. SAT0218 Efficacy and safety of baricitinib in mtx-ir patients with rheumatoid arthritis: 52 week results from a phase 3 study (RA-BALANCE). Presented at the Annual European Congress of Rheumatology (EULAR 2018); 16.6.18; Netherlands. *Ann Rheum Dis* 2018;77(Suppl2):969-970.

[75] Takeuchi T, Tanaka Y, Tanaka S, Kawakami A, Iwasaki M, Katayama K, et al. Efficacy and safety of peficitinib (ASP015K) in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III randomised, double-blind, placebo-controlled trial (RAJ4) in Japan. *Ann Rheum Dis* 2019;78(10):1305-1319.

[76] Keystone E, Heijde D, Mason D, Jr., Landewe R, Vollenhoven RV, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 2008;58(11):3319-29.

[77] Smolen J, Landewe RB, Mease P, Brzezicki J, Mason D, Luijtens K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis* 2009;68(6):797-804.

[78] Peterfy C, Emery P, Tak PP, Ostergaard M, DiCarlo J, Otsa K, et al. MRI assessment of suppression of structural damage in patients with rheumatoid arthritis receiving rituximab: results from the randomised, placebo-controlled, double-blind RA-SCORE study. *Ann Rheum Dis* 2016;75(1):170-7.

[79] Huizinga TW, Fleischmann RM, Jasson M, Radin AR, van Adelsberg J, Fiore S, et al. Sarilumab, a fully human monoclonal antibody against IL-6Ralpha in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. *Ann Rheum Dis* 2014;73(9):1626-34.

[80] Fleischmann R. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double- blind, randomized controlled trial. *Arthritis Rheumatol* 2019;71(11):788–1800.

[81] Burmester GR. A phase 3 randomized, placebo-controlled, double-blind study of upadacitinib (ABT-494), a selective JAK-1 inhibitor, in patients with active rheumatoid arthritis with inadequate response to conventional synthetic Dmards. *2017 ACR/ARHP Annual Meeting*, 2018.

[82] Burmester GR, Kremer JM, Van den Bosch F, Kivitz A, Bessette L, Li Y, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2018;391(10139):2503-2512.

[83] Emery P, Deodhar A, Rigby WF, Isaacs JD, Combe B, Racewicz AJ, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). *Ann Rheum Dis* 2010;69(9):1629-35.

[84] Tanaka Y, Emoto K, Tsujimoto M, Schlichting DE, Macias W. 12-week results of a phase 2b dose-ranging study of baricitinib, an oral JAK1/JAK2 inhibitor in Japanese patients with rheumatoid arthritis on background methotrexate therapy. Presented at the American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting (ACR/ARHP 2013); October 2013; San Diego: US. *Arthritis Rheum* 2013;65(Suppl10):S765.

[85] Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum* 2008;58(10):2968-80.

[86] Weinblatt M. A trial of etanercept, a recombinant tumor necrosis factor receptor Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999;340(4).

[87] Genovese M. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor A inhibition. *N Engl J Med* 2005(353).

[88] Kivitz A, Olech E, Borofsky MA, Zazueta B, Navarro-Sarabia F, Radominski SC, et al. Two-year efficacy and safety of subcutaneous tocilizumab in combination with disease-modifying antirheumatic drugs including escalation to weekly dosing in rheumatoid arthritis. *J Rheumatol* 2018;45(4):456-464.

[89] Genovese MC, Kalunian K, Gottenberg JE, Mozaffarian N, Bartok B, Matzkies F, et al. Effect of filgotinib vs placebo on clinical response in patients with moderate to severe rheumatoid arthritis refractory to disease-modifying antirheumatic drug therapy: the FINCH 2 randomized clinical trial. *JAMA* 2019;322(4):315-325.

[90] Schiff MH, von Kempis J, Goldblum R, Tesser JR, Mueller RB. Rheumatoid arthritis secondary non-responders to TNF can attain an efficacious and safe response by switching to certolizumab pegol: a phase IV, randomised, multicentre, double-blind, 12-week study, followed by a 12-week open-label phase. *Ann Rheum Dis* 2014;73(12):2174-7.

[91] Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, et al. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med* 2016;374(13):1243-52.

[92] Zamani O. Efficacy and safety of baricitinib in patients with active rheumatoid arthritis and inadequate response to tumour necrosis factor inhibitors: summary results from the 24-week phase III RA-Beacon study. 2016.

[93] Smolen JS, Kremer JM, Gaich CL, DeLozier AM, Schlichting DE, Xie L, et al. Patient-reported outcomes from a randomised phase III study of baricitinib in patients with rheumatoid arthritis and an inadequate response to biological agents (RA-BEACON). *Ann Rheum Dis* 2017;76(4):694-700.

[94] Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008;67(11):1516-23.

[95] Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum* 2006;54(9):2793-806.

[96] Keystone E, Burmester GR, Furie R, Loveless JE, Emery P, Kremer J, et al. Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. *Arthritis Rheum* 2008;59(6):785-93.

[97] Genovese M, Fleischmann R, Combe B, Hall S, Zhang Y, Zhou Y, et al. Upadacitinib (ABT-494) in patients with active rheumatoid arthritis and inadequate response or intolerance to biological

DMARDs: a phase 3 randomized, placebo controlled, double-blind study of a selective JAK-1 inhibitor. Presented at the Annual European Congress of Rheumatology (EULAR 2018); June 2018; Netherlands. *Ann Rheum Dis* 2017;77(Suppl 2):970.

[98] Fleischmann R, Geraldo Da R, Brzezicki J, Hrycaj P, Lin Y, Van Adelsberg J, et al. Efficacy and safety of sarilumab in combination with csdmards in patients with active rheumatoid arthritis who were inadequate responders or intolerant of anti-TNF-I therapy: results from a phase 3 study. Presented at the 57th Annual Scientific Meeting of the Australian Rheumatology Association in conjunction with the Rheumatology Health Professionals Association; April 2016; Australia. *Intern Med J* 2015;46(Suppl2):41.

[99] Dias S, Welton N, Sutton A, Ades1 A. *NICE DSU Technical Support Document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. Report by the Decision Support Unit [Internet]*, August 2011 (updated September 2016) [accessed 21.7.20]. 98p. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/A-general-linear-modelling-framework-for-pair-wise-and-network-meta-analysis-of-randomised-controlled-trials..pdf

[100] Gilead Sciences. *Filgotinib for treating moderate to severe rheumatoid arthritis [ID1632]. Appendix G: Published cost-effectiveness studies [Word document provided by the company]*: Gilead Sciences, 16th April 2020 [accessed 14.7.20]. 72p.

[101] Gilead Sciences. *Filgotinib for treating moderate-to-severe rheumatoid arthritis [ID1632]. Appendix I: Cost and healthcare resource identification, measurement and valuation [Word document provided by the company]*: Gilead Sciences, 16th April 2020 [accessed 21.4.20]. 52p.

[102] Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J, et al. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. *Health Technol Assess* 2016;20(35):1-610.

[103] 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] [Internet]*. London: NICE, 26.1.16 [accessed 7.7.20] Available from: https://www.nice.org.uk/guidance/ta375

[104] Norton S, Fu B, Scott DL, Deighton C, Symmons DP, Wailoo AJ, et al. Health Assessment Questionnaire disability progression in early rheumatoid arthritis: systematic review and analysis of two inception cohorts. *Semin Arthritis Rheum* 2014;44(2):131-44.

[105] Hernandez Alava M, Wailoo A, Wolfe F, Michaud K. The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2013;52(5):944-50.

[106] National Institute for Health and Care Excellence. *Filgotinib for treating moderate to severe rheumatoid arthritis [ID1632]: clarification questions [Word document]*. London: NICE, May 2020 [accessed 4.6.20]. 9p.

[107] National Institute for Health and Care Excellence. *Upadacitinib for previously treated moderate to severe active rheumatoid arthritis [ID1400]. Committee Papers [Internet]*. London: NICE, 31.1.20 [accessed 7.7.20] Available from: https://www.nice.org.uk/guidance/gid-ta10389/documents/committee-papers

[108] Office for National Statistics. National life tables, UK: 2015 to 2017.

[109] Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* 2011(2):CD008794.

[110] Oppong R, Kaambwa B, Nuttall J, Hood K, Smith RD, Coast J. The impact of using different tariffs to value EQ-5D health state descriptions: an example from a study of acute cough/lower respiratory tract infections in seven countries. *Eur J Health Econ* 2013;14(2):197-209.

[111] Malottki K, Barton P, Tsourapas A, Uthman AO, Liu Z, Routh K, et al. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. *Health Technol Assess* 2011;15(14):1-278.

[112] Monthly Index of Medical Specialities (MIMS). 2020. Available from: http://www.mims.co.uk/

[113] Kaltenthaler E, Carroll C, Hill-McManus D, Scope A, Holmes M, Rice S, et al. The use of exploratory analyses within the National Institute for Health and Care Excellence single technology appraisal process: an evaluation and qualitative analysis. *Health Technol Assess* 2016;20(26):1-48.

[114] Schiff M, Weinblatt ME, Valente R, van der Heijde D, Citera G, Elegbe A, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. *Ann Rheum Dis* 2014;73(1):86-94.

[115] Greenwald MW, Shergy WJ, Kaine JL, Sweetser MT, Gilder K, Linnik MD. Evaluation of the safety of rituximab in combination with a tumor necrosis factor inhibitor and methotrexate in patients with active rheumatoid arthritis: results from a randomized controlled trial. *Arthritis Rheum* 2011;63(3):622-32.

[116] Dougados M, Kissel K, Sheeran T, Tak PP, Conaghan PG, Mola EM, et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). *Ann Rheum Dis* 2013;72(1):43-50.

[117] Kremer JM, Blanco R, Brzosko M, Burgos-Vargas R, Halland A-M, Vernon E, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. *Arthritis Rheum* 2011;63(3):609-21.

[118] Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumour necrosis factor alpha given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis* 2009;68(6):789-96.

[119] Edwards JCW. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004(350).

[120] Kremer JM, Westhovens R, Leon M, Di Giorgio E, Alten R, Steinfeld S, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med* 2003;349(20):1907-15.

[121] Kameda H, Ueki Y, Saito K, Nagaoka S, Hidaka T, Atsumi T, et al. Etanercept (ETN) with methotrexate (MTX) is better than ETN monotherapy in patients with active rheumatoid arthritis despite MTX therapy: a randomized trial. *Mod Rheumatol* 2010;20(6):531-8.

[122] Fleischmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. *Ann Rheum Dis* 2009;68(6):805-11.

[123] Takeuchi T, Harigai M, Tanaka Y, Yamanaka H, Ishiguro N, Yamamoto K, et al. Golimumab monotherapy in Japanese patients with active rheumatoid arthritis despite prior treatment with disease-modifying antirheumatic drugs: results of the phase 2/3, multicentre, randomised, double-blind, placebo-controlled GO-MONO study through 24 weeks. *Ann Rheum Dis* 2013;72(9):1488-95.

[124] van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med* 2012;367(6):508-19.

[125] Miyasaka N, Change Study Investigators. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. *Modern Rheumatology* 2008;18(3):252-62.

[126] Smolen JS, Kay J, Doyle MK, Landewe R, Matteson EL, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet* 2009;374(9685):210-21.

[127] Keystone EC, Wang MM, Layton M, Hollis S, McInnes IB, Team DCS. Clinical evaluation of the efficacy of the P2X7 purinergic receptor antagonist AZD9056 on the signs and symptoms of rheumatoid arthritis in patients with active disease despite treatment with methotrexate or sulphasalazine. *Ann Rheum Dis* 2012;71(10):1630-5.

[128] Taylor PC, Steuer A, Gruber J, Cosgrove DO, Blomley MJK, Marsters PA, et al. Comparison of ultrasonographic assessment of synovitis and joint vascularity with radiographic evaluation in a randomized, placebo-controlled study of infliximab therapy in early rheumatoid arthritis. *Arthritis Rheum* 2004;50(4):1107-16.

[129] Kim J, Ryu H, Yoo D-H, Park S-H, Song G-G, Park W, et al. A clinical trial and extension study of infliximab in Korean patients with active rheumatoid arthritis despite methotrexate treatment. *J Korean Med Sci* 2013;28(12):1716-22.

[130] van Vollenhoven RF, Kinnman N, Vincent E, Wax S, Bathon J. Atacicept in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase II, randomized, placebo-controlled trial. *Arthritis Rheum* 2011;63(7):1782-92.

[131] Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med* 1999;130(6):478-86.

[132] Genentech. A study of the safety and efficacy of rituximab in patients with moderate to severe rheumatoid arthritis receiving methotrexate. NCT00243412. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2011 [accessed 1.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00243412

[133] Bristol-Myers Squibb. A phase III study of BMS-188667 in subjects with active rheumatoid arthritis. NCT00048932. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2011 [accessed 1.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00048932

[134] Yazici Y, Curtis JR, Ince A, Baraf H, Malamet RL, Teng LL, et al. Efficacy of tocilizumab in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study. *Ann Rheum Dis* 2012;71(2):198-205.

[135] Genovese MC, Cohen S, Moreland L, Lium D, Robbins S, Newmark R, et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum* 2004;50(5):1412-9.

[136] van Vollenhoven RF, Ernestam S, Geborek P, Petersson IF, Coster L, Waltbrand E, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. *Lancet* 2009;374(9688):459-66.

[137] De Filippis L, Caliri A, Anghelone S, Scibilia G, Lo Gullo R, Bagnato G. Improving outcomes in tumour necrosis factor a treatment: comparison of the efficacy of the tumour necrosis factor a blocking agents etanercept and infliximab in patients with active rheumatoid arthritis. *Panminerva Med* 2006;48(2):129-35.

[138] Jobanputra P, Maggs F, Deeming A, Carruthers D, Rankin E, Jordan AC, et al. A randomised efficacy and discontinuation study of etanercept versus adalimumab (RED SEA) for rheumatoid arthritis: a pragmatic, unblinded, non-inferiority study of first TNF inhibitor use: outcomes over 2 years. *BMJ OPEN* 2012;2(6).

[139] Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003;48(1):35-45.

[140] Johnsen AK, Schiff MH, Mease PJ, Moreland LW, Maier AL, Coblyn JS, et al. Comparison of 2 doses of etanercept (50 vs 100 mg) in active rheumatoid arthritis: a randomized double blind study. *J Rheumatol* 2006;33(4):659-64.

[141] van de Putte LBA, Atkins C, Malaise M, Sany J, Russell AS, van Riel PLCM, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis* 2004;63(5):508-16.

[142] Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004;363(9410):675-81.

[143] Shim SC, Park SH, Bae SC, Song YW, MacAraeg GM, Delvaux A, et al. Efficacy and safety of abatacept in Korean patients with active rheumatoid arthritis and inadequate response to methotrexate: a phase III, multicenter, randomized, double-blind, placebo-controlled bridging study. Presented at 14th Congress of Asia Pacific League of Associations for Rheumatology, APLAR; 11-15 Jul 2010; Hong Kong: Hong Kong. *Int J Rheum Dis* 2010;13:101.

[144] Emery P, Smolen JS, Samborski W, Berenbaum F, Davies O, Ambrugeat J, et al. Efficacy and safety of certolizumab pegol after incomplete response to dmards in rheumatoid arthritis patients with low moderate disease activity: results from certain, a phase IIIB study. Presented at British Society for Rheumatology and British Health Professionals in Rheumatology Annual Meeting 2012, Rheumatology 2012; 1-3 May 2012; Glasgow, U.K. *Rheumatology* 2012;51:iii134.

[145] Hoffmann-La Roche. A study of RoActemra/Actemra (tocilizumab) versus adalimumab in combination with methotrexate in patients with moderate to severe active rheumatoid arthritis and an inadequate response to treatment with only one TNF-Inhibitor. NCT01283971. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 1.5.14]. Available from: http://ClinicalTrials.gov/show/NCT01283971

[146] Pfizer, Amgen. Open-label study comparing etanercept to conventional disease modifying antirheumatic drug (DMARD) therapy. NCT00848354. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 1.5.14]. Available from: http://ClinicalTrials.gov/show/NCT00848354

[147] Hoffmann-La Roche. A study to compare subcutaneous versus intravenous administration of RoActemra/Actemra (tocilizumab) in patients with moderate to severe active rheumatoid arthritis. NCT01194414. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 [accessed 1.5.14]. Available from: http://ClinicalTrials.gov/show/NCT01194414

[148] Ogata A. [Usefulness of the subcutaneous formulation of tocilizumab: results of phase III trial in Japan]. *Japn Pharmacol Ther* 2013;41(10):951-8.

[149] Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet* 2013;381(9877):1541-1550.

[150] Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. *Arthritis Rheum* 2006;54(9):2807-16.

[151] Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Efficacy and safety of certolizumab pegol without methotrexate co-administration in japanese patients with active rheumatoid arthritis. Presented at Annual Scientific Meeting of the American College of Rheumatology and Association of Rheumatology Health Professionals; 4-9 Nov 2011; Chicago, IL: United States. *Arthritis Rheum* 2011;63(10 suppl 1).

[152] Shi Q, Zhao Y, Bao C-d, Li X-F, Huang F, Zhu P, et al. [The efficacy and safety of tocilizumab combined with disease-modifying anti-rheumatoid drugs in the treatment of active rheumatoid arthritis: a multi-center, randomized, double-blinded, placebo-controlled trial]. *Chung Hua Nei Ko Tsa Chih* 2013;52(4):323-9.

[153] Genovese MC, Covarrubias A, Leon G, Mysler E, Keiserman M, Valente R, et al. Subcutaneous abatacept versus intravenous abatacept: a phase IIIb noninferiority study in patients with an inadequate response to methotrexate. *Arthritis Rheum* 2011;63(10):2854-2864.

[154] Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. *Mod Rheumatol* 2009;19(1):12-9.

[155] Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. *Ann Rheum Dis* 2007;66(9):1162-7.

[156] Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol* 2003;30(12):2563-71.

[157] Tanaka Y, Harigai M, Takeuchi T, Yamanaka H, Ishiguro N, Yamamoto K, et al. Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study. *Ann Rheum Dis* 2012;71(6):817-24.

[158] Burmester GR, Rubbert-Roth A, Cantagrel A, Hall S, Leszczynski P, Feldman D, et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study). *Ann Rheum Dis* 2014;73(1):69-74.

[159] Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999;354(9194):1932-9.

Appendix 1: Inclusion criteria for the systematic review of clinical effectiveness

Variable	Inclusion criteria	Exclusion criteria
Population	Adult (≥ 18 years) patients with moderate to severe active RA (including patients with early and established RA): • Treatment-naïve patients or those intolerant or contraindicated to methotrexate (MTX-naïve) • Patients who had intolerance or inadequate response to prior cDMARDs including MTX (MTX-IR) • Patients who had intolerance or inadequate response to previous bDMARDs (bDMARD-IR) If the disease severity of included patients is not clearly stated in the article, the following approach will be used (as described in TA466(2)): if DAS28 scores were reported, then DAS28 scores of > 3.2 will be considered to be moderate RA; DAS28 scores of > 5.1 will be considered to be severe RA. If DAS28 scores are not reported, then swollen and tender joint counts both > 6 will be considered to be a proxy for moderate to severe RA	• Juvenile idiopathic arthritis • Studies that include only juveniles • Patients with mild RA; if the study population is mixed (i.e. mild to severe), exclude those studies in which data are not reported separately for moderate or severely active RA • Patients without RA • Non-human studies
Interventions	**cDMARDs** (including MTX and at least one other DMARD, such as sulfasalazine or leflunomide) • MTX (Trexall, Rheumatrex, amethopterin, Rasuvo, Otrexup) • Sulfasalazine (Azulfidine, Salazopyrin, Sulazine, sulfazine) • Leflunomide (Arabloc, Arava, Lunava, Respo) • Hydroxychloroquine (Plaquenil, Axemal, Dolquine, Quensyl, Quineprox) All **bDMARDs** (in combination with MTX or as monotherapy) • Infliximab (Remicade) • Adalimumab (Humira, Trudexa, ABP 501, BI695501, CHS-1420, GP2017, M923, PF-06410293) • Certolizumab pegol (Cimzia) • Golimumab (Simponi) • Etanercept (Enbrel, Avent, BX2922, CHS-0214, ENIA11, Etacept, Etanar, GP2013,	• Studies that do not have an intervention of interest in more than 1 arm • Non-pharmacological studies, e.g., exercise, Chinese medicine, etc. • Azathioprine (Azasan, Imuran) • Studies comparing conventional DMARDs to non-DMARD treatments, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids • Sirukumab‡

Variable	Inclusion criteria	Exclusion criteria
	GP2015, HD203, LBEC0101, M923, PRX-106, SB4, TuNEX, Yisaipu) • Abatacept (Orencia) • Anakinra (Kineret) • Rituximab (Rituxan, Mabthera, Zytux, Reditux) • Tocilizumab (Actemra, RoActemra, atlizumab) • Sarilumab (Kevzara) All **tsDMARDs** (in combination with MTX or as monotherapy) • Baricitinib (Olumiant) • Tofacitinib (Xeljanz) • Upadacitinib (UPA) • Filgotinib (GLPG0634, GS-6034) • Peficitinib (ASP015K) **Biosimilars** • Adalimumab biosimilar • Amjevita/ABP-501; Cyltezo/BI 695501; SB5 • Etanercept biosimilar • Erelzi/GP2015; SB4 • Rituximab biosimilars • Rituxan; Truxima/CT-P10; Rixathon • Infliximab biosimilars • Remsima; Inflectra; Flixabi; Renflexis®SB2, CT-P13; PF-06438179; PF-06438179; ABP501	
Comparators	Any comparison between any of the listed interventions and each other or placebo	Studies not reporting on at least one of the interventions of interest

Outcomes	• Studies reporting efficacy and safety data, HRQOL, WPAI-RA, or MRI studies that specifically mention the Sharp/Van der Heijde bone erosion score • †To be included in the review, a study must report at least 1 of the following outcomes of interest: †**Efficacy measurements**: • †ACR criteria • †ACR score • †Proportion of patients achieving an ACR20 response • †Proportion of patients achieving an ACR50 response • †Proportion of patients achieving an ACR70 response • †ACR remission • †Proportion of patients achieving an ACR50 response in the subgroup of patients who are TNFi naïve, have inadequate response to TNF or other biologics, or who are intolerant to TNF or other biologics (if reported) • †Proportion of patients achieving an ACR20 response in the subgroup of patients who are TNF inhibitor naïve, have inadequate response to TNF or other biologics or who are intolerant to TNF or other biologics (if reported) • †Individual components of the ACR: o HAQ-DI o Pain VAS o Tender joint count o Swollen joint count o Physician's Global Assessment of Disease Activity o Patient's Global Assessment of Disease Activity o Patient's assessment of physical function assessed by HAQ or HAQ-DI • Radiographic scoring system scores o Modified Total Sharp score o Erosion score o Joint space narrowing score	Studies that report only MRI outcomes and do not specifically mention the Sharp/Van der Heijde bone erosion score Studies that report only bone mineral density Studies that investigate ultrasound and radiography in assessing bone damage

	• DAS28 ESR for RA • DAS28 CRP for RA • SDAI • CDAI • †Endpoints measuring the following: o Morning joint stiffness (severity and duration) and/or joint pain (may be assessed by different instruments) o Tiredness or fatigue (may be assessed by different instruments) • † EULAR or ACR remission defined as: o CDAI score ≤ 2.8 o SDAI score ≤ 3.3 o DAS28 < 2.6 o RAPID3 ≤ 1 o DAS-44 < 1.6 o Boolean definition of remission (EULAR or ACR where all measures must be < 1) • WPAI-RA • †HRQOL outcomes from the following: o EQ-5D o SF-36 • †**Safety outcomes reported at study endpoint**: o Overall rate of AEs o Overall rate of serious AEs o Discontinuations due to o Lack of efficacy o AEs o Individual AEs, such as the following: o Specific myelosuppressive events, e.g., anaemia, leukopenia, neutropenia, or thrombocytopaenia or lymphopenia or lymphocytopenia o Thrombocytosis	

Variable	Inclusion criteria	Exclusion criteria
	○ Serious infections including herpes zoster ○ Opportunistic infections ○ Malignancies ○ Cardiovascular events ○ Venous thromboembolism, deep vein thrombosis, or pulmonary embolism ○ Elevations in ALT or AST (> 3 times upper limit of normal) with total bilirubin (> 2 times upper limit of normal) ○ Injection-related combinations ○ Intravenous reactions ○ Death ○ Initial or prolonged inpatient hospitalisation	
Study design	• Randomised, controlled, prospective clinical trials (above Phase I) • Long-term follow-up studies (e.g. open-label follow-up studies with continuation of treatments in their respective randomised group)	• Phase I randomised, controlled, prospective clinical trials • Non-randomised clinical trials • Single-arm studies • Long-term follow-up or extension studies of RCTs in which patients do not remain in their respective randomised group • Maintenance studies and step-down treatment studies • Preclinical studies • Phase I studies • Prognostic studies • Retrospective studies • Prospective observational studies • Case reports • Commentaries and letters (publication type)

Variable	Inclusion criteria	Exclusion criteria
		• Consensus reports • Pooled analyses • Post hoc analyses • Non-systematic reviews • Systematic reviews (including meta-analyses)* • Secondary analyses • Animal models
Language restrictions	• English language only	• Studies published in languages other than English
Date restriction	• 1999 to present	• Prior to 1999

Source: Appendix D of the CS

Footnote: †Additional criteria used during the full text review process.

*Systematic reviews and meta-analyses will be used for identification of primary studies that may have been missed in the electronic searches

ǂ On 26 October 2017, Janssen-Cilag International NV officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for sirukumab (Plivensia), for the treatment of RA Therefore, sirukumab is not considered an active comparator.

ACR: American College of Rheumatology; ACR20/50/70: 20/50/70% improvement in ACR criteria; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate transaminase; bDMARD: biologic DMARD; CDAI: clinical disease activity index; CRP: high-sensitivity C-reactive protein; cDMARD: conventional DMARD; DAS28: disease activity score modified to include the 28 diarthrodial joint count; DAS-44: disease activity score modified to include the 44 diarthrodial joint count; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; EQ-5D: EuroQoL 5 dimensions; HAQ: health assessment questionnaire; HAQ-DI: health assessment questionnaire-disability index; HRQoL: health related quality of life; IR: intolerant or inadequate response; MRI: magnetic resonance imaging; MTX: methotrexate; NSAIDs: nonsteroidal anti-inflammatory drugs; RA: rheumatoid arthritis; RAPID3: routine assessment of patient index data 3; RCT: randomised controlled trial; SF-36; 36-Item Short Form Health Survey; SDAI: Simplified Disease Activity Index; TNF: tumour necrosis factor; TNFi: tumour necrosis factor inhibitor; tsDMARD; targeted synthetic DMARD; VAS: visual analogue scale; WPAI-RA: Work Productivity and Activity Index-Rheumatoid Arthritis

Appendix 2: Subgroup results (Moderately active RA and Severely active RA)

Table A2.1: Baseline characteristics in FINCH 1 and 2 – Moderately active RA (DAS28 score of 3.2-5.1)

Baseline characteristics	**FINCH 1**				**FINCH 2**		
	Filgotinib 200mg (n = 104)	Filgotinib 100mg (n = 121)	Adalimumab (n = 72)	Placebo (n = 128)	Filgotinib 200mg (n = 33)	Filgotinib 100mg (n = 34)	Placebo (n = 28)
Age (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Duration of RA (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
hsCRP (mg/L), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
RF-positive, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
1 cDMARD, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
≥2 cDMARDs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
bDMARD-naïve, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
DAS28 (CRP), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
SJC66, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
TJC68, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR

Baseline characteristics	FINCH 1				FINCH 2		
SGA (mm), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
PGA (mm), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Pain (mm), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
HAQ-DI, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR

Source: Table 7 of the CS and Response to clarification
ACR = American College of Rheumatology; bDMARD = biologic disease-modifying antirheumatic drug; cDMARD = conventional synthetic disease-modifying antirheumatic drug; DAS28 (CRP) = Disease Activity Score for 28 joints with C-reactive protein; HAQ-DI = Health Assessment Questionnaire Disability Index; hsCRP = high sensitivity C-reactive protein; PGA = Physician's Global Assessment of Disease Activity; RA = rheumatoid arthritis; RF = rheumatoid factor; SAS = safety analysis set; SD = standard deviation; SGA = Subject's Global Assessment of Disease Activity; SJC66 = swollen joint count based on 66 joints; TJC66 = tender joint count based on 68 joints.

Table A2.2: Baseline characteristics in FINCH 1 and 2 – Severely active RA (DAS28 score > 5.1)

Baseline characteristics	FINCH 1				FINCH 2		
	Filgotinib 200mg (n = 369)	Filgotinib 100mg (n = 358)	Adalimumab (n = 251)	Placebo (n = 347)	Filgotinib 200mg (n = 114)	Filgotinib 100mg (n = 119)	Placebo (n = 120)
Age (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Duration of RA (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
hsCRP (mg/L), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
RF-positive, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
1 cDMARD, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
≥2 cDMARDs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
bDMARD-naïve, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
DAS28 (CRP), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
SJC66, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
TJC68, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
SGA (mm), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR

Baseline characteristics	FINCH 1				FINCH 2		
PGA (mm), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Pain (mm), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
HAQ-DI, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR

Source: Table 7 of the CS and Response to clarification
ACR = American College of Rheumatology; bDMARD = biologic disease-modifying antirheumatic drug; cDMARD = conventional synthetic disease-modifying antirheumatic drug; DAS28 (CRP) = Disease Activity Score for 28 joints with C-reactive protein; HAQ-DI = Health Assessment Questionnaire Disability Index; hsCRP = high sensitivity C-reactive protein; PGA = Physician's Global Assessment of Disease Activity; RA = rheumatoid arthritis; RF = rheumatoid factor; SAS = safety analysis set; SD = standard deviation; SGA = Subject's Global Assessment of Disease Activity; SJC66 = swollen joint count based on 66 joints; TJC66 = tender joint count based on 68 joints.

Table A2.3: Efficacy results of FINCH 1 and FINCH 2 – Moderately active RA (DAS28 score of 3.2-5.1)

Outcomes (mean, SD or %)	FINCH 1				FINCH 2		
	Filgotinib 200mg + MTX (N=104)	Filgotinib 100mg + MTX (N=121)	Adalimumab + MTX (N=72)	Placebo + MTX (N=128)	Filgotinib 200mg + cDMARDs (N=33)	Filgotinib 100mg + cDMARDs (N=34)	Placebo + cDMARDs (N=28)
12-week results							
ACR20 response	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
ACR50 response	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
ACR70 response	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
EULAR Response	NR	NR	NR	NR	NR	NR	NR
% DAS28-CRP <2.6 (remission)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
% DAS28-CRP ≤3.2 (LDA)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Change from baseline in HAQ-DI	NR	NR	NR	NR	NR	NR	NR
Change from baseline in SF-36 PCS	NR	NR	NR	NR	NR	NR	NR
Change from baseline in FACIT-Fatigue score	NR	NR	NR	NR	NR	NR	NR
Change from Baseline in patient's pain assessment	NR	NR	NR	NR	NR	NR	NR
24-week results							
ACR20 response	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
ACR50 response	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
ACR70 response	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
EULAR Response	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR

Outcomes (mean, SD or %)	FINCH 1				FINCH 2		
	Filgotinib 200mg + MTX (N=104)	Filgotinib 100mg + MTX (N=121)	Adalimumab + MTX (N=72)	Placebo + MTX (N=128)	Filgotinib 200mg + cDMARDs (N=33)	Filgotinib 100mg + cDMARDs (N=34)	Placebo + cDMARDs (N=28)
% DAS28-CRP <2.6 (remission)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
% DAS28-CRP ≤3.2 (LDA)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Change from baseline in HAQ-DI	NR	NR	NR	NR	NR	NR	NR
Change from baseline in mTSS	NR	NR	NR	NR	NR	NR	NR

Source: CS, Sections 2.6.1 and 2.6.2

*P<0.05; **P<0.01; ***P<0.001; versus placebo. †P<0.05; ††P<0.01; †††P<0.001; versus adalimumab. #P value is nominal. Square brackets indicate analyses versus adalimumab.

ADA=adalimumab; cDMARD=conventional synthetic disease-modifying antirheumatic drug; DAS28-CRP=Disease Activity Score based on 28 joints and C reactive protein value; FACIT=Functional Assessment of Chronic Illness Therapy; FIL=filgotinib; HAQ-DI=Health Assessment Questionnaire-Disability Index; LDA=Low disease activity; mTSS=modified total Sharp score; MTX=methotrexate; NR=not reported; QD=once per day; SD=standard deviation; SF-36 PCS=36-item Short Form Health Survey Physical Component Summary.

Table A2.4: Efficacy results of FINCH 1 and FINCH 2 – Severely active RA (DAS28 score > 5.1)

Outcomes (mean, SD or %)	FINCH 1				FINCH 2		
	Filgotinib 200mg + MTX (N=369)	Filgotinib 100mg + MTX (N=358)	Adalimumab + MTX (N=251)	Placebo + MTX (N=347)	Filgotinib 200mg + cDMARDs (N=114)	Filgotinib 100mg + cDMARDs (N=119)	Placebo + cDMARDs (N=120)
12-week results							
ACR20 response	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
ACR50 response	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
ACR70 response	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
EULAR Response	NR	NR	NR	NR	NR	NR	NR
% DAS28-CRP <2.6 (remission)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
% DAS28-CRP ≤3.2 (LDA)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Change from baseline in HAQ-DI	NR	NR	NR	NR	NR	NR	NR
Change from baseline in SF-36 PCS	NR	NR	NR	NR	NR	NR	NR
Change from baseline in FACIT-Fatigue score	NR	NR	NR	NR	NR	NR	NR
Change from Baseline in patient's pain assessment	NR	NR	NR	NR	NR	NR	NR
24-week results							
ACR20 response	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
ACR50 response	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
ACR70 response	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
EULAR Response	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR

Outcomes (mean, SD or %)	FINCH 1				FINCH 2		
	Filgotinib 200mg + MTX (N=369)	Filgotinib 100mg + MTX (N=358)	Adalimumab + MTX (N=251)	Placebo + MTX (N=347)	Filgotinib 200mg + cDMARDs (N=114)	Filgotinib 100mg + cDMARDs (N=119)	Placebo + cDMARDs (N=120)
% DAS28-CRP <2.6 (remission)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
% DAS28-CRP ≤3.2 (LDA)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Change from baseline in HAQ-DI	NR	NR	NR	NR	NR	NR	NR
Change from baseline in mTSS	NR	NR	NR	NR	NR	NR	NR

Source: CS, Sections 2.6.1 and 2.6.2 and Appendix E.

*P<0.05; **P<0.01; ***P<0.001; versus placebo. †P<0.05; ††P<0.01; †††P<0.001; versus adalimumab. #P value is nominal. Square brackets indicate analyses versus adalimumab.

ADA=adalimumab; cDMARD=conventional synthetic disease-modifying antirheumatic drug; DAS28-CRP=Disease Activity Score based on 28 joints and C reactive protein value; FACIT=Functional Assessment of Chronic Illness Therapy; FIL=filgotinib; HAQ-DI=Health Assessment Questionnaire-Disability Index; LDA=Low disease activity; mTSS=modified total Sharp score; MTX=methotrexate; NR=not reported; QD=once per day; SD=standard deviation; SF-36 PCS=36-item Short Form Health Survey Physical Component Summary.

Appendix 3: Studies not included in the NMAs

Table A3.1: Excluded studies within the NICE scope

Study ID	Comparisons
AMPLE[114]	ABT+MTX vs ADA+MTX
TAME[115]	RTX+MTX vs MTX+PLA
ACT-RAY[116]	TCZ+MTX vs TCZ+PLA
LITHE[117]	TCZ+MTX vs TCZ+MTX vs MTX+PLA
GO-FORWARD[118]	GLM+MTX vs GLM+MTX vs GLM-mono vs MTX+PLA
Edwards 2004[119]	RTX+MTX vs RTX-mono vs RTX-mono vs MTX+PLA
Kremer 2003[120]	ABT+MTX vs ABT+MTX vs MTX+PLA
JESMR[121]	ETN+MTX vs ETN-mono
FAST4WARD[122]	CZP-mono vs PLA
Takeuchi 2013[60]	ETN-mono vs ETN-mono vs MTX+PLA
GO-MONO[123]	GLM-mono vs GLM-mono vs PLA
ORAL STANDARD[124]	ADA+MTX vs MTX+PLA
CHANGE[125]	ADA-mono vs ADA-mono vs ADA-mono vs PLA
GO-AFTER[126]	GLM-mono vs GLM-mono vs PLA
CREATE[127]	ETN-mono vs PLA
Taylor 2004[128]	IFX+MTX vs MTX+PLA
Kim 2013[129]	IFX-mono vs PLA
AUGUST II[130]	Atacicept-mono vs Atacicept-mono vs ADA-mono vs PLA
Moreland 1999[131]	ETN-mono vs ETN-mono vs PLA
RUMBA[132]	RTX+MTX vs RTX+MTX
NCT00048932[133]	ABT-mono vs PLA
ROSE[134]	TCZ+DMARDs vs DMARDs+PLA
20000223[135]	ETN+anakinra vs ETN+anakinra vs ETN-mono
Swefot[136]	sulfasalazine+MTX vs IFX+MTX
De Filippis 2006[137]	ETN+MTX vs IFX+MTX
RED SEA[138]	ADA-mono vs ETN-mono
ARMADA[139]	ADA+MTX vs ADA+MTX vs ADA+MTX vs MTX+PLA
Johnsen 2006[140]	ETN-mono vs ETN-mono
Van de Putte 2004[141]	ADA-mono vs ADA-mono vs ADA-mono vs ADA-mono
TEMPO[142]	ETN-mono vs ETN+MTX vs MTX+PLA
NCT00409838[143]	ABT+MTX vs MTX+PLA
CERTAIN[144]	CZP+DMARDs vs DMARDs+PLA
NCT01283971[145]	TCZ+MTX vs ADA+MTX
NCT00848354[146]	ETN+MTX vs DMARDs+MTX
NCT01194414[147]	TCZ-mono vs TCZ-mono
MUSASHI[148]	TCZ-mono vs TCZ-mono

ADACTA[149]	TCZ-mono vs ADA-mono
ASSURE[150]	ABT-mono vs PLA
NCT00791921[151]	CZP-mono vs PLA
Shi 2013[152]	TCZ-mono vs PLA
ACQUIRE[153]	ABT+MTX vs ABT+MTX
SATORI[154]	TCZ-mono vs PLA+MTX
SAMURAI[155]	TCZ-mono vs DMARDs
STAR[156]	ADA+DMARDs vs DMARDs+PLA
GO-FORTH[157]	GLM+MTX vs GLM+MTX vs MTX+PLA
SUMMACTA[158]	TCZ-mono vs TCZ-mono
ATTRACT[159]	PLA+MTX vs IFX+MTX vs IFX+MTX vs IFX

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Filgotinib for treating moderate to severe rheumatoid arthritis [ID1632]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Tuesday 11 August 2020** 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.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 – Populations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Stated that the CS does not separate the severe and the moderate populations. In Section 1.2 Summary of the key issues in the clinical effectiveness evidence (Page 12). The ERG stated : "*The NICE scope lists different comparators for people with moderately active RA and for people with severely active RA.* ***The CS does not separate these two populations.***"	Gilead requests the following amendment: "*The NICE scope lists different comparators for people with moderately active RA and for people with severely active RA. The CS separates these two populations*."	As per Section B3.2.1 (p131) of the CS: The cost-effectiveness analysis models patients with moderately to severely active RA. Patients are categorised into subpopulations depending on their disease severity, line of treatment and tolerance to guideline-recommended treatments. Broadly, patients encompass three main groups: 1. Adults with moderate RA (DAS28 of 3.2-5.1) who have had inadequate response to or are intolerant to csDMARDs (moderate cDMARD-IR) 2. Adults with severe RA (DAS28 >5.1) who have an inadequate response to csDMARDs only (severe cDMARD-IR) 3. Adults with severe RA (DAS28 >5.1) who have an inadequate response to bDMARDs (severe bDMARD-IR) 4. In line with NICE treatment	Not a factual inaccuracy. This statement in the ERG report pertains to the clinical effectiveness evidence, where neither of the NMAs used to make the comparison with those treatments listed in the scope differentiated between moderate and severe subgroups and the filgotinib efficacy data used for these NMAs was obtained from the FINCH 1 and 2 trials, each one of which contained a mixture of moderate and severe patients.

		guidelines, patients are further sub-categorised providing a total of eight individually analysed populations. Therefore, this cost-effectiveness analysis reflects the use of filgotinib within its anticipated Marketing Authorisation, the populations outlined in the NICE scope, and clinical practice in the UK.	

Issue 2 – Glucorticoids as comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Stated that glucocorticoids are within the scope of this submission. In Section 1.2, Summary of the key issues in the clinical section effectiveness (Page 12) *"The NICE scope does not mention glucocorticoids (GCs) as a comparator or as a possible previous treatment, even though*	Gilead request for the underlined text to be removed.	Glucocorticoids (GCs) are recommended to consider as short-term bridging treatment when starting a new cDMARD, for short term treatment of flare management or when all other treatment options (including bDMARD and tsDMARDs) have been offered and the long-term complications of GC therapy have been fully discussed with the patient. Moreover, the ERG mentions	Amended accordingly.

NICE recommends them. According to our clinical expert treatment with cDMARD plus glucocorticoids (GC) is a much more effective treatment than one cDMARD alone because it stops the progression of the underlying joint destruction. ***Therefore, GC plus cDMARD is the most effective treatment in newly diagnosed RA; and should be the main comparator in this appraisal.****"* In Section 2.2.,Critique of company's description of the underlying health problem (Page 23), and Section 3.3, Comparators, (Page 32) The ERG stated: "*It should also be noted that glucocorticoids (GCs) have not been included as a comparator or mentioned as a possible previous treatment in the NICE scope,* even though NICE recommends them. *According to our clinical expert treatment with cDMARD plus glucocorticoids is a much more*		Glucorticoids are the most effective treatment in newly diagnosed patients, which are outside of the scope of this submission. Therefore, glucocorticoids are not within the NICE scope, which includes patients with moderately or severely active rheumatoid arthritis that have not responded adequately to therapy with conventional DMARDs.	

effective treatment than one cDMARD alone because it stops the progression of the underlying joint destruction. ***Therefore, GC plus cDMARD is the most effective treatment in newly diagnosed RA; and should be the main comparator in this appraisal.****"*			

Issue 3 – NMA inclusion criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
NMA inclusion criteria incorrectly stated. On page 13, the ERG report describes the NMA in the following way: *"Several relevant comparators mentioned in the scope were not included in the NMAs because of lack of data. This is partly due to the inclusion criteria used by the company (no monotherapy* ***and only patients who failed on two or more DMARDs****). As a result, these comparators have also not been included in the economic*	Page 13: Gilead request for the underlined text to be removed, and the two bullet points around the NMA inclusion criteria including only patients that have failed two or more DMARDs. Additionally, Gilead want to note that the text referring to the NMA should be *"For the NMA used to inform the cost-effectiveness model for the moderate population"* as opposed to *"For the NMA in the moderately active RA population (cDMARD-IR)".* Page 15: Gilead request for this text to be removed	Studies included in the NMA and SLR are not limited to studies including patients that have failed two DMARDs. The ERG cites Table 1, page 15 of the CS *"in the moderately active RA population the company submission is limited to patients following two or more cDMARD failures, this restriction is applied on the basis of clinical opinion and expected cost-effectiveness"* This does not apply to the NMA.	Amended accordingly.

model." The following two bullet points are also on page 13: *"the company only included studies in which patients had failed at least two DMARDs"* and *"For the NMA in the moderately active RA population (cDMARD-IR) the company included studies with patients that had failed on two or more cDMARDs for the comparators. However, for the intervention, the company included the FINCH 1 study in which patients had failed on one or more DMARDs. As far as the ERG is aware the company did not adjust the results of the FINCH 1 study for this difference in populations."* On page 15: *"The company used the FINCH trial programme to inform effectiveness of filgotinib, which also included patients who had only one prior csDMARD (as opposed to studies included in the NMA), which led to a discrepancy*	Page 31: Gilead request for the underlined text to be removed Page 63: Gilead request for the following amendment *"The company used different inclusion criteria from the NICE scope. Firstly, all monotherapy studies were excluded. This was because the FINCH 1 and 2 trials did not have monotherapy arms. However, the NICE scope mentions several monotherapy comparators which could still have been included.* ***Secondly, the search was limited to studies after 1999.*** *However, many cDMARD studies were performed before 1999. Therefore, potentially relevant studies were excluded from the NMAs."* Page 78: Gilead request for the underlined text to be removed Page 80: Gilead request for the following amendment *"Firstly, all monotherapy studies were excluded. This was because the FINCH 1 and 2 trials did not have monotherapy arms. However, the NICE scope mentions several monotherapy*	The inclusion criteria for the cDMARD-IR SLR in section 1.6 of Appendix D is *"Patients who had intolerance or inadequate response to prior csDMARDs including MTX".* Additionally, Gilead note that there was no NMA performed separately for the moderate population, and hence the NMA for the cDMARD-IR population is incorrectly referred to as *"the NMA in the moderately active RA population"* (see section B2.9.8 of the CS, and response to clarification question A20).	

between effectiveness results of filgotinib and comparators." On page 31: *"As a result of this decision by the company and because of the inclusion criteria used by the company (no monotherapy studies **and only patients who failed on two or more DMARDs**)"* On page 63: *"The company used different inclusion criteria from the NICE scope. Firstly, all monotherapy studies were excluded. This was because the FINCH 1 and 2 trials did not have monotherapy arms. However, the NICE scope mentions several monotherapy comparators which could still have been included. **Secondly, the company only included studies in which patients had failed at least two DMARDs. The NICE scope only mentions one DMARD, and patients in the FINCH 1 trial had failed on one or more DMARDs. Thirdly, the search was limited to studies after 1999.** However, many*	*comparators which could still have been included. **Secondly, the search was limited to studies after 1999**."*		

cDMARD studies were performed before 1999. Therefore, potentially relevant studies were excluded from the NMAs." On page 78: *"This is partly due to the inclusion criteria used by the company (no monotherapy **and only patients who failed on two or more DMARDs**)."* On page 80: *"Firstly, all monotherapy studies were excluded. This was because the FINCH 1 and 2 trials did not have monotherapy arms. However, the NICE scope mentions several monotherapy comparators which could still have been included. **Secondly, the company only included studies in which patients had failed at least two DMARDs. The NICE scope only mentions one DMARD, and patients in the FINCH 1 trial had failed on one or more DMARDs. Thirdly, the search was limited to studies after 1999**."*			

Issue 4 – Comparators included in the submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Stated that comparators were excluded from the NMA. Stated that tofacitinib is not included in the economic model. On page 14: "*Data for certolizumab pegol and tofacitinib **were not included in the NMA in the relevant populations** or at the 24-week assessment time point."* On page 31: *"several interventions **were not included in the NMAs and** were not included in the economic model (infliximab, certolizumab pegol, upadacitinib, golimumab**, and tofacitinib (for cDMARD-IR**))."* Table 5.5 on page 92 on the model comparators states the following: *"Not all relevant comparators have been included (e.g.*	Page 14: Gilead request for the following amendment "*Data for certolizumab pegol and tofacitinib were not available from the NMA at the 24-week assessment time point."* Page 31: Gilead request for the following amendment "*several interventions were not included in the economic model (infliximab, certolizumab pegol, upadacitinib, golimumab)."* Table 5.5, page 92: *"Not all relevant comparators have been included (e.g. certolizumab pegol)."* Page 100: *"According to Table 1, several comparators mentioned in the scope, and included in the NMA (infliximab, certolizumab pegol, upadacitinib, golimumab) were not included in the economic model."* Page 153:	The treatments noted by the ERG were all included in the submitted NMA. Infliximab, certolizumab pegol, upadacitinib, golimumab and tofacitinib were all included in the cDMARD-IR ACR at 12 weeks NMA. (see CS section B2.9.5) Infliximab, certolizumab pegol and upadacitinib were included in the cDMARD-IR ACR at 24 weeks NMA. Additionally, certolizumab pegol, upadacitinib, and tofacitinib were all included in the bDMARD-IR ACR at 12 weeks NMA. Treatment sequences included in the economic analysis were chosen based on market share data and expert opinion (see section B3.2.5. of the CS). The ERG are correct to note that infliximab, certolizumab pegol, upadacitinib and golimumab were not included as comparators in the model.	Amended to improve accuracy. The ERG would also like to point out that results for certolizumab pegol, were not included in the bDMARD-IR ACR at 12 weeks NMA.

*certolizumab pegol**, tofacitinib**).”* On page 100: *“According to Table 1, several comparators mentioned in the scope, and included in the NMA (infliximab, certolizumab pegol, upadacitinib, golimumab**, tofacitinib**) were not included in the economic model.”* On page 153: *“**Data for certolizumab pegol and tofacitinib were not included in the NMA**.”*	Gilead request for this to be removed	Tofacitinib was included as a comparator in the economic model. The ERG are correct that tofacitinib was not included in the cDMARD-IR population economic analysis, but tofacitinib monotherapy was however used as a comparator in the bDMARD-IR population.	

Issue 5 – Statistical analysis - power

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Discrepancy between the statistical analysis description in the ERG report, and CS. In Section 4.2.2 Statistical analysis of the included filgotinib studies (Page 46) The ERG stated: “*In FINCH 1 a sample of 450 patients in each group provided over **95%** power*	Gilead requests the following amendment: “*In FINCH 1 a sample of 450 patients in each group provided over **90%** power to detect an increase in ACR20 response rate of 45% to 65% between the placebo control group and the filgotinib group, respectively, using a two-sided 0.05-level test*”	This is most likely a typographical error. This can be found in the CS in Table 8. Summary of statistical analysis in RCTs (Page 58).	There is no discrepancy: Table 8 in the CS states 95%.

to detect an increase in ACR20 response rate of 45% to 65% between the placebo control group and the filgotinib group, respectively, using a two-sided 0.05-level test"			

Issue 6 – Safety Results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
A typographical error in copying over the safety results. In Section 4.2.7 Safety results (Page 56) The ERG has copied: "FINCH 2, TEAE leading to premature discontinuation of study drug, n (%): o Filgotinib 200mg: 32 (21.8%) o Filgotinib 100mg: 29 (19.0%) o Placebo: 23 (15.5%)"	Gilead requests the following amendment: *"TEAE leading to premature discontinuation of study drug, n (%)* which are as follows: o Filgotinib 200mg: 5 (3.4%); o Filgotinib 100mg: 6 (3.9%); o Placebo: 3 (2.0%)"	The ERG seems to have copied the values for "*TEAE related to study drug, n (%)"* rather than the values for "*TEAE leading to premature discontinuation of study drug, n (%)".* This information can be found on page 123 of the CS and on page 134 of FINCH 2 CSR.	Corrected.

Issue 7 – PAS prices

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect PAS referenced in the ERG report. Page 15: *"The company's pricing was unclear as there is differential pricing for patients with moderately to severely active RA and severely active RA and the company only used the former in the model. The ERG changed the price used in the severely active RA model population to that proposed for the severely active RA population."* Page 16: *"Filgotinib price not implemented in line with company's Patient Access Scheme (PAS) proposed for the severe population in the CS."* Page 117, point c): *"In the CS, a PAS was provided by the company reducing list prices for moderately to severely*	Page 15: Gilead request for this text to be removed Page 16: Gilead request for this text to be removed Page 117: Gilead request for point c) to be removed Page 120: Gilead request for this text to be removed	The pricing approach presented in the CS was agreed prior to submission with NICE and PASLU. The base case uses [redacted] for both moderate and severe populations under the condition that both populations receive reimbursement. As discussed and agreed with NICE and PASLU, in the event that only severe disease is reimbursed the price would default to [redacted]. Therefore, a scenario analysis using [redacted] is provided in Appendix J. This also results in the changes to the severe base cases presented in the ERG report, section 7.2, being incorrect.	Not a factual error. This arrangement was not communicated in the company submission. As of now (with filgotinib not being recommended for the moderate population), the use of the price for the severely active RA population in the severely active RA model population is not an error. However, the ERG has added a scenario using the lower price for the severe population.

active RA to [redacted] per year and for severely active RA only to [redacted] per year. In the model, however, the list prices of [redacted] per year was used for both for moderately to severely active RA and severely active RA only. Hence, the ERG has adjusted this in their base case analyses." Page 129: *"FE: Severe population: Filgotinib price not implemented in line with company's PAS"*			

Issue 8 – AIC markings

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
AIC marking incorrectly implemented. Page 15: Moderate subgroup baseline data from FINCH 1 not marked AIC	Page 15: Gilead request for this to be marked AIC Page 52: Gilead request for the AIC marking to be removed	As per updated Appendix H sent to NICE on June 29th2020 (ID1632_Filgotinib_STA_Appendix_K_v4.0), efficacy data from FINCH 1 are not marked AIC, with the exception of subgroup analyses. NMA data are marked AIC.	Addressed.

Page 52: FINCH 1 data marked AIC Page 74: NMA results for filgotinib 100mg ACR at 12 weeks for the bDMARD-IR population not marked AIC	Page 74: Gilead request for this to be marked AIC		

Issue 9 – Generation of patient profiles

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect description of the generation of patient profiles in the model. Page 15: *"The company used the same distributions (i.e. means and standard errors) to produce patient profiles for the moderate and severe cDMARD as well as the bDMARD populations. The ERG would prefer for the patient characteristics to reflect each*	Page 15: Gilead request for this text to be removed Page 108: Gilead request for the underlined text to be removed	As described in section B3.3.1. in the CS, and clarification question B6, population characteristics stratified by severity were used to generate the different patient cohorts in the model. Different means and standard errors were used (as shown in table 44 in the CS, section B3.3.1).	We thank the company for this clarification. An error in the model's interface (on the 'Main Settings' sheet) evoked this impression. When switching to different populations, it appears that the means and standard deviations for each population are overwritten with the average FINCH I trial data, see Reset Default sub (for example *Range("rngRandomCohortSummary*

<table>
<tr>
<td>patient population."

Page 108:

"The company used different sets of patient profiles for the moderate and severe csDMARD and bDMARD populations, <u>however, these were generated based on the same values of patient characteristics (derived from both FINCH trials), probably using a different seed. This means that differences in the populations are not captured in the model, which may lead to bias that could not be quantified</u>."

Page 153:

"The company used the same distributions (i.e. means and standard errors) to produce patient profiles for the moderate and severe cDMARD as well as the bDMARD populations. The ERG would prefer for the patient characteristics to reflect each patient population."

Results from scenario analysis 1, pages 141-146, tables 7.21-7.31.</td>
<td>Page 153:

Gilead request for this text to be removed</td>
<td>Results from scenario analysis:

Gilead believe that the ERG may have implemented scenario 1 incorrectly, possibly by using different baseline characteristics than the ones applied in the CS (table 44, section B3.3.1).

Gilead were able to replicate the ERG base case for the moderate population (population 1b, moderate RA after 2 cDMARD failures, MTX eligible), using MTX (cDMARDs) as a comparator.

However, Gilead were unable to replicate the results of scenario 1. To verify this finding, Gilead generated 5 different sets of patient profiles, consistent with the ERG analysis for scenario 1.

Results from the 5 randomly generated patient populations are reported below.

<table>
<tr><th>Analysis no</th><th>FIL costs (£)</th><th>FIL QALYs</th><th>MTX costs (£)</th></tr>
</table>
</td>
<td>Mean").Value = Application.Transpose(Array(XX,XX, XX,X))

). Thus, any newly generated patient profiles appear to use these values (FINCH I, both moderate and severe). It should be noted that there are several errors introduced in the Main Settings sheet once the population is changed multiple times. This made it extremely difficult to assess what values were used. If these issues could be resolved, this would be very much appreciated for any future submissions.

The ERG has removed the corresponding statements from the report, but added that the possibility of generating new patient profiles using correct values for the different patient populations was not implemented correctly in the model.

The text on page 15 has been removed and been replaced by the following: "The model file contained some errors in the VBA underlying the 'Main Settings' sheet that made amendments difficult. In particular, it was unclear how new patient profiles could be generated using differential distributions for each patient population (FINCH 1 moderate only, FINCH 1, severe only, and FINCH 2)."</td>
</tr>
</table>

ERG base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,977	0.288	27,676
ERG scenario 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,042	0.382	36,715
Gilead: scenario 1 replication 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,942	0.294	27,021
Gilead: scenario 1 replication 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,886	0.285	26,921
Gilead: scenario 1 replication 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,523	0.287	26,195
Gilead: scenario 1 replication 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,796	0.285	27,398
Gilead: scenario 1 replication 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	7,471	0.284	26,261

Abbreviations: FIL, filgotinib; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALY, quality adjusted life year

The ERG scenario 1 analysis resulted in a QALY difference of 1.564 (12.5%) from the ERG base

The text on page 108 has been removed.

The text on page 153 has been removed.

Scenario 1 and any related conclusions have been removed. As described above, the patient characteristics used for these alternative profiles were likely based on FINCH 1 averages and therefore are not applicable to any specific population. This may have caused results to be significantly different, whilst they may not be (as demonstrated by the company). For reassurance, it may be valuable if the company could provide results using alternative sets of patient profiles (like done here); and as mentioned in the report a larger number of patient profiles going forward.

Results of Scenario 1 have been replaced by the new Scenario 1 that uses the alternative filgotinib PAS for the severely active RA population.

		case. However, for Gilead's replication the maximum QALY difference for filgotinib from the ERG base case across all 5 analyses was 0.275 (2.2%). The incremental costs and QALYs remained similar in each case. Therefore, Gilead believe there may have been an error in the ERG analysis as we are unable to reproduce the level of variability obtained. Therefore, Gilead believe the resulting ICER and level of uncertainty may have been overstated.	

NICE National Institute for Health and Care Excellence

Technical engagement response form

Filgotinib for treating moderate to severe rheumatoid arthritis [ID1632]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **is 5pm on Monday 2 November**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted

under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Gilead Sciences Inc.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NA**

Questions for engagement

Issue 1: Relevant comparators and treatment sequences	
Are any important relevant comparators missing from the company submission (see Table 1 in the appendix)?	
Are treatment sequences modelled in the company submission appropriate for decision-making (see Table 2 in the appendix)? What subsequent treatments (i.e. second- and third-line bDMARDs) are used in routine NHS practice, for patients who are methotrexate eligible and ineligible? Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, and so on.	
What is the most appropriate second-line therapy for methotrexate-ineligible population (2a): abatacept, IL-6 inhibitors (tocilizumab or sarilumab), or rituximab monotherapy?	
Issue 2: Generalisability of FINCH trials	
Would the treatment effect of filgotinib (or other bDMARDs) be expected to be similar for people who have received 1 or more prior csDMARDs, compared with those who received 2 or more prior csDMARDs?	

Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ depending on the prior therapy received (csDMARDs in combination with corticosteroids versus csDMARD alone)?	
Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ between people with moderate-severe and those with severe disease?	
Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ when it is given as a monotherapy, or in combination with csDMARDs?	
Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ depending on the line of advanced therapy (e.g. first- vs second vs third-line)?	
Issue 3: Rate of progression from moderate to severe RA	
What is the expected DAS28 score among people with moderate RA in UK clinical practice? Is there any published evidence to support this estimate?	
What is the expected annual rate of progression from moderate to severe RA with the current BSC at 1, 2, 10 years, and lifelong risk of progression? Is there any published evidence to support these estimates?	
Issue 4: Treatment sequence upon progression from moderate to severe RA	
What is the most relevant bDMARDs treatment sequence for people progressing from moderate to severe RA?	

Does the treatment sequence depend on the prior treatment received for moderate disease? In particular: **a.** If people received filgotinib for moderate disease, would the treatment sequence for severe disease be different compared to people who did not receive prior filgotinib (e.g. alternative third-line biologic received upon progression)? **b.** If people received only csDMARDs for their moderate disease, would filgotinib be used once disease progresses to severe state?	
Issue 5: Modelling best supportive care	
What is the current BSC for people with moderate RA whose disease responded inadequately to, or who are intolerant of 2 or more csDMARDs?	
What is the expected treatment effect of current BSC given after failure of 2 or more csDMARDs?	

NICE National Institute for Health and Care Excellence

Appendix

These two tables are a submission summary provided by the NICE technical team. They are not part of the additional evidence provided by the company. Additional evidence submitted by the company is presented in Appendices 2 and 3.

Table 1. Comparison of relevant comparators listed in the scope and included by the company in their economic model. Note: Comparators that were listed in the final scope but not included in the company submission are underlined.

Population	Disease severity	Line of advanced therapy[a]	MTX eligible?	Comparators listed in the scope	Comparators included by the company
1a	Moderate	First	No	BSC[b]	BSC
1b	Moderate	First	Yes	BSC[b]	BSC
2a	Severe	First	No	Adalimumab, etanercept, certolizumab pegol, tocilizumab, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (as monotherapy)	Adalimumab, etanercept, baricitinib, tocilizumab (as monotherapy)
2b	Severe	First-line	Yes	Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (with MTX)	Adalimumab, etanercept, baricitinib (with MTX)
3a	Severe	Second	No	Adalimumab, etanercept, certolizumab pegol, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (as monotherapy)	Tofacitinib, baricitinib, abatacept[c] (as monotherapy)
3b	Severe	Second	Yes	Adalimumab, etanercept, infliximab, abatacept, tocilizumab, certolizumab pegol, golimumab, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (with MTX)	Abatacept, tocilizumab, baricitinib, sarilumab (with MTX)
4	Severe	Second	Yes	Rituximab with MTX	Rituximab with MTX
5	Severe	Third	Yes	Tocilizumab, sarilumab, upadacitinib[c] (with MTX)	Tocilizumab, sarilumab (with MTX)

[a] after failure of 2 or more csDMARDs; [b] focusing on population in company submission (after failure of 2 or more csDMARDs); [c] Ongoing technology appraisal, not a relevant comparator; [c] abatacept is not recommended as monotherapy for methotrexate-ineligible population in TA195 and was not included in the scope); csDMARD = conventional disease-modifying antirheumatic drugs; MTX = methotrexate.

Table 2. Treatment sequences used in the company model

Population	Line of advanced therapy (after failure of 2 more csDMARDs)			
	First	**Second**	**Third**	**Subsequent**
1a	FIL or csDMARDs	BSC		
1b	FIL (with MTX) or csDMARDs	BSC		
2a	FIL, ADA, ETN, BAR or TCZ CS	ABC SC	BSC	
2b1	FIL, ADA, ETN or BAR (all with MTX)	RTX (with MTX)	TCZ SC (with MTX)	BSC
2b2	FIL, ADA, ETN or BAR (all with MTX)	TCZ SC (with MTX)	BSC	
2b3	FIL, ADA, ETN or BAR (all with MTX)	ABC SC (with MTX)	BSC	
3a		FIL, ABC SC, BAR, TOF	BSC	
3b		FIL, ABC SC, TCZ SC, SAR, BAR (all with MTX)	BSC	
4		FIL or RTX (with MTX)	TCZ SC (with MTX)	BSC
5			FIL, TCZ SC, SAR (all with MTX)	BSC

ABC = abatacept; ADA = adalimumab; BAR = baricitinib; BSC = best supportive care; csDMARDs = conventional synthetic disease modifying antirheumatic drug; ETN = etanercept; FIL = filgotinib; MTX = methotrexate; RTX = rituximab; SAR = sarilumab; TCZ = tocilizumab

Source: Company submission, tables 35-43.

Appendix 2 – Additional evidence submitted by the company

The technical team requested for a revised base case for the moderate population (population 1a and 1b) to be provided by the company. All analyses presented below are conducted using the revised base case.

The changes applied are summarised in Table 3.

Table 3: Updates made to the submitted base case for the moderate population

Company submission base case	Revised base case
Filgotinib compared to BSC in first line, to which patients are assumed to have no response.	Filgotinib compared to placebo/MTX first line, to which patients can have a response, followed by subsequent BSC. Patients are assumed to have no response to the subsequent BSC.
Using efficacy estimates from the MTX-IR NMA for the moderate to severe population	Using head-to-head trial data for the whole moderate population from FINCH 1 to inform efficacy in the moderate population for filgotinib and placebo/MTX
Applying costs of BSC from MTA375	Applying costs of MTX to subsequent BSC in the moderate population
Sampling patient cohort using DAS28 score of 4.1, i.e. the midpoint of the defined moderate DAS28 scores interval (3.2 to 5.1)	Sampling patient cohort using DAS28 baseline score from the moderate population of FINCH 1

Issue 1: Relevant comparators and treatment sequences	
Technical Team Preliminary Judgement	Company response
The technical team accepts the change in the target patient population proposed by the company. The use of biological DMARD therapies (bDMARDs) after failure of 2 or more csDMARDs is aligned with the current use of bDMARDs in severe RA population (for example in TA375). However, the technical team notes that this creates uncertainty since it is not in line with the trial population (only 49% of patients with moderate RA in FINCH 1 study had 2 or more csDMARDs before entering the study; 51% had only 1 prior csDMARD; table 13 in the company submission). The company should provide justification for the use of clinical effectiveness data from a different population.	The company is now providing a pairwise comparison of moderate patients who have received 1 prior csDMARD and moderate patients who have received 2 or more csDMARDs (please see Appendix 3). At week 12, the proportion of patients achieving ACR20 response (primary endpoint of FINCH 1) in the filgotinib 200mg arm is higher in the 1 prior csDMARD exposure subgroup. 73.6% of patients achieved ACR20 response in the >=2 prior csDMARDs exposure group and 82.4% achieved it in the 1 prior csDMARD exposure group. Similarly, at week 24, 75.5% of patients achieved ACR20 response in the >=2 prior csDMARDs exposures group and 68.6% % achieved it in the 1 prior csDMARD exposures group. It should be noted that these comparisons are not statistically significant and that patient numbers in these groups are low. FINCH 1 was not powered to allow for this analysis.

The technical team would like to request subgroup analysis for people who received 1 prior csDMARDs, compared with those who received 2 or more csDMARDs to assess if clinical effectiveness is similar in the 2 groups.	
Issue 2: Relevant comparators and treatment sequences (severe RA)	
Technical Team Preliminary Judgement	Company response
The technical team requests a scenario analysis assuming IL-6 (tocilizumab or sarilumab) as a second-line advanced treatment in population 2a (methotrexate-ineligible), instead of subcutaneous abatacept.	Scenarios using both tocilizumab and sarilumab in second line for population 2a are provided below. **Scenario 1: Population 2a (Severe RA patients in first line advanced therapy treatment (MTX ineligible)) - 2nd line SAR** The sequences run for Scenario 1 are summarised in Table 4. Results are shown in Table 5.

Table 4: Sequences applied in Scenario 1

Sequence	First-line treatment	Second-line treatment	Third-line treatment
1	***FIL***	***SAR***	***BSC***
2	ADA	SAR	BSC
3	ETN	SAR	BSC
4	BAR	SAR	BSC
5	TCZ SC	SAR	BSC

Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; MTX, methotrexate; TCZ, tocilizumab

Table 5: Results for Scenario 1

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL	[redacted]	14.639	[redacted]	-	-	-	-	-
ADA	[redacted]	14.639	[redacted]	18,315.80	0.000	-0.013	Dominated	Dominated
ETN	[redacted]	14.639	[redacted]	4,173.34	0.000	0.079	341,862.50 SW	52,901.05
BAR	[redacted]	14.639	[redacted]	7,546.06	0.000	-0.041	1,208,117.65 SW	Dominated
TCZ SC	[redacted]	14.639	[redacted]	4,390.29	0.000	-0.050	Dominated	Dominated

Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Scenario 2: Population 2a (Severe RA patients in first line advanced therapy treatment (MTX ineligible)) - 2nd line TCZ

The sequences run for Scenario 2 are summarised in Table 6. Results are shown in Table 7. For scenario 2, TCZ is excluded as a first line comparator, as it is included in second line.

Table 6: Sequences applied in Scenario 2

Sequence	First-line treatment	Second-line treatment	Third-line treatment
1	***FIL***	***TCZ SC***	***BSC***
2	ADA	TCZ SC	BSC
3	ETN	TCZ SC	BSC

4	BAR	TCZ SC	BSC

Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; MTX, methotrexate

Table 7: Results for Scenario 2

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
FIL	[redacted]	14.639	[redacted]	-	-	-	-	-
ADA	[redacted]	14.639	[redacted]	18,278	0.000	-0.014	Dominated	Dominated
ETN	[redacted]	14.639	[redacted]	4,510	0.000	0.086	317,669.12 SW	52,727.09
BAR	[redacted]	14.639	[redacted]	7,355	0.000	-0.045	1,109,972.59 SW	Dominated

Abbreviations: ABC, abatacept; ADA, adalimumab; BAR, baricitinib; BSC, best supportive care; ETN, etanercept; FIL, filgotinib; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Issue 3: Generalisability of FINCH trials to the decision problem and UK clinical practice

Technical Team Preliminary Judgement	Company response
The technical team requests subgroup data from the severe population of the FINCH 2 study.	FINCH 2 severe subgroup baseline characteristics can be found in Table 8.

Table 8. Baseline characteristics for the severe RA subgroup in the FINCH 2 trial

[redacted]	[redacted]	[redacted]	[redacted]
Age (years), mean (SD)	[redacted]	[redacted]	[redacted]

Female, n (%)			
Duration of RA (years), mean (SD)			
hsCRP (mg/L), mean (SD)			
RF-positive, n (%)			
1 csDMARD, n (%)			
≥2 csDMARDs, n (%)			
bDMARD-naïve, n (%)			
DAS28 (CRP), mean (SD)			
SJC66, mean (SD)			
TJC68, mean (SD)			
SGA (mm), mean (SD)			
PGA (mm), mean (SD)			
Pain (mm), mean (SD)			
HAQ-DI, mean (SD)			

bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28 (CRP), Disease Activity Score for 28 joints with C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; hsCRP, high sensitivity C-reactive protein; placebo, placebo; PGA, Physician's Global Assessment of Disease Activity; RA, rheumatoid arthritis; RF, rheumatoid factor; SAS, safety analysis set; SD, standard deviation; SGA, Subject's Global Assessment of Disease Activity; SJC66, swollen joint count based on 66 joints; TJC66, tender joint count based on 68 joints.

Summary efficacy results for the FINCH 2 severe RA subgroup can be found in Table 9.

Table 9. Summary of efficacy outcomes for the severe RA subgroup in the FINCH 2 trial

Efficacy assessment	Time point	Filgotinib 200mg (N=147)	Filgotinib 100mg (N=153)	Placebo (N=148)
ACR 20 response rate (SD) [95%CI]	week 12	[redacted]	[redacted]	[redacted]
	p-value	[redacted]	[redacted]	[redacted]
	week 24	[redacted]	[redacted]	[redacted]
	p-value	[redacted]	[redacted]	[redacted]
ACR 50 response rate (SD) [95%CI]	week 12	[redacted]	[redacted]	[redacted]
	p-value	[redacted]	[redacted]	[redacted]
	week 24	[redacted]	[redacted]	[redacted]
	p-value	[redacted]	[redacted]	[redacted]
ACR 70 response rate (SD) [95%CI]	week 12	[redacted]	[redacted]	[redacted]
	p-value	[redacted]	[redacted]	[redacted]
	week 24	[redacted]	[redacted]	[redacted]
	p-value	[redacted]	[redacted]	[redacted]
EULAR response %	week 12 (Good Responder)	[redacted]	[redacted]	[redacted]
	week 12 (Moderate Responder)	[redacted]	[redacted]	[redacted]
	week 12 (Non-Responder)	[redacted]	[redacted]	[redacted]
	week 24 (Good Responder)	[redacted]	[redacted]	[redacted]

		week 24 (Moderate Responder)	[redacted]	[redacted]	[redacted]
		week 24 (Non-Responder)	[redacted]	[redacted]	[redacted]
	Proportion of patients who achieved DAS28-CRP ≤3.2 (%) [95% CI]	week 12	[redacted]	[redacted]	[redacted]
		p-value	[redacted]	[redacted]	[redacted]
		week 24	[redacted]	[redacted]	[redacted]
		p-value	[redacted]	[redacted]	[redacted]
	Proportion of patients who achieved DAS28-CRP <2.6 (%) [95%CI]	week 12	[redacted]	[redacted]	[redacted]
		p-value	[redacted]	[redacted]	[redacted]
		week 24	[redacted]	[redacted]	[redacted]
		p-value	[redacted]	[redacted]	[redacted]

p-value: pairwise comparison versus placebo

ACR: American college of Rheumatology score; CI: Confidence interval; EULAR: European League Against Rheumatism; DAS28 (CRP), Disease Activity Score for 28 joints with C-reactive protein; SD: Standard deviation;

Issue 4: Network meta-analysis

Technical Team Preliminary Judgement	Company response
The technical team requests company rationale for excluding studies that were identified as potentially relevant by the ERG.	Reason for exclusion for some of the studies identified by the ERG are provided in Table 10. **Table 10: Studies excluded from the NMA as identified by the ERG and reasons for exclusion**

Study ID	Reason for exclusion

	AMPLE	No 12/24 week data
	TAME	Excluded from the SLR as could not be confirmed that the population is moderate to severe: tender/swollen joints <6
	ACT-RAY	Monotherapies not assessed
	LITHE	Data available from NCT website, but only peer reviewed publications were in scope
	GO-FORWARD	Excluded in NMA due to swollen joint count <6
	JESMR	Monotherapies not assessed
	FAST4WARD	Monotherapies not assessed
	Takeuchi 2013	Monotherapies not assessed
	GO-MONO	Monotherapies not assessed
	CHANGE	Monotherapies not assessed
	GO-AFTER	Monotherapies not assessed
	CREATE	Data available from NCT website, but only peer reviewed publications were in scope
	Taylor 2004	Excluded from the SLR as could not be confirmed that the population is moderate to severe: tender/swollen joints <6
	AUGUST II	Excluded from the SLR as atacicept not considered as a comparator
	Moreland 1999	Monotherapies not assessed
	RUMBA	Data available from NCT website, but only peer reviewed publications were in scope
	ROSE	Data available from NCT website, but only peer reviewed publications were in scope
	20000223	Could not be linked into the network
	Swefot	No 12/24 week data
	RED SEA	Excluded from the SLR as could not be confirmed that the population is moderate to severe
	Van de Putte 2004	Monotherapies not assessed
	NCT00409838	Data available from NCT website, but only peer reviewed publications were in scope
	CERTAIN	Excluded from the SLR as the population is not moderate to severe

NCT01283971	Data available from NCT website, but only peer reviewed publications were in scope
MUSASHI	Excluded based on study type
ADACTA	Monotherapies not assessed
ASSURE	Excluded from the SLR as could not be confirmed that the population is moderate to severe
NCT00791921	Monotherapies not assessed
Shi 2013	Excluded from SLR due to language not English
ACQUIRE	Excluded from SLR due to comparator not relevant
SATORI	Monotherapies not assessed
SAMURAI	Monotherapies not assessed
GO-FORTH	Excluded from the SLR as could not be confirmed that the population is moderate to severe: tender/swollen joints <6
SUMMACTA	Monotherapies not assessed
ATTRACT	No 12/24 week data

A review of recent technical appraisals (TA10389, TA485, TA480, TA466, TA375 (1-5)) found that NMAs conducted have varied in terms of included studies. However, the results of the analyses are not comparable as point estimates are not available in the published committee papers.

Fakhouri et al. recently published an NMA which is an update of the NMA submitted as part of the baricitinib submission (TA466) for patients with moderate to severe RA and inadequate response to methotrexate (4, 6). The outcome considered is ACR at week 24. As such, a comparison of the published NMA to the ACR outcome at 24 weeks in the filgotinib cDMARD-IR population NMA was feasible.

The comparison is conducted using an analysis labelled as “Sensitivity analysis 1” in Fakhouri et al., as this analysis was included as the company base case in TA466, and did not exclude studies where less than 20% of patients had been previously exposed to bDMARDs, as in the base case presented in the recent publication (4, 6).

Table 11 summarises the 14 studies that were included in both networks, while Table 12 and Table 13 summarise the studies that were included in one network, and not the other.

Table 11: Studies included in both Fakhouri et al. and filgotinib NMA

Study	Reference
AIM (NCT00048568)	Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2006;144(12):865-876.
ATTEST (NCT00095147)	Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis. 2008;67(8):1096-1103.
RA-BEAM (NCT01710358)	Taylor PC KE, Van Der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. . N Engl J Med 2017 Feb 16;376(7):652-62. 2017
Keystone 2004	Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004;50(5):1400-1411
Kim 2007	Kim HY LS, Song YW, Yoo DH, Koh EM, Yoo B. A randomized, double-blind, placebocontrolled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR Journal of Rheumatology 2007;10(1):9-16. 2007.

MOBILITY (NCT01061736)	Genovese MC, Fleischmann R, Kivitz AJ, et al. Sarilumab Plus Methotrexate in Patients With Active Rheumatoid Arthritis and Inadequate Response to Methotrexate: Results of a Phase III Study. Arthritis Rheumatol. 2015;67(6):1424-1437
RA-SCORE (NCT00578305)	Peterfy C, Emery P, Tak PP, et al. MRI assessment of suppression of structural damage in patients with rheumatoid arthritis receiving rituximab: results from the randomised, placebo-controlled, double-blind RA-SCORE study. Ann Rheum Dis. 2016;75(1):170-177.
RAPID-C (NCT02151851)	Bi L, Li Y, He L, et al. Efficacy and safety of certolizumab pegol in combination with methotrexate in methotrexate-inadequate responder Chinese patients with active rheumatoid arthritis: 24-week results from a randomised, double-blind, placebo controlled phase 3 study. Clin Exp Rheumatol. 2018
SERENE	Emery P, Deodhar A, Rigby WF, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). Ann Rheum Dis. 2010;69(9):1629-1635
Kang 2013	Kang YM PW, Park YE, Choe JY, Bae SC, Cho CS. Efficacy and safety of certolizumab pegol (CZP) with concomitant methotrexate (MTX) in korean rheumatoid arthritis (RA) patients (PTS) with an inadequate response to MTX. Annals of the Rheumatic Disease 2013;71(Suppl 3):666
OPTION (NCT00106548)	Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008;371(9617):987-997
RACAT (NCT00405275)	O'Dell JR, Mikuls TR, Taylor TH, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 2013;369(4):307-318
RAPID 1 (NCT00152386)	Keystone E, Burmester GR, Furie R, et al. Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum. 2008;59(6):785-793
RAPID 2 (NCT00175877)	Smolen J, Landewe RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009;68(6):797-804

Table 12: Studies included in Fakhouri et al. and excluded in filgotinib NMA

Study	Reference	Included in ERG list of excluded studies
AMPLE (NCT00929864)	Schiff M, Weinblatt ME, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Ann Rheum Dis. 2014;73(1):86-94	Yes
ATTRACT	Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999;354(9194):1932-1939.	Yes
Edwards 2004	Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004;350(25):2572-2581.	Yes
GO-FORTH (NCT00727987)	Tanaka Y, Harigai M, Takeuchi T, et al. Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study. Ann Rheum Dis. 2012;71(6):817-824.	Yes
GO-FORWARD (NCT00264550)	Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumour necrosis factor (alpha) given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. 2009;68(6):789-796	Yes
LITHE (NCT00106535)	Kremer JM, Blanco R, Brzosko M, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheum. 2011;63(3):609-621	Yes
ORAL STANDARD (NCT00853385)	van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367(6):508-519	Yes
ARMADA	Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003;48(1):35-45	No
Li 2013 (NCT01248780)	Li Z ZF, Kay J, Fei K, Han C, Zhuang Y. Safety and efficacy of subcutaneous golimumab in Chinese patients with active rheumatoid arthritis despite MTX	No

	therapy: Results from a randomized, placebo-controlled, phase 3 trial. Arthritis and Rheumatism. Arthritis and Rheumatism 2013;65(Suppl 10):S598-S9. 2013.	
Machado 2014 (NCT00848354)	Machado DA, Guzman RM, Xavier RM, et al. Open-label observation of addition of etanercept versus a conventional disease-modifying antirheumatic drug in subjects with active rheumatoid arthritis despite methotrexate therapy in the Latin American region. J Clin Rheumatol. 2014;20(1):25-33	No
START	Westhovens R, Cole JC, Li T, et al. Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial. Rheumatology (Oxford). 2006;45(10):1238-1246	No
Weinblatt 1999	Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. 1999;340(4):253-259.	No
J-RAPID (NCT00791999)	Yamamoto K, Takeuchi T, Yamanaka H, et al. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. Mod Rheumatol. 2014;24(5):715-724	No
ORAL SCAN (NCT00847613)	van der Heijde D, Tanaka Y, Fleischmann R, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four month phase III randomized radiographic study. Arthritis Rheum. 2013;65(3):559-570	No
ORAL STRATEGY (NCT02187055)	Fleischmann R, Mysler E, Hall S, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet. 2017;390(10093):457-468.	No

Table 13: Studies included in filgotinib NMA and excluded from Fakhouri et al.

Study	Reference
Baek et al.	Baek HJ, Lim MJ, Park W, et al. Efficacy and safety of tocilizumab in Korean patients with active rheumatoid arthritis. Korean J Intern Med. 2018.
Cohen et al.	Cohen SB, Moreland LW, Cush JJ, et al. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. Ann Rheum Dis. 2004;63(9):1062-8.

DANCER	Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum. 2006;54(5):1390-400.
Etanercept 309	Combe B, Codreanu C, Fiocco U, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis. 2006;65(10):1357-62.
FINCH 1	Kivitz A. A Randomized, Double-blind, Placebo- and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 weeks in Combination with Methotrexate to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate. (FINCH 1). 2019.
KAKEHASI	Tanaka Y, Wada K, Takahashi Y, et al. Efficacy and safety of sarilumab plus methotrexate in a phase 3 trial in Japanese patients with active rheumatoid arthritis (KAKEHASI). APLAR Conference 2018. 2018.
Kremer et al.	Kremer JM, Genovese MC, Cannon GW, et al. Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2002;137(9):726-33.
Lim et al.	Lim MJ, Park SH, Shim SC, et al. A double-blind, placebo-controlled, multicenter trial of tocilizumab in moderate to severe active RA patients with inadequate response to methotrexate in Korean population. Annals of the Rheumatic Disease. 2013;71.
NCT00345748	Takeuchi T, Miyasaka N, Zang C, et al. A phase 3 randomized, double-blind, multicenter comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity, and safety in Japanese subjects with active rheumatoid arthritis. Mod Rheumatol. 2013;23(4):623-33.
NCT00544154	Choy E, McKenna F, Vencovsky J, et al. Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. Rheumatology (Oxford). 2012;51(7):1226-34.
NCT00993317	Kang YP, Y-E.; Park, W.; Choe, J-Y.; Cho, C-S.; Shim, S-C. Rapid onset of efficacy predicts response to therapy with certolizumab plus methotrexate in patients with active rheumatoid arthritis. Korean J Intern Med. 2018.
NCT01758198	Matsubara T, Inoue H, Nakajima T, et al. Abatacept in combination with methotrexate in Japanese biologic-naive patients with active rheumatoid arthritis: a randomised placebo-controlled phase IV study. RMD Open. 2018;4(2):e000813.
NCT02557100	Rigby W, Buckner J, Bridges L, et al. LB0008 THE EFFECT OF HLA-DRB1 RISK ALLELES ON THE CLINICALEFFICACY OF ABATACEPT AND ADALIMUMAB IN SEROPOSITIVE BIOLOGIC-NAÏVE PATIENTSWITH EARLY, MODERATE-TO-SEVERE RA: DATA FROM A HEAD-TO-HEAD SINGLEBLINDEDTRIAL. Ann Rheum Dis. 2019;78(Suppl 2).

RA BUILD	Dougados M, van der Heijde D, Chen YC, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. Ann Rheum Dis. 2017;76(1):88-95.
SELECT-COMPARE	Fleischmann R, Pangan AL, Song IH, et al. Upadacitinib Versus Placebo or Adalimumab in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Results of a Phase III, Double-Blind, Randomized Controlled Trial. Arthritis Rheumatol. 2019.
TOWARD	Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. 2008;58(10):2968-80.

A comparison of the results for all relevant comparators included in the Fakhouri et al. NMA is provided in Table 14. All estimate differences are within 10%, except ABT SC + MTX, where the company NMA resulted in higher estimates of efficacy than Fakhouri et al. Thus, despite some differences in the studies included, the results are broadly similar.

Table 14: Comparison of ACR20/ACR50/ACR70 results at 24 weeks for the cDMARD-IR population from Fakhouri et al. and filgotinib NMA

	Fakhouri et al.			Filgotinib NMA		
	ACR20	**ACR50**	**ACR70**	**ACR20**	**ACR50**	**ACR70**
BARI 4mg + MTX	65.9%	41.0%	21.8%	[redacted]	[redacted]	[redacted]
ADA 40mg + MTX	58.2%	38.3%	17.1%	[redacted]	[redacted]	[redacted]
CZP 200mg + MTX	70.2%	46.1%	27.2%	[redacted]	[redacted]	[redacted]
ETN + MTX	71.8%	49.2%	23.6%	[redacted]	[redacted]	[redacted]
IFX 3mg + MTX	55.5%	33.4%	14.3%	[redacted]	[redacted]	[redacted]
ABT IV 10mg + MTX	57.8%%	33.8%	13.0%	[redacted]	[redacted]	[redacted]

	ABT SC + MTX	59.1%	38.5%	16.6%	[redacted]	[redacted]	[redacted]
	RTX + MTX	56.1%	32.2%	11.6%	[redacted]	[redacted]	[redacted]
	SARI 200mg +MTX	60.8.1%	38.7%	16.3%	[redacted]	[redacted]	[redacted]
	TCZ 8mg IV + MTX	57.3%	40.4%	25.9%	[redacted]	[redacted]	[redacted]
	PBO/MTX	27.3%	12.3%	4.3%	[redacted]	[redacted]	[redacted]

The technical team notes NMA data may not be applicable to the moderate population, and prefers to use direct head to head data in the base case analyses for the moderate subgroup.	Analyses using direct head-to-head trial data are provided in the response to Issue 7 below.
Issue 5: Rate of progression from moderate to severe RA	
Technical Team Preliminary Judgement	Company response
The technical team would like the company to explore alternative extrapolation methods, to align with the rates expected in clinical practice. It appears that the ERG's approach may overestimate and the company's approach may underestimate progression to severe disease. Alternatively, both ERG's and company's approaches may need to be considered together,	The company submitted base case applied a linear mixed model for repeated measures, consistent with TA10389. Non-linear mixed models were also explored, using a second and third order polynomial but, as the resulting additional coefficients were not statistically significant, these were not considered appropriate for the cost-effectiveness analysis. An updated cost-effectiveness analysis is provided in response to Issue 7, which incorporates an alternative progression as described below. The revised approach considers MTX/placebo using efficacy estimates from FINCH 1 as a first line comparator, to which patients can have a response and remain on treatment, followed by BSC in second line, to which patients are assumed to have no response. This is in line with the technical team preferred

with the true rate of progression somewhere in between.

approach. Upon progression to severe disease, patients receive biologic treatment. The mean baseline DAS28 score of the moderate subgroup in the FINCH 1 trial was applied. This is detailed in the response to Issue 7.

The introduction of a placebo effect to the comparator sequence reduced the rate of progression to a severe state. In addition, applying the baseline DAS28 score from the FINCH 1 trial, increases the rate of progression rapidly. As such, the updated analysis results in a progression rate that lies in between the company's submitted base case rate and the ERG base case rate. This is shown in Table 15.

Table 15: Cumulative percentage of patients in the CEM progressing to severe RA from moderate RA on BSC

Time	Company submitted base case: linear mixed model, gamma using midpoint DAS28 mean	ERG base case: linear mixed model, gamma using FINCH 1 DAS28 mean	Company's updated analysis: linear mixed model, gamma using FINCH1 DAS28 mean with placebo effect incorporated
Year 2	5%	26%	11%
Year 3	12%	44%	23%
Year 4	14%	49%	29%
Year 5	24%	59%	39%

Kiely et al. reported data on 302 newly diagnosed patients, predominantly treated with csDMARDs or csDMARD combinations, in the ERAN database who were followed up for 2 years. The study found that after 2 years 19% of patients had exceeded the DAS28 severe threshold of 5.1 (7).

In the updated analysis, approximately 11% of patients had progressed to severe disease after 2 years, and 24% after 3 years. Although this rate of progression is lower than observed in the ERAN database, the rate observed in the

	revised base case analysis likely resembles clinical practice more closely than the submitted base case. This analysis can however be considered conservative, compared to the rate observed in the ERAN database. The results of the revised cost-effectiveness analysis are provided in the response Issue 7.
Issue 6: Treatment sequence upon progression from moderate to severe RA	
Technical Team Preliminary Judgement	Company response
The technical team requests scenario analyses exploring the following treatment sequences: • Patients with severe RA previously treated with filgotinib when in moderate RA will be treated with subcutaneous abatacept rather than tocilizumab • Patients with severe RA not previously treated with filgotinib when in moderate RA will be treated with filgotinib rather than tocilizumab	The analyses requested by the technical team are summarised below. These analyses are conducted using the base case as described in Issue 7 below, and at the beginning of Appendix 2, and by varying the treatment sequence upon progression to a severe disease. The sequences applied for moderate patients all compare filgotinib to placebo/MTX in first line, followed by BSC, as detailed in the response to Issue 7. The company notes that for scenarios 2 and 3 below, the sequences do not evaluate the cost-effectiveness of filgotinib compared to BSC, considering that different sequence "tails" are used in each treatment arm. Rather the cost-effectiveness of the entire sequence is assessed and any differences in costs or QALYs cannot be attributed to a single agent. Moreover, the two sequences apply treatments of differing mechanisms of action, e.g. tocilizumab (IL-6) and abatacept (CD80) as second line advanced therapies, depending on whether filgotinib is used first-line. **<u>Population 1a – Moderate RA patients after 2 cDMARD failures (MTX ineligible)</u>** **Scenario 1: Treatment sequence for severe disease not affected by treatment received in moderate disease** a. Adalimumab → tocilizumab → BSC

• Sarilumab is used instead of tocilizumab	b. Adalimumab→ sarilumab → BSC **Scenario 2: Patients with severe RA previously treated with filgotinib when in moderate RA will be treated with subcutaneous abatacept rather than tocilizumab** a. Adalimumab → tocilizumab[a] or abatacept[b] → BSC b. Adalimumab → sarilumab[a] or abatacept[b] → BSC Where: [a] Patient did not receive filgotinib for moderate disease; [b] Patient received filgotinib for moderate disease *The company note that in the requested sequences, two different mechanisms of action are applied in second-line advanced therapies (IL-6 and CD80), and that these analyses do not evaluate the cost-effectiveness of filgotinib compared to BSC, but rather compare the cost-effectiveness of two different sequences, given the different treatment sequence "tails". The company would not expect that the choice of filgotinib or BSC in first-line moderate therapy would result in an alternative choice of mechanism of action at second-line severe.* **Scenario 3: Patients with severe RA not previously treated with filgotinib when in moderate RA will be treated with filgotinib rather than tocilizumab** a. Adalimumab → filgotinib[a] or tocilizumab[b] → BSC b. Adalimumab → filgotinib[a] or sarilumab[b] → BSC Where: [a] Patient did not receive filgotinib for moderate disease; [b] Patient received filgotinib for moderate disease *The company note that in the requested sequences, two different mechanisms of action are applied in second-line advanced therapies (IL-6 and JAK inhibitor), and that these analyses do not evaluate the cost-effectiveness of filgotinib compared to BSC, but rather compare the cost-effectiveness of two different sequences, given the different treatment sequence "tails".*

Population 1b – Moderate RA patients after 2 cDMARD failures (MTX eligible)

Scenario 1: Treatment sequence for severe disease is not affected by treatment received for moderate disease

a. Adalimumab → rituximab→ tocilizumab → BSC
b. Adalimumab → rituximab→ sarilumab → BSC

Scenario 2: Patients with severe RA previously treated with filgotinib when in moderate RA will be treated with subcutaneous abatacept rather than tocilizumab

a. Adalimumab → rituximab → tocilizumab[a] or abatacept[b] → BSC
b. Adalimumab → rituximab → sarilumab[a] or abatacept[b] → BSC

Where: [a] Patient did not receive filgotinib for moderate disease; [b] Patient received filgotinib for moderate disease

The company note that in the requested sequences, two different mechanisms of action are applied in third-line advanced therapies (IL-6 and CD80), and that these analyses do not evaluate the cost-effectiveness of filgotinib compared to BSC, but rather compare the cost-effectiveness of two different sequences, given the different treatment sequence "tails". The company would not expect that the choice of filgotinib or BSC in first-line moderate therapy would result in an alternative choice of mechanism of action at second-line severe.

Scenario 3: Patients with severe RA not previously treated with filgotinib when in moderate RA will be treated with filgotinib rather than tocilizumab

a. Adalimumab → rituximab → filgotinib[a] or tocilizumab[b] → BSC
b. Adalimumab → rituximab → filgotinib[a] or sarilumab[b] → BSC

Where: [a] Patient did not receive filgotinib for moderate disease; [b] Patient received filgotinib for moderate disease

The company note that in the requested sequences, two different mechanisms of action are applied in second-line advanced therapies (IL-6 and JAK inhibitor), and that these analyses do not evaluate the cost-effectiveness of filgotinib compared to BSC, but rather compare the cost-effectiveness of two different sequences, given the different treatment sequence "tails".

Results: Population 1a – Moderate RA patients after 2 cDMARD failures (MTX ineligible)

Table 16: Scenario 1a results

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.810	[redacted]	-	-	-	25,450.83	-
FIL	[redacted]	15.810	[redacted]	12,186.38	0.000	0.479	-	25,450.83

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Table 17: Scenario 1b results

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.810	[redacted]	-	-	-	24,956.07	-
FIL	[redacted]	15.810	[redacted]	11,710.73	0.000	0.469	-	24,956.07

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Table 18: Scenario 2a results

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.810	[redacted]	-	-	-	40,917.53	-

FIL	[redacted]	15.810	[redacted]	22,067.49	0.000	0.539	-	40,917.53

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Table 19: Scenario 2b results

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.810	[redacted]	-	-	-	39,726.90	-
FIL	[redacted]	15.810	[redacted]	19,797.50	0.000	0.498	-	39,726.90

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Table 20: Scenario 3a results

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.810	[redacted]	-	-	-	53,043.74	-
FIL	[redacted]	15.810	[redacted]	24,874.27	0.000	0.469	-	53,043.74

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Table 21: Scenario 3b results

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.810	[redacted]	-	-	-	53,300.07	-
FIL	[redacted]	15.810	[redacted]	26,668.61	0.000	0.500	-	53,300.07

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Results: Population 1b – Moderate RA patients after 2 cDMARD failures (MTX eligible)

Table 22: Scenario 1a results

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.810	[redacted]	-	-	-	26,135.50	-
FIL	[redacted]	15.810	[redacted]	11586.57	0.000	0.443	-	26,135.50

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Table 23: Scenario 1b results

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.810	[redacted]	-	-	-	25,865.27	-
FIL	[redacted]	15.810	[redacted]	11,287.58	0.000	0.436	-	25,865.27

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Table 24: Scenario 2a results

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.810	[redacted]	-	-	-	38,780.62	-
FIL	[redacted]	15.810	[redacted]	18,961.76	0.000	0.489	-	38,780.62

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Table 25: Scenario 2b results

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.810	[redacted]	-	-	-	37,466.38	-
FIL	[redacted]	15.810	[redacted]	17,063.13	0.000	0.455	-	37,466.38

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Table 26: Scenario 3a results

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.810	[redacted]	-	-	-	47,525.10	-
FIL	[redacted]	15.810	[redacted]	20,618.88	0.000	0.434	-	47,525.10

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Table 27: Scenario 3b results

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.810	[redacted]	-	-	-	48,254.04	-
FIL	[redacted]	15.810	[redacted]	22,218.52	0.000	0.460	-	48,254.04

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; QALY, quality adjusted life year

Issue 7: Modelling best supportive care in the moderate population

<table>
<tr><th>Technical Team Preliminary Judgement</th><th>Company response</th></tr>
<tr><td>

- The technical team agrees with the ERG that it is not appropriate to assume 0% clinical efficacy for the initial BSC, while assuming the full clinical efficacy for the filgotinib arm. This is because the efficacy observed in the placebo arm is likely related to the placebo effect or natural fluctuation in disease activity. The same effect is likely to be present in the filgotinib arm. Therefore the technical team prefers the ERG approach to modelling the cost and efficacy of the BSC.
- The technical team agrees that subsequent BSC is unlikely to have any clinical benefit, and therefore it is appropriate to assume 0% effectiveness.
- The technical team requests that the base case analysis is based on the direct head-to-head trial data (moderate subgroup) to inform the efficacy of both filgotinib and the initial BSC.

</td><td>

An updated base case analysis is conducted using the following changes as accepted by the technical team:

- Baseline characteristics and efficacy were informed using head-to-head trial data from the whole FINCH 1 moderate subgroup (i.e. 1+ csDMARD failures). This is summarised in Appendix 3. These data informed efficacy for both for filgotinib 200mg, and placebo/MTX in the moderate population.
  - No efficacy was assumed for the subsequent BSC, and the NMA was used to inform efficacy of the advanced treatments upon progression to severe disease
- Applying costs of MTX to subsequent BSC in the moderate population
- Sampling patient cohort using DAS28 baseline score from the moderate FINCH 1 subgroup

Using the DAS28 baseline score from the FINCH 1 trial, as opposed to using the midpoint of 4.15 (i.e. the midpoint of the defined moderate DAS28 upper and lower bounds) as in the company submitted base case, results in moderate patients progressing rapidly to severe disease. However, introducing placebo/MTX as a first line comparator to which patients can achieve a response slows down the rate of progression, and as a result, the rate of progression for the updated analysis is a rate between the ERG and the submitted company base case. This is detailed in Issue 5 above.

The treatment sequences used for the analysis are summarised in Table 28 through Table 31.

Population 1a - Moderate RA patients after 2 cDMARD failures (MTX ineligible)

Table 28: Treatment sequences considered in moderately active cDMARD-IR patients (population 1a)

Sequence	First-line treatment	Second-line treatment
1	***FIL***	***BSC***
2	PBO/BSC	BSC

</td></tr>
</table>

Abbreviations: BSC, best supportive care; FIL, filgotinib; PBO, placebo

Table 29: Severe treatment sequences considered upon progression in moderately active cDMARD-IR patients (population 1a)

Sequence	First-line treatment	Second-line treatment	Third-line treatment
1 & 2	ADA	ABC SC	BSC
Abbreviations: ABC, abatacept; ADA, adalimumab; BSC, best supportive care; SC, subcutaneous			

Population 1b - Moderate RA patients after 2 cDMARD failures (MTX eligible)

Table 30: Treatment sequences considered in moderately active cDMARD-IR patients (population 1b)

Sequence	First-line treatment	Second-line treatment
1	***FIL***	***BSC***
2	PBO/BSC	BSC
Abbreviations: BSC, best supportive care; FIL, filgotinib; PBO, placebo		

Table 31: Severe treatment sequences considered upon progression in moderately active cDMARD-IR patients (population 1b)

Sequence	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment
1 & 2	ADA + MTX	RTX + MTX	TCZ SC + MTX	BSC
Abbreviations: ADA, adalimumab; BSC, best supportive care; MTX, methotrexate; RTX, rituximab; SC, subcutaneous; TCZ, tocilizumab				

Results

Population 1a - Moderate RA patients after 2 csDMARD failures (MTX ineligible)

The results of the base case analysis for the moderate, MTX ineligible patient population after at least two csDMARD failures are presented in Table 32. Compared to BSC, filgotinib 200mg monotherapy was associated with QALY gains (0.464), and increased costs (£9,986), generating an incremental cost-effectiveness ratio (ICER) of £21,510 per QALY.

Table 32: Two csDMARD failure, MTX ineligible, moderate RA – versus FIL 200mg monotherapy (base case using overall FINCH 1 moderate subgroup data)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.810	[redacted]	-	-	-	21,509.64	-
FIL	[redacted]	15.810	[redacted]	9,986.06	0.000	0.464	-	21,509.64

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year

Population 1b - Moderate RA patients after 2 csDMARD failures (MTX eligible)

The results of the base case analysis for the moderate, MTX eligible patient population after at least two csDMARD failures are presented in Table 33. Compared to BSC, filgotinib 200mg combination therapy was associated with QALY gains (0.443), and increased costs (£11,587), generating an incremental cost-effectiveness ratio (ICER) of £26,136 per QALY.

Table 33: Two csDMARD failure, MTX eligible, moderate RA – versus FIL 200mg combination therapy (base case using overall FINCH 1 moderate subgroup data)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.810	[redacted]	-	-	-	26,135.50	-
FIL + MTX	[redacted]	15.810	[redacted]	11,586.57	0.000	0.443	-	26,135.50

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year

Scenario 1: Using efficacy data for FINCH 1 moderate subgroup with at least 2 cDMARD exposures

A scenario using the efficacy data for the FINCH 1 moderate subgroup with least 2 cDMARD exposures is presented below. It should be noted that the FINCH 1 study is not powered for these subgroup analyses, and only 49% of moderate RA patients (209 patients) had experience with 2 or more csDMARDs before entering the study. The cost-effectiveness analyses should thus be treated with caution, as the efficacy of filgotinib 200mg is informed by 53 patients, and the efficacy of placebo is informed by 66 patients. Due to the low patient numbers, the efficacy data from the overall moderate subgroup was preferred as the updated base case.

Population 1a - Moderate RA patients after 2 csDMARD failures (MTX ineligible)

The results of the scenario analysis for the moderate, MTX ineligible patient population after at least two csDMARD failures are presented in Table 32. Compared to BSC, filgotinib 200mg monotherapy was associated with QALY gains (0.462), and increased costs (£10,286), generating an incremental cost-effectiveness ratio (ICER) of £22,286 per QALY.

Table 34: Two csDMARD failure, MTX ineligible, moderate RA – versus FIL 200mg monotherapy (Scenario 1 using data for FINCH 1 moderate subgroup with at least 2 cDMARD exposures

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.946	[redacted]	-	-	-	22,286.28	-
FIL	[redacted]	15.946	[redacted]	10,286.37	0.000	0.462	-	22,286.28

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year

Population 1b - Moderate RA patients after 2 csDMARD failures (MTX eligible)

The results of the scenario analysis for the moderate, MTX eligible patient population after at least two csDMARD failures are presented in Table 33. Compared to BSC, filgotinib 200mg combination therapy was associated with QALY gains (0.438), and increased costs (£11,898), generating an incremental cost-effectiveness ratio (ICER) of £27,163 per QALY.

Table 35: Two csDMARD failure, MTX eligible, moderate RA – versus FIL 200mg combination therapy (Scenario 1 using data for FINCH 1 moderate subgroup with at least 2 cDMARD exposures

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.946	[redacted]	-	-	-	27,163.19	-
FIL + MTX	[redacted]	15.946	[redacted]	11,898.21	0.000	0.438	-	27,163.19

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year

Scenario 2: Using efficacy data for FINCH 1 moderate subgroup with at least 2 cDMARD failures

Using efficacy data for the FINCH 1 moderate subgroup that had failed at least 2 cDMARD failures at baseline, as opposed to patients that had 2 cDMARD exposures at baseline, was also explored, given this is the target population. Failed treatment was defined as prior csDMARD discontinuation due to inadequate response, loss of response or intolerance which included allergic response, whereas exposure can be successful treatment or failed treatment.

The number of patients that met the 2+ cDMARD failures criteria in the FINCH 1 moderate subgroup was low. The efficacy of filgotinib 200mg is informed by 19 patients, and the efficacy of placebo is informed by 32 patients.

Due to the low patient numbers, the efficacy data from the overall moderate subgroup was preferred as the updated base case.

Population 1a - Moderate RA patients after 2 csDMARD failures (MTX ineligible)

The results of the scenario analysis for the moderate, MTX ineligible patient population after at least two csDMARD failures are presented in Table 36. Compared to BSC, filgotinib 200mg monotherapy was associated with QALY gains (0.556), and increased costs (£9,578), generating an incremental cost-effectiveness ratio (ICER) of £17,216 per QALY.

Table 36: Two csDMARD failure, MTX ineligible, moderate RA – versus FIL 200mg monotherapy (Scenario 2 using data for FINCH 1 moderate subgroup with at least 2 cDMARD failures

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.946	[redacted]	-	-	-	17,216.12	-
FIL	[redacted]	15.946	[redacted]	9,578.17	0.000	0.556	-	17,216.12

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year

Population 1b - Moderate RA patients after 2 csDMARD failures (MTX eligible)

The results of the scenario analysis for the moderate, MTX eligible patient population after at least two csDMARD failures are presented in Table 37. Compared to BSC, filgotinib 200mg combination therapy was associated with QALY gains (0.527), and increased costs (£11,842), generating an incremental cost-effectiveness ratio (ICER) of £22,487 per QALY.

Table 37: Two csDMARD failure, MTX eligible, moderate RA – versus FIL 200mg combination therapy (Scenario 2 using data for FINCH 1 moderate subgroup with at least 2 cDMARD failures)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.946	[redacted]	-	-	-	22,486.62	-
FIL + MTX	[redacted]	15.946	[redacted]	11,842.04	0.000	0.527	-	22,486.62

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year

Issue 8: Utility values	
Technical Team Preliminary Judgement	Company response
The technical team agrees with the ERG that the empirical EQ-5D data collected in the trial	EQ-5D data are available from the FINCH 1 and FINCH 2 trials for the following treatments: • Filgotinib 200mg (FINCH 1 and FINCH 2)

should be used in a scenario analysis.

- Adalimumab (FINCH 1)
- MTX/Placebo (FINCH 1 and FINCH 2)

For the following timepoints:

- Baseline (FINCH 1 and FINCH 2)
- Week 24 (FINCH 1 and FINCH 2)
- Week 52 (filgotinib and adalimumab in FINCH 1)

According to the latest NICE recommendation, the responses to the EQ-5D-5L in FINCH 1 and FINCH 2 were converted to health utilities using the cross-walk algorithm mapped onto the UK EQ-5D-3L value set (8).

Utility inputs used in the analysis are summarised in Table 38 through Table 40.

Table 38: Mean utility of the moderate population of FINCH 1

	Filgotinib 200mg	Adalimumab	Placebo
Baseline (overall moderate population of FINCH 1)	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	N/A*

*Placebo patients switched to either filgotinib 200mg or 100 mg at week 24

Table 39: Mean utility of the severe population of FINCH 1

	Filgotinib 200mg	Adalimumab	Placebo
Baseline (overall moderate population of FINCH 1)	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	N/A*

*Placebo patients switched to either filgotinib 200mg or 100 mg at week 24

Table 40: Mean utility of the total population of FINCH 2

	Filgotinib 200mg	Placebo
Baseline (overall population of FINCH 2)	[redacted]	[redacted]
Week 24	[redacted]	[redacted]

By way of validation, scenario analysis comparing filgotinib to adalimumab and MTX was conducted for the MTX-IR population, and comparing filgotinib to MTX in the bDMARD-IR population.

At baseline, the utility values of the overall population (i.e. including all treatment arms) were applied, to reflect that an identical cohort for each arm is simulated in the cost-effectiveness model. For the MTX-IR population, the utility associated with filgotinib and adalimumab was assumed constant and equal to the utility at week 52 throughout the model, and the utility associated with placebo was assumed constant after week 24 (patients discontinued placebo treatment at week 24 in FINCH 1).

For the bDMARD-IR population, the utility associated with filgotinib and placebo was assumed constant and equal to the utility at week 52 throughout the model.

To inform the efficacy of subsequent BSC treatment, the mapping algorithm by Hernandez-Alava et al. as applied in the company base case was used, due to lack of long term data for BSC (9).

The results of the analyses are shown in Table 41 through Table 43.

Table 41: QALY outputs for the moderate MTX-IR population (FINCH 1)

	Filgotinib 200mg	Adalimumab	Placebo

Total QALYs using mapping algorithm by Hernandez-Alava et al.	[redacted]	[redacted]	[redacted]
Total QALYs using empirical trial data	[redacted]	[redacted]	[redacted]

Table 42: QALY outputs for the severe MTX-IR population (FINCH 1)

	Filgotinib 200mg	Adalimumab	Placebo
Total QALYs using mapping algorithm by Hernandez-Alava et al.	[redacted]	[redacted]	[redacted]
Total QALYs using empirical trial data	[redacted]	[redacted]	[redacted]

Table 43: QALY outputs for the severe bDMARD-IR population (FINCH 2)

	Filgotinib 200mg	Placebo
Total QALYs using mapping algorithm by Hernandez-Alava et al.	[redacted]	[redacted]
Total QALYs using empirical trial data	[redacted]	[redacted]

In addition to the scenario analysis, a correction to Table 50 which was provided as a response to ERG question B18c is provided below. In the previous table, aggregated baseline data from FINCH I (overall cohort) and FINCH II were mapped to utility values and averaged using an EQ-5D-5L value set for England described in Devlin et al., accessed from the EuroQoL website (10).

The updated table reports results from applying the cross-walk algorithm on individual patient data as per the latest NICE recommendation (8).

The updated utility outputs from the trial are similar to the model outputs using the mapping from Hernandez-Alava et al (9).

Table 44: Average baseline utility outputs from the FINCH trials, and the two mappings included in the model

Average utilities	cDMARD-IR (FINCH I)	bDMARD-IR (FINCH II)
From trial	[redacted]	[redacted]
Output from model using mapping from Hernandez-Alava et al.	[redacted]	[redacted]
Output from model using mapping from Malottki et al.	[redacted]	[redacted]

Appendix 3 – Company additional evidence - ISSUE 1 Relevant Populations

CEM inputs – base case analysis

The inputs used for the cost-effectiveness analysis are provided below in Table 45 and Table 46.

Table 45: Patient baseline characteristics used in the CEM – Overall FINCH 1 moderate population

Characteristics	Mean (SD)	Source
Age (years)	[redacted]	FINCH 1
Proportion female	[redacted]	
Duration of disease (years)	[redacted]	
Number of prior DMARDs	[redacted]	
Baseline HAQ-DI	[redacted]	
Baseline Pain (VAS)	[redacted]	
Weight (kg)	[redacted]	
DAS28	[redacted]	
RF (positive)	[redacted]	
IMD quartile	2.37	Norton et al. (11)
ACR (positive)	0.71	

Table 46: Treatment efficacy used in the CEM – Overall FINCH 1 moderate population

Treatments	ACR20 – number of responders (%)	ACR50 – number of responders (%)	ACR70 – number of responders (%)
Filgotinib 200mg (n=104)	[redacted]	[redacted]	[redacted]
Adalimumab (n=72)	[redacted]	[redacted]	[redacted]
Placebo/MTX (n=128)	[redacted]	[redacted]	[redacted]
After mapping to EULAR			
Treatments	**No response (%)**	**Moderate response (%)**	**Good response (%)**
Filgotinib 200mg	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Placebo/MTX	[redacted]	[redacted]	[redacted]

CEM inputs – scenario analyses 1 and 2

The baseline characteristics used for scenario analyses 1 and 2 are provided in Table 47. The efficacy inputs are provided in Table 48 and Table 49.

Table 47: Patient baseline characteristics used in the CEM – FINCH 1 moderate subgroup with at least 2 cDMARD exposures applied for both scenario analyses 1 and 2)

Characteristics	Mean (SD)	Source
Age (years)	[redacted]	FINCH 1
Proportion female	[redacted]	
Duration of disease (years)	[redacted]	
Number of prior DMARDs	[redacted]	
Baseline HAQ-DI	[redacted]	
Baseline Pain (VAS)	[redacted]	
Weight (kg)	[redacted]	
DAS28	[redacted]	
RF (positive)	[redacted]	
IMD quartile	2.37	Norton et al. (11)
ACR (positive)	0.71	

Table 48: Treatment efficacy used in the CEM – FINCH 1 moderate subgroup with at least 2 cDMARD exposures

Treatments	**ACR20 – number of responders (%)**	**ACR50 – number of responders (%)**	**ACR70 – number of responders (%)**
Filgotinib 200mg (n=53)	[redacted]	[redacted]	[redacted]
Placebo/MTX (n=66)	[redacted]	[redacted]	[redacted]
After mapping to EULAR			
Treatments	**No response (%)**	**Moderate response (%)**	**Good response (%)**
Filgotinib 200mg	[redacted]	[redacted]	[redacted]
Placebo/MTX	[redacted]	[redacted]	[redacted]

Table 49: Treatment efficacy used in the CEM – FINCH 1 moderate subgroup with at least 2 cDMARD failures

Treatments	**ACR20 – number of responders (%)**	**ACR50 – number of responders (%)**	**ACR70 – number of responders (%)**
Filgotinib 200mg (n=19)	[redacted]	[redacted]	[redacted]
Placebo/MTX (n=32)	[redacted]	[redacted]	[redacted]
After mapping to EULAR			
Treatments	**No response (%)**	**Moderate response (%)**	**Good response (%)**
Filgotinib 200mg	[redacted]	[redacted]	[redacted]
Placebo/MTX	[redacted]	[redacted]	[redacted]

Subgroup data

A summary of the comparison between moderate RA patients who have received 1 prior csDMARD and moderate patients who have received 2 or more csDMARDs is presented below for ACR20, ACR50, ACR70, DAS28-CRP <2.6 and DAS28-CRP ≤3.2 endpoints is provided below.

Table 50. Pairwise comparison of moderate RA patients with >= 2 prior csDMARDs versus moderate RA patients with 1 prior csDMARD, ACR20 week 12

ACR20	Filgotinib 200mg		Filgotinib 100mg		Adalimumab		Placebo	
Week 12	Moderate RA with >=2 prior csDMARDs (N=53)	Moderate RA with 1 prior csDMARDs (N=51)	Moderate RA with >=2 prior csDMARDs (N=55)	Moderate RA with 1 prior csDMARD (N=66)s	Moderate RA with >=2 prior csDMARDs (N=35)	Moderate RA with 1 prior csDMARDs (N=37)	Moderate RA with a prior csDMARDs (N=66)	Moderate RA with >1 prior csDMARDs (N=62)
Number of responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of non-responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of Non-Responders Observed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Imputed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in Response Rates vs-Subjects with 1 Prior csDMARDs [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 51. Pairwise comparison of moderate RA patients with >= 2 prior csDMARDs versus moderate RA patients with 1 prior csDMARD, ACR20 week 24

ACR20	Filgotinib 200mg		Filgotinib 100mg		Adalimumab		Placebo	
Week 24	Moderate RA with >=2 prior csDMARDs (N=53)	Moderate RA with 1 prior csDMARDs (N=51)	Moderate RA with >=2 prior csDMARDs (N=53)	Moderate RA with 1 prior csDMARDs (N=51)	Moderate RA with >=2 prior csDMARDs (N=55)	Moderate RA with 1 prior csDMARDs (N=66)	Moderate RA with >=2 prior csDMARDs (N=35)	Moderate RA with 1 prior csDMARDs (N=37)
Number of responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of non-responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Observed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Imputed (%)								
Difference in Response Rates vs-Subjects with 1 Prior csDMARDs [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 52. Pairwise comparison of moderate RA patients with >= 2 prior csDMARDs versus moderate RA patients with 1 prior csDMARD, ACR20 week 52

ACR20	Filgotinib 200mg		Filgotinib 100mg		Adalimumab	
Week 52	**Moderate RA with >=2 prior csDMARDs (N=53)**	**Moderate RA with 1 prior csDMARDs (N=51)**	**Moderate RA with >=2 prior csDMARDs (N=55)**	**Moderate RA with 1 prior csDMARDs (N=66)**	**Moderate RA with >=2 prior csDMARDs (N=35)**	**Moderate RA with 1 prior csDMARDs (N=37)**
Number of respond	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ers (%) [95% CI]						
Number of non-responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Observed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Imputed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in Response Rates vs-Subjects with 1 Prior csDMARDs [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 53. Pairwise comparison of moderate RA patients with >= 2 prior csDMARDs versus moderate RA patients with 1 prior csDMARD, ACR50 week 12

ACR50	Filgotinib 200mg		Filgotinib 100mg		Adalimumab		Placebo	
Week 12	Moderate RA with >=2 prior csDMARDs (N=53)	Moderate RA with 1 prior csDMARDs (N=51)	Moderate RA with >=2 prior csDMARDs (N=53)	Moderate RA with 1 prior csDMARDs (N=51)	Moderate RA with >=2 prior csDMARDs (N=55)	Moderate RA with 1 prior csDMARDs (N=66)	Moderate RA with >=2 prior csDMARDs (N=35)	Moderate RA with 1 prior csDMARDs (N=37)
Number of responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of non-responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Observed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Imputed (%)								
Difference in Response Rates vs-Subjects with 1 Prior csDMARDs [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 54. Pairwise comparison of moderate RA patients with >= 2 prior csDMARDs versus moderate RA patients with 1 prior csDMARD, ACR50 week 24

ACR50	Filgotinib 200mg		Filgotinib 100mg		Adalimumab		Placebo	
Week 24	**Moderate RA with >=2 prior csDMARDs (N=53)**	**Moderate RA with 1 prior csDMARDs (N=51)**	**Moderate RA with >=2 prior csDMARDs (N=53)**	**Moderate RA with 1 prior csDMARDs (N=51)**	**Moderate RA with >=2 prior csDMARDs (N=55)**	**Moderate RA with 1 prior csDMARDs (N=66)**	**Moderate RA with >=2 prior csDMARDs (N=35)**	**Moderate RA with 1 prior csDMARDs (N=37)**

Number of responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of non-responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Observed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Imputed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in Response Rates vs-Subje	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

cts with 1 Prior csDMARDs [95% CI]								
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 55. Pairwise comparison of moderate RA patients with >= 2 prior csDMARDs versus moderate RA patients with 1 prior csDMARD, ACR50 week 52

ACR50	Filgotinib 200mg		Filgotinib 100mg		Adalimumab	
Week 52	Moderate RA with >=2 prior csDMARDs (N=53)	Moderate RA with 1 prior csDMARDs (N=51)	Moderate RA with >=2 prior csDMARDs (N=55)	Moderate RA with 1 prior csDMARDs (N=66)	Moderate RA with >=2 prior csDMARDs (N=35)	Moderate RA with 1 prior csDMARDs (N=37)
Number of responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of non-responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of Non-Responders Observed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Imputed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in Response Rates vs-Subjects with 1 Prior csDMARDs [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 56. Pairwise comparison of moderate RA patients with >= 2 prior csDMARDs versus moderate RA patients with 1 prior csDMARD, ACR70 week 12

ACR70	Filgotinib 200mg	Filgotinib 100mg	Adalimumab	Placebo

Week 12	Moderate RA with >=2 prior csDMARDs (N=53)	Moderate RA with 1 prior csDMARDs (N=51)	Moderate RA with >=2 prior csDMARDs (N=53)	Moderate RA with 1 prior csDMARDs (N=51)	Moderate RA with >=2 prior csDMARDs (N=55)	Moderate RA with 1 prior csDMARDs (N=66)	Moderate RA with >=2 prior csDMARDs (N=35)	Moderate RA with 1 prior csDMARDs (N=37)
Number of responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of non-responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Observed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Imputed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Difference in Response Rates vs-Subjects with 1 Prior csDMARDs [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 57. Pairwise comparison of moderate RA patients with >= 2 prior csDMARDs versus moderate RA patients with 1 prior csDMARD, ACR70 week 24

ACR70	Filgotinib 200mg		Filgotinib 100mg		Adalimumab		Placebo	
Week 24	**Moderate RA with >=2 prior csDMARDs (N=53)**	**Moderate RA with 1 prior csDMARDs (N=51)**	**Moderate RA with >=2 prior csDMARDs (N=53)**	**Moderate RA with 1 prior csDMARDs (N=51)**	**Moderate RA with >=2 prior csDMARDs (N=55)**	**Moderate RA with 1 prior csDMARDs (N=66)**	**Moderate RA with >=2 prior csDMARDs (N=35)**	**Moderate RA with 1 prior csDMARDs (N=37)**
Number of responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of non-responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Observed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Imputed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in Response Rates vs-Subjects with 1 Prior csDMARDs [95% CI]	[redacted]		[redacted]		[redacted]			

P value	[redacted]							

Table 58. Pairwise comparison of moderate RA patients with >= 2 prior csDMARDs versus moderate RA patients with 1 prior csDMARD, ACR70 week 52

ACR70	Filgotinib 200mg		Filgotinib 100mg		Adalimumab	
Week 52	Moderate RA with >=2 prior csDMARDs (N=53)	Moderate RA with 1 prior csDMARDs (N=51)	Moderate RA with >=2 prior csDMARDs (N=55)	Moderate RA with 1 prior csDMARDs (N=66)	Moderate RA with >=2 prior csDMARDs (N=35)	Moderate RA with 1 prior csDMARDs (N=37)
Number of responders (%) [95% CI]	[redacted]					
Number of non-responders (%) [95% CI]	[redacted]					
Number of Non-Responders Observed (%)	[redacted]					

Number of Non-Responders Imputed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in Response Rates vs-Subjects with 1 Prior csDMARDs [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 59. Pairwise comparison of moderate RA patients with >= 2 prior csDMARDs versus moderate RA patients with 1 prior csDMARD, DAS28-CRP <2.6 week 12

DAS28-CRP <2.6	Filgotinib 200mg		Filgotinib 100mg		Adalimumab		Placebo	
Week 12	**Moderate RA with >=2 prior csDMARDs (N=53)**	**Moderate RA with 1 prior csDMARDs (N=51)**	**Moderate RA with >=2 prior csDMARDs (N=55)**	**Moderate RA with 1 prior csDMARDs (N=66)**	**Moderate RA with >=2 prior csDMARDs (N=35)**	**Moderate RA with 1 prior csDMARDs (N=37)**	**Moderate RA with a prior csDMARDs (N=66)**	**Moderate RA with >1 prior csDMARDs (N=62)**

Number of responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of non-responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Observed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Imputed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in Response Rates vs-Subjects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

with 1 Prior csDMARDs [95% CI]								
P-value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 60. Pairwise comparison of moderate RA patients with >= 2 prior csDMARDs versus moderate RA patients with 1 prior csDMARD, DAS28-CRP <2.6 week 24

DAS28-CRP <2.6	**Filgotinib 200mg**		**Filgotinib 100mg**		**Adalimumab**		**Placebo**	
Week 24	**Moderate RA with >=2 prior csDMARDs (N=53)**	**Moderate RA with 1 prior csDMARDs (N=51)**	**Moderate RA with >=2 prior csDMARDs (N=55)**	**Moderate RA with 1 prior csDMARDs (N=66)**	**Moderate RA with >=2 prior csDMARDs (N=35)**	**Moderate RA with 1 prior csDMARDs (N=37)**	**Moderate RA with a prior csDMARDs (N=66)**	**Moderate RA with >1 prior csDMARDs (N=62)**
Number of responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of non-responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of Non-Responders Observed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Imputed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in Response Rates vs-Subjects with 1 Prior csDMARDs [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 61. Pairwise comparison of moderate RA patients with >= 2 prior csDMARDs versus moderate RA patients with 1 prior csDMARD, DAS28-CRP <2.6 week 52

DAS28-CRP <2.6	Filgotinib 200mg		Filgotinib 100mg		Adalimumab	
Week 52	Moderate RA with >=2 prior csDMARDs (N=53)	Moderate RA with 1 prior csDMARDs (N=51)	Moderate RA with >=2 prior csDMARDs (N=55)	Moderate RA with 1 prior csDMARDs (N=66)	Moderate RA with >=2 prior csDMARDs (N=35)	Moderate RA with 1 prior csDMARDs (N=37)
Number of responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of non-responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Observed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Imputed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in Response Rates vs-Subjects with 1 Prior csDMAR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Ds [95% CI]						
P-value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 62. Pairwise comparison of moderate RA patients with >= 2 prior csDMARDs versus moderate RA patients with 1 prior csDMARD, DAS28-CRP ≤3.2 week 12

DAS28-CRP ≤3.2	Filgotinib 200mg		Filgotinib 100mg		Adalimumab		Placebo	
Week 12	**Moderate RA with >=2 prior csDMARDs (N=53)**	**Moderate RA with 1 prior csDMARDs (N=51)**	**Moderate RA with >=2 prior csDMARDs (N=53)**	**Moderate RA with 1 prior csDMARDs (N=51)**	**Moderate RA with >=2 prior csDMARDs (N=55)**	**Moderate RA with 1 prior csDMARDs (N=66)**	**Moderate RA with >=2 prior csDMARDs (N=35)**	**Moderate RA with 1 prior csDMARDs (N=37)**
Proportion of patients who achieved DAS28-CRP ≤3.2 (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of non-responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Observed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Imputed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in Response Rates vs-Subjects with 1 Prior csDMARDs [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 63. Pairwise comparison of moderate RA patients with >= 2 prior csDMARDs versus moderate RA patients with 1 prior csDMARD, DAS28-CRP ≤3.2 week 24

DAS28-CRP ≤3.2	**Filgotinib 200mg**		**Filgotinib 100mg**		**Adalimumab**		**Placebo**	
Week 24	**Moderate RA with >=2 prior csDMARDs (N=53)**	**Moderate RA with 1 prior csDMARDs (N=51)**	**Moderate RA with >=2 prior csDMARDs (N=53)**	**Moderate RA with 1 prior csDMARDs (N=51)**	**Moderate RA with >=2 prior csDMARDs (N=55)**	**Moderate RA with 1 prior csDMARDs (N=66)**	**Moderate RA with >=2 prior csDMARDs (N=35)**	**Moderate RA with 1 prior csDMARDs (N=37)**
Proportion of patients who achieved DAS28-CRP ≤3.2 (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of non-responders (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[95% CI]								
Number of Non-Responders Observed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Imputed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in Response Rates vs-Subjects with 1 Prior csDMARDs [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 64. Pairwise comparison of moderate RA patients with >= 2 prior csDMARDs versus moderate RA patients with 1 prior csDMARD, DAS28-CRP ≤3.2 week 52

DAS28-CRP ≤3.2	Filgotinib 200mg		Filgotinib 100mg		Adalimumab	
Week 52	Moderate RA with >=2 prior csDMARDs (N=53)	Moderate RA with 1 prior csDMARDs (N=51)	Moderate RA with >=2 prior csDMARDs (N=55)	Moderate RA with 1 prior csDMARDs (N=66)	Moderate RA with >=2 prior csDMARDs (N=35)	Moderate RA with 1 prior csDMARDs (N=37)
Proportion of patients who achieved DAS28-CRP ≤3.2 (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of non-responders (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders Observed (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Non-Responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Imputed (%)						
Difference in Response Rates vs-Subjects with 1 Prior csDMARDs [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 65. Moderate RA patients with 1 prior csDMARD - European League Against Rheumatism (EULAR) Responses at Week 12, Week 24 and Week 52

EULAR	Filgotinib 200mg	Filgotinib 100mg	Adalimumab	Placebo
	Moderate RA with 1 prior csDMARDs (N=51)	**Moderate RA with 1 prior csDMARDs (N=66)**	**Moderate RA with 1 prior csDMARDs (N=37)**	**Moderate RA with 1 prior csDMARDs (N=62)**
Week 12				
Good response	[redacted]	[redacted]	[redacted]	[redacted]
Moderate response	[redacted]	[redacted]	[redacted]	[redacted]
No Response	[redacted]	[redacted]	[redacted]	[redacted]

Week 24				
Good response	[redacted]	[redacted]	[redacted]	[redacted]
Moderate response	[redacted]	[redacted]	[redacted]	[redacted]
No Response	[redacted]	[redacted]	[redacted]	[redacted]
Week 52				
Good response	[redacted]	[redacted]	[redacted]	[redacted]
Moderate response	[redacted]	[redacted]	[redacted]	[redacted]
No Response	[redacted]	[redacted]	[redacted]	[redacted]

Table 66. Moderate RA patients with >= 2 prior csDMARD - European League Against Rheumatism (EULAR) Responses at Week 12, Week 24 and Week 52

EULAR	Filgotinib 200mg	Filgotinib 100mg	Adalimumab	Placebo
	Moderate RA with >= 2 csDMARDs (N=49)	Moderate RA with >= 2 csDMARDs (N=51)	Moderate RA with >= 2 csDMARDs (N=33)	Moderate RA with >= 2 csDMARDs (N=60)

Week 12				
Good response	[redacted]	[redacted]	[redacted]	[redacted]
Moderate response	[redacted]	[redacted]	[redacted]	[redacted]
No Response	[redacted]	[redacted]	[redacted]	[redacted]
Week 24				
Good response	[redacted]	[redacted]	[redacted]	[redacted]
Moderate response	[redacted]	[redacted]	[redacted]	[redacted]
No Response	[redacted]	[redacted]	[redacted]	[redacted]
Week 52				
Good response	[redacted]	[redacted]	[redacted]	[redacted]
Moderate response	[redacted]	[redacted]	[redacted]	[redacted]
No Response	[redacted]	[redacted]	[redacted]	[redacted]

Appendix 4 – Additional scenarios requested by the technical team

In the company responses to technical engagement, the ACR response rates from the FINCH 1 trial were mapped to EULAR responses and used to inform the efficacy of filgotinib and placebo. Following submission of the revised base case, the technical team requested a scenario using the EULAR data directly from the FINCH 1 trial, as these data are available. The inputs used and the results from these analyses are reported below.

CEM inputs – Additional scenario analysis using EULAR responses from FINCH 1

This scenario analysis applies direct EULAR responses for the FINCH 1 overall moderate subgroup for both filgotinib and placebo, which are summarised in Table 67**Error! Reference source not found.**.

Table 67: Treatment efficacy used in the CEM – Scenario: direct EULAR responses for the overall FINCH 1 moderate subgroup

Treatments	No response (%)	Moderate response (%)	Good response (%)
Filgotinib 200mg (n=89)	[redacted]	[redacted]	[redacted]
Placebo/MTX (n=98)	[redacted]	[redacted]	[redacted]

Additional scenario: Using direct EULAR efficacy data for the FINCH 1 moderate subgroup

The base case analysis applies ACR rates from the FINCH 1 trial using the FINCH 1 overall moderate subgroup. As the model applies EULAR response rates, the ACR response rates were mapped to EULAR using a mapping algorithm from TA375, which is detailed in the company submission and response to ERG questions. This is consistent with the methodology applied for the severe population.

This scenario analysis applies the EULAR responses directly from the FINCH 1 trial, for the overall moderate subgroup.

Results

Population 1a - Moderate RA patients after 2 csDMARD failures (MTX ineligible)

The results of the scenario analysis for the moderate, MTX ineligible patient population after at least two csDMARD failures are presented in Table 68. Compared to BSC, filgotinib 200mg monotherapy was associated with QALY gains (0.643), and increased costs (£15,633), generating an incremental cost-effectiveness ratio (ICER) of £24,294.84 per QALY.

Table 68: Two csDMARD failure, MTX ineligible, moderate RA – versus FIL 200mg monotherapy (Scenario using direct EULAR efficacy from FINCH 1 moderate subgroup data)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.946	[redacted]	-	-	-	24,294.84	-
FIL	[redacted]	15.946	[redacted]	15,632.72	0.000	0.643	-	24,294.84

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year

Population 1b - Moderate RA patients after 2 csDMARD failures (MTX eligible)

The results of the scenario analysis for the moderate, MTX eligible patient population after at least two csDMARD failures are presented in Table 69. Compared to BSC, filgotinib 200mg combination therapy was associated with QALY gains (0.620), and increased costs (£17,243), generating an incremental cost-effectiveness ratio (ICER) of £27,818 per QALY.

Table 69: Two csDMARD failure, MTX eligible, moderate RA – versus FIL 200mg combination therapy (Scenario using direct EULAR efficacy from FINCH 1 moderate subgroup data)

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
PBO/BSC	[redacted]	15.946	[redacted]	-	-	-	27,818.35	-
FIL + MTX	[redacted]	15.946	[redacted]	17,243.38	0.000	0.620	-	27,818.35

Abbreviations: BSC, best supportive care; FIL, filgotinib; ICER, incremental cost-effectiveness ratio; LYG, life year gained; MTX, methotrexate; PBO, placebo; QALY, quality adjusted life year

References

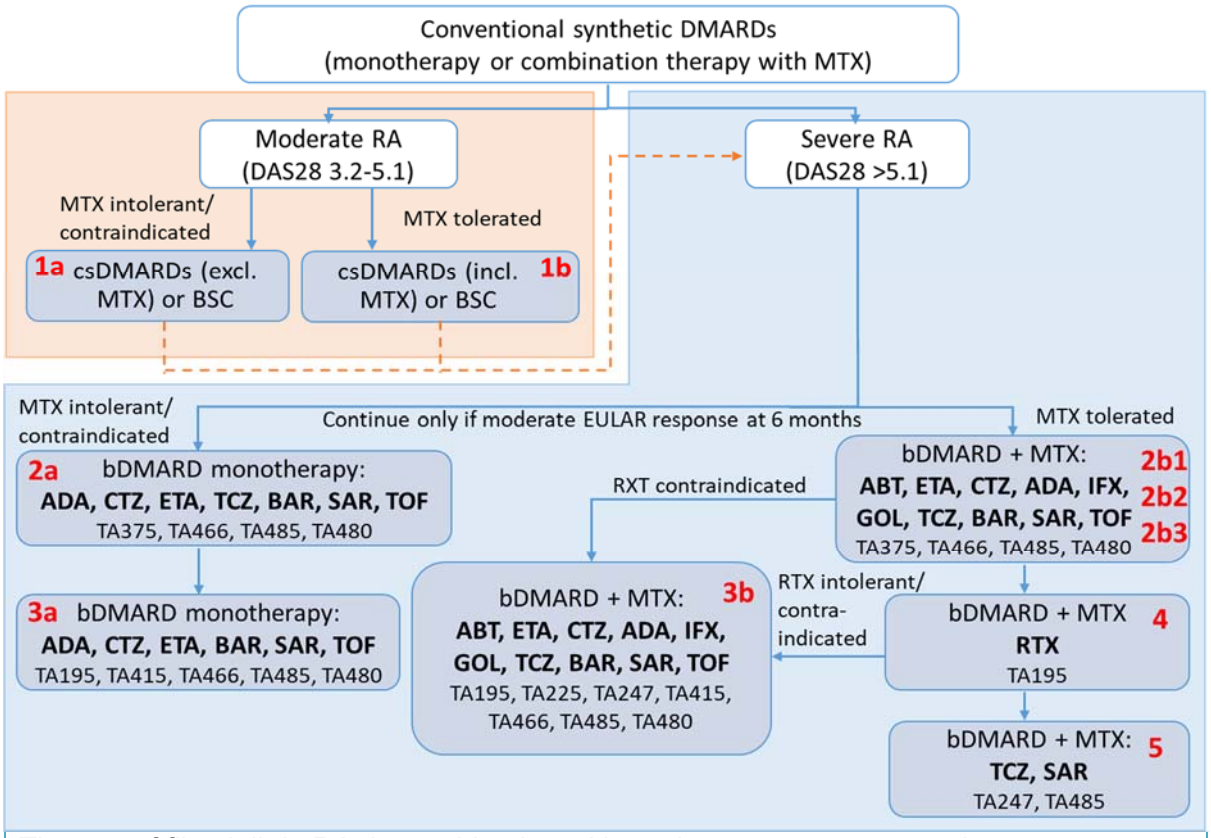
1. Excellence NIfHaC. Single Technology Appraisal: Upadacitinib for previously treated moderate to severe active rheumatoid arthritis [ID1400]. Committee Papers. 2019.
2. National Institute for Health and Care Excellence. Overview | Sarilumab for moderate to severe rheumatoid arthritis | Guidance | NICE.
3. National Institute for Health and Care Excellence. Overview | Tofacitinib for moderate to severe rheumatoid arthritis | Guidance | NICE.
4. National Institute for Health and Care Excellence. Overview | Baricitinib for moderate to severe rheumatoid arthritis | Guidance | NICE.
5. Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J, et al. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. Health Technol Assess. 2016;20(35):1-610.
6. Fakhouri W, Wang X, de La Torre I, Nicolay C. A Network Meta-Analysis to Compare Effectiveness of Baricitinib and Other Treatments in Rheumatoid Arthritis Patients with Inadequate Response to Methotrexate. J Health Econ Outcomes Res. 2020;7(1):10-23.
7. Kiely PD, Jayakumar K, Norton S, Williams R, Walsh D, Young A, editors. Relation between year 1 DAS28 status and 2 year disease activity, function and employment in DMARD treated RA patients in the Early Rheumatoid Arthritis Network (ERAN). Rheumatology; 2009: OXFORD UNIV PRESS GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND.
8. van Hout B, Janssen Mf Fau - Feng Y-S, Feng Ys Fau - Kohlmann T, Kohlmann T Fau - Busschbach J, Busschbach J Fau - Golicki D, Golicki D Fau - Lloyd A, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. (1524-4733 (Electronic)).
9. Hernandez Alava M, Wailoo A, Wolfe F, Michaud K. The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis. Rheumatology (Oxford). 2013;52(5):944-50.
10. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. Health Econ. 2018;27(1):7-22.
11. Norton S, Fu B, Scott DL, Deighton C, Symmons DP, Wailoo AJ, et al. Health Assessment Questionnaire disability progression in early rheumatoid arthritis: systematic review and analysis of two inception cohorts. Semin Arthritis Rheum. 2014;44(2):131-44.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Questions for technical engagement

1 Background information

Figure 1. Proposed positioning of filgotinib within current NICE treatment pathway. Relevant patient populations are marked in red and annotated below.



The use of filgotinib in RA, in combination with methotrexate or as monotherapy (methotrexate-ineligible population), was modelled in 10 patient populations:

- **1a:** moderate RA, MTX ineligible population (as first-line bDMARD monotherapy after failure of 2 or more cDMARDs)
- **1b:** moderate RA, MTX eligible population (as first-line bDMARD, with MTX, after failure of 2 or more cDMARDs)
- **2a:** severe RA, MTX ineligible population (as first-line bDMARD monotherapy)
- **2b:** severe RA, MTX eligible population (as first-line bDMARD with MTX); further divided into 3 subgroups based on the use of the subsequent second-line bDMARD (**2b1:** RTX; **2b2:** IL-6 [tocilizumab]; **2b3:** CD80 [abatacept])
- **3a:** severe RA, MTX ineligible population (as second-line bDMARD monotherapy)
- **3b:** severe RA, MTX eligible, RTX ineligible population (as second-line bDMARD with MTX)
- **4:** severe RA, MTX eligible, RTX eligible population (as second-line bDMARD with MTX)
- **5:** severe RA, after the failure of RTX+MTX (as third-line bDMARD with MTX)

ADA = adalimumab; ABA = abatacept; BAR = baricitinib; bDMARD = biological DMARD; BSC = best supportive care; csDMARD = conventional synthetic DMARD; CZP = certolizumab pegol; DAS = Disease Activity Score; DMARD = disease modifying antirheumatic drug; ETA = etanercept; GOL = golimumab; IFX = infliximab; MTX = Methotrexate; RA = Rheumatoid arthritis; RTX = Rituximab; TOC = tocilizumab; TOF = tofacitinib.
Source: Adapted from the ERG report, Figure 2.1.

2 Questions for engagement

Relevant comparators and treatment sequences

1. Are any important relevant comparators missing from the company submission (see Table 1)?

Table 1. Comparison of relevant comparators listed in the scope and included by the company in their economic model. Note: Comparators that were listed in the final scope but not included in the company submission are underlined.

Population	Disease severity	Line of advanced therapy[a]	MTX eligible?	Comparators listed in the scope	Comparators included by the company
1a	Moderate	First	No	BSC[b]	BSC
1b	Moderate	First	Yes	BSC[b]	BSC
2a	Severe	First	No	Adalimumab, etanercept, certolizumab pegol, tocilizumab, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (as monotherapy)	Adalimumab, etanercept, baricitinib, tocilizumab (as monotherapy)
2b	Severe	First-line	Yes	Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (with MTX)	Adalimumab, etanercept, baricitinib (with MTX)
3a	Severe	Second	No	Adalimumab, etanercept, certolizumab pegol, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (as monotherapy)	Tofacitinib, baricitinib, abatacept[c] (as monotherapy)
3b	Severe	Second	Yes	Adalimumab, etanercept, infliximab, abatacept, tocilizumab, certolizumab pegol, golimumab, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (with MTX)	Abatacept, tocilizumab, baricitinib, sarilumab (with MTX)
4	Severe	Second	Yes	Rituximab with MTX	Rituximab with MTX
5	Severe	Third	Yes	Tocilizumab, sarilumab, upadacitinib[c] (with MTX)	Tocilizumab, sarilumab (with MTX)

[a] after failure of 2 or more csDMARDs; [b] focusing on population in company submission (after failure of 2 or more csDMARDs); [c] Ongoing technology appraisal, not a relevant comparator; [c] abatacept is not recommended as monotherapy for methotrexate-ineligible population in TA195 and was not included in the scope).

csDMARD = conventional disease-modifying antirheumatic drugs; MTX = methotrexate.

2. Are treatment sequences modelled in the company submission appropriate for decision-making? What subsequent treatments (i.e. second- and third-line bDMARDs) are used in routine NHS practice, for patients who are methotrexate eligible and ineligible? Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, and so on.

Table 2. Treatment sequences used in the company model

Population	**Line of advanced therapy (after failure of 2 more csDMARDs)**			
	First	**Second**	**Third**	**Subsequent**
1a	Filgotinib[a] or csDMARDs	BSC		
1b	Filgotinib[b] or csDMARDs	BSC		
2a	Filgotinib[a] or bDMARD[a,b]	Abatacept[a]	BSC	
2b1	Filgotinib[c] or bDMARD[b,c]	Rituximab[c]	Tocilizumab[c]	BSC
2b2	Filgotinib[c] or bDMARD[b,c]	Tocilizumab[c]	BSC	
2b3	filgotinib[c] or bDMARD[b,c]	Abatacept[c]	BSC	
3a		Filgotinib[a] or bDMARD[a,b]	BSC	
3b		Filgotinib[c] or bDMARD[b,c]	BSC	
4		Filgotinib[c] or rituximab[c]	Tocilizumab[c]	BSC
5			Filgotinib[c] or bDMARD[b,c]	BSC

bDMARD = biologic DMARD; BSC = best standard care; csDMARDs = conventional synthetic DMARD; DMARD = disease modifying antirheumatic drug.

[a] as monotherapy; [b] relevant bDMARDs are listed in Table 1; [c] with methotrexate.

Generalisability of FINCH trials

3. Would the treatment effect of filgotinib be expected to be similar for people who have received 1 or more prior csDMARDs, and those who received 2 or more prior csDMARDs?Yes, by enlarge

4. Would the treatment effect of filgotinib and other cDMARDs/bDMARDs be expected to differ depending on the prior therapy received (for example, csDMARDs in combination with glucocorticoids versus glucocorticoids alone)? Yes, due to disease duration and/or impact of prior therapy

5. Would the treatment effect of filgotinib and other bDMARDs be expected to differ between people with moderate and severe disease?

6. Would the treatment effect be expected to differ when filgotinib (or other bDAMRDs) is given as a monotherapy, or in combination with csDMARDs?

7. Would the treatment effect of filgotinib or other bDMARDs be expected to differ depending on the line of advanced therapy (e.g. first- vs second vs third-line)?

Modelling progression from moderate to severe RA

8. What is the expected DAS28 score among people with moderate RA in UK clinical practice? Is there any published evidence to support this estimate?Approx 4.3 (Hyrich K, et al. Rheum 2009; 48(10)

9. What is the expected annual rate of progression from moderate to severe RA with the current BSC at 1, 2, 10 years, and lifelong risk of progression? Is there any published evidence to support these estimates? Accurate data are lacking.

10. What is the most relevant bDMARDs treatment sequence for people progressing from moderate to severe RA? Not sure what the question is asking exactly. If it is what would be the typical bDMARD sequence in moderate RA patients – I would say most would adopt a consistent approach to that taken in severe RA i.e. first TNFi, then RTX if seropositive or tocilizumab/IL-6 targeted subsequently and abatacept.

    If the question is, what bDMARD sequence is associated with progression from moderate to severe RA – no good UK data as unable to prescribe. But wouldn't necessarily anticipate a specific sequence is associated with this

Modelling best supportive care

11. What is the current BSC for people with moderate RA whose disease responded inadequately to, or who are intolerant of 2 or more csDMARDs?Lef + MTX, addition of low dose steroid

12. What is the expected treatment effect of current BSC given after failure of 2 or more csDMARDs?30% response

NICE National Institute for Health and Care Excellence

Technical engagement response form

Filgotinib for treating moderate to severe rheumatoid arthritis [ID1632]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **is 5pm on Monday 2 November**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Ailsa Bosworth**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**National Rheumatoid Arthritis Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Relevant comparators and treatment sequences	
Are any important relevant comparators missing from the company submission (see Table 1 in the appendix)?	**NRAS agrees with the comparators listed by NICE within the current NICE treatment pathway. There are comparators missing in severe disease in the company submission**
Are treatment sequences modelled in the company submission appropriate for decision-making (see Table 2 in the appendix)? What subsequent treatments (i.e. second- and third-line bDMARDs) are used in routine NHS practice, for patients who are methotrexate eligible and ineligible? Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, and so on.	**This question is more directed at the clinical expert than the patient experts, however, I do wish to state that I do not believe that BSC as a third line option makes any sense at all nor do I believe that a patient who has not responded to or been intolerant of 2 biologic/advanced treatments post failure of csDMARDs would be given BSC as a realistic option.**
What is the most appropriate second-line therapy for methotrexate-ineligible population (2a): abatacept, IL-6 inhibitors (tocilizumab or sarilumab), or rituximab monotherapy?	**This question is inappropriate for patient experts**
Issue 2: Generalisability of FINCH trials	
Would the treatment effect of filgotinib (or other bDMARDs) be expected to be similar for people who have received 1 or more prior csDMARDs, compared with those who received 2 or more prior csDMARDs?	**In my opinion yes. The reality is that if you fail to respond to MTX, you are less likely to respond to a second csDMARD so I wouldn't have thought there would be a significant difference between the two states.**

Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ depending on the prior therapy received (csDMARDs in combination with corticosteroids versus csDMARD alone)?	**This is a clinical expert question, but in my opinion it would not differ.**
Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ between people with moderate-severe and those with severe disease?	**This is a question for the clinical expert, however we have noted the comments in the technical engagement report in FINCH1 regarding the high baseline DAS28 scores (close to the severe spectrum of disease) and that all interventions were approx.. 20% less effective in severe disease than in moderate disease.**
Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ when it is given as a monotherapy, or in combination with csDMARDs?	**The company has assumed similar efficacy when given as mono or combination therapy which is aligned with previous TAs, but my understanding as a patient on their 9th advanced therapy that whether it is a biologic or a JAK, the efficacy is enhanced when taken with MTX**
Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ depending on the line of advanced therapy (e.g. first- vs second vs third-line)?	**My understanding is that for patients with prior exposure to TNF-α inhibitors, the likelihood of response to subsequent treatment with biologic agents declines with the increasing number of previous treatments with TNF-α inhibitors. For this reason general practice has evolved to not switch a patient to a second TNF but to give them a different target altogether. So my opinion would be that yes it would differ dependent on the line.**
Issue 3: Rate of progression from moderate to severe RA	
What is the expected DAS28 score among people with moderate RA in UK clinical practice? Is there any published evidence to support this estimate?	**In my opinion as lay expert, I would say that there is not an 'expected' DAS score amongst moderate patients as some patients will be progressing towards a DAS of 5.1 or greater, and then move onto a biologic, some will remain near the low end of the threshold of 3.2 and others can be in mid or upper-range between 3.2 and 5.1. There is helpful evidence in the BSR paper authored by Frank McKenna submitted to NICE in July 2019 in regard to the request by NRAS and the BSR for a review of TA375. In this paper Frank looks at data from a number of key databases.**

What is the expected annual rate of progression from moderate to severe RA with the current BSC at 1, 2, 10 years, and lifelong risk of progression? Is there any published evidence to support these estimates?	**Again I would refer NICE to the above submission on behalf of the BSR authored by Frank McKenna which specifically addresses this subject.**
Issue 4: Treatment sequence upon progression from moderate to severe RA	
What is the most relevant bDMARDs treatment sequence for people progressing from moderate to severe RA?	In the real world, my experience is that most clinicians would start a biologic naïve patient on an Anti-TNF biosimilar as they have the most experience with TNF-a. Some are now starting people on a JAK if there are clinical reasons or patient choice/lifestyle reasons to start in this class,
Does the treatment sequence depend on the prior treatment received for moderate disease? In particular: **a.** If people received filgotinib for moderate disease, would the treatment sequence for severe disease be different compared to people who did not receive prior filgotinib (e.g. alternative third-line biologic received upon progression)? **b.** If people received only csDMARDs for their moderate disease, would filgotinib be used once disease progresses to severe state?	a) Yes potentially it would if filgotinib was given in moderate disease, say after failure of MTX mono or combination cs DMARDs. I would guess that we don't have the data to inform definitive clinical decision-making when in comes to a third line biologic under these circumstances? b) It could be absolutely in my opinion and as far as I know is being used as first line advanced therapy.
Issue 5: Modelling best supportive care	
What is the current BSC for people with moderate RA whose disease responded inadequately to, or who are intolerant of 2 or more csDMARDs?	Intensive treatment, per TITRATE trial is an option but in the current climate unlikely to happen due pressure on NHS resources, especially nurses. Use of steroids but long term this is bad for patients due damage from long term steroid use. Using more csDMARDs after failure of MTX +1

	other is unlikely to have any effect. NRAS has a paper out for peer review on the impact of disease on patients who have not progressed to a biologic therapy authored by Prof. P Kiely and Dr. E. Nikiphorou et al. which shows clearly • In established RA patients not on advanced therapies, PROMs indicate high levels of suffering. • The rheumatoid arthritis impact of disease (RAID) acceptable state is very uncommon. • High levels of pain, physical disability, sleep difficulties and fatigue are prominent symptoms. This paper has been submitted to NICE as part of NRAS submission to review of TA375.
What is the expected treatment effect of current BSC given after failure of 2 or more csDMARDs?	As a patient who has been in this situation personally for a long time prior to the advent of biologics in 1999/2000, my experience has been very negative with huge amounts of irreversible joint damage having occurred necessitating to date 20 mostly major operations and a significant level of disability

Appendix

Table 1. Comparison of relevant comparators listed in the scope and included by the company in their economic model. Note: Comparators that were listed in the final scope but not included in the company submission are underlined.

Population	Disease severity	Line of advanced therapy[a]	MTX eligible?	Comparators listed in the scope	Comparators included by the company
1a	Moderate	First	No	BSC[b]	BSC
1b	Moderate	First	Yes	BSC[b]	BSC
2a	Severe	First	No	Adalimumab, etanercept, certolizumab pegol, tocilizumab, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (as monotherapy)	Adalimumab, etanercept, baricitinib, tocilizumab (as monotherapy)
2b	Severe	First-line	Yes	Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (with MTX)	Adalimumab, etanercept, baricitinib (with MTX)
3a	Severe	Second	No	Adalimumab, etanercept, certolizumab pegol, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (as monotherapy)	Tofacitinib, baricitinib, abatacept[c] (as monotherapy)
3b	Severe	Second	Yes	Adalimumab, etanercept, infliximab, abatacept, tocilizumab, certolizumab pegol, golimumab, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (with MTX)	Abatacept, tocilizumab, baricitinib, sarilumab (with MTX)
4	Severe	Second	Yes	Rituximab with MTX	Rituximab with MTX
5	Severe	Third	Yes	Tocilizumab, sarilumab, upadacitinib[c] (with MTX)	Tocilizumab, sarilumab (with MTX)

[a] after failure of 2 or more csDMARDs; [b] focusing on population in company submission (after failure of 2 or more csDMARDs); [c] Ongoing technology appraisal, not a relevant comparator; [c] abatacept is not recommended as monotherapy for methotrexate-ineligible population in TA195 and was not included in the scope); csDMARD = conventional disease-modifying antirheumatic drugs; MTX = methotrexate.

Table 2. Treatment sequences used in the company model

Population	Line of advanced therapy (after failure of 2 more csDMARDs)			
	First	**Second**	**Third**	**Subsequent**
1a	FIL or csDMARDs	BSC		
1b	FIL (with MTX) or csDMARDs	BSC		
2a	FIL, ADA, ETN, BAR or TCZ CS	ABC SC	BSC	
2b1	FIL, ADA, ETN or BAR (all with MTX)	RTX (with MTX)	TCZ SC (with MTX)	BSC
2b2	FIL, ADA, ETN or BAR (all with MTX)	TCZ SC (with MTX)	BSC	
2b3	FIL, ADA, ETN or BAR (all with MTX)	ABC SC (with MTX)	BSC	
3a		FIL, ABC SC, BAR, TOF	BSC	
3b		FIL, ABC SC, TCZ SC, SAR, BAR (all with MTX)	BSC	
4		FIL or RTX (with MTX)	TCZ SC (with MTX)	BSC
5			FIL, TCZ SC, SAR (all with MTX)	BSC

ABC = abatacept; ADA = adalimumab; BAR = baricitinib; BSC = best supportive care; csDMARDs = conventional synthetic disease modifying antirheumatic drug; ETN = etanercept; FIL = filgotinib; MTX = methotrexate; RTX = rituximab; SAR = sarilumab; TCZ = tocilizumab

Source: Company submission, tables 35-43.

Moderate RA and TNF inhibitors

[redacted] BA MD FRCP

25.07.19

Background

NICE Guideline NG 100 recommends that patients with rheumatoid arthritis (RA) should be treated to a target of remission of low disease activity in all patients. In those who fail conventional synthetic disease modifying anti-rheumatoid drugs (csDMARDs) and have a disease activity score (DAS28) >5.1 MTA375 recommends biologic DMARDs (bDMARDs). In those with persistent moderate disease with a DAS28 >3.2 and $\leq$ 5.1, MTA375 did not approve bDMARDs. However, patients with persistent moderate disease have increasing disability from observations in several studies. Conaghan et al (Rheumatology 2010;49:1894–1899) found that even over a 6 month period, up to 25% of those with moderate disease had progressive disability. In the ERAN study, Kiely et al (*Rheumatology* 2011;50:926–31) found that only 52% of 170 patients with moderate disease achieved a Health Assessment Questionnaire score (HAQ) < 1.25 after 2 years despite csDMARDs , compared with 79% of 161 patients who had low disease activity or remission. In a further analysis of the ERAS and ERAN database, Nikiphorou et al (*Ann Rheum Dis* 2016;75:2080–2086) found significant progression over time of HAQ independent of whether the DAS score was at the higher or lower part of the moderate range. However, those in the higher range required more orthopaedic surgery.

Patients with moderate disease have a similar response to treatment with TNFi compared with patients with severe disease. In a review of the BSR biologics register Hyrich KL et al (*Rheumatology* 2009;48:1323–1327) evaluated the response to a TNF inhibitor (TNFi) in 224 patients with moderate disease compared with 4,687 with severe disease and found the magnitude of improvement in HAQ was similar. They concluded that improvement in HAQ score 12 months after start of anti-TNF therapy was not dependent on baseline DAS28 scores suggesting that substantial benefits may also be gained by treating those with moderately active disease despite standard DMARD therapy. More recently a total of 1,754 patients with moderate RA in the BSR biologics register were assessed: 211 who had received a TNFi were compared with 1,543 who had only received csDMARDs. Those treated with a TNFi at baseline tended toward a higher DAS28 score but had a greater reduction in DAS28 and Health Assessment Questionnaire scores from treatment; disease remission occurred more often with less progression with the TNFi confirming the benefit of TNFi in those with moderate disease (Kotak S et al. Value Health 2015;18:817-23).

In their paper discussing the health economics of MTA375, Stevenson et al from ScHARR (*J Rheumatol* 2017;44:973-980 stated that if the price of bDMARDs fell by 50%, the ICER for moderate DAS would be £31,500, just above the upper limit of the NICE threshold for innovative technologies. With the reduction in price of TNF inhibitors following the introduction of biosimilar compounds, the ICERs for moderate disease would now fall under the £30,000/QALY threshold.

Prevalence of moderate disease

There may be concern regarding the potential effect on local drug budgets from widening access. We have undertaken a review of a number of databases in order to determine how many patients in England and Wales may be eligible for a TNFi if criteria included all RA patients with a DAS28 >3.2. In order to address this we have reviewed:

- ERAS database
- Data from recent large phase 3 studies with a novel disease modifying drug (commercial in confidence)
- Independent databases from Newcastle, Norwich and Swindon. Two databases have evaluated a cohort of patients who have been followed from diagnosis and one has taken a 4 week 'snapshot' of patients attending a rheumatology unit.

ERAS database

The Early Rheumatoid Arthritis Study (ERAS) is a multicentre inception cohort which recruited 1,465 patients with early RA (<2 years disease duration, no prior csDMARD) between 1986 and 1999 from nine hospitals in England, followed yearly for up to 25 years (median follow-up 10 years). We have commissioned a detailed analysis of the database. We were able to undertake a detailed analysis on patients who had received methotrexate or received at least two non-methotrexate DMARDs or received at least 1 combination DMARD. For those patients who received a TNF inhibitor during the study, only data up the year prior to the receipt of the TNF inhibitor was included in the analysis.

We analysed patients who would be eligible for a biologic drug from MTA375 compared with those with persistently moderate disease. There were 899 patients who either had a median DAS28 >5.1 (317) or had a DAS28 of 3.2 to 5.1 and had flares of disease with DAS28 >5.1 (582). There were 868 patients who had a mean DAS28 in the moderate range, but only 119 patients of these patients had a DAS28 that was never >5.1 (13% of those not in low disease state or remission). The database was also examined to determine HAQ progression. The dataset presented HAQ values of patients at 17 timepoints: baseline (year 0), 6 months (year 0.5), and yearly data from year 1 to year 15. Annual average HAQ progression in the whole cohort was 0.012. In the whole ERAS dataset, 602 patients had high HAQ progression, defined as a progression rate ≥0.06. Of these 602 patients, 319 had a mean DAS28 ≥3.2 and ≤5.1 (53.0% of those with high HAQ progression and 36.8% of the 868 patients with a mean DAS28 in the moderate range). Also from this cohort, only 39 patients had a DAS28 score that was always moderate (6.5% of high HAQ progression, 32.8% of those who never had a DAS28 >5.1). Average HAQ progression in those with DAS28 >5.1 at

every time point (84 patients) was 0.057. These data strengthen the argument for aggressive treatment of both severe and moderate RA.

Phase 3 studies in RA

A novel targeted synthetic DMARD (tsDMARD) has recently been evaluated in a number of studies evaluating active drug with either a placebo or with a comparator bDMARD. The tsDMARD is indicated for the treatment of moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more csDMARDs. The data is Commercial in Confidence. Entry criteria required patients with RA to have either moderate or severe disease and to have failed at least one csDMARD. Recruitment was undertaken worldwide in over 40 countries. Some studies were undertaken with patients who had failed on a bDMARD and were excluded from this analysis. Overall, 2,504 patients were entered into a study with a DAS28 at baseline. There were 631 patients (25%) with a DAS28 between 3.2 and 5.1. The remainder had a DAS28 >5.1.

Independent databases

Database A has up to 10 year follow up of 218 patients with RA taking DMARDs under the care of a single rheumatologist; 199 remain under regular follow up. At the last follow up 16% had been prescribed biologic drugs and only 11% had persistent moderate disease taking cDMARDs. Only 67% of those with moderate disease were considered suitable for a TNFi ie 7.6% of the total cohort.

Database B includes 513 patients with up to 7 years follow up. 358 were treated with methotrexate at baseline. Of these 40% have had a DAS28 > 5.1 whilst on treatment. The database does not clarify whether all these patients received a biologic drug. From the total cohort only 10.1% have persistently moderate disease. At present in this unit there are 203 patients with RA treated with bDMARDs. If bDMARDs were available for moderate patients and 67% were suitable for a TNFi then prescribing of bDMARDs in this unit would increase by approximately 10%.

Database C evaluated all patients attending a rheumatology clinic over a 4 week period and recorded DAS scores. DAS28 was recorded in 312 patients. 53.5% of patients had a DAS28<3.2 and 11.9% had a DAS> 5.1. Of the remaining 35% who had moderate disease 53% did not have an increase in DMARD therapy. If bDMARDs were available for moderate patients then from this data it can be extrapolated that up to 16% of patients may be elegible for a bDMARD. However, some of these patients may respond to increasing csDMARDs

Discussion

Current guidance allows treatment of any patient with RA with a DAS28 > 5.1 at one time point. It would be unusual for these patients not to have active synovitis in many joints. However, the DAS28 is weighted towards pain and tenderness and not all patients with a moderate DAS28 will have active synovitis. Some may have pain from previous joint damage. Others may have co-existent fibromyalgia and may be treated inappropriately with bDMARDS. In one study of 162 patients with RA, 64% of the 25 patients with 'fibromyalgic' RA were treated with bDMARDs compared with 32% of the remainder (Lage-Hansen PR et al Scand J Rheumatol 2016;45:45–48). We would therefore recommend that bDMARDs should only be prescribed in moderate RA in those with at least some joint swelling as well as tender joints.

It is noteworthy that in database A, only two thirds of those with a moderate DAS28 were considered suitable for a bDMARD. We also note that in both database A and B, the proportion of those with moderate disease (of 10-11%) was similar to the 13% of patients in the ERAS database who had persistent moderate disease without a flare making them eligible for a bDMARD. In contrast the 35% of patients in the 'snapshot' of a clinic in database C appears to indicate a greater need. However only half of these patients required a change in drug therapy and not all would have failed cDMARDs. In the recent large pharmaceutical studies with open recruitment of patients with active disease, 25% of patients had moderate disease. However, we recognise that in a worldwide recruitment of patients for these studies, many patients are recruited without being subject to tight control that is recommended in the current NICE guideline.

We believe that the individual databases reflect real world data and would estimate that prescribing of TNFi for RA may increase by approximately 15-20% if access is widened to include moderate RA. Of these patients at least 20% would have primary failure and be discontinued. A further 50% would be discontinued for secondary failure after a mean of 3 years (Soliman MM et alAnn Rheum Dis. 2011;70: 583-9). From this small sample it can be calculated that approximately 15% of the total cohort would be continued on a TNFi after 6 months and 7.5% would continue after 3 years. From the data available it is likely that TNFi prescribing in RA would increase by less than 20% falling to less than an additional 10% after 3 years.

We believe this review gives some confidence of the number of patients in England and Wales who may be eligible for a TNFi if MTA 375 is revised to allow prescribing to patients with RA who have a DAS28 >3.2 and have failed csDMARDs including methotrexate. The individual databases give real world data that are strengthened by the larger databases from ERAS and the pharmaceutical studies.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Filgotinib for treating moderate to severe rheumatoid arthritis [ID1632]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **is 5pm on Monday 2 November**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	British Society for Rheumatology
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No disclosures**

Questions for engagement

Issue 1: Relevant comparators and treatment sequences	
Are any important relevant comparators missing from the company submission (see Table 1 in the appendix)?	no
Are treatment sequences modelled in the company submission appropriate for decision-making (see Table 2 in the appendix)? What subsequent treatments (i.e. second- and third-line bDMARDs) are used in routine NHS practice, for patients who are methotrexate eligible and ineligible? Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, and so on.	Treatment sequences are adequate but as mentioned in the proposal certolizumab and golimumab are not included in tablet 2 – ctz I believe has more of a market share in women of child bearing age in particular therefore would be useful to include – I note included in table 1 and was listed in the final scope. I also note the comparison to sc abatacept as second line – I would agree that a further comparison should be made to IL-6 inhibition. Subsequent second and third line DMARDS – 1. Methotrexate eligible – csDMARD-ir Initial: bDMARD Baricitinib or Tofacitinib 30%, TNF 70% (adalimumab or etanercept) Secondary: Rituximab (if seropositive) 40%, JAK-i if not used above 20%, Tocilizumab 20%, Abatacept 20% Third line: Tocizilumab / Sarilumab 50% or Abatacept 50% 2. Methotrexate ineligible: Initial bDMARD: Adalimumab 70% or JAK 30% Secondary: Toc / Sarilumab 70% or Abatacept 30% Third: JAK inhibitor, Toc / Sarilumab / Abatacept 33.3 each
What is the most appropriate second-line therapy for methotrexate-ineligible population (2a): abatacept, IL-6 inhibitors (tocilizumab or sarilumab), or rituximab monotherapy?	IL-6 inhibition, followed by abatacept, I would also consider rituximab in combination with leflunomide rather than as monotherapy

Issue 2: Generalisability of FINCH trials	
Would the treatment effect of filgotinib (or other bDMARDs) be expected to be similar for people who have received 1 or more prior csDMARDs, compared with those who received 2 or more prior csDMARDs?	"only 49% of patients with moderate RA in FINCH 1 study had 2 or more csDMARDs before entering the study; 51% had only 1 prior csDMARD" I would expect the treatment effect for both of these to be similar – although I have not seen the original data.
Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ depending on the prior therapy received (csDMARDs in combination with corticosteroids versus csDMARD alone)?	This depends on disease duration and the duration of corticosteroid therapy. Those who have received more corticosteroid therapy may have more aggressive disease, and therefore have more in the way of structural damage at baseline however I would not expect the treatment effect to differ given the data presented in comparison to adalimumab or monotherapy.
Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ between people with moderate-severe and those with severe disease?	Trial data is based on ACR responses –ACR 50/70 responses are much harder to reach in severe disease. I would not expect the treatment effect to differ from other bDMARDs but there are other factors, such as pain scores to be taken into account in severe disease.
Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ when it is given as a monotherapy, or in combination with csDMARDs?	Data from FINCH2 would suggest that monotherapy is not significantly different to combination therapy in csDMARD naïve individuals. There is however no head to head or superiority data to compare this with.
Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ depending on the line of advanced therapy (e.g. first- vs second vs third-line)?	Yes, previous studies would suggest that the more therapies that are used (including JAK inhibitors 3rd or 4th line) efficacy appears to be diminished the more bDMARDs that are used (BSR registry data, 2018) – overall refractory disease being 6%.Kearsley Fleet et al, ARD. Most bDMARD refractory patients had cycled through at least 3 other bDMARD agents – therefore there is a possibility that the treatment effect of filgotinib would be diminished as a 3rd or 4th line agent, but this is not specific to the drug.

Issue 3: Rate of progression from moderate to severe RA	
What is the expected DAS28 score among people with moderate RA in UK clinical practice? Is there any published evidence to support this estimate?	DAS-28 4.34, sd 0.5, range 3.2-5.1. as published in Pan Y, Norton S, Gwinnutt JM, et al. Not all moderate disease is the same - Identification of disability trajectories among patients with rheumatoid arthritis and moderate disease activity [published correction appears in PLoS One. 2020 Apr 2;15(4):e0231481]. *PLoS One*. 2019;14(5)
What is the expected annual rate of progression from moderate to severe RA with the current BSC at 1, 2, 10 years, and lifelong risk of progression? Is there any published evidence to support these estimates?	47-53% over 5 years Schneider et al, 2013, summarised in Edwards et al, Rheumatology advanced practice 2019 – but with multiple contributory factors .Radiographic progression – 2.02 Carpenter et al, 2016 Rheumatology
Issue 4: Treatment sequence upon progression from moderate to severe RA	
What is the most relevant bDMARDs treatment sequence for people progressing from moderate to severe RA?	1. JAK inhibition (baricitinib, tofactinib, upadacitnib) OR TNF (ada, etanercept, ctz, gol, ifx) 2. Rituximab (seropositive+MTX) OR IL-6 inhibition (tocilizumab or sarilumab) 3. Abatacept
Does the treatment sequence depend on the prior treatment received for moderate disease? In particular: **a.** If people received filgotinib for moderate disease, would the treatment sequence for severe disease be different compared to people who did not receive prior filgotinib (e.g.	a. No, would still follow this order – TNF, RTX OR IL-6, Abatacept – this would only change the likelihood of considering another less selective JAK inhibitor such as tofactinib or baricitinib

alternative third-line biologic received upon progression)? **b.** If people received only csDMARDs for their moderate disease, would filgotinib be used once disease progresses to severe state?	b. Filgotinib would be considered in the same order if used for severe disease (DAS>5.1), dependent on safety data for men wishing to conceive
Issue 5: Modelling best supportive care	
What is the current BSC for people with moderate RA whose disease responded inadequately to, or who are intolerant of 2 or more csDMARDs?	This is not really an issue in practice as we would move on to biologics in those with moderate - severe disease as second line. If best supportive care were to be carried out this would consist of steroid use for flares – which is very dependent on individual patient factors such as age and comorbidity
What is the expected treatment effect of current BSC given after failure of 2 or more csDMARDs?	If we are confining the definition of BSC to no medication – progression of disease and disability, including adverse effects to steroids.

Appendix

Table 1. Comparison of relevant comparators listed in the scope and included by the company in their economic model. Note: Comparators that were listed in the final scope but not included in the company submission are underlined.

Population	Disease severity	Line of advanced therapy[a]	MTX eligible?	Comparators listed in the scope	Comparators included by the company
1a	Moderate	First	No	BSC[b]	BSC
1b	Moderate	First	Yes	BSC[b]	BSC
2a	Severe	First	No	Adalimumab, etanercept, certolizumab pegol, tocilizumab, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (as monotherapy)	Adalimumab, etanercept, baricitinib, tocilizumab (as monotherapy)
2b	Severe	First-line	Yes	Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (with MTX)	Adalimumab, etanercept, baricitinib (with MTX)
3a	Severe	Second	No	Adalimumab, etanercept, certolizumab pegol, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (as monotherapy)	Tofacitinib, baricitinib, abatacept[c] (as monotherapy)
3b	Severe	Second	Yes	Adalimumab, etanercept, infliximab, abatacept, tocilizumab, certolizumab pegol, golimumab, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (with MTX)	Abatacept, tocilizumab, baricitinib, sarilumab (with MTX)
4	Severe	Second	Yes	Rituximab with MTX	Rituximab with MTX
5	Severe	Third	Yes	Tocilizumab, sarilumab, upadacitinib[c] (with MTX)	Tocilizumab, sarilumab (with MTX)

[a] after failure of 2 or more csDMARDs; [b] focusing on population in company submission (after failure of 2 or more csDMARDs); [c] Ongoing technology appraisal, not a relevant comparator; [c] abatacept is not recommended as monotherapy for methotrexate-ineligible population in TA195 and was not included in the scope); csDMARD = conventional disease-modifying antirheumatic drugs; MTX = methotrexate.

Table 2. Treatment sequences used in the company model

Population	Line of advanced therapy (after failure of 2 more csDMARDs)			
	First	**Second**	**Third**	**Subsequent**
1a	FIL or csDMARDs	BSC		
1b	FIL (with MTX) or csDMARDs	BSC		
2a	FIL, ADA, ETN, BAR or TCZ CS	ABC SC	BSC	
2b1	FIL, ADA, ETN or BAR (all with MTX)	RTX (with MTX)	TCZ SC (with MTX)	BSC
2b2	FIL, ADA, ETN or BAR (all with MTX)	TCZ SC (with MTX)	BSC	
2b3	FIL, ADA, ETN or BAR (all with MTX)	ABC SC (with MTX)	BSC	
3a		FIL, ABC SC, BAR, TOF	BSC	
3b		FIL, ABC SC, TCZ SC, SAR, BAR (all with MTX)	BSC	
4		FIL or RTX (with MTX)	TCZ SC (with MTX)	BSC
5			FIL, TCZ SC, SAR (all with MTX)	BSC

ABC = abatacept; ADA = adalimumab; BAR = baricitinib; BSC = best supportive care; csDMARDs = conventional synthetic disease modifying antirheumatic drug; ETN = etanercept; FIL = filgotinib; MTX = methotrexate; RTX = rituximab; SAR = sarilumab; TCZ = tocilizumab

Source: Company submission, tables 35-43.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Filgotinib for treating moderate to severe rheumatoid arthritis [ID1632]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **is 5pm on Monday 2 November**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**AbbVie**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Questions for engagement

Issue 1: Relevant comparators and treatment sequences	
Are any important relevant comparators missing from the company submission (see Table 1 in the appendix)?	AbbVie believe that the following comparators should be used for filgotinib in moderate RA after the failure of two or more csDMARDs, in line with the MTA in RA (TA375), and the three NICE appraisals in RA published subsequent to that appraisal: • csDMARD → BSC compared to FILGO → csDMARD → BSC
Are treatment sequences modelled in the company submission appropriate for decision-making (see Table 2 in the appendix)? What subsequent treatments (i.e. second- and third-line bDMARDs) are used in routine NHS practice, for patients who are methotrexate eligible and ineligible? Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, and so on.	AbbVie believe that the following treatment sequence in severe RA is reflective of clinical practice: • Adalimumab combo → rituximab combo → sarilumab combo, in MTX eligible patients • Adalimumab mono → rituximab mono → sarilumab mono, in MTX ineligible patients Model outputs are sensitive to treatment sequencing scenarios and it is important that reimbursement decisions are based on a treatment pathway that mirrors UK clinical practice as much as possible. It is also important to note that the preferred ERG sequencing for severe RA (etanercept as the first-line comparator) may not be as conservative as the one suggested above (adalimumab as the first-line comparator) once commercial discounts of all products are taken into account.
What is the most appropriate second-line therapy for methotrexate-ineligible population (2a): abatacept, IL-6 inhibitors (tocilizumab or sarilumab), or rituximab monotherapy?	AbbVie believe that the following treatment sequence in severe RA for methotrexate ineligible patients is reflective of clinical practice: • Adalimumab mono → rituximab mono → sarilumab mono

Issue 2: Generalisability of FINCH trials	
Would the treatment effect of filgotinib (or other bDMARDs) be expected to be similar for people who have received 1 or more prior csDMARDs, compared with those who received 2 or more prior csDMARDs?	
Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ depending on the prior therapy received (csDMARDs in combination with corticosteroids versus csDMARD alone)?	
Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ between people with moderate-severe and those with severe disease?	AbbVie believe that it would be most appropriate to use the moderate RA subgroup to estimate the efficacy of filgotinib and of csDMARD in moderate RA patients since there is evidence from upadacitinib studies (a drug in the same class) to support that treatment effect is expected to differ between moderate and severe RA patients. AbbVie anticipate that the same trend in benefit may be seen in filgotinib trials.
Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ when it is given as a monotherapy, or in combination with csDMARDs?	
Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ depending on the line of advanced therapy (e.g. first- vs second vs third-line)?	For first line therapies, it would seem to be most appropriate to use the advanced therapy naïve NMA from the manufacturer's submission (csDMARD IR NMA that uses FINCH 1 as the evidence base) and for subsequent positions the advanced therapy experienced NMA (bDMARD IR NMA that uses FINCH 2 as the evidence base).
Issue 3: Rate of progression from moderate to severe RA	
What is the expected DAS28 score among people with moderate RA in UK clinical practice? Is there any published evidence to support this estimate?	

What is the expected annual rate of progression from moderate to severe RA with the current BSC at 1, 2, 10 years, and lifelong risk of progression? Is there any published evidence to support these estimates?	Published data from the UK ERAN dataset suggests 19% of moderate RA patients transition to severe RA at two years [Deighton et al 2010 and Kiely et al 2009]. • Deighton C, Hyrich K, Ding T, Ledingham J, Lunt M, Luqmani R, et al. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. Rheumatology (Oxford). 2010. • Kiely PD, Jayakumar K, Norton S, Williams R, Walsh D, Young A, editors. Relation between year 1 DAS28 status and 2 year disease activity, function and employment in DMARD treated RA patients in the Early Rheumatoid Arthritis Network (ERAN). Rheumatology; 2009: OUP. Data is aligned with time-point progression projections from an AbbVie analysis of UK registry data from the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) which further supports the two-year progression rate.
Issue 4: Treatment sequence upon progression from moderate to severe RA	
What is the most relevant bDMARDs treatment sequence for people progressing from moderate to severe RA?	AbbVie believe that the following treatment sequence in severe RA is reflective of clinical practice: • Adalimumab combo → rituximab combo → sarilumab combo, in MTX eligible patients • Adalimumab mono → rituximab mono →sarilumab mono, in MTX ineligible patients
Does the treatment sequence depend on the prior treatment received for moderate disease? In particular: **a.** If people received filgotinib for moderate disease, would the treatment sequence for severe disease be different compared to people who did not receive prior filgotinib (e.g.	

alternative third-line biologic received upon progression)? **b.** If people received only csDMARDs for their moderate disease, would filgotinib be used once disease progresses to severe state?	
Issue 5: Modelling best supportive care	
What is the current BSC for people with moderate RA whose disease responded inadequately to, or who are intolerant of 2 or more csDMARDs?	AbbVie believe that the csDMARD that has been shown to work best and is established UK practice in those moderate RA patients that have failed two or more csDMARDs is reflective of clinical practice.
What is the expected treatment effect of current BSC given after failure of 2 or more csDMARDs?	Using the treatment effect of placebo + csDMARD from the control arm of FINCH 1 would seem an appropriate estimate of the efficacy of csDMARD that are used in existing practice after the failure of two or more DMARDs. The appropriate estimate of the efficacy of csDMARD after the failure of filgotinib would be the placebo + csDMARD arm of FINCH 2, since this trial consists of those who have had an inadequate response or are intolerant to at least one advanced therapy.

Appendix

Table 1. Comparison of relevant comparators listed in the scope and included by the company in their economic model. Note: Comparators that were listed in the final scope but not included in the company submission are underlined.

Population	Disease severity	Line of advanced therapy[a]	MTX eligible?	Comparators listed in the scope	Comparators included by the company
1a	Moderate	First	No	BSC[b]	BSC
1b	Moderate	First	Yes	BSC[b]	BSC
2a	Severe	First	No	Adalimumab, etanercept, certolizumab pegol, tocilizumab, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (as monotherapy)	Adalimumab, etanercept, baricitinib, tocilizumab (as monotherapy)
2b	Severe	First-line	Yes	Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (with MTX)	Adalimumab, etanercept, baricitinib (with MTX)
3a	Severe	Second	No	Adalimumab, etanercept, certolizumab pegol, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (as monotherapy)	Tofacitinib, baricitinib, abatacept[c] (as monotherapy)
3b	Severe	Second	Yes	Adalimumab, etanercept, infliximab, abatacept, tocilizumab, certolizumab pegol, golimumab, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (with MTX)	Abatacept, tocilizumab, baricitinib, sarilumab (with MTX)
4	Severe	Second	Yes	Rituximab with MTX	Rituximab with MTX
5	Severe	Third	Yes	Tocilizumab, sarilumab, upadacitinib[c] (with MTX)	Tocilizumab, sarilumab (with MTX)

[a] after failure of 2 or more csDMARDs; [b] focusing on population in company submission (after failure of 2 or more csDMARDs); [c] Ongoing technology appraisal, not a relevant comparator; [c] abatacept is not recommended as monotherapy for methotrexate-ineligible population in TA195 and was not included in the scope); csDMARD = conventional disease-modifying antirheumatic drugs; MTX = methotrexate.

Table 2. Treatment sequences used in the company model

Population	Line of advanced therapy (after failure of 2 more csDMARDs)			
	First	**Second**	**Third**	**Subsequent**
1a	FIL or csDMARDs	BSC		
1b	FIL (with MTX) or csDMARDs	BSC		
2a	FIL, ADA, ETN, BAR or TCZ CS	ABC SC	BSC	
2b1	FIL, ADA, ETN or BAR (all with MTX)	RTX (with MTX)	TCZ SC (with MTX)	BSC
2b2	FIL, ADA, ETN or BAR (all with MTX)	TCZ SC (with MTX)	BSC	
2b3	FIL, ADA, ETN or BAR (all with MTX)	ABC SC (with MTX)	BSC	
3a		FIL, ABC SC, BAR, TOF	BSC	
3b		FIL, ABC SC, TCZ SC, SAR, BAR (all with MTX)	BSC	
4		FIL or RTX (with MTX)	TCZ SC (with MTX)	BSC
5			FIL, TCZ SC, SAR (all with MTX)	BSC

ABC = abatacept; ADA = adalimumab; BAR = baricitinib; BSC = best supportive care; csDMARDs = conventional synthetic disease modifying antirheumatic drug; ETN = etanercept; FIL = filgotinib; MTX = methotrexate; RTX = rituximab; SAR = sarilumab; TCZ = tocilizumab

Source: Company submission, tables 35-43.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Filgotinib for treating moderate to severe rheumatoid arthritis [ID1632]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **is 5pm on Monday 2 November**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Pfizer Ltd.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Questions for engagement

Issue 1: Relevant comparators and treatment sequences	
Are any important relevant comparators missing from the company submission (see Table 1 in the appendix)?	Pfizer agrees with the NICE technical team that the analyses by Gilead omitted important and relevant comparators. In line with the current methods guide (Guide to the methods of technology appraisal 2013) and with the final scope developed by the NICE technical team Xeljanz® (tofacitinib) should be included as a comparator in the analyses for population 2a, 2b, 3a, 3b. Xeljanz® (tofacitinib) is indicated for moderate to severe rheumatoid arthritis as per the marketing authorisation and has been recommended by NICE as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with a combination of conventional disease-modifying anti-rheumatic drugs (DMARDs) in TA480 (Tofacitinib for moderate to severe rheumatoid arthritis). As outlined by the ERG, market access data does not reflect clinical usefulness and the opinion of one UK rheumatologist cannot be considered as a general reflection of the opinion of UK clinical community or availability of treatment options. It is also worth acknowledging that tofacitinib and filgotinib belong to the same drug class, the Janus kinase inhibitors (JAKs), and therefore exhibit the same mechanism of action. Based on the mechanism of action it is highly unlikely that clinicians would position filgotinib differently in clinical practice to currently available JAKs recommended by NICE, especially since filgotinib has lesser efficacy benefits than current established JAKs (NMA results section B2.9.13 of company submission). Considering all of the above points, Pfizer believes that tofacitinib (Xeljanz®)should be included as a comparator for population 2a, 2b, 3a and 3b, as part of NICE decision making for the current technology appraisal of filgotinib in moderate to severe rheumatoid arthritis.

Are treatment sequences modelled in the company submission appropriate for decision-making (see Table 2 in the appendix)? What subsequent treatments (i.e. second- and third-line bDMARDs) are used in routine NHS practice, for patients who are methotrexate eligible and ineligible? Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, and so on.	No comments.
What is the most appropriate second-line therapy for methotrexate-ineligible population (2a): abatacept, IL-6 inhibitors (tocilizumab or sarilumab), or rituximab monotherapy?	No comments.
Issue 2: Generalisability of FINCH trials	
Would the treatment effect of filgotinib (or other bDMARDs) be expected to be similar for people who have received 1 or more prior csDMARDs, compared with those who received 2 or more prior csDMARDs?	No comments.
Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ depending on the prior therapy received (csDMARDs in combination with corticosteroids versus csDMARD alone)?	No comments.
Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ between people with moderate-severe and those with severe disease?	No comments.

Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ when it is given as a monotherapy, or in combination with csDMARDs?	No comments.
Would the treatment effect of filgotinib (or other bDMARDs) be expected to differ depending on the line of advanced therapy (e.g. first- vs second vs third-line)?	No comments.
Issue 3: Rate of progression from moderate to severe RA	
What is the expected DAS28 score among people with moderate RA in UK clinical practice? Is there any published evidence to support this estimate?	No comments.
What is the expected annual rate of progression from moderate to severe RA with the current BSC at 1, 2, 10 years, and lifelong risk of progression? Is there any published evidence to support these estimates?	No comments.
Issue 4: Treatment sequence upon progression from moderate to severe RA	
What is the most relevant bDMARDs treatment sequence for people progressing from moderate to severe RA?	No comments.
Does the treatment sequence depend on the prior treatment received for moderate disease? In particular: **a.** If people received filgotinib for moderate disease, would the treatment sequence for severe disease be different compared to people who did not receive prior filgotinib (e.g.	No comments.

alternative third-line biologic received upon progression)? **b.** If people received only csDMARDs for their moderate disease, would filgotinib be used once disease progresses to severe state?	
Issue 5: Modelling best supportive care	
What is the current BSC for people with moderate RA whose disease responded inadequately to, or who are intolerant of 2 or more csDMARDs?	No comments.
What is the expected treatment effect of current BSC given after failure of 2 or more csDMARDs?	No comments.

Appendix

Table 1. Comparison of relevant comparators listed in the scope and included by the company in their economic model. Note: Comparators that were listed in the final scope but not included in the company submission are underlined.

Population	Disease severity	Line of advanced therapy[a]	MTX eligible?	Comparators listed in the scope	Comparators included by the company
1a	Moderate	First	No	BSC[b]	BSC
1b	Moderate	First	Yes	BSC[b]	BSC
2a	Severe	First	No	Adalimumab, etanercept, certolizumab pegol, tocilizumab, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (as monotherapy)	Adalimumab, etanercept, baricitinib, tocilizumab (as monotherapy)
2b	Severe	First-line	Yes	Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (with MTX)	Adalimumab, etanercept, baricitinib (with MTX)
3a	Severe	Second	No	Adalimumab, etanercept, certolizumab pegol, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (as monotherapy)	Tofacitinib, baricitinib, abatacept[c] (as monotherapy)
3b	Severe	Second	Yes	Adalimumab, etanercept, infliximab, abatacept, tocilizumab, certolizumab pegol, golimumab, sarilumab, tofacitinib, baricitinib, upadacitinib[c] (with MTX)	Abatacept, tocilizumab, baricitinib, sarilumab (with MTX)
4	Severe	Second	Yes	Rituximab with MTX	Rituximab with MTX
5	Severe	Third	Yes	Tocilizumab, sarilumab, upadacitinib[c] (with MTX)	Tocilizumab, sarilumab (with MTX)

[a] after failure of 2 or more csDMARDs; [b] focusing on population in company submission (after failure of 2 or more csDMARDs); [c] Ongoing technology appraisal, not a relevant comparator; [c] abatacept is not recommended as monotherapy for methotrexate-ineligible population in TA195 and was not included in the scope); csDMARD = conventional disease-modifying antirheumatic drugs; MTX = methotrexate.

Table 2. Treatment sequences used in the company model

Population	Line of advanced therapy (after failure of 2 more csDMARDs)			
	First	**Second**	**Third**	**Subsequent**
1a	FIL or csDMARDs	BSC		
1b	FIL (with MTX) or csDMARDs	BSC		
2a	FIL, ADA, ETN, BAR or TCZ CS	ABC SC	BSC	
2b1	FIL, ADA, ETN or BAR (all with MTX)	RTX (with MTX)	TCZ SC (with MTX)	BSC
2b2	FIL, ADA, ETN or BAR (all with MTX)	TCZ SC (with MTX)	BSC	
2b3	FIL, ADA, ETN or BAR (all with MTX)	ABC SC (with MTX)	BSC	
3a		FIL, ABC SC, BAR, TOF	BSC	
3b		FIL, ABC SC, TCZ SC, SAR, BAR (all with MTX)	BSC	
4		FIL or RTX (with MTX)	TCZ SC (with MTX)	BSC
5			FIL, TCZ SC, SAR (all with MTX)	BSC

ABC = abatacept; ADA = adalimumab; BAR = baricitinib; BSC = best supportive care; csDMARDs = conventional synthetic disease modifying antirheumatic drug; ETN = etanercept; FIL = filgotinib; MTX = methotrexate; RTX = rituximab; SAR = sarilumab; TCZ = tocilizumab

Source: Company submission, tables 35-43.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Filgotinib for moderate to severe rheumatoid arthritis

ADDENDUM: Critique of the company's response to Technical Engagement

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

Authors
Rob Riemsma, Reviews Manager, Kleijnen Systematic Reviews Ltd, UK
Sabine Grimm, Health Economist, Maastricht UMC, the Netherlands
Ben Wijnen, Health Economist, Maastricht UMC
Debra Fayter, Systematic Reviewer, KSR Ltd
Sue O'Meara, Systematic Reviewer, KSR Ltd
Nigel Armstrong, Health Economist, KSR Ltd
Charlotte Ahmadu, Health Economist, KSR Ltd
Lloyd Brandts, Health Economist, Maastricht UMC
Gill Worthy, Statistician, KSR Ltd
Kate Misso, Information Specialist, KSR Ltd
John Kirwan, Emeritus Professor of Rheumatic Diseases, University of Bristol
Manuela Joore, Health Economist, Maastricht UMC
Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University

Correspondence to Rob Riemsma, Kleijnen Systematic Reviews
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, UK
YO19 6FD

Date completed 26/11/2020

1. Company's response to technical engagement

The purpose of this addendum is to provide a critique of the new evidence submitted by the company as part of their response to the technical engagement report.[1]

In their response to technical engagement, the company submitted responses to the key issues raised in the Technical Report written by the NICE technical team, and some additional evidence relevant to these issues.[1] The company also provided a new base-case cost effectiveness analysis for the moderate population, along with several scenario analyses requested by NICE. It should be noted that the company did not submit a new economic model that enables the selection of this new base-case and the different scenarios. Upon request, the company provided a model file, which included the data for the new base-case, but which still did not permit the running of most scenarios or the original base-case analysis for model validation. A log file with model changes was submitted later upon request, and the company provided additional clarifications, which then allowed the ERG to reproduce the company's base-case. The delay caused by this lack of transparency meant that timelines were delayed and that doing the analyses was extremely challenging to the ERG. This emphasizes the need for transparency in any updates in response to technical engagement.

-

The company response to the technical engagement issues and the new evidence presented in relation to these issues will be discussed in Section 1 of this addendum. Section 2 will provide the ERG's updated base-case and scenario analyses, in response to the company changes. A conclusion will be given in Section 3.

1.1 Relevant comparators and treatment sequences

The company has provided a pairwise comparison of moderate patients who have received 1 prior csDMARD and moderate patients who have received 2 or more csDMARDs (See Appendix 3 of the company Response to TE).[1] At week 12, the proportion of patients achieving ACR20 response (primary endpoint of FINCH 1) in the filgotinib 200mg arm is higher in the 1 prior csDMARD exposure subgroup. [redacted] of patients achieved ACR20 response in the >=2 prior csDMARDs exposure group and [redacted] achieved it in the 1 prior csDMARD exposure group. At week 24, [redacted] of patients achieved ACR20 response in the >=2 prior csDMARDs exposures group and [redacted] achieved it in the 1 prior csDMARD exposures group.

The company does state that "*it should be noted that these comparisons are not statistically significant and that patient numbers in these groups are low*" and that FINCH 1 was not powered to allow for this analysis.

ERG comment:

The Technical Report stated that "The company should provide justification for the use of clinical effectiveness data from a different population". No such justification has been provided. Instead the company provided a pairwise comparison of moderate patients who have received 1 prior csDMARD and moderate patients who have received 2 or more csDMARDs. Also, despite the company asserting that there was similarity between the two populations, the difference between filgotinib and BSC is in opposing directions at 12 and 24 weeks. This is confusing.

As stated by the company, some results are more favourable in the filgotinib 200mg arm in the 1 prior csDMARD exposure subgroup when compared to the >=2 prior csDMARDs exposure group. However, the same applies to adalimumab: At week 12, the proportion of patients achieving ACR20 response (primary endpoint of FINCH 1) in the adalimumab arm is higher in the 1 prior csDMARD exposure subgroup. [redacted] of patients achieved ACR20 response in the >=2 prior csDMARDs exposure group and [redacted] achieved it in the 1 prior csDMARD exposure group. Therefore, the relative effectiveness of filgotinib versus adalimumab and other comparators is unclear. Also, other outcomes, such as the proportion of patients achieving ACR20 at week 24, show the opposite: At week 24, the proportion of patients achieving ACR20 response in the filgotinib 200mg arm is lower in the 1 prior csDMARD exposure subgroup. [redacted]% of patients achieved ACR20 response in the >=2 prior csDMARDs exposure group and [redacted]% achieved it in the 1 prior csDMARD exposure group.

Therefore, these results are ambiguous and the uncertainty referred to by NICE in their question still exists. The company's analyses in the ≥2 prior csDMARDs exposure group (n=53 and n=66 in filgotinib and placebo arms) show slightly increased ICERs, whilst the company's analyses in the ≥2 prior csDMARDs failure group (n=19 and n=32 in the filgotinib and placebo arms) show significantly decreased ICERs compared with the company's base-case. EULAR response rates were not provided for these populations, hence the ERG base-case could not be reproduced with these – but the ERG considers that these subgroup analyses may be relevant.

1.2 Relevant comparators and treatment sequences (severe RA)

The technical team requested scenarios using tocilizumab or sarilumab in second line in population 2a. The company provided both scenarios.

ERG comment: The ERG assumes that these scenario analyses were conditional on the company's base-case using their moderate to severe PAS price, in the absence of detail provided by the company. Compared with the company's base-case results in population 2a, when sarilumab is used in second line, costs and QALY gains for all comparators are reduced and filgotinib remains the cheapest treatment option. Etanercept remains the only other treatment that is not dominated and its ICER in the incremental analysis is higher. The same applies when tocilizumab is used in second line.

1.3 Generalisability of FINCH trials to the decision problem and UK clinical practice

The Technical Report requested subgroup data from the severe population of the FINCH 2 study. The company provided baseline characteristics for the severe RA subgroup in the FINCH 2 trial and results in terms of ACR20, 50, 70 EULAR response and proportion of patients who achieved DAS28-CRP ≤3.2 and <2.6.

ERG comment: The numbers are slightly confusing in that the total numbers at the top of the table (Filgotinib 200mg (N=147), Filgotinib 100mg (N=153), Placebo (N=148)) are those for the full FINCH 2 population. However, baseline characteristics are different from those presented in Table 7 of the CS; therefore, these characteristics are probably for the severe population only.

At week 12 the results for ACR20, 50 and 70 are very similar when compared to the full trial population. However, EULAR response (good response) at week 12 is lower in the severe subgroup than in the total population: [redacted]% for Filgotinib 200mg, [redacted]% for Filgotinib 100mg and [redacted]% for placebo in the severe subgroup compared to [redacted]%, [redacted]% and [redacted]%, respectively in the total population. The same applies to

the week 24 results. Therefore, in terms of EULAR response results differ considerably between the two populations.

1.4 Network meta-analysis

The NICE technical team requested a company rationale for excluding studies that were identified as potentially relevant by the ERG. The company provided a table with reasons for exclusion for some of the studies identified by the ERG. The company listed 35 out of 47 studies identified by the ERG and provided a rationale for these. It is not clear why the remaining 12 studies were ignored.

ERG comment: In total, the ERG considers the reasons for exclusion for 13 of the 35 studies to be valid reasons ('No 12/24 week data' (3x), 'it could not be confirmed that the population is moderate to severe' (7x), and 'could not be linked into the network' (3x)). However, 22 of the 35 studies were excluded for other reasons: 'monotherapy' (14x), 'data available from NCT website, but only peer reviewed publications were in scope' (6x), 'Atacicept not relevant comparator' (but trial also included ADA-mono vs PLA) (1x), and 'language not English' (1x). Monotherapy studies were excluded by the company; yet, the NICE scope explicitly included several monotherapy treatment options.

In addition, it is not clear why the company did not provide a rationale for excluding 12 out of 47 studies listed by the ERG as potentially relevant. Therefore, the ERG still believes that potentially relevant studies were excluded from the NMA.

1.5 Rate of progression from moderate to severe RA

The company's new cost effectiveness analysis in the moderate population uses the efficacy estimates for placebo in FINCH 1. The company states that the introduction of a placebo effect to the comparator sequence reduced the rate of progression to a severe state. As a result, the updated analysis results in a progression rate that lies in between the company's submitted base case rate and the ERG base case rate.

ERG comment: The ERG is satisfied that the company's new approach uses trial data from FINCH 1, and that it results in a progression rate that is closer to that observed in the ERAN database than their original analysis. However, it is noteworthy that the company's analysis results in a rate of progression at 2 years of 11%, which is still lower than ERAN database 19%. Slower progression results in increased ICERs for filgotinib vs BSC (see scenarios, using the DAS midpoint progression rates are lower, Table 15 of company response). Quicker progression appears to result in higher QALY gain (regardless of treatment arm), which is somewhat counter-intuitive and could be a result of patients being treated with bDMARDs upon progression, which improve their health-related quality of life.

1.6 Treatment sequence upon progression from moderate to severe RA

In response to NICE's request, the company provided scenarios with alternative treatment sequences for severe disease after progression from moderate disease. These scenarios are based on the company's updated base-case analysis.

ERG comment: All but scenario 1 in population 1b increased the ICERs and scenario 3b, that is alternative sequences where patients with severe RA not previously treated with filgotinib when in moderate RA will be treated with filgotinib rather than tocilizumab, increased ICERs the most. The company highlights that these scenarios do not evaluate the cost-effectiveness of filgotinib compared to BSC, but rather compare the cost-effectiveness of two different sequences, given the different treatment sequence "tails". However, a

comparison between filgotinib and BSC in the index population, regardless of what which treatments follow, does provide for the evaluation of the cost-effectiveness of filgotinib, as long as any such sequence is applied to both intervention and comparator according to rules that could be plausible in clinical practice. Such a sequence could include filgotinib on the understanding that it might be recommended for the severe population. There could also be variation in the sequences between intervention and comparator if treatments were chosen based on history i.e. the use of one treatment precludes the use of another treatment at later line. If such sequences were demanded in the Technical Report then they must have been considered plausible. Therefore, the ERG considers that these results cast doubt over the cost effectiveness of filgotinib in the moderate population.

1.7 Modelling best supportive care in the moderate population

In response to NICE's request, the company provided an updated cost effectiveness model using head-to-head trial data from the FINCH 1 moderate subgroup (1+ csDMARD failures), comparing filgotinib 200mg with placebo/MTX. For this, ACR response rates from FINCH 1 (moderate subgroup) were converted to EULAR response rates using the previously described mapping algorithm. In addition, the company applied costs of MTX to subsequent BSC in the moderate population, as requested by the ERG. The mean DAS28 score from the moderate FINCH 1 subgroup was used to estimate progression to severe disease (as discussed above in Issue 5). Treatment sequences in the company's base-case are in line with their original base-case (see response to Issue 6 for alternative treatment sequences).

ERG comment: The ERG considers the described analyses appropriate, with one notable exception: the use of ACR response rates mapped to EULAR response rates, instead of using EULAR response rates from the trial. The ERG is concerned that the mapping may introduce unnecessary noise into the resulting EULAR estimates and would have preferred the use of trial EULAR response rates directly. This analysis was provided by the company subsequently, but only for the base-case population, i.e. the whole moderate population, and not for the ≥2 prior csDMARD exposure or failure populations. The ERG uses EULAR response rates directly from FINCH in its new base-case for the moderate population. It is to be noted that the EULAR response rates directly obtained from FINCH appear more favourable for both filgotinib and placebo arms than those mapped from the ACR score.

1.8 Utility values

In response to NICE's request, the company explored the use of FINCH trial programme utility data for filgotinib, adalimumab and placebo as an alternative to the mapping algorithm by Hernandez-Alava et al. The company presents QALY model outputs for moderate and severe population for filgotinib, placebo and adalimumab (only in the severe population) comparing the use of utilities from the clinical trial and using the mapping algorithm.

ERG comment: The ERG is satisfied that QALY outputs are fairly similar using the two methods. In addition, the ERG's concern arose partly because of Table 50 submitted by the company in response to clarification question 18c, where significant differences could be observed between trial utility values and output from mapping algorithm. The company provided an updated Table 50, where instead of using aggregated baseline data from FINCH 1, individual patient data were used as per NICE recommendation and this analysis also results in similar values for trial and mapped utilities. In conclusion, the ERG's

reservations about the mapping algorithm used and also the inclusion of pain mapped from the HAQ score are no longer relevant. The ERG is no longer making any adjustments to the estimation of utilities in its base-case.

2. ERG analyses

The following tables present the ERG base-case and scenario analyses for the moderate population:

- Company base-case replication
- Company base-case, but using DAS midpoint instead of mean DAS from FINCH 1
- ERG base-case: conditional on company's base-case but using EULAR response rates directly from FINCH
- Scenarios for both population 1a and 1b (conditional on ERG base-case):
    - 1: Progression based on DAS midpoint score
    - 2: Utilities estimated based on baseline pain from FINCH
    - 3: First-line etanercept in severe
- Scenarios for population 1a:
    - 4a: Second-line tocilizumab in severe
    - 5a: Second-line abatacept in FIL arm and tocilizumab in BSC arm
    - 6a: Second-line tocilizumab in FIL arm and filgotinib in BSC arm
- Scenarios for population 1b:
    - 4b: Third-line sarilumab in severe
    - 5b: Third-line abatacept in FIL arm and tocilizumab in BSC arm
    - 6b: Third-line abatacept in FIL arm and sumab in BSC arm
    - 7b: Third-line tocilizumab in FIL arm and filgotinib in BSC arm
    - 8b: Third-line sarilumab in FIL arm and filgotinib in BSC arm

Table 1: ERG analyses population 1a

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) vs BSC	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
Company's base-case								
BSC	[redacted]	[redacted]					4.926	6.474
FIL (200mg) monotherapy	[redacted]	[redacted]	0.464	£4,430	£9,543	NA	5.169	6.791
Company's base-case, using DAS midpoint								
BSC	[redacted]	[redacted]					5.786	6.967
FIL (200mg) monotherapy	[redacted]	[redacted]	0.504	£6,547	£13,002	NA	5.962	7.252
ERG base-case								
BSC	[redacted]	[redacted]					5.300	6.756
FIL (200mg) monotherapy	[redacted]	[redacted]	0.668	£8,246	£12,348	NA	5.556	7.148
Scenario 1: Progression based on DAS midpoint score								

BSC	[redacted]	[redacted]					5.939	7.110
FIL (200mg) monotherapy	[redacted]	[redacted]	0.709	£10,339	£14,584	NA	6.131	7.474
Scenario 2: Utilities based on baseline pain								
BSC	[redacted]	[redacted]					7.911	9.367
FIL (200mg) monotherapy	[redacted]	[redacted]	0.515	£8,246	£15,996	NA	8.015	9.607
Scenario 3: First line etanercept								
BSC	[redacted]	[redacted]					5.270	6.746
FIL (200mg) monotherapy	[redacted]	[redacted]	0.659	£7,883	£11,966	NA	5.534	7.142
Scenario 4: Second line tocilizumab								
BSC	[redacted]	[redacted]					5.781	7.052
FIL (200mg) monotherapy	[redacted]	[redacted]	0.689	£10,888	£15,801	NA	5.926	7.378
Scenario 5: Second line abatacept and tocilizumab								
BSC	[redacted]	[redacted]					5.781	7.052
FIL (200mg) monotherapy	[redacted]	[redacted]	0.741	£19,324	£26,080	NA	5.556	7.148
Scenario 6: Second line tocilizumab and filgotinib								
BSC	[redacted]	[redacted]					6.431	7.488
FIL (200mg) monotherapy	[redacted]	[redacted]	0.680	£23,709	£34,878	NA	5.926	7.378

Table 2: ERG analyses population 1b

Technologies	Total QALYs	Total costs	Incremental QALYs	Incremental Costs	ICER (£/QALY) vs BSC	ICER (£/QALY) incremental	NHB (20k) (QALYs)	NHB (30k) (QALYs)
Company's base-case								
BSC	[redacted]	[redacted]					5.401	6.826
FIL (200mg) + csDMARDs	[redacted]	[redacted]	0.443	£6,031	£13,604	NA	5.543	7.069
Company's base-case, using DAS midpoint								
BSC	[redacted]	[redacted]					6.056	7.168

FIL (200mg) + csDMARDs	[redacted]	[redacted]	0.486	£7,728	£15,907	NA	6.155	7.396
ERG base-case								
BSC	[redacted]	[redacted]					5.729	7.072
FIL (200mg) + csDMARDs	[redacted]	[redacted]	0.645	£9,807	£15,198	NA	5.883	7.391
Scenario 1: Progression based on DAS midpoint score								
BSC	[redacted]	[redacted]					6.210	7.312
FIL (200mg) + csDMARDs	[redacted]	[redacted]	0.687	£11,631	£16,924	NA	6.316	7.612
Scenario 2: Utilities based on baseline pain								
BSC	[redacted]	[redacted]					8.313	9.657
FIL (200mg) + csDMARDs	[redacted]	[redacted]	0.500	£9,807	£19,616	NA	8.322	9.830
Scenario 3: First line etanercept								
BSC	[redacted]	[redacted]					5.673	7.045
FIL (200mg) + csDMARDs	[redacted]	[redacted]	0.637	£9,409	£14,759	NA	5.840	7.369
Scenario 4: Third line sarilumab								
BSC	[redacted]	[redacted]					5.675	7.046
FIL (200mg) + csDMARDs	[redacted]	[redacted]	0.638	£9,531	£14,932	NA	5.836	7.367
Scenario 5: Third line abatacept and tocilizumab								
BSC	[redacted]	[redacted]					5.729	7.072
FIL (200mg) + csDMARDs	[redacted]	[redacted]	0.686	£16,177	£23,589	NA	5.605	7.219
Scenario 6: Third line abatacept and sarilumab								
BSC	[redacted]	[redacted]					5.675	7.046
FIL (200mg) + csDMARDs	[redacted]	[redacted]	0.656	£14,507	£22,110	NA	5.605	7.219
Scenario 7: Third line tocilizumab and filgotinib								
BSC	[redacted]	[redacted]					6.202	7.391

FIL (200mg) + csDMARDs	[redacted]	[redacted]	0.637	£19,107	£30,010	NA	5.883	7.391
Scenario 8: Third line sarilumab and filgotinib								
BSC	[redacted]	[redacted]					6.202	7.391
FIL (200mg) + csDMARDs	[redacted]	[redacted]	0.659	£20,501	£31,092	NA	5.836	7.367

3. ERG conclusions

In conclusion, the company have finally provided the relevant requested analyses, with the exception of EULAR response rates from the subgroups. There remains some doubt over the cost effectiveness of filgotinib in the moderate population, given that alternative treatment sequences in the severe population have a significant impact on the ICERs, and given some doubts over the progression from the moderate to the severe population.

REFERENCES:

[1] National Institute for Health and Care Excellence. *Technical engagement response form. Filgotinib for treating moderate to severe rheumatoid arthritis [ID1632] (Version 2)*. London: NICE, 6th November 2020 [accessed 11.11.20]. 66p.