NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Filgotinib for treating moderately to severely active ulcerative colitis [ID3736]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Filgotinib for treating moderately to severely active ulcerative colitis [ID3736]

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 **Galapagos**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Crohn's & Colitis UK
   b. UKCPA

4. **Evidence Review Group report** prepared by **Kleijnen Systematic Reviews**

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from **Galapagos**

7. **Technical engagement response & expert statement from experts:**
   a. Gordon Moran – clinical expert, nominated by the British Society of Gastroenterology

8. **Technical engagement response from consultees and commentators:**
   a. British Society of Gastroenterology
   b. British Society of Gastroenterology IBD section

9. **Evidence Review Group critique of company response to technical engagement** prepared by **Kleijnen Systematic Reviews**
   a. Critique
   b. Addendum

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 moderately to severely active ulcerative colitis [ID3736]

Document B

Company evidence submission

File name	Version	Contains confidential information	Date
ID3736_Filgotinib_Document B_ACIC redacted_v3.0	**3.0**	**Yes**	**19th April, 2021**

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Tables and figures

List of abbreviations

Abbreviation	Definition
1L	First-line
2L	Second-line
3L	Third-line
5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
AE	Adverse event
ATP	Adenosine triphosphate
CD	Crohn's disease
CDSR	Cochrane Database of Systematic Reviews
CE	Cost-effectiveness
CEM	Cost-effectiveness model
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CrCl	Creatinine clearance
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
DIC	Deviance information criterion
EBS	Endoscopy/bleeding/stool
ECCO	European Crohn's and Colitis Organisation
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	EuroQol-5 Dimension Scale
EQ-5D-5L	EuroQoL-5D-5L
ESR	Erythrocyte sedimentation rate
EU	European Union
FAS	Full Analysis Set
FWER	Family-wise type I error rate
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HR	Heart rate
HRQoL	Health-related quality of life
hs-CRP	High sensitivity C-reactive protein
HTA	Health Technology Assessment database
IBD	Inflammatory bowel disease
IBDQ	Irritable Bowel Disease Questionnaire
IFN-γ	Interferon-gamma
IL	Interleukin
IM	Intramuscular
IQR	Interquartile range
IV	Intravenous
JAK	Janus kinase
Kg/m^2	Kilogram per square meter

Abbreviation	Definition
LOR	Loss of response
LTE	Long-term extension
MCS	Mayo clinic score
MCS	Mental component summary
Mg/L	Milligrams per litre
MHRA	Medicines & Health products Regulatory Agency
MTX	Methotrexate
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Non-responders
ONS	Office of National Statistics
OR	Odds ratio
PCS	Physical component summary
PGA	Physician's Global Assessment
PICOS	Population, intervention, comparator, outcomes and study design
PK	Pharmacokinetic
PP	Per-protocol
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
QALY	Quality-adjusted life year
QD	Once a day
QoL	Quality of life
RB	Rectal bleeding
RCT	Randomised controlled trials
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF	Stool frequency
SLR	Systematic literature review
STAT	Signal transducers and activators of transcription
TA	Technical appraisal
TB	Tuberculosis
TBC	To be confirmed
TNF	Tumour necrosis factor
TNFα	Tumour necrosis factor-alpha
TYK	Tyrosine kinase
UC	Ulcerative colitis
UK	United Kingdom
US	United States
VAS	Visual analogue scale
VTE	Venous thromboembolism
WPAI	Work Productivity and Activity Impairment
µg/g	Micrograms per litre

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

B.1.1 Decision problem

Filgotinib is a next-generation JAK (Janus kinase) inhibitor that is a preferential and reversible inhibitor of JAK1, a member of the JAK/STAT signalling pathway, which is known to be involved in chronic inflammation.

Filgotinib is currently indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying antirheumatic drugs (DMARDs); it may be used as monotherapy or in combination with methotrexate.

Requests to vary the Marketing Authorisation for filgotinib were validated by the European Medicines Agency (EMA) and the Medicines & Healthcare products Regulatory Agency (MHRA) in [redacted] and [redacted], respectively, and are currently under review. The variation applied for adds the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent.

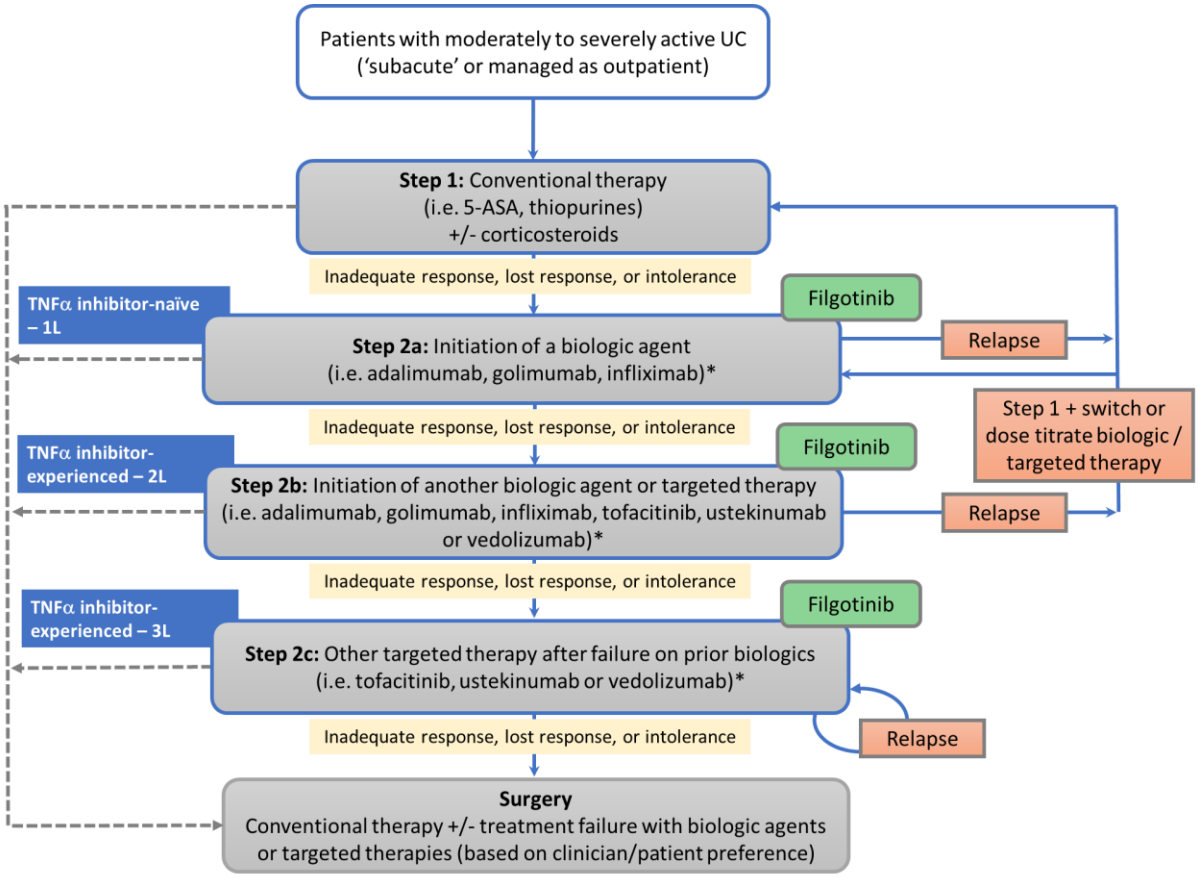
This submission covers filgotinib's whole patient population included in the UC therapeutic indication, including the following two subgroups of adult patients with moderately to severely active UC:

1. Biologic-naïve (no previous exposure to biologic therapy tumour necrosis factor-alpha [TNFα] inhibitor or vedolizumab)

2. Biologic-experienced (previous exposure to biologic therapy TNFα inhibitor or vedolizumab).

The position of filgotinib within the current treatment pathway based on expert advice is represented in Figure 1.

Figure 1. Proposed positioning of filgotinib within NICE treatment pathway



*Patients in response/remission remain on therapy with 12-month review

Abbreviations: 1L, first-line advanced; 2L, second-line advanced; 3L, third-line advanced; 5-ASA, 5-aminosalicylate; JAK, Janus kinase; NICE, National Institute for Health and Care Excellence; TNFα, tumour necrosis factor-alpha; UC, ulcerative colitis.

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	People with moderately to severely active ulcerative colitis who have had an inadequate response, loss of response or were intolerant to conventional therapy (oral corticosteroids and/or immunomodulators), or a biologic agent (TNF-alpha inhibitor or vedolizumab).	Aligned with NICE scope	NA
Intervention	Filgotinib	Aligned with NICE scope	NA
Comparator(s)	• Conventional therapies, without biological treatments • TNF-alpha inhibitors (infliximab, adalimumab and golimumab) • Tofacitinib • Ustekinumab • Vedolizumab	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
Outcomes	The outcome measures to be considered include: • mortality • measures of disease activity • rates of and duration of response, relapse and remission • rates of hospitalisation • rates of surgical intervention • endoscopic healing • mucosal healing (combines endoscopic and histological healing) • corticosteroid-free remission • achieving mucosal healing • adverse effects of treatment • health-related quality of life.	Aligned with final NICE scope (except where noted). • mortality	SELECTION (the pivotal trial in the filgotinib UC programme) does not provide data on filgotinib's effect on mortality due to UC. The remaining outcomes are included.
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	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
	the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • people who have been previously treated with one or more biologics; • and people who have not received prior biologics therapy.	Aligned with NICE scope	NA

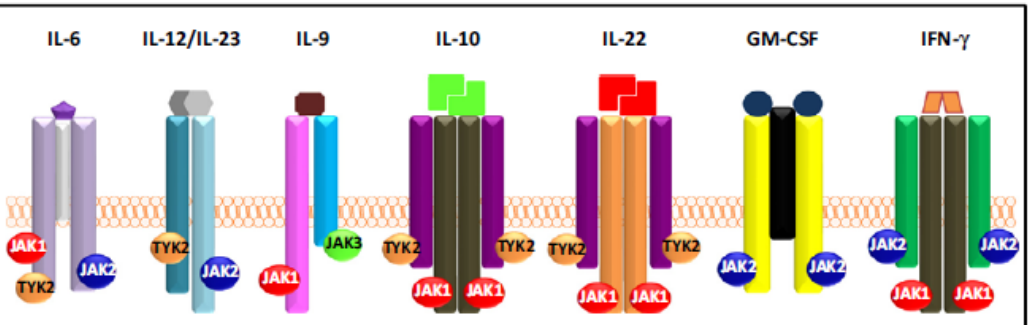
B.1.2 Description of the technology being appraised

B.1.2.1 Mechanism of action

Filgotinib is a next-generation JAK inhibitor that is a preferential and reversible inhibitor of JAK1. There are four known JAK types (JAK1, JAK2, JAK3, and TYK2), which are involved in the JAK/STAT pathway that mediate cytokine signalling. JAKs are also involved in other intracellular signalling pathways including erythropoietin signalling through JAK2 (1).

Within the JAK/STAT signalling pathway, cytokine binding to its cell surface receptor leads to receptor polymerisation and autophosphorylation of associated JAKs. Activated JAKs phosphorylate the receptors that dock STATs. The phosphorylated STATs, then dimerise and move to the nucleus to activate new gene transcription. The four JAKs arrange in various combinations, to trigger further downstream signalling of cytokines or growth factors that are involved in immune system regulation, epithelial barrier homeostasis, or both (see Figure 2). For example, JAK1, JAK2 and TYK2 combine to control signalling of one of the key pro-inflammatory cytokines, interleukin (IL)-6, which is produced by mononuclear cells of the lamina propria as well as by intestinal epithelial cells (2, 3). IL-6 concentration is increased in the plasma of IBD patients and several studies found an association between the amount of IL-6 expression and disease activity in both CD and UC patients (4, 5). Multiple pro-inflammatory cytokines have been found to play a role in the pathogenesis of UC by activating immune cells (6). These include IL-5, IL-9, IL-13, IL-33, IL-6, IL-17A/F, IL-21, IL-22, IL-23, and tumour necrosis factor cytokines (6). Janus kinase inhibition therefore leads to modulation of pro-inflammatory cytokine activity (6).

Figure 2. Scheme of the cytokine pathways and their activity in IBD



Main JAK driver	JAK1	TYK2	JAK1	JAK1	JAK1	JAK2	JAK1
Main activity in the gut	inflammation wound healing	inflammation	deleterous	anti-inflammatory	wound healing	protective	inflammation

Abbreviations: IBD, inflammatory bowel disease; IL, interleukin; GM-CSF, granulocyte-macrophage colony-stimulating factor, IFN-γ, interferon gamma. JAK, Janus kinase; TYK, tyrosine kinase.
References: Galien, 2016 (7).

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). The JAKs have mainly discrete but also some overlapping functions, therefore, filgotinib's preferential inhibition of JAK1 is expected to result in reduced off-target effects and an improved safety profile (1). Other broad JAK inhibitor agents with specificity for more than one JAK type have been associated with adverse effects (8).

In biochemical assays, filgotinib preferentially inhibited the activity of JAK1 and showed greater than five-fold higher potency of filgotinib for JAK1 over JAK2, JAK3 and TYK2. In human cellular assays, filgotinib preferentially inhibited JAK1/JAK3 -mediated signalling downstream of the heterodimeric cytokine receptors for IL-2, IL-4 and IL-15, JAK1/2-mediated IL-6, and JAK1/TYK2-mediated type I interferons, with functional selectivity over cytokine receptors that signal via pairs of JAK2 or JAK2/TYK2 (9).

B.1.2.2 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.

Table 2. Technology being appraised

UK approved name and brand name	Filgotinib (Jyseleca®)
Mechanism of action	Filgotinib is a next-generation JAK inhibitor that is a preferential and reversible inhibitor of JAK1. It modulates the cytokine signalling pathway by preventing the phosphorylation and activation of STATs by JAKs. For a detailed overview of the mechanism of action, see Section B.1.2.1.
Marketing authorisation/CE mark status	Variation to the Marketing Authorisation for filgotinib in the treatment of adults with UC was validated by the EMA in [redacted] and the MHRA in [redacted]. The anticipated date of regulatory approvals is between [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Filgotinib will have two indications, however, this appraisal is for UC only. Filgotinib is indicated for the treatment of: • adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent. • moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Filgotinib may be used as monotherapy or in combination with methotrexate (MTX). Contraindications: • Hypersensitivity to the active substance or to any of the excipients • Active tuberculosis or active serious infections • Pregnancy

	For the full draft SmPC, see Appendix C.
Method of administration and dosage	Filgotinib is orally administered, and the starting recommended dose is 200mg once daily. Film-coated tablets are available in 100mg or 200mg strengths. A dose of 100mg of filgotinib once daily is recommended for patients with moderate or severe renal impairment (CrCl 15 to <60 mL/min).
Additional tests or investigations	Patients taking filgotinib will be monitored in line with patients on other currently available JAK inhibitors and biologic therapies. No additional tests or investigations are expected to be required. 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

Definition of UC

Ulcerative colitis is the most common form of inflammatory bowel disease (10-12). The intestinal inflammation in IBD is controlled by a complex interplay of innate and adaptive immune mechanisms. Cytokines play a key role in IBD that determine T cell differentiation of Th1, Th2, T regulatory and Th17 cells. Cytokines levels orchestrate the development, recurrence and exacerbation of the inflammatory process in IBD (9). A combination of hereditary, immunological factors and environmental triggers have been proposed contributing to the aetiology, however, the cause of UC is unknown (13).

Ulcerative colitis is a chronic, progressive, systemic disorder, which is characterised by confluent areas of ulceration, with the inflammation confined to the mucosa, that extend proximally from the rectum into the colon (14-16).

Clinical presentation

Ulcerative colitis can develop at any age, but primarily presents in late adolescence or early adulthood (17). The onset of UC is usually insidious; symptoms are often present for weeks or even months before patients seek medical advice. The initial presentation of UC is characterised by symptoms relating to an inflamed rectum such as, rectal bleeding, urgency, and tenesmus (sensation of incomplete defecation and pressure) (15). In patients with severe disease at presentation, symptoms may also include incontinence, fatigue, increased frequency of bowel movements, nocturnal defecations, fever, and weight loss (16). Approximately 15% of patients have an initial presentation of severe disease, and ~30% of patients demonstrate extensive disease at diagnosis (16, 18).

Ulcerative colitis follows a relapsing and remitting course, which includes periods of disease flare, where patients experience disease symptoms of varying severity, and remissions, where patients experience few symptoms (15-17). The frequency of

relapse (i.e., pattern of disease) is usually defined during the first three years, and may be characterised as continuous (persistent UC symptoms without remission), frequent (≥2 relapses/year) or infrequent (≤1 relapse/year) (15, 19).

Disease progression often leads to hospitalisation and intensive therapy; in addition, approximately up to 10% of patients require surgery (e.g., colectomy), which can lead to chronic and debilitating complications (16, 17, 20). Complications of UC that often necessitate colectomy include intestinal perforation, uncontrolled haemorrhage, thromboembolism, toxic megacolon, dysplasia, or colorectal cancer (17, 20).

Diagnosis of UC

The diagnosis of UC is typically made on the basis of a combination of clinical factors, endoscopy, imaging, histopathology, and stool tests, as well as exclusion of other diagnoses (such as infectious colitis) (21). All of these components can be used to classify the severity and extent of UC, which then determines the appropriate treatment pathway.

The majority of treatment approaches in UC are considered based on disease severity, classified as mild, moderate, or severe (22). However, there are no clinically validated definitions of disease severity in UC (22, 23).

The most frequently used endoscopic scoring system for monitoring of UC is the Mayo Clinic Score (MCS) (23) (Table 3). Endoscopy is the standard for reassessment of UC during severe relapse, persistent disease activity, newly developed symptoms, and when considering treatment switch (23). Mucosal healing, or endoscopic remission (a Mayo Clinic endoscopic sub score of 0 or 1), has become an important endpoint in evaluating UC treatments, as it has been shown to be associated with clinical remission, corticosteroid-free remission, and the avoidance of hospitalisation and colectomy (23, 24). Current guidelines endorse mucosal healing for the assessment of treatment response (21, 23).

Table 3. Mayo clinic score for ulcerative colitis

Score	0	1	2	3
Stool frequency	Normal	1-2 per day greater than normal	3-4 per day greater than normal	5 per day greater than normal
Rectal bleeding	None	Streaks	Obvious	Mostly blood
Endoscopic / mucosa	Normal	Mild friability	Moderate friability	Spontaneous bleeding
Physician's global assessment	Normal	Mild	Moderate	Severe

Reference: Sturm et al. 2018 (23)

B.1.3.2 Epidemiology

Incidence of UC

The England-specific incidence rate of UC has been reported to be 11.3 per 100,000 persons in a prospective cohort study across five urban centres published in 2019 (25). Applying the latest population figures (26), approximately 5,300 new adult patients are estimated to be diagnosed with UC each year in England and Wales.

The incidence of UC does not differ significantly for male (54%) versus female (46%) patients (except for the age group of 5–9 years) until age 45 years; thereafter, men have a significantly higher incidence of ulcerative colitis than women (27). In terms of age, the peak incidence of UC is between 15 and 25 years of age, with a small secondary peak between 55 and 65 years of age (28, 29).

Prevalence of UC

Prevalence rate estimates of UC for England have been reported as 243.4 cases per 100,000 persons (95% confidence interval [CI]: 217.4 to 269.4) (30). Based on current population figures (26), this equates to approximately 115,000 prevalent adult patients in England and Wales.

Moderate to severe UC patients

It is estimated that 52% of UC patients have moderate to severe disease (31). Applying the latest population figures (26), approximately 60,000 adult patients are estimated to have moderate to severe UC each year in England and Wales.

B.1.3.3 Disease burden

Clinical burden

The clinical burden of UC is substantial, due to disease flares or relapses that cause severe, often debilitating symptoms and diminished quality of life (17, 32-35). As a lifelong and progressive disease, the burden of UC increases with time, with worsening symptoms and disease activity leading to hospitalisation and intensive therapy. As a systemic disease, multiple organs of the body are typically affected, adding to the clinical burden.

Disease progression and complications

Patients with UC experience a relapsing and remitting course of disease and have the potential for irreversible structural damage and disability (16, 36, 37). Clinical worsening of disease (i.e., flares) and involvement of more proximal segments of the colon characterise disease progression in UC and often require more intensive treatment, including biologic therapies, targeted therapies (such as JAK inhibitors), immunosuppressants, and/or surgery (16, 17).

Due to treatment failure or disease complications, approximately 10% of patients with UC will require surgery (e.g., colectomy) within a five to ten-year follow-up period (33, 38). Post-surgical complications are common, debilitating, and often chronic (22). In particular venous thromboembolism (VTE) is a notable and common complication of surgery for UC (39, 40).

Patients with UC have a significantly increased risk of colorectal cancer, particularly those with more extensive disease, severe inflammation, and longer duration of disease (37, 41, 42).

Extra-intestinal manifestations and comorbidities

Extra-intestinal manifestations (EIM) of disease are common among patients with UC and can affect multiple organ systems, including musculoskeletal, ophthalmologic, mucocutaneous, dermatologic, hepatobiliary, cardiovascular, and pulmonary systems (43). The risk of EIMs increases with disease duration; the development of EIMs often parallels disease activity and disease flares (43). Approximately 35% to 55% of patients with UC experience at least one EIM, such as, anaemia, VTE and arthritis (43-45).

A European-wide prospective study reported that approximately 34% of UC patients present with anaemia at diagnosis (46). Anaemia was the most common complication of UC reported in a 2012 Swiss IBD cohort study (44), affecting approximately 75% of patients at any point during the 4-year follow-up (44).

Venous thromboembolism and cardiovascular disease (specifically, coronary heart disease) have been reported in approximately 5% and 6% of patients with UC, respectively (12, 47). Although these EIMs are less commonly seen than anaemia and musculoskeletal/inflammatory manifestations, they are associated with substantial morbidity and mortality in UC and are important contributors to the overall burden of disease. Given the wide clinical spectrum of affected organ systems, EIMs have a negative impact on the QoL of UC patients and, in some cases, can be life-threatening (43).

Corticosteroid use and dependency in UC patients

Long-term treatment of patients with UC with corticosteroids is not recommended; however, a substantial proportion of patients are steroid dependent. Up to 24% of patients with UC received steroids for greater than 3 months in a 12-month period, and 12% of patients with UC were treated with steroids for ≥6 months (48). Corticosteroid-free remission is a key treatment goal as more is understood about the potential long-term side effect profile of corticosteroids.

Steroid dependency is associated with a wide range of side-effects (15, 49, 50). In the short-term, common side effects include ecchymosis, infections, acne, and moon face/Cushingoid appearance (49). Long-term side effects of corticosteroid use

include steroid associated osteoporosis, glaucoma, cataracts, hypertension, and new-onset diabetes mellitus (49).

A UK-based study investigating steroid use in UC patients (n=575) found that 42.6% of moderate to severe UC patients demonstrated steroid dependency or excess use of steroids (50).

Mortality

Patients with IBD are associated with an increased risk of mortality in the UK, caused by the disease itself and by the complications of UC, however, most IBD patients will die of unrelated causes in a pattern much akin to the general population. A 2017 matched cohort study conducted in patients with IBD (n=20,293) and matched non-IBD patients (n=83,261) from general practice data in the UK found that patients with UC had a higher overall mortality rate versus matched controls (16.4 vs 13.7 per 1,000 person-years; adjusted HR 1.3 [95% CI: 1.3, 1.4]) (51). Common causes of death for patients with UC included circulatory or respiratory diseases (42.9%) which could be related to EIMs, and neoplastic causes (26.2%) (51).

Humanistic burden

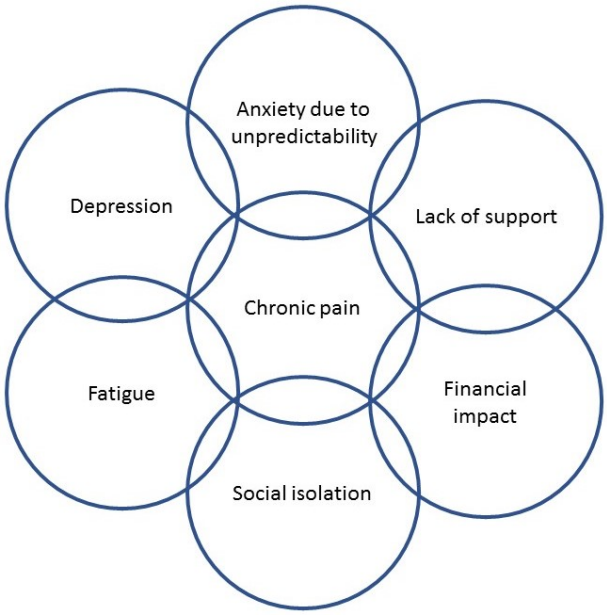
IBD has a substantial impact on many aspects of patients' lives (Figure 3), and the impact of UC is profound yet often "hidden" (52). Patients with UC experience debilitating physical symptoms (e.g. rectal bleeding, bowel urgency, abdominal cramping, fatigue) and negative emotional responses, which together impair patients' ability to engage in daily activities spanning the personal, family, social, and professional dimensions (52, 53).

A review of qualitative evidence from 23 studies (including 11 from the UK) published between 2000 and 2017 reported that the life experience of patients with UC is markedly affected by fatigue, fear, stigma, and isolation (54). The physical symptoms of UC prevent patients from living a 'normal' life in terms of their daily activities when compared to people of a similar age, socioeconomic status and geographical region (55). Additional factors contributing to the impairment of QoL in patients with UC include EIMs and comorbidities. The disease worsens with increasing severity of

flares (43), and once UC treatments have been exhausted, the only remaining option for patients is surgery, which has a negative impact on QoL (56).

Caregivers of patients with UC also experience reduced QoL, with their daily lives adversely affected by the physical and mental burdens entailed (53, 57).

Figure 3. The multifaceted impact of IBD disease burden on patients' lives



Abbreviations: IBD, inflammatory bowel disease.
References: Ghosh et al, 2015 (52).

Economic burden

In 2019/20, the cost of UC admissions (excluding drug costs) in England was estimated at £70 million. Of the 108,000 UC-related hospital admissions, 80% of patients admitted could be considered to be economically active (58). The substantial UC related work disability experienced by individual patients translates into the economic burden due to productivity loss at the societal level. Indirect costs (e.g., lost work productivity) account for between 54% and 68% of the total economic burden of UC (59).

Ulcerative colitis is a cost-intensive disease to manage, due to pharmacotherapy, hospitalisations, physician visits, and outpatient visits (60, 61). A 2019 study of the Epi-IBD European cohort found that 23% of patients with UC of all severity levels (n=717) were hospitalised at least once due to UC during the first 5 years after

diagnosis. The median time to first hospitalisation was 10 months (IQR 3–23 months) (38).

Moderate-to-severe disease activity, relapses, and UC complicated by EIMs lead to high-cost burden (59). Healthcare costs are higher for patients with UC on suboptimal therapy and in those requiring biologic dose escalation, than for patients on stable doses of effective therapy (60).

A significant proportion of UC patients (50% aged 15-44 years; 30% aged 45-64 years) are of working age, therefore indirect costs are high due to productivity loss. Patients with active disease have significantly higher indirect costs compared to patients in remission (62). This highlights the importance of having rapid and efficacious therapies for the treatment of flares and maintenance of remission in managing the wider healthcare costs associated with UC.

B.1.3.4 Current treatment guidelines

The overarching aim of treating active UC patients with pharmacotherapies is to dampen disease symptoms and to induce remission as quickly as possible. Following the control of the inflammatory disease flare (or relapse), patients remain on a maintenance therapy.

Recommendations for the management of UC and treatment pathways in the UK are available from the 2019 NICE guideline [NG130] (63), the 2019 British Society of Gastroenterology consensus IBD guidelines (64), and the 2017 European Crohn's and Colitis Organisation (ECCO) guideline (20).

Several factors considered together determine the choice of treatment for the patient throughout the course of their disease, these include:

- disease severity (i.e. mild to moderate, moderate to severe, or severe)
- site of the disease
- frequency of relapse
- response to previous therapies.

NICE guideline

Figure 4 summarises the clinical treatment pathway for patients with moderately to severely active UC, as recommended by NICE (63).

Step 1: Patients with moderately to severely active UC are first treated with conventional therapy (aminosalicylates, corticosteroids or thiopurines), with the primary treatment goal of inducing remission.

Step 2a: When conventional therapy cannot be tolerated, or the disease has responded inadequately to or lost response to treatment, patients may be initiated on biologics (i.e. TNFα inhibitors [TA329]).

- TNFα inhibitor-naïve patients may initiate first-line TNFα inhibitor therapy with adalimumab, golimumab or infliximab (28).

Step 2b: When the disease has responded inadequately to or lost response to the first-line TNFα inhibitor, patients may initiate another biologic or other advanced therapy, i.e. anti-integrin (vedolizumab [TA342]), a JAK inhibitor (tofacitinib [TA547]), or anti-interleukin (ustekinumab [TA633]).

- TNFα inhibitor experienced-patients can be initiated on a second-line TNFα inhibitor (adalimumab, golimumab or infliximab) or other advanced therapy (vedolizumab, tofacitinib or ustekinumab) (28, 65-67).

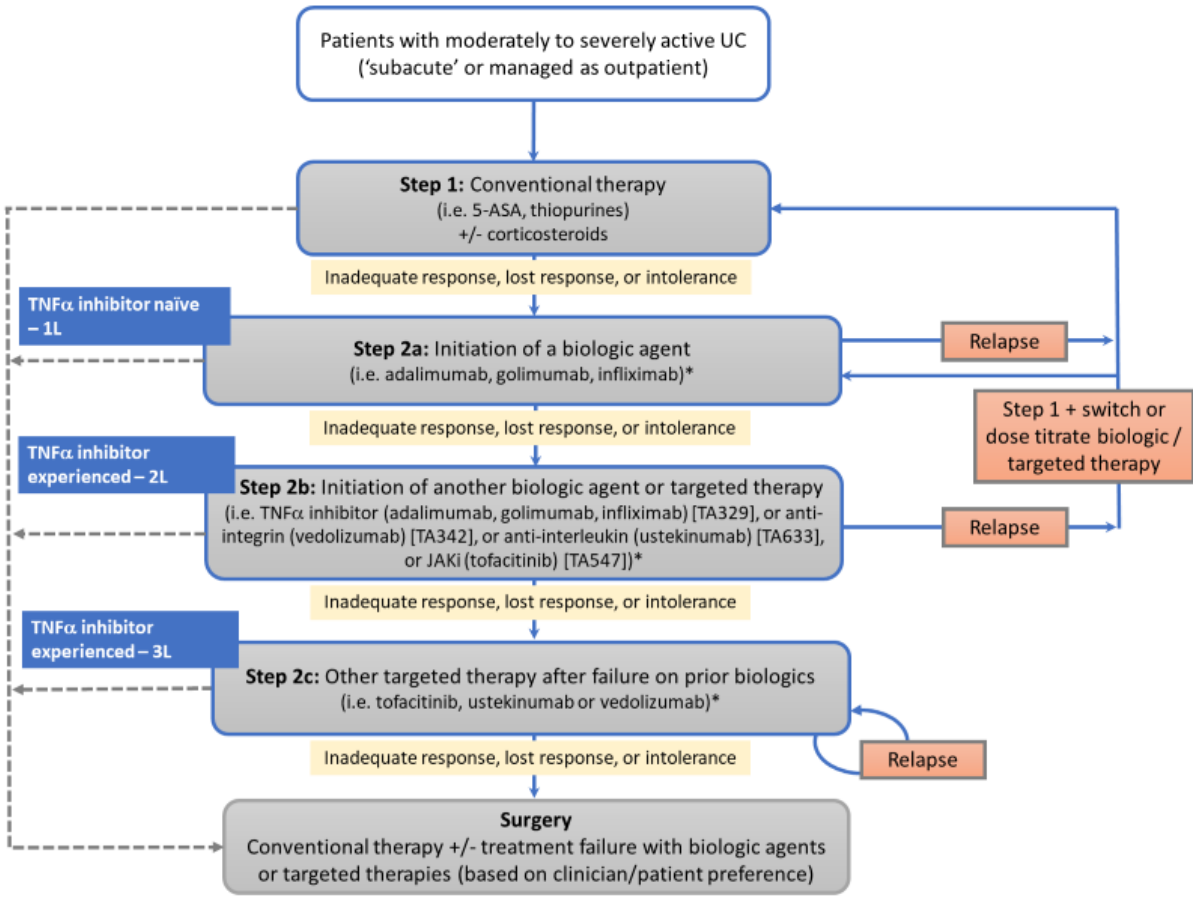
Step 2c: When the disease has responded inadequately to or lost response to the second-line TNFα inhibitor treatment or other advanced therapy, patients may initiate ustekinumab or another advanced therapy.

- TNFα inhibitor-experienced patients can be initiated on a third-line advanced therapy (vedolizumab, tofacitinib or ustekinumab) (65-67).

*If during **Step 2** patients do not respond adequately to, are intolerant of, or lose response to a biologic or other advanced therapy, patients may switch biologic/other advanced treatments, discontinue biologic or advanced treatments, or proceed to surgery.*

Surgery: If patients have been cycled through different biologics and have failed all treatments as described in Step 2 (i.e. TNFα inhibitors (adalimumab, infliximab, golimumab), anti-integrin (vedolizumab), JAK inhibitor (tofacitinib), anti-interleukin (ustekinumab)) surgery may be considered. A small number of patients may elect to have surgery at any stage, due to personal preferences (20, 63).

Figure 4. Current NICE treatment guidance on treatment of moderately to severely active UC



Abbreviations: 1L, first-line advanced; 2L, second-line advanced; 3L, third-line advanced; 5-ASA, 5-aminosalicylate; JAK, Janus kinase; NICE, National Institute for Health and Care Excellence; TA, technical appraisal; TNFα, tumour necrosis factor-alpha; UC, ulcerative colitis.
References; NICE: ulcerative colitis: management 2019 (63)**;** NICE: Infliximab, adalimumab and golimumab for treating moderately-to-severely active ulcerative colitis after the failure of conventional therapy 2015 (28);
Notes: The British Society of Gastroenterology suggests the following treatment options for failure of initial biologic therapy: increase dose, shorten dosage interval, switch to alternative biologic, or switch to a different drug class (64).

ECCO guideline

The current ECCO guidelines for UC management were published in 2017, prior to the approval of tofacitinib for the treatment of patients with moderate to severe UC (20). In the outpatient setting, the recommended treatment for moderate to severe UC is based on the site of disease or the course/behaviour of the disease (20). As first-line treatment, biologics (TNFα inhibitor or vedolizumab) are recommended for the treatment of moderately to severely active UC that is refractory to oral corticosteroids or immunomodulators, and for the maintenance of UC remission (20).

Key differences between NICE and ECCO guidelines

In the UK, the British Society of Gastroenterology published consensus guidelines in 2019 on the management of IBD in adults and suggests treatment options based on disease activity, disease severity, site of disease (e.g. proctitis) and response to previous therapies (64), with reference to the NICE and ECCO guidelines (20, 63).

There are differing recommendations for the treatment of moderate-to-severe disease between the ECCO and NICE guidelines, summarised in Table 4.

Table 4. NICE guideline recommendations for the treatment of moderate-to-severe UC not requiring hospitalisation differing from ECCO guideline

Disease stage	Recommended treatments
Induction of remission • Proctitis and proctosigmoiditis	• First-line treatment is oral or rectal 5-ASA, or both in combination • Topical corticosteroids or oral corticosteroids if 5-ASA are contraindicated or not effective • If patients are non-responsive to oral corticosteroids, consider adding oral tacrolimus • If patients are non-responsive to or contraindicated for any other medication, consider TNFα inhibitors
Induction of remission • **Left-sided UC and extensive UC**	• First-line treatment is high-dose oral 5-ASA and rectal 5-ASA or oral corticosteroid • Oral prednisolone if aminosalicylates are contraindicated or not effective, or the patient has subacute UC • If patients are non-responsive to oral prednisolone, consider adding oral tacrolimus • If patients are non-responsive to or contraindicated for any other medication, consider TNFα inhibitors • If patients are non-responsive to TNFα inhibitors, or TNFα inhibitor treatment has failed, vedolizumab or tofacitinib should be considered for induction of remission

Disease stage	Recommended treatments
Maintenance of remission	• Oral or topical 5-ASA • If 5-ASA does not maintain remission consider switching to thiopurine, TNFα inhibitors, vedolizumab or tofacitinib • The choice of drug should be determined by clinical factors, patient choice, cost, likely adherence and local infusion capacity

Abbreviations: 5-ASA, 5-aminosalicylate; NICE, National Institute for Health and Care Excellence; TNFα, tumour necrosis factor-alpha; UC, ulcerative colitis; UK, United Kingdom.
References: British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults (64) 2019; NICE: ulcerative colitis: management (63) 2019; NICE: Infliximab, adalimumab and golimumab for treating moderately-to-severely active ulcerative colitis after the failure of conventional therapy (28) 2015.

Related NICE technology appraisals

A summary of all related NICE Technology Appraisals (TAs) is presented in Table 5.

Table 5. Summary of related NICE Technology Appraisals

Technology and indication	Year
Published Technology Appraisals	
Ustekinumab for treating moderately to severely active ulcerative colitis (NICE TA633) (67)	2020
Tofacitinib for moderately to severely active ulcerative colitis (NICE TA547) (66)	2018
Vedolizumab for treating moderately to severely active ulcerative colitis (NICE TA342) (65)	2015
Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (NICE TA329) (28)	2015
Appraisals in development	
Ozanimod for treating moderate to severe ulcerative colitis (NICE TA guidance [ID3841]) (68)	Expected TBC
Etrolizumab for treating moderately to severely active ulcerative colitis (NICE TA guidance [ID3827]) (69)	Expected TBC

Abbreviations: NICE, National Institute for Health and Care Excellence; TA, Technology Appraisal; TBC, to be confirmed.

Limitations of current treatments

Management of UC has markedly improved over recent years due to biologics and other targeted therapies, however, the management of symptoms and disease activity remains suboptimal. Currently available therapies have several limitations (Table 6) with points for moderately to severely active disease including:

- primary non-response to induction (all therapy options)
- secondary non-response (TNFα inhibitor, anti-integrin agent)

- slow onset of action (anti-integrin agent, immunomodulators)
- therapeutic drug monitoring for optimisation requiring outpatient visits (immunomodulators, TNFα inhibitor)
- lack of suitability as a long-term maintenance therapy (corticosteroids)
- lack of oral options (all biologics)
- sub-optimal efficacy and reduced durability of response over time (TNFα inhibitor, anti-integrin agent)
- Healthcare resource intensive e.g. nursing time for monitoring, infusion chair capacity challenges, homecare service management
- Tolerability and side-effect concerns (all therapy options).

There remains an unmet need for novel treatments to increase therapeutic options for patients with UC.

Table 6. Key limitations of currently available therapies for moderately to severely active UC

Therapy (Route of administration)	Key limitations
Corticosteroids (oral and IV)	• Not suitable for long-term maintenance use due to side effects (70) • Significant side effects including endocrine, metabolic, musculoskeletal, neurologic, dermatologic and infection-related complications (70) • Steroid dependency and reduced response in around 50% of patients over 1 year after receiving first course of corticosteroids (71)
Immunomodulators • **Azathioprine (72)** • **6-mercaptopurine (72)**	• Slow therapeutic response that may take several months, making it unsuitable for induction therapy (73) • Safety concerns including pancreatitis, serious infections, myelosuppression, hepatotoxicity, lymphoma, non-melanoma skin cancer, other possible malignancies (73)
TNFα inhibitor agents • **Adalimumab (SC)** • **Golimumab (SC)** • **Infliximab (IV/SC)**	• Primary non-response (i.e. failure to respond to induction therapy) in around 33% to 50% of patients (74-76) • Secondary non-response (i.e. loss of response to

Therapy (Route of administration)	Key limitations
	therapy over time) in up to 50% of initial responders (77, 78) • Therapeutic drug monitoring for optimisation in both induction and maintenance treatment adds burden to physicians and patients (79) • Safety concerns including serious infections (e.g. bacterial, tuberculosis and opportunistic infections) and malignancy (80) • Need for concomitant immunosuppressants, especially with infliximab, to optimise efficacy and/or reduce immunogenicity (81, 82) • No oral options; regular visits for IV infusions and need for refrigeration; potential infusion site reactions
Anti-integrin agent • **Vedolizumab (IV/SC)**	• Slow onset of action (~six weeks) in moderately to severely active UC patients (83, 84) • Bridging therapy is common (often with steroids or cyclosporine) until vedolizumab takes effect • No oral options; regular visits for IV infusions and need for refrigeration; potential infusion site reactions
JAK inhibitor • **Tofacitinib (72)**	• Not recommended for usage with potent immunosuppressants (e.g. azathioprine and cyclosporine) (85) • Increased risk of herpes zoster infection (79, 80) • VTE safety concerns in patients at high risk of blood clots, including pulmonary embolism and deep vein thrombosis (8)
IL-12/IL-23 inhibitor • **Ustekinumab (IV/SC)**	• Safety concerns including serious bacterial, fungal and viral infections and malignancy (86) • No oral options; regular visits for IV infusions and need for refrigeration; potential infusion site reactions (86)

Abbreviations: IL, interleukin; IV, intravenous; SC, subcutaneous; TNFα, tumour necrosis factor-alpha; UC, ulcerative colitis.

B.1.3.5 Unmet need with current treatments

The unmet need of patients with UC includes efficacy, safety and tolerability, and quality of life. There is evidence of patient preference for additional UC treatment options that improve symptom control and reduced risk of malignancy in patients with moderately to severely active disease (87). For physicians, symptom control was also the most important attribute (87).

Efficacy issues

Real-world evidence demonstrates that a majority of the UC patient population are not optimally treated, with the 2017 ECCO guideline stating that long-term studies show remission rates of less than 50% (20). Inadequate response to therapy or drug intolerance (i.e. primary non-response), and loss of response over time (i.e. secondary loss of response) caused by the formation of anti-drug antibodies (immunogenicity) to biologic therapies or mechanistic escape often leads to treatment discontinuation (88).

Clinical and real-world studies have reported that 18% to 50% of UC patients experience primary non-response to biologic therapies (43, 75, 76, 89, 90). Secondary loss of response (11) resulting in an increased rate of dose escalation over time was reported, with 16% at 6 months, 28% at 12 months, 40% at 24 months and 44% at 36 months in biologic-naïve UC patients (91). Uncontrolled UC despite biologic dose escalation, interval shortening between doses and cycling through treatments leaves the patient with limited options other than treatment discontinuation, hospitalisation and surgery (64).

There is an unmet need for more effective therapies that have a rapid onset and durable response, to ensure that patients recover quickly from disease and maintain response. Filgotinib provides a faster response to improvement of symptoms within 10 weeks (92, 93), see Sections B.2.6.1 and B.2.6.2. Given that a UK-based study found that 42.6% of moderate to severe UC patients demonstrated steroid dependency or excess use of steroids, and the increasing importance of steroid-free remission as a clinical endpoint, there is a need for therapies offering the potential for steroid-free remission (50). Filgotinib has demonstrated symptom control without corticosteroids for 6 months or more (92, 93), see Section B.2.6.3.

Safety and tolerability issues

Real-world studies demonstrate that AEs are a major cause of treatment discontinuation in UC. Rates of biologic discontinuation due to AEs range from 4% to 34% in studies of patients with UC (94). Recently, increased risk of thromboembolic events has been associated with tofacitinib in patients who are already at high risk

(8). Thus, AEs due to both biologic therapies and targeted agents may lead to subsequent loss of remission when patients discontinue treatment.

Discontinuation of biologic therapy may lead to a higher risk of disease relapse following remission. Fiorino et al evaluated outcomes among patients with UC discontinuing infliximab treatment and found that almost half (47.7%) of patients who discontinued infliximab subsequently experienced disease relapse (95).

There is an unmet need for new treatment options that provide sustained remission, including mucosal healing, and have an acceptable risk-benefit profile. Filgotinib offers UC patients an alternative treatment option to first-line biologics which are limited by sub-optimal efficacy and lack of durability. Filgotinib is well tolerated and offers an improved safety profile in terms of VTE risk.

Quality of life issues

Ulcerative colitis is associated with debilitating symptoms that result in decreased QoL for patients and result in an impaired ability to engage in work and daily activities (53, 83, 96-100). Withdrawal from work also carries a considerable economic burden (101). The physical symptoms of UC (e.g. rectal bleeding, bowel urgency, abdominal cramping, fatigue) also have a significant and detrimental impact on the social aspect and mental wellbeing of patients' lives. These symptoms prevent patients from living a 'normal' life in terms of their daily activities when compared to people of a similar age, socioeconomic status and geographical region (55). Therefore, there is a need for an efficacious, well-tolerated therapy that can achieve rapid and sustained remission in order to improve patient QoL, avoid severe disease-associated complications and comorbidities, and minimise the substantial socioeconomic burden. Filgotinib demonstrated improvements in health-related QoL (HRQoL) from baseline compared to placebo across all measures (i.e., physical and emotional health, work productivity and activity impairment, general and IBD specific health status); demonstrating the ability of filgotinib to alleviate the burden of moderately to severely active UC on patient's personal, professional, and social life (102).

Patient preference for oral over parenteral treatments

Patients with UC often have poor adherence to biologic therapy regimens, which require subcutaneous (SC) or intravenous (IV) dosing (103). Non-adherence to UC treatments has negative clinical consequences for patients, including increased disease activity and disease flares (104, 105). Low adherence may also lead to loss of response to treatment (104). Non-adherence to biologic therapy has been associated with higher healthcare utilisation (i.e. poor outcomes) and increased costs, compared to patients who are adherent to therapy (106). Therefore, patients require treatments with simple dosing regimens and manageable risk-benefit profiles to support adherence to therapy. Boeri et al conducted a discrete choice experiment in 200 patients with moderate to severe UC and found they preferred oral to subcutaneous or intravenous administration (relative importance, 0.47 vs 0.11 and 0.18, respectively) (87). Filgotinib is an oral therapy that is simple and convenient for patients; one tablet a day, taken at home. Current NHS service challenges due to COVID-19 means that 'out-of-hospital' care is preferred to reduce visits and keep patients away from hospitals.

B.1.3.6 Positioning of filgotinib within the current treatment pathway

As described in Section B.1.1 filgotinib is a next-generation JAK inhibitor that is a preferential and reversible inhibitor of JAK1. Filgotinib can be used as first-line therapy in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent. 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

A systematic literature review (SLR) was conducted to determine the clinical efficacy of existing interventions for the treatment of moderately to severely active UC in patients who are either biologic-naïve or biologic-experienced.

Comprehensive literature searches were undertaken in electronic databases (MEDLINE, Embase, the Cochrane library, the Cochrane Database of Systematic Reviews [CDSR], the University of York Centre for Reviews and Dissemination [CRD] and the Health Technology Assessment [HTA] database) for studies published from inception to 8th of May 2019, as well as conference proceedings and websites of national reimbursement and HTA organisations. An update was performed that searched these databases from 8th of May 2019 to 2nd of November 2020. Data from eligible studies was extracted and assessed for methodological quality and applicability.

In total, the reviews identified 51 publications describing 39 clinical trials that met review inclusion criteria for clinical effectiveness of interventions for the treatment of moderately to severely active UC.

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

SELECTION is the phase 2b/3, randomised, double-blind, placebo-controlled pivotal clinical programme of induction and maintenance trials informing the safety and efficacy of filgotinib in moderately to severely active UC patients.

Table 7. Clinical effectiveness evidence: SELECTION clinical programme

Study	**SELECTION (NCT02914522)**
Study design	Combined phase 2b/3, randomised, double-blind, placebo-controlled, parallel assignment trial
Population	Adults with moderately to severely active UC with previous

	inadequate response, loss of response, or intolerance to at least one of the following agents: • Corticosteroids • Immunomodulators • TNFα inhibitors • Vedolizumab		
Intervention(s)	Induction study (10 weeks): • **Filgotinib 200mg** once daily • **Filgotinib 100mg** once daily Subjects from the induction studies who were eligible for the maintenance study were re-randomised. Subjects receiving filgotinib 200mg or 100mg in the induction studies were randomised in a 2:1 manner to either continue on the assigned filgotinib regimen or to placebo for the duration of the maintenance study. Maintenance study (weeks 10 to 58): • **Filgotinib 200mg** once daily • **Filgotinib 100mg** once daily		
Comparator(s)	Induction study (10 weeks) • Placebo-to-match filgotinib 200mg once daily • Placebo-to-match filgotinib 100mg once daily. Maintenance study (weeks 10 to 58) • Placebo-to-match filgotinib 200mg once daily • Placebo-to-match filgotinib 100mg once daily.		
Background treatment	Subjects entering either of the two induction studies may have been on a stable dose of the following: • Oral 5-aminosalicylate (5-ASA) compounds • Azathioprine • 6-mercaptopurine (6-MP) • MTX (dose must have been stable 4 weeks prior to randomisation through 10 weeks after randomisation) • Oral corticosteroid therapy (prednisolone prescribed at a stable dose ≤30mg/day • Budesonide prescribed at a stable dose of ≤9mg/day, prescribed dose must have been stable for 2 weeks prior to randomisation through 14 weeks after randomisation).		
Trial supports application for Marketing Authorisation?	Yes	**Indicate if trial used in the economic model**	Yes
Rationale for use/non-use in the model	This pivotal study provides evidence of the efficacy of filgotinib and was included in the network meta-analysis used in the economic model.		
Reported outcomes specified in the decision problem	• Measures of disease activity (Mayo score) • Rates of duration of response, relapse and remission (Mayo score)		

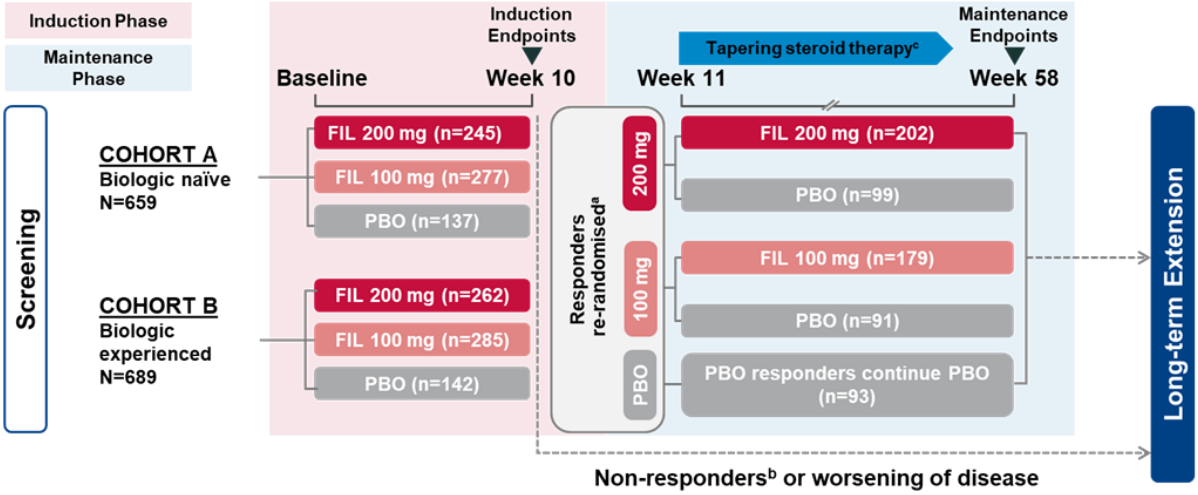
	• Mucosal healing (endoscopic sub score of 0 or 1) • Endoscopic healing • Corticosteroid-free remission • Adverse effects of treatment • Rates of hospitalisation and of surgical intervention due to ulcerative colitis • Health-related quality of life: IBDQ, SF-36, EQ-5D and WPAI.
All other reported outcomes	• PK plasma concentrations of filgotinib and its metabolite.

Abbreviations: EBS, endoscopy/bleeding/stool; EQ5D, EuroQol-5D; HRQoL, health related quality of life; IBDQ, Inflammatory Bowel Disease Questionnaire; MTX, methotrexate; PK, pharmacokinetics; SF36, Short Form 36; TNFα inhibitors, tumour necrosis factor alpha inhibitors; WPAI, Work Productivity and Activity Impairment Questionnaire.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107).

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

The SELECTION clinical programme was conducted under a single protocol but designed and analysed as three separate studies: two induction studies and a maintenance study. The population of the induction period was stratified by biologic-naïve (cohort A) and biologic-experienced (cohort B) patients, resulting in the two induction studies. The clinical programme's design is summarised in Figure 5 below.

Figure 5. Trial design of the SELECTION randomised clinical programme for patients with moderately to severely active UC*



Abbreviations: UC, ulcerative colitis; N, number; FIL, filgotinib; PBO, placebo; mg, milligram.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107).
Notes: [a] Participants from Cohorts A and B who achieved either EBS remission or MCS response at Week 10, upon induction phase completion, were re-randomized upon entering the maintenance study at Week 11.
[b] Non-responders were those that did not achieve both EBS remission and MCS response at Week 10.
[c] Participants that enter maintenance phase and on concomitant steroids were required to begin tapering steroid therapy, starting at Week 14 of the study.

The primary objective of the two induction studies was to evaluate the efficacy of filgotinib as compared with placebo in establishing endoscopy/bleeding/stool frequency (EBS) remission at week 10. EBS is a composite measure of three variables: an endoscopic sub score of 0 or 1, rectal bleeding sub score of 0, and at least one point decrease in stool frequency from baseline to achieve a sub score of 0 or 1. The primary objective of the maintenance study was to evaluate the efficacy of filgotinib when compared to placebo in establishing EBS remission at week 58.

A summary of the methods used in the SELECTION clinical programme is provided in Table 8.

Table 8. Summary of SELECTION clinical programme methodology

Study	SELECTION (NCT02914522)
Trial design	SELECTION is a combined phase 2b/3, double-blind, randomised, placebo-controlled programme of trials evaluating the efficacy and safety of filgotinib 200mg or 100mg in the induction and maintenance of remission in subjects with moderately to severely active UC. Two 650-subject induction studies (cohort A and B) were conducted. Enrolled subjects could be males or nonpregnant, nonlactating females between 18 and 75 years of age (inclusive) with moderately to severely active UC. Following screening (days −30 to −1), eligible subjects were randomised (day 1) and took part in the blinded induction studies (day 1 to week 11). Subjects who were assigned to active treatment, completed the induction studies and achieved either EBS remission or MCS response at week 10 were re-randomised into the maintenance study at week 11 and took part in the blinded maintenance study (weeks 11 to 58). Subjects were re-randomised into the maintenance study as follows: • Subjects who received filgotinib 200mg in the induction studies were re-randomised to receive filgotinib 200mg or placebo • Subjects who received filgotinib 100mg in the induction studies were re-randomised to receive filgotinib 100mg or placebo. Subjects who received placebo in the induction studies and achieved either EBS remission or MCS response at week 10 continued to

	receive placebo in the maintenance study. Subjects who did not achieve EBS remission or MCS response at week 10 had the option to enter a separate, SELECTION LTE study (NCT02914535). Subjects who met disease worsening criteria in the maintenance study were discontinued from blinded treatment and had the option to receive open-label filgotinib in the LTE study. Subjects who completed the week 58 visit had the option to continue study drug in a blinded fashion in the LTE study.
Eligibility criteria for participants	<u>General eligibility criteria for the induction studies (cohorts A & B):</u> Eligible subjects met all the following inclusion criteria for participation in the cohort A or cohort B induction studies: • Males or nonpregnant, nonlactating females, aged 18 to 75 years (inclusive) based on the date of the screening visit • Documented diagnosis of UC of at least 6 months and with a minimum disease extent of 15cm from the anal verge • Moderately to severely active UC as determined by a centrally read endoscopy score ≥2, a rectal bleeding score ≥1, a stool frequency score ≥1, and Physician's Global Assessment of ≥2 as determined by the Mayo Clinic scoring system with endoscopy occurring during screening; total score between 6 and 12, inclusive • A surveillance colonoscopy was required prior to screening in subjects with a history of UC for 8 or more years, if one was not performed in the prior 24 months • Must not have had Crohn's disease, indeterminate colitis, ischemic colitis, fulminant colitis, isolated ulcerative proctitis, or toxic mega-colon • Must not have had active TB or history of latent TB that had not been treated. <u>Additional eligibility criteria for cohort A (biologic-naïve) Induction study:</u> • Previously demonstrated an inadequate clinical response, loss of response to, or intolerance to at least one of the following agents (depending on current country treatment recommendations/guidelines): ○ Corticosteroids: active disease despite a history of at least an induction regimen of a dose equivalent to oral prednisolone 30mg daily for 2 weeks or intravenously (IV) for 1 week, or 2 failed attempts to taper steroids below a dose equivalent to 10mg daily prednisolone, or a history of steroid intolerance

	○ Immunomodulators: active disease despite a history of at least a 12-week regimen of oral azathioprine (≥2mg/kg/day) or 6-MP (≥1mg/kg/day), or MTX (25mg subcutaneously [SC] or intramuscularly [IM] per week for induction and ≥15mg IM per week for maintenance), or a history of intolerance to at least one immunomodulator. • No prior or current use of any TNFα inhibitor • No prior or current use of vedolizumab at any time. <u>Additional eligibility criteria for cohort B (biologic-experienced) Induction study:</u> • Previously demonstrated an inadequate clinical response, loss of response to, or intolerance of at least one of the following agents (depending on current country treatment recommendations/guidelines): ○ TNFα inhibitors: active disease despite a history of at least one induction regimen of a TNFα inhibitor: infliximab (minimum induction regimen of 5mg/kg at 0, 2, and 6 weeks [in the EU, duration of treatment of 14 weeks]); adalimumab (8-week induction regimen consisting of 160mg [four 40mg injections in 1 day or two 40mg injections per day for two consecutive days] on day 1, followed by a second dose two weeks later of 80mg and a 40mg dose two weeks later, followed by a 40mg dose every other week until week 8); golimumab (minimum induction duration of six weeks [12 weeks in EU] including a 200mg SC injection at week 0, followed by 100mg at week 2, and then 100mg every 4 weeks), or a recurrence of symptoms during maintenance therapy with any of these agents, or a history of intolerance to any TNFα inhibitors ○ Vedolizumab: active disease despite a history of at least a 14-week (ten weeks in EU) induction regimen consisting of 300mg IV at weeks 0, 2, and 6, or a history of intolerance to vedolizumab. • Must not have used any TNFα inhibitor or vedolizumab ≤8 weeks prior to screening or any other biologic agent ≤8 weeks prior to screening or within five times the half-life of the biologic agent prior to screening, whichever was longer. <u>Main Eligibility Criteria for maintenance study:</u> Subjects must have completed the cohort A or cohort B induction study with an MCS response or EBS remission based on week 10 assessments.
Settings and locations where	This study was conducted at 341 study centres in 40 countries:

the data were collected	Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Czech Republic, France, Germany, Greece, Hong Kong, Hungary, India, Ireland, Israel, Italy, Japan, Malaysia, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Republic of Georgia, Republic of Korea, Romania, Russian Federation, Serbia, Singapore, Slovakia, South Africa, Spain, Sweden, Switzerland, Taiwan, Ukraine, United Kingdom, and the United States.
Trial drugs	Cohort A induction study: **Interventions** • Filgotinib 200mg once daily (n=245) • Filgotinib 100mg once daily (n=277). **Comparator** • Placebo once daily to match filgotinib 200mg + placebo to match filgotinib 100mg (n=137). Cohort B induction study: **Interventions** • Filgotinib 200mg once daily (n=262) • Filgotinib 100mg once daily (n=285). **Comparator** • Placebo once daily to match filgotinib 200mg + placebo to match filgotinib 100mg (n=142). Maintenance study: **Interventions** Induction filgotinib 200mg group: • Maintenance filgotinib 200mg (n=202) Induction filgotinib 100mg group: • Maintenance filgotinib 100mg (n=179). **Comparator** Induction filgotinib 200mg group: • Maintenance placebo once daily (n=99) Induction filgotinib 100mg group: • Maintenance placebo once daily (n=91) Induction placebo group: • Maintenance placebo once daily (n=93).
Permitted and disallowed concomitant medications	Provided that they are maintained at a stable dose for the noted time without dosing alteration or discontinuation, permitted concomitant medications for ulcerative colitis were: • Oral 5-ASA compounds provided the dose prescribed has been stable for at least 4 weeks prior to randomisation; dose must be stable for the first 10 weeks after randomisation • Azathioprine, 6-MP, or MTX provided the dose prescribed has

	been stable for 4 weeks prior to randomisation; dose must be stable for the first 10 weeks after randomisation • Oral corticosteroid therapy (prednisone prescribed at a stable dose ≤30mg/day or budesonide prescribed at a stable dose of ≤9mg/day) provided the dose prescribed has been stable for 2 weeks prior to randomisation; dose must be stable for the first 14 weeks after randomisation. Prohibited medications included anticonvulsants, antimycobacterials, corticosteroids, TNFα inhibitors, Integrin antagonists, Lymphocyte-depleting therapies.
Primary outcomes (including scoring methods and timings of assessments)	Induction study endpoints were assessed at week 10 and maintenance study endpoints were assessed at week 58. <u>Primary endpoint for induction and maintenance studies</u>: • Proportion of patients achieving EBS remission.

Other outcomes used in the economic model/specified in the scope	**Secondary endpoints:**
	<u>Induction studies:</u>
	• Mayo Clinic Score remission
	• Mayo Clinic Score response
	• Mucosal healing
	• Endoscopic sub score of 0
	• Histologic remission
	• Mayo Clinic Score remission (alternative definition).
	<u>Maintenance study:</u>
	• As above, plus
	  ○ Sustained EBS remission
	  ○ 6-month corticosteroid-free remission (components of Mayo Clinic Score).

Pre-planned subgroups	Four types of subgroup analyses were performed for the primary efficacy endpoints for each individual study (cohort A induction study, cohort B induction study, and maintenance study).
	
	• Stratification factors:
	  ○ Concomitant use of systemic corticosteroids at baseline
	  ○ Concomitant use of immunomodulators at baseline
	  ○ Prior exposure to biologic agents approved for ulcerative colitis (cohort B only)
	  ○ Participation in the cohort A induction study or the cohort B induction study (maintenance only)
	
	• History of biologic agent use: (cohort B induction study and maintenance study only)

	○ Previous exposure to TNFα inhibitors ○ Prior failure of TNFα inhibitors ○ Previous exposure to vedolizumab ○ Prior failure of vedolizumab Dual refractory (prior failure of TNFα inhibitors and vedolizumab). • Demographic factors: ○ Age at baseline ○ Sex at birth ○ Race ○ Geographic region. • Baseline disease characteristics: ○ hs-CRP at baseline ○ Faecal calprotectin at baseline ○ Duration of ulcerative colitis ○ Mayo clinic score at screening.

Abbreviations: CRP, C-Reactive Protein; EBS, endoscopy/bleeding/stool; IBDQ, Inflammatory Bowel Disease Questionnaire; IV, intravenous; LTE, long-term extension; MCS, Mayo clinic score; MTX, methotrexate; QD, once a day; TNFα inhibitors, tumour necrosis factor alpha inhibitors; UC, ulcerative colitis; 5-ASA, aminosalicylic acids; 6 MP, 6-mercaptopurine; TB, tuberculosis; EU, European Union.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107).

Demographic and disease characteristics of subjects for all three studies are presented in Table 9 for induction study cohort A, in Table 10 for induction study cohort B and in Table 11 for the maintenance study.

Table 9. Demographics and disease baseline characteristics, induction study cohort A (Safety Analysis Set)

Characteristic	Filgotinib 200mg (N=245)	Filgotinib 100mg (N=277)	Placebo (N=137)	Total (N=659)
Age, mean (SD)	42 (13.1)	42 (13.3)	41 (12.9)	42 (13.1)
Sex at birth, Female, n (%)	122 (49.8%)	120 (43.3%)	50 (36.5%)	292 (44.3%)
Weight in kg, mean (SD)	70.1 (17.89)	69.6 (17.69)	69.5 (15.89)	69.7 (17.39)
Body Mass Index in kg/m^2, mean (SD)	24.7 (5.82)	24.2 (4.91)	24.0 (4.31)	24.3 (5.16)
Race				
American Indian or Alaska Native, n (%)	1 (0.4%)	0	0	1 (0.2%)

Characteristic	Filgotinib 200mg (N=245)	Filgotinib 100mg (N=277)	Placebo (N=137)	Total (N=659)
Asian, n (%)	77 (31.4%)	79 (28.5%)	38 (27.7%)	194 (29.4%)
Black or African American, n (%)	2 (0.8%)	3 (1.1%)	1 (0.7%)	6 (0.9%)
Native Hawaiian or Pacific Islander, n (%)	0	0	0	0
White, n (%)	165 (67.3%)	192 (69.3%)	95 (69.3%)	452 (68.6%)
Other, n (%)	0	2 (0.7%)	2 (1.5%)	4 (0.6%)
Not Permitted, n (%)	0	1 (0.4%)	1 (0.7%)	2 (0.3%)
Geographic Region				
United States, n (%)	14 (5.7%)	33 (11.9%)	19 (13.9%)	66 (10.0%)
Non-US, n (%)	231 (94.3%)	244 (88.1%)	118 (86.1%)	593 (90.0%)
UC History				
Duration of UC in years, mean (SD)	7.2 (6.87)	6.7 (7.41)	6.4 (7.39)	6.8 (7.20)
Mayo Clinic Score, mean (SD)	8.6 (1.31)	8.6 (1.43)	8.7 (1.32)	8.6 (1.36)
Partial Mayo Clinic Score, mean (SD)	6.0 (1.24)	5.9 (1.31)	6.1 (1.29)	6.0 (1.28)
Endoscopy Score of 3, n (%)	133 (54.3%)	159 (57.4%)	76 (55.5%)	368 (55.8%)
Faecal calprotectin in µg/g, mean (SD)	2059 (2639.1)	2001 (3447.8)	2231 (2916.9)	2070 (3055.5)
C-Reactive protein in hs-CRP, mg/L; mean (SD)	8.63 (16.274)	7.75 (17.384)	5.82 (7.600)	7.67 (15.426)
Concomitant use of systemically absorbed corticosteroids and immunomodulators				
Systemic corticosteroids only, n (%)	54 (22.0%)	67 (24.2%)	34 (24.8%)	155 (23.5%)
Immunomodul	53 (21.6%)	63 (22.7%)	33 (24.1%)	149 (22.6%)

Characteristic	Filgotinib 200mg (N=245)	Filgotinib 100mg (N=277)	Placebo (N=137)	Total (N=659)
ators only, n (%)				
Both systemic corticosteroids and immunomodulators, n (%)	20 (8.2%)	19 (6.9%)	8 (5.8%)	47 (7.1%)
Neither systemic corticosteroids nor immunomodulators, n (%)	118 (48.2%)	128 (46.2%)	62 (45.3%)	308 (46.7%)

Abbreviations: hs-CRP, high-sensitivity C-Reactive Protein; kg/m^2, kilogram per square meter; n, number; µg/g, microgram/gram; mg/L, milligrams per litre; SD, standard deviation; UC, ulcerative colitis**.**
References: Gilead SELECTION clinical study report, 2020 (data on file) (107).

Table 10. Demographic and disease baseline characteristics, induction study cohort B, Safety Analysis Set

Characteristic	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)	Total (N=689)
Age, mean (SD)	43 (14.2)	43 (14.3)	44 (14.9)	43 (14.4)
Sex at birth, Female, n (%)	114 (43.5%)	99 (34.7%)	56 (39.4%)	269 (39.0%)
Weight in kg, mean (SD)	73.1 (18.68)	74.7 (17.01)	73.1 (16.74)	73.8 (17.61)
Body Mass Index in kg/m^2, mean (SD)	25.1 (5.70)	25.0 (4.90)	24.7 (5.28)	25.0 (5.29)
Race				
American Indian or Alaska Native, n (%)	0	0	0	0
Asian, n (%)	50 (19.1%)	51 (17.9%)	27 (19.0%)	128 (18.6%)
Black or African American, n (%)	4 (1.5%)	6 (2.1%)	3 (2.1%)	13 (1.9%)
Native Hawaiian or Pacific Islander, n (%)	0	0	0	0
White, n (%)	190 (72.5%)	212 (74.4%)	98 (69.0%)	500 (72.6%)
Other, n (%)	0	0	1 (0.7%)	1 (0.1%)

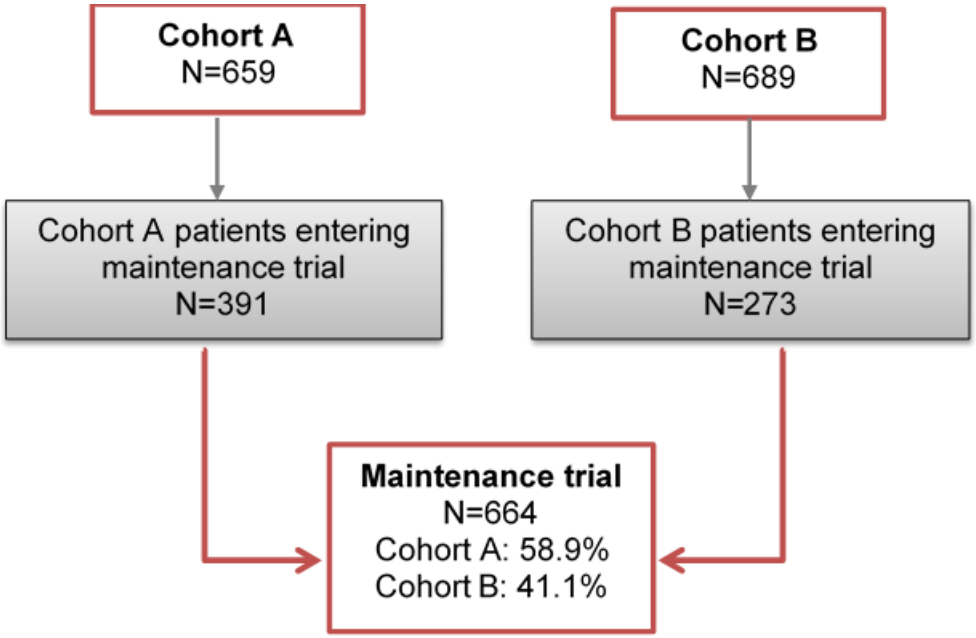
Characteristic	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)	Total (N=689)
Not Permitted, n (%)	18 (6.9%)	16 (5.6%)	13 (9.2%)	47 (6.8%)
Geographic Region				
United States, n (%)	36 (13.7%)	58 (20.4%)	21 (14.8%)	115 (16.7%)
Non-US, n (%)	226 (86.3%)	227 (79.6%)	121 (85.2%)	574 (83.3%)
UC History				
Duration of UC in years, mean (SD)	9.8 (7.64)	9.7 (7.15)	10.2 (8.22)	9.8 (7.56)
Mayo Clinic Score, mean (SD)	9.2 (1.39)	9.3 (1.27)	9.3 (1.42)	9.3 (1.35)
Partial Mayo Clinic Score, mean (SD)	6.5 (1.38)	6.4 (1.26)	6.4 (1.40)	6.4 (1.33)
Endoscopy Score of 3, n (%)	203 (77.5%)	222 (77.9%)	111 (78.2%)	536 (77.8%)
Faecal calprotectin in µg/g, mean (SD)	2845 (4076.5)	2236 (3094.9)	2479 (3571.4)	2517 (3596.7)
C-Reactive protein in hs-CRP, mg/L; mean (SD)	12.21 (14.850)	11.72 (17.986)	13.98 (24.280)	12.37 (18.405)
Number of prior Biologic Agents				
0, n (%)	3 (1.1%)	2 (0.7%)	3 (2.1%)	8 (1.2%)
1, n (%)	80 (30.5%)	98 (34.4%)	46 (32.4%)	224 (32.5%)
2, n (%)	90 (34.4%)	109 (38.2%)	45 (31.7%)	244 (35.4%)
≥ 3, n (%)	89 (34.0%)	76 (26.7%)	48 (33.8%)	213 (30.9%)
Prior use of TNFα inhibitor				
Yes, n (%)	242 (92.4%)	266 (93.3%)	130 (91.5%)	638 (92.6%)
1, n (%)	126 (48.1%)	136 (47.7%)	66 (46.5%)	328 (47.6%)
2, n (%)	90 (34.4%)	117 (41.1%)	54 (38.0%)	261 (37.9%)
≥ 3, n (%)	26 (9.9%)	13 (4.6%)	10 (7.0%)	49 (7.1%)
Prior use of vedolizumab				
Yes, n (%)	164 (62.6%)	145 (50.9%)	85 (59.9%)	394 (57.2%)
Treatment failure worst outcome, n (%)	148 (56.5%)	132 (46.3%)	76 (53.5%)	356 (51.7%)

Characteristic	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)	Total (N=689)
Intolerance worst outcome, n (%)	11 (4.2%)	9 (3.2%)	2 (1.4%)	22 (3.2%)
Other, n (%)	11 (4.2%)	4 (1.4%)	7 (4.9%)	16 (2.3%)
Prior Use of both TNFα inhibitor and vedolizumab				
Prior Use of both TNFα inhibitor and vedolizumab, Yes, n (%)	147 (56.1%)	128 (44.9%)	76 (53.5%)	351 (50.9%)
Concomitant use of systemically absorbed corticosteroids and immunomodulators				
Systemic corticosteroids only, n (%)	94 (35.9%)	103 (36.1%)	51 (35.9%)	248 (36.0%)
Immunomodulators only, n (%)	34 (13.0%)	34 (11.9%)	21 (14.8%)	89 (12.9%)
Both systemic corticosteroids and immunomodulators, n (%)	28 (10.7%)	28 (9.8%)	11 (7.7%)	67 (9.7%)
Neither systemic corticosteroids nor immunomodulators, n (%)	106 (40.5%)	120 (42.1%)	59 (41.5%)	285 (41.4%)

Abbreviations: hs-CRP, high-sensitivity C-Reactive Protein; kg/m^2, kilogram per square meter; n, number; µg/g, microgram/gram; mg/L, milligrams per litre; SD, standard deviation; UC, ulcerative colitis; TNFα, tumour necrosis factor alpha.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107).

Across treatment groups, 58.9% of subjects entered the maintenance study from the cohort A induction study (biologic-naïve subjects) and 41.1% entered the maintenance study from the cohort B induction study (biologic-experienced subjects) (Figure 6). For detailed information on patient disposition in each trial, please see Appendix D.

Figure 6. Proportion of patients in the maintenance trial originating from each induction study



Abbreviation: N, number.

Table 11. Demographic and disease baseline characteristics, maintenance study, Safety Analysis Set

SELECTION (NCT02914522)	Induction filgotinib 200mg			Induction filgotinib 100mg			Induction Placebo	Overall Total (N=664)
	Maintenance filgotinib 200mg (N=202)	Maintenance placebo (N=99)	Total (N=301)	Maintenance filgotinib 100mg (N=179)	Maintenance placebo (N=91)	Total (N=270)	Maintenance placebo (N=93)	
Age, mean (SD)	43 (13.8)	42 (13.0)	43 (13.5)	42 (12.6)	43 (15.1)	42 (13.5)	43 (13.0)	43 (13.4)
Sex at birth, Female, n (%)	107 (53.0%)	51 (51.5%)	158 (52.5%)	78 (43.6%)	42 (46.2%)	120 (44.4%)	44 (47.3%)	322 (48.5%)
Weight in kg, mean (SD)	71.2 (18.31)	73.0 (18.12)	71.8 (18.24)	72.3 (19.97)	73.7 (18.06)	72.8 (19.32)	69.2 (16.03)	71.8 (18.41)
Body Mass Index in kg/m^2, mean (SD)	71.8 (18.41)	25.7 (5.54)	25.1 (5.63)	24.9 (5.39)	25.2 (5.51)	25.0 (5.42)	24.0 (4.17)	24.9 (5.37)
Race								
American Indian or Alaska Native, n (%)	0	0	0	0	0	0	0	0
Asian, n (%)	56 (27.7%)	29 (29.3%)	85 (28.2%)	41 (22.9%)	19 (20.9%)	60 (22.2%)	28 (30.1%)	173 (26.1%)
Black or African American, n (%)	4 (2.0%)	0	4 (1.3%)	4 (2.2%)	0	4 (1.5%)	0	8 (1.2%)
Native Hawaiian or Pacific Islander, n (%)	0	0	0	0	0	0	0	0
White, n (%)	138 (68.3%)	68 (68.7%)	206 (68.4%)	130 (72.6%)	71 (78.0%)	201 (74.4%)	63 (67.7%)	470 (70.8%)
Other, n (%)	0	0	0	1 (0.6%)	0	1 (0.4%)	1 (1.1%)	2 (0.3%)
Not Permitted, n (%)	4 (2.0%)	2 (2.0%)	6 (2.0%)	3 (1.7%)	1 (1.1%)	4 (1.5%)	1 (1.1%)	11 (1.7%)
Geographic Region								

SELECTION (NCT02914522)	Induction filgotinib 200mg			Induction filgotinib 100mg			Induction Placebo	Overall Total (N=664)
	Maintenance filgotinib 200mg (N=202)	Maintenance placebo (N=99)	Total (N=301)	Maintenance filgotinib 100mg (N=179)	Maintenance placebo (N=91)	Total (N=270)	Maintenance placebo (N=93)	
United States, n (%)	19 (9.4%)	12 (12.1%)	31 (10.3%)	29 (16.2%)	12 (13.2%)	41 (15.2%)	8 (8.6%)	80 (12.0%)
Non-US, n (%)	183 (90.6%)	87 (87.9%)	270 (89.7%)	150 (83.8%)	79 (86.8%)	229 (84.8%)	85 (91.4%)	584 (88.0%)
UC History								
Duration of UC in years, mean (SD)	8.4 (7.37)	8.9 (7.61)	8.6 (7.44)	8.9 (8.40)	7.5 (7.45)	8.4 (8.10)	7.0 (6.78)	8.3 (7.64)
Faecal calprotectin in µg/g, mean (SD)	627 (944.9)	934 (2621.7)	728 (1692.4)	662 (1291.2)	760 (1474.7)	695 (1353.9)	1043 (1545.9)	758 (1544.3)
C-Reactive protein in hs-CRP, mg/L; mean (SD)	3.74 (10.131)	2.72 (4.443)	3.41 (8.686)	3.04 (5.721)	3.53 (5.392)	3.21 (5.607)	3.30 (5.299)	3.31 (7.127)
Participated cohort A, n (%)	109 (54.0%)	54 (54.5%)	163 (54.2%)	107 (59.8%)	54 (59.3%)	161 (59.6%)	67 (72.0%)	391 (58.9%)
Participated cohort B, n (%)	93 (46.0%)	45 (45.5%)	138 (45.8%)	72 (40.2%)	37 (40.7%)	109 (40.4%)	26 (28.0%)	273 (41.1%)
Number of prior biologic agents used								
0, n (%)	110 (54.5%)	55 (55.6%)	165 (54.8%)	106 (59.2%)	56 (61.5%)	162 (60.0%)	68 (73.1%)	395 (59.5%)
1, n (%)	36 (17.8%)	16 (16.2%)	52 (17.3%)	32 (17.9%)	9 (9.9%)	41 (15.2%)	12 (12.9%)	105 (15.8%)
2, n (%)	31 (15.3%)	10 (10.1%)	41 (13.6%)	22 (12.3%)	15 (16.5%)	37 (13.7%)	4 (4.3%)	82 (12.3%)

SELECTION (NCT02914522)	Induction filgotinib 200mg			Induction filgotinib 100mg			Induction Placebo	Overall Total (N=664)
	Maintenance filgotinib 200mg (N=202)	Maintenance placebo (N=99)	Total (N=301)	Maintenance filgotinib 100mg (N=179)	Maintenance placebo (N=91)	Total (N=270)	Maintenance placebo (N=93)	
≥ 3, n (%)	25 (12.4%)	18 (18.2%)	43 (14.3%)	19 (10.6%)	11 (12.1%)	30 (11.1%)	9 (9.7%)	82 (12.3%)
Prior use of TNFα antagonist								
Yes	84 (41.6%)	43 (43.4%)	127 (42.2%)	68 (38.0%)	32 (35.2%)	100 (37.0%)	21 (22.6%)	248 (37.3%)
1, n (%)	47 (23.3%)	21 (21.2%)	68 (22.6%)	37 (20.7%)	9 (9.9%)	46 (17.0%)	10 (10.8%)	124 (18.7%)
2, n (%)	29 (14.4%)	19 (19.2%)	48 (15.9%)	26 (14.5%)	21 (23.1%)	47 (17.4%)	9 (9.7%)	104 (15.7%)
≥3, n (%)	8 (4.0%)	3 (3.0%)	11 (3.7%)	5 (2.8%)	2 (2.2%)	7 (2.6%)	2 (2.2%)	20 (3.0%)
Prior use of vedolizumab								
Yes, n (%)	49 (24.3%)	24 (24.2%)	73 (24.3%)	32 (17.9%)	16 (17.6%)	48 (17.8%)	15 (16.1%)	136 (20.5%)
Treatment Failure worst outcome, n (%)	40 (19.8%)	21 (21.2%)	61 (20.3%)	28 (15.6%)	14 (15.4%)	42 (15.6%)	12 (12.9%)	115 (17.3%)
Intolerance worst outcome, n (%)	5 (2.5%)	3 (3.0%)	8 (2.7%)	3 (1.7%)	1 (1.1%)	4 (1.5%)	2 (2.2%)	14 (2.1%)
Other, n (%)	4 (2.0%)	0	4 (1.3%)	1 (0.6%)	1 (1.1%)	2 (0.7%)	1 (1.1%)	7 (1.1%)
Prior Use of both TNFα inhibitors and vedolizumab								
Prior Use of both TNFα inhibitors and vedolizumab, Yes, n (%)	41 (20.3%)	23 (23.2%)	64 (21.3%)	27 (15.1%)	13 (14.3%)	40 (14.8%)	11 (11.8%)	115 (17.3%)

SELECTION (NCT02914522)	Induction filgotinib 200mg			Induction filgotinib 100mg			Induction Placebo	Overall Total (N=664)
	Maintenance filgotinib 200mg (N=202)	Maintenance placebo (N=99)	Total (N=301)	Maintenance filgotinib 100mg (N=179)	Maintenance placebo (N=91)	Total (N=270)	Maintenance placebo (N=93)	
Concomitant use of systemically absorbed corticosteroids and immunomodulators								
Systemic corticosteroids only, n (%)	61 (30.2%)	31 (31.3%)	92 (30.6%)	62 (34.6%)	28 (30.8%)	90 (33.3%)	25 (26.9%)	207 (31.2%)
Immunomodulators only, n (%)	35 (17.3%)	18 (18.2%)	53 (17.6%)	27 (15.1%)	15 (16.5%)	42 (15.6%)	23 (24.7%)	118 (17.8%)
Both systemic corticosteroids and immunomodulators, n (%)	19 (9.4%)	9 (9.1%)	28 (9.3%)	17 (9.5%)	9 (9.9%)	26 (9.6%)	7 (7.5%)	61 (9.2%)
Neither systemic corticosteroids nor immunomodulators, n (%)	87 (43.1%)	41 (41.4%)	128 (42.5%)	73 (40.8%)	39 (42.9%)	112 (41.5%)	38 (40.9%)	278 (41.9%)

Abbreviations: hs-CRP, high-sensitivity C-Reactive Protein; kg/m^2, kilogram per square meter; mg/L, milligrams per litre; µg/g, milligrams per gram; n, number; SD, standard deviation; TNFα, tumour necrosis factor-alpha; UC, ulcerative colitis.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107).

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

B.2.4.1 Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) for each induction study included all randomised subjects who took at least one dose of study drug in the corresponding induction study.

The FAS for the maintenance study included all subjects randomised to either filgotinib 200mg or filgotinib 100mg treatment groups in the induction studies who achieved EBS remission or MCS response at week 10, were re-randomised, and took at least one dose of study drug in the maintenance study. The FASs were the primary analysis sets for the efficacy analyses.

Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set for each induction study included subjects in the respective FAS who met the following criteria:

- Documented diagnosis of UC of at least 6 months with a minimum disease extent of 15 cm from the anal verge and moderately to severely active UC as described in the statistical analysis plan (SAP)
- Moderately to severely active UC as determined by a centrally read endoscopy score ≥2, a rectal bleeding (RB) score ≥1, a stool frequency (SF) score ≥1, and Physician's Global Assessment (PGA) of ≥2 as determined by the Mayo clinic scoring system with endoscopy occurring during screening; total score must have been between 6 and 12, inclusive
- On-treatment adherence of at least 80% for both study drugs (filgotinib and placebo-to-match) during the induction studies
- Had sufficient data to evaluate EBS remission at week 10 or met treatment failure criteria for week 10 EBS remission outcome

- For the Cohort A induction study, were never exposed to any biologics; for the Cohort B induction study, were exposed to at least 1 of the biologics.

The PP Analysis Set for the maintenance study included subjects in the FAS who met the following criteria:

- Met the key eligibility criteria from the induction studies, as stated above
- On-treatment adherence of at least 80% for both study drugs (filgotinib and placebo-to-match) during the maintenance study
- Had sufficient data to evaluate EBS remission or met treatment failure criteria for EBS remission outcome at week 58 or discontinued study drug due to protocol-specified disease worsening criterion.

Safety Analysis Set

The Safety Analysis Set for each induction study included all subjects who took at least one dose of study drug in the corresponding induction study.

The Safety Analysis Set for the maintenance study included all subjects who took at least one dose of study drug in the maintenance study.

The Overall Safety Analysis Set for the study included all subjects who took at least one dose of study drug in either of the induction studies or the maintenance study.

The Safety Analysis Sets were the primary analysis sets for safety analyses.

B.2.4.2 Statistical information

The statistical analysis methods and definitions of study groups used in the SELECTION clinical programme are described in below in Table 12.

Table 12. Summary of statistical analyses in SELECTION

	SELECTION (NCT02914522) induction studies	SELECTION (NCT02914522) maintenance study
Objective	To evaluate the efficacy of filgotinib as compared with placebo in establishing endoscopy/bleeding/stool frequency (EBS) remission at week 10	To evaluate the efficacy of filgotinib as compared with placebo in establishing EBS remission at week 58
Multiple Comparisons/Multiplicity	The graphical approach presented by Bretz 2009 (108) to sequentially reject the null hypotheses in multiple test procedures was used to control a family-wise type I error rate (FWER) at 5% (i.e., α=0.05) for each individual study (cohort A induction study, cohort B induction study, and the maintenance study). This procedure strongly protects the FWER on all the primary and key secondary endpoints.	
Statistical analysis for primary endpoints	The primary analyses consisted of a superiority test of filgotinib 200mg compared with placebo and filgotinib 100mg compared with placebo based on the primary endpoint. For each induction study, a stratified Cochran-Mantel-Haenszel (CMH) test was used to compare the treatment effect between the filgotinib 200mg group and placebo and between the filgotinib 100mg group and placebo, separately. The CMH tests were stratified by concomitant use of oral, systemic corticosteroids at day 1, and	A CMH test was used to compare the treatment effect between filgotinib 200mg and placebo and between filgotinib 100mg and placebo. The CMH test was stratified by participation in cohort A or cohort B, concomitant use of oral, systemic corticosteroids at re-baseline, and concomitant use of immunomodulators at re-baseline. A CMH test with the same stratification factors was used to compare the treatment effect between filgotinib 100mg and placebo among the subjects from the cohort A and B induction studies combined

	SELECTION (NCT02914522) induction studies	SELECTION (NCT02914522) maintenance study
	concomitant use of immunomodulators at day 1 for the cohort A induction study, and were stratified by concomitant use of oral, systemic corticosteroids at day 1, concomitant use of immunomodulators at day 1, and exposure to biologic agents (≤1, >1) for the cohort B induction study. The stratified CMH chi-square p-value was provided for each of the above comparisons. Strata with low numbers of subjects may have been aggregated for the CMH test. The two-sided 95% CI of EBS remission rate based on normal approximation method with a continuity correction was provided for each treatment group. In addition, non-stratified risk difference estimated along with its two-sided 95% CI using the normal approximation (i.e., the Wald method) with a continuity correction for the difference in proportions was provided. Stratification variables based on the eCRF data were used for the analysis.	being treated with filgotinib 100mg. The stratified CMH chi-square p-value was provided for each of the above comparisons. Strata with low numbers of subjects may have been aggregated for the CMH test. The two-sided 95% CI of EBS remission rate based on normal approximation method with a continuity correction was provided for each treatment group. In addition, non-stratified risk difference estimated along with its two-sided 95% CI using the normal approximation (i.e., the Wald method) with a continuity correction for the difference in proportions was provided. Stratification variables based on the eCRF data were used for the analysis.
Statistical analysis secondary endpoints	The same statistical method described for testing the primary efficacy endpoint was used for testing the key secondary efficacy endpoints.	

	SELECTION (NCT02914522) induction studies	SELECTION (NCT02914522) maintenance study
Sample size, power calculation	Sample size was chosen to ensure that a clinically meaningful difference in EBS remission rate at week 10 could be detected when comparing filgotinib with placebo within each induction study. A sample size of 130 subjects in the placebo group and 260 subjects in each filgotinib dose (200mg or 100mg) group (N=650 per cohort) provided 90% power for each filgotinib dose group comparison with placebo at a two-sided 0.025 significance level to detect a treatment difference in EBS remission rate of 15% (25% on filgotinib and 10% on placebo).	Assuming a response rate of 55% among subjects receiving filgotinib 200mg or 100mg in the induction studies, approximately 285 subjects from each filgotinib dose group from cohorts A and B combined would have been eligible to be re-randomised into the maintenance study. Sample size was chosen to ensure that a clinically meaningful difference in EBS remission rate at week 58 could be detected when comparing each filgotinib dose group with placebo in the maintenance study. A sample size of 95 subjects in the placebo group and 190 subjects in the filgotinib group at the same dose level as the induction dose provided more than 85% power for each filgotinib dose group comparison with placebo at a two-sided 0.025 significance level to detect a treatment difference in maintenance EBS remission rate of 20% (40% on filgotinib and 20% on placebo).
Data management, patient withdrawals	To evaluate the impact from missing data on the EBS remission rates at week 10 and week 58, the following missing value imputations were used: <u>Observed cases only</u> Observed cases were used for analysis without any imputation. Only subjects in the FAS with both baseline and week 10 (or week 58) data were included for analysis. <u>Missing=Success</u>	

	SELECTION (NCT02914522) induction studies	SELECTION (NCT02914522) maintenance study
	Subjects in the FAS who did not have sufficient data to decide on EBS remission status were imputed as having achieved EBS remission. <u>Missing=Success for the placebo and Missing=Failure for the filgotinib groups</u> Subjects in the FAS who did not have sufficient data to decide on EBS remission status were imputed as having achieved EBS remission for the placebo group and not having achieved EBS remission for the filgotinib groups. <u>Multiple imputation</u> Subjects in the FAS who did not have sufficient data to decide on EBS remission status at week 10 for the induction studies or week 58 for the maintenance study were imputed using the multiple imputation procedure. A logistic regression model was used to perform the imputation with baseline values of EBS sub scores, treatment, and stratification factors as independent variables.	

Abbreviations: EBS, endoscopy/bleeding/stool remission; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; SAP, statistical analysis plan.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107); Bretz, 2009 (108).

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The quality assessment of the SELECTION clinical programme is presented in Table 13. The clinical programme was 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 13. Quality assessment results for the SELECTION clinical programme

Study question	SELECTION (NCT02914522)
Was randomisation carried out appropriately?	Yes (Table 8)
Was the concealment of treatment allocation adequate?	Yes (Table 8)
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes (Table 8)
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes (Table 8)
Were there any unexpected imbalances in drop-outs between groups?	No (Table 12)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No (Table 7, Table 8)
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 (Table 12)

B.2.6 Clinical effectiveness results of the relevant trials

The SELECTION programme of induction and maintenance trials demonstrated that statistically significantly higher proportions of patients taking filgotinib 200mg achieved key efficacy endpoints compared to patients taking placebo in both the induction and the maintenance studies. Improvements in clinical outcomes were

accompanied by reductions in inflammatory biomarkers and improvements in health-related quality of life measures (102). The definitions of the efficacy endpoints applied in the trial are presented in Table 14.

Table 14. Definition of efficacy endpoints

Endpoint	Definition	Used in economic model
EBS remission	An endoscopic sub score of 0 or 1, RB sub score of 0, and at least one-point decrease in SF from baseline to achieve a sub score of 0 or 1	No
Sustained EBS remission	EBS remission at both weeks 10 and 58	No
MCS response	A MCS reduction of ≥3 points and at least 30% from baseline score with an accompanying decrease in RB sub score of ≥1 point or an absolute RB sub score of 0 or 1	Yes
MCS remission	A MCS of 2 or less and no single sub score higher than 1	Yes
MCS remission (alternative definition)	RB, SF, and PGA sub scores of 0 and an endoscopic sub score of 0 or 1; overall MCS of ≤1	No
Mucosal healing	An endoscopic sub score of 0 or 1	No
Endoscopic sub score of 0	And endoscopic sub score of 0	No
Geboes Histologic remission	Based on the Geboes Scale, all of the following must have been met to be considered in Geboes histologic remission at: Grade 0 of ≤0.3, Grade 1 of ≤1.1, Grade 2a of ≤2A.3, Grade 2b of 2B.0, Grade 3 of 3.0, Grade 4 of 4.0, and Grade 5 of 5.0	No
6-months corticosteroid-free remission	EBS remission with no corticosteroid use for the indication of UC for at least 6 months prior to week 58 among subjects who are on corticosteroid at re-baseline (baseline of maintenance study). Subjects who weaned off steroids but required re-initiation within 6 months prior to week 58 assessment were considered to have not met this endpoint.	No

Abbreviations: EBS, endoscopy/bleeding/stool frequency; MCS, Mayo Clinic Score; PGA, Physician's Global Assessment; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.
References: Gilead SELECTION clinical study report (data on file) (107); Geboes, 2000 (109).

B.2.6.1 Cohort A induction study

Primary Endpoint

The cohort A induction study met its primary endpoint. A statistically significantly higher proportion of subjects achieved EBS remission at week 10 in the filgotinib 200mg group compared with the placebo group. At week 10, 26.1% [CI=20.4% to 31.8%] of patients in the filgotinib 200mg and 15.3% [CI=8.9% to 21.7%] of patients in the placebo group achieved EBS remission (p=0.0157). A numerically higher proportion of subjects achieved EBS remission at week 10 in the filgotinib 100mg (19.1% [CI=14.3% to 23.9%]) compared with the placebo group (15.3% [CI=8.9% to 21.7%]) (p=0.3379).

Key secondary endpoints

Similarly, in cohort A induction study, filgotinib 200mg also demonstrated statistically significantly better efficacy over placebo for a number of key secondary efficacy endpoints including MCS response, MCS remission, and mucosal healing and endoscopic sub score of zero.

At week 10, 66.5% [CI=60.4% to 72.6%] of patients receiving filgotinib 200mg achieved MCS response, compared with 46.7% [CI=38.0% to 55.4%] in the placebo group (p=0.0002). MCS remission was achieved by 24.5% [CI=18.9% to 30.1%] of patients receiving 200mg, compared with 12.4% [CI=6.5% to 18.3%] in the placebo group (p=0.0053) at week 10.

Mucosal healing was achieved by 33.9% [CI=27.7% to 40.0%] of patients receiving filgotinib 200mg, compared with 20.4% [CI=13.3% to 27.6%] in the placebo group (p=0.0055) at week 10. An endoscopic sub score of 0 was achieved by 12.2% [CI=7.9% to 16.6%] of patients receiving filgotinib 200mg, compared with 3.6% [CI=9.5% to 22.6%] in the placebo group (p=0.0047) at week 10.

A summary of key efficacy endpoints is presented in Table 15.

Table 15. Summary of main efficacy outcomes for cohort A induction study, week 10 (Non-responders' imputation; Full Analysis Set)

Endpoint	Filgotinib 200mg (n=245)	Filgotinib 100mg (n=277)	Placebo (n=137)
EBS remission n (%) [95%CI]	64 (26.1%) [20.4% to 31.8%]	53 (19.1%) [14.3% to 23.9%]	21 (15.3%) [8.9% to 21.7%]
p-value*	0.0157	0.3379	NA
MCS response n (%) [95%CI]	163 (66.5%) [60.4% to 72.6%]	164 (59.2%) [53.2% to 65.2%]	64 (46.7%) [38.0% to 55.4%]
p-value	0.0002	0.0173	NA
MCS remission n (%) [95%CI]	60 (24.5%) [18.9% to 30.1%]	47 (17.0%) [12.4% to 21.6%]	17 (12.4%) [6.5% to 18.3%]
p-value	0.0053	0.2295	NA
Mucosal healing n (%) [95%CI]	83 (33.9%) [27.7% to 40.0%]	73 (26.4%) [21.0% to 31.7%]	28 (20.4%) [13.3% to 27.6%]
p-value	0.0055	0.1760	NA
Endoscopic sub score of 0, n (%) [95%CI]	30 (12.2%) [7.9% to 16.6%]	16 (5.8%) [2.8% to 8.7%]	5 (3.6%) [0.1% to 7.2%]
p-value	0.0047	0.3495	NA
Geboes Histologic remission, n(%) [95%CI]	86 (35.1%) [28.9% to 41.3%]	66 (23.8%) [18.6% to 29.0%]	22 (16.1%) [9.5% to 22.6%]
p-value	<0.0001	0.0672	NA
MCS remission (alternative definition) n (%) [95%CI]	30 (12.2%) [7.9% to 16.6%]	24 (8.7%) [5.2% to 12.2%]	6 (4.4%) [0.6% to 8.2%]
p-value	0.0105	0.1062	NA

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; MCS, Mayo Clinic Score; n, number; NA, not applicable.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107).
Notes: *p-values from Stratified Cochran-Mantel-Haenszel Test.

Patient-reported outcomes

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a disease specific instrument which represents several dimensions of quality of life that are pivotal to the patient experience. These include general activities of daily living, specific intestinal function such as bowel habit and abdominal pain as well as social

performance, personal interactions, and emotional status. Importantly, a clinically meaningful improvement has been identified as a >16 point improvement from baseline on the IBDQ scale (110). In the cohort A induction study, at week 10, the mean (SD) total IBDQ score change from baseline was 52 points (37.8) for patients receiving filgotinib 200mg compared with 34 points (40.5) in the placebo group ($p<0.0001$). Clinically meaningful improvements from baseline in total IBDQ score were therefore reached for patients taking filgotinib 200mg.

The SF-36 is a chronic disease specific questionnaire comprised of two component summaries: the physical component summary (PCS) and the mental component summary. SF-36 is measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. In general, a change of 2 to 3 points in each component summary indicates a clinically meaningful improvement. In the cohort A induction study, at week 10, mean (SD) improvements in the PCS and mental component summary scores were clinically meaningful and statistically significantly higher in the filgotinib 200mg group (110). Patients taking filgotinib 200mg had a 6.78 (6.850) points change from baseline for the PCS, compared to the placebo group who reported a 5.69 (7.430) points change from baseline for PCS ($p<0.0001$). Patients taking filgotinib 200mg had an 8.04 (10.178) points change from baseline for the mental component summary, compared to the placebo group which reported a 6.81 (10.613) points change from baseline ($p=0.0013$).

The EQ-5D VAS is a component of the EQ-5D, a generic HRQoL instrument. EQ-5D VAS score is obtained through a visual analogue scale (VAS) that has endpoints labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state” (110). In the cohort A induction study, at week 10, mean (SD) improvements in the EQ-5D VAS scores were statistically significantly higher in the filgotinib 200mg group (17 points [21.5]) as compared to the placebo group (9 points [21.3]) ($p<0.0001$).

Detailed results of the EQ-5D index individual dimensions and of the Work Productivity And Impairment (WPAI) questionnaire are presented in Appendix L. A summary of patients’ reported outcomes is presented in Table 16.

Table 16. Summary of health-related quality of life results for cohort A induction study, week 10

Endpoint	Filgotinib 200mg (n=245)	Filgotinib 100mg (n=277)	Placebo (n=137)
IBDQ total score, mean (SD)			
Baseline	119 (30.5)	117 (34.2)	114 (32.4)
Change from baseline	52 (37.8)	49 (40.2)	34 (40.5)
p-value	<0.0001	<0.0001	NA
SF-36, mean (SD)			
Baseline physical component	42.22 (6.804)	42.25 (7.037)	42.49 (6.908)
Change from baseline physical component	6.78 (6.850)	5.69 (7.430)	3.10 (7.309)
p-value	<0.0001	0.0005	NA
Baseline mental component	39.50 (9.467)	39.50 (10.640)	37.65 (9.546)
Change from baseline mental component	8.04 (10.178)	6.81 (10.613)	6.12 (9.319)
p-value	0.0013	0.0693	NA
EQ-5D VAS, mean (SD)			
Baseline	54 (18.9)	54 (19.3)	52 (19.1)
Change from Baseline	17 (21.5)	16 (21.4)	9 (21.3)
p-value	<0.0001	<0.0001	NA

Abbreviations: EQ-5D, European quality of life 5 dimensions; IBDQ, inflammatory bowel disease questionnaire; NA, not applicable; SD, standard deviation; SF-36, 36 item short form survey; VAS, visual analogue scale.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107).
Notes: *p-values from Stratified Cochran-Mantel-Haenszel Test.

B.2.6.2 Cohort B induction study

Primary Endpoint

The cohort B induction study met its primary endpoint. A statistically significantly higher proportion of subjects achieved EBS remission at week 10 in the filgotinib 200mg group compared with the placebo group. At week 10, EBS remission was achieved by 11.5% [CI=7.4% to 15.5] of patients in the filgotinib 200mg and 4.2% [CI=0.6% to 7.9%] of patients in the placebo group (p=0.0103). A numerically higher proportion of subjects achieved EBS remission at week 10 in the filgotinib 100mg (9.5% [CI=5.9% to 13.0%]) compared with the placebo group (4.2% [CI=0.6% to 7.9%]) (p=0.0645).

Key secondary endpoints

Similarly, in the cohort B induction study, filgotinib 200mg also demonstrated statistically significantly better efficacy over placebo for a number of key secondary efficacy endpoints including MCS response, MCS remission, and mucosal healing and endoscopic sub score of zero.

At week 10, MCS response was achieved by 53.1% [CI=46.8% to 59.3%] of patients receiving filgotinib 200mg, compared with 17.6% [CI=11.0% to 24.2%] in the placebo group (p<0.0001). At week 10, MCS remission was achieved by 9.5% [CI=5.8% to 13.3%] of patients receiving 200mg, compared with 4.2% [CI=0.6% to 7.9%] in the placebo group (p=0.5308).

At week 10, 17.2% [CI=12.4% to 21.9%] of patients receiving filgotinib 200mg achieved mucosal healing compared with 7.7% [CI=3.0% to 12.5%] in the placebo group (p=0.0053). Similarly, at week 10, 3.4% [CI=1.0% to 5.8%] of patients receiving filgotinib 200mg achieved an endoscopic sub score of 0 compared with 2.1% [CI=0.0% to 4.8%] in the placebo group (p=0.4269).

A summary of key efficacy endpoints is presented in Table 17.

Table 17. Summary of efficacy outcomes for cohort B induction study (Non-responders' imputation; Full Analysis Set)

Endpoint	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)
EBS remission n (%) [95%CI]	30 (11.5%) [7.4% to 15.5%]	27 (9.5%) [5.9% to 13.0%]	6 (4.2%) [0.6% to 7.9%]
p-value	0.0103	0.0645	NA
MCS response n (%) [95%CI]	139 (53.1%) [46.8% to 59.3%]	102 (35.8%) [30.0% to 41.5%]	25 (17.6%) [11.0% to 24.2%]
p-value	<0.0001	0.0001	NA
MCS remission n (%) [95%CI]	25 (9.5%) [5.8% to 13.3%]	17 (6.0%) [3.0% to 8.9%]	6 (4.2%) [0.6% to 7.9%]
p-value	0.0393	0.5308	NA
Mucosal healing n (%) [95%CI]	45 (17.2%) [12.4% to 21.9%]	37 (13.0%) [8.9% to 17.1%]	11 (7.7%) [3.0% to 12.5%]
p-value	0.0053	0.1138	NA

Endpoint	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)
Endoscopic sub score 0 n (%) [95%CI]	9 (3.4%) [1.0% to 5.8%]	6 (2.1%) [0.3% to 3.9%]	3 (2.1%) [0.0% to 4.8%]
p-value	0.4269	0.9987	NA
Geboes Histologic remission n (%) [95%CI]	52 (19.8%) [14.8% to 24.9%]	39 (13.7%) [9.5% to 17.8%]	12 (8.5%)
p-value	0.0019	0.1286	NA
MCS remission (alternative definition) n (%) [95%CI]	10 (3.8%) [1.3% to 6.3%]	6 (2.1%) [0.3% to 3.9%]	3 (2.1%) [0.0% to 4.8%]
p-value	0.3084	0.9109	NA

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; MCS, Mayo Clinic Score; n, number; NA, not applicable.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107).
Notes: *p-values from Stratified Cochran-Mantel-Haenszel Test.

Patient-reported outcomes

Patients in the cohort B induction study also demonstrated a statistically significantly increase in the main patient reported outcome measures when taking filgotinib 200mg or filgotinib 100mg, compared to placebo. Clinically meaningful improvements from baseline in total IBDQ score, SF-36 PCS and SF-36 mental component summary scores were reached for patients taking filgotinib 200mg and patients taking filgotinib 100mg (110). A summary of patients' reported outcomes is presented in Table 18.

Detailed results of the EQ-5D index individual dimensions and of the WPAI questionnaire are presented in Appendix L.

Table 18. Summary of Health-related Quality of Life results for cohort B induction study, week 10

Endpoint	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)
IBDQ total score, mean (SD)			
Baseline	112 (32.1)	118 (30.9)	118 (33.1)
Change from baseline	46 (37.7)	29 (36.9)	13 (35.2)
p-value	<0.0001	<0.0001	NA
SF-36, mean (SD)			
Baseline physical component	40.55 (7.768)	41.85 (7.376)	40.10 (8.134)

Endpoint	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)
Change from baseline physical component	6.61 (7.278)	4.16 (6.622)	2.44 (8.062)
p-value	<0.0001	0.0011	NA
Baseline mental component	37.93 (10.895)	40.55 (9.943)	39.94 (10.341)
Change from baseline mental component	7.92 (10.409)	3.85 (9.512)	1.66 (9.540)
p-value	<0.0001	0.0113	NA
EQ-5D VAS, mean (SD)			
Baseline	48 (20.5)	51 (19.8)	49 (18.9)
Change from baseline	19 (22.2)	10 (21.2)	6 (20.2)
p-value	<0.0001	0.0051	NA

Abbreviations: EQ-5D, European quality of life 5 dimensions; IBDQ, inflammatory bowel disease questionnaire; NA, not applicable; SD, standard deviation; SF-36, 36 item short form survey.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107).
Notes: *p-values from Stratified Cochran-Mantel-Haenszel Test.

Healthcare resource use (cohort A and cohort B)

During the induction phase, for cohort A and cohort B combined, the hospitalisation rate was [redacted] and [redacted] for the placebo and filgotinib 200mg groups, respectively. Additionally, [redacted] of filgotinib 200mg patients had outpatient surgeries or procedures, while in the placebo arm, the percentage of patients undergoing outpatient surgeries was [redacted]

B.2.6.3 Maintenance study

Primary Endpoint

The maintenance study also met its primary endpoint. A statistically significantly higher proportion of subjects achieved EBS remission at week 58 in the filgotinib 200mg group compared with the placebo group. At week 58, 37.2% [CI=30.2% to 44.2%] of patients in the filgotinib 200mg and 11.2% [CI=4.5% to 18.0%] of patients in the placebo group achieved EBS remission (P<0.0001). A statistically significantly higher proportion of subjects achieved EBS remission at week 58 in the filgotinib

100mg (23.8% [CI=17.2% to 30.5%]) compared with the placebo group (13.5% [CI=5.8% to 21.1%]) (p=0.0420).

Key secondary endpoints

Similarly, in the maintenance study, filgotinib 200mg also demonstrated statistically significantly better efficacy over placebo for a number of key secondary efficacy endpoints including sustained EBS response, MCS response, MCS remission, and mucosal healing, endoscopic sub score of zero, and 6-month corticosteroid-free remission.

At week 58, sustained EBS remission was achieved by 18.1% [CI=12.5% to 23.7%] of patients receiving filgotinib 200mg, compared to 5.1% [CI=0.2% to 10.0%] in the placebo group (p=0.0024).

At week 58, 66.8% [CI=60.0% to 73.6%] of patients receiving filgotinib 200mg achieved MCS response, compared with 32.7% [CI=22.9% to 42.4%] in the placebo group (p<0.0001). Similarly, at week 58, 34.7% [CI=27.8% to 41.5%] of patients receiving 200mg achieved MCS remission, compared with 9.2% [CI=3.0% to 15.4%] in the placebo group (p<0.0001).

At week 58, 40.7% [CI=33.6% to 47.8%] of patients receiving filgotinib 200mg achieved mucosal healing compared with 15.3% [CI=7.7% to 22.9%] in the placebo group (p<0.0001). Similarly, at week 58, 15.6% [CI=10.3% to 20.9%] of patients receiving filgotinib 200mg achieved an endoscopic sub score of 0 compared with 6.1% [CI=0.9% to 11.4%] in the placebo group (p=0.0157).

Finally, 27.2% [17.5% to 36.8%] of patients receiving filgotinib 200mg achieved 6-month corticosteroid-free remission compared to 6.4% [0.0% to 14.4%] of patients receiving placebo (p=0.0005).

A summary of key efficacy endpoints is presented in Table 19.

Table 19. Summary of efficacy outcomes for maintenance study, week 58 (Non-responders' imputation; Full Analysis Set)

Endpoint	Induction filgotinib 200mg	Induction filgotinib 100mg

	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib (n=172)	Maintenance placebo (n=89)
EBS remission n (%) [95%CI]	74 (37.2%) [30.2% to 44.2%]	11 (11.2%) [4.5% to 18.0%]	41 (23.8%) [17.2% to 30.5%]	12 (13.5%) [5.8% to 21.1%]
p-value	<0.0001	NA	0.0420	NA
Sustained EBS remission n (%) [95%CI]	36 (18.1%) [12.5% to 23.7%]	5 (5.1%) [0.2% to 10.0%]	15 (8.7%) [4.2% to 13.2%]	7 (7.9%) [1.7% to 14.0%]
p-value	0.0024	NA	0.7951	NA
MCS response n (%) [95%CI]	133 (66.8%) [60.0% to 73.6%]	32 (32.7%) [22.9% to 42.4%]	87 (50.6%) [42.8% to 58.3%]	35 (39.3%) [28.6% to 50.0%]
p-value	<0.0001	NA	0.0703	NA
MCS remission n (%) [95%CI]	69 (34.7%) [27.8% to 41.5%]	9 (9.2%) [3.0% to 15.4%]	39 (22.7%) [16.1% to 29.2%]	12 (13.5%) [5.8% to 21.1%]
p-value	<0.0001	NA	0.0658	NA
Mucosal healing n (%) [95%CI]	81 (40.7%) [33.6% to 47.8%]	15 (15.3%) [7.7% to] 22.9%	46 (26.7%) [19.8% to 33.6%]	17 (19.1%) [10.4% to 27.8%]
p-value	<0.0001	NA	0.1625	NA
Endoscopic sub score 0 n (%) [95%CI]	31 (15.6%) [10.3% to 20.9%]	6 (6.1%) [0.9% to 11.4%]	23 (13.4%) [8.0% to 18.7%]	7 (7.9%) [1.7% to 14.0%]
p-value	0.0157	NA	0.1808	NA
Geboes Histologic remission n (%) [95%CI]	76 (38.2%) [31.2% to 45.2%]	13 (13.3%) [6.0% to 20.5%]	48 (27.9%) [20.9% to 34.9%]	16 (18.0%) [9.4% to 26.5%]
p-value	<0.0001	NA	0.0521	NA
MCS remission (alternative definition) n (%) [95%CI]	44 (22.1%) [16.1% to 28.1%]	6 (6.1%) [0.9% to 11.4%]	21 (12.2%) [7.0% to 17.4%]	7 (7.9%) [1.7% to 14.0%]
p-value	0.0005	NA	0.2946	NA
6-months corticosteroid-free remission n (%) [95%CI]**	25 (27.2%) [17.5% to 36.8%]	3 (6.4%) [0.0% to 14.4%]	11 (13.6%) [5.5% to 21.7%]	2 (5.4%) 0.0% to 14.0%
p-value	0.0055	NA	0.1265	NA

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; MCS, Mayo Clinic Score; NA, not applicable.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107).

Notes: *p-values from Stratified Cochran-Mantel-Haenszel Test.
**Denominator of percentage is the number of Full Analysis Set subjects who were on corticosteroid at maintenance baseline.

Patient-reported outcomes

Patients re-randomised to the maintenance study demonstrated a statistically significantly increase in the main patient-reported outcome measures when taking filgotinib 200mg.

Detailed results of the EQ-5D index individual dimensions and of the WPAI questionnaire are presented in Appendix L. A summary of patients' reported outcomes is presented in Table 20.

Table 20. Summary of Health-related Quality of Life endpoints for maintenance study, week 47

Endpoint	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 200mg (n=172)	Maintenance placebo (n=89)
IBDQ total score, mean (SD)				
Baseline	178 (28.4)	182 (25.6)	176 (30.8)	176 (27.0)
Change from baseline	9 (27.3)	-5 (26.5)	8 (26.0)	5 (21.5)
p-value	<0.0001	NA	0.0834	NA
SF-36, mean (SD)				
Baseline physical component	49.99 (7.393)	49.51 (6.652)	49.30 (7.596)	48.57 (6.658)
Change from baseline physical component	2.45 (5.745)	1.90 (5.506)	1.45 (6.536)	1.68 (5.437)
p-value	0.0027	NA	0.3037	NA
Baseline mental component	48.67 (9.451)	49.52 (8.124)	48.54 (9.219)	47.88 (8.621)
Change from baseline mental component	1.45 (8.980)	-0.99 (8.572)	1.44 (6.973)	1.86 (7.769)
p-value	0.0057	NA	0.9623	NA
EQ-5D VAS, mean (SD)				
Baseline mean	73 (17.8)	75 (13.2)	74 (15.1)	73 (15.3)

Endpoint	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 200mg (n=172)	Maintenance placebo (n=89)
Change from baseline	5 (17.0)	1 (12.5)	2 (15.9)	4 (14.6)
p-value	0.0030	NA	0.4235	NA

Abbreviations: EQ-5D, European quality of life 5 dimensions; IBDQ, inflammatory bowel disease questionnaire; NA, not applicable; SD, standard deviation; SF-36, 36 item short form survey.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107).
Notes: *p-values from Stratified Cochran-Mantel-Haenszel Test.

Healthcare resource use

During the maintenance study, [redacted]. Moreover, [redacted] of patients in the maintenance study had outpatient surgeries or procedures in the filgotinib 200mg group, with [redacted] in the placebo group.

B.2.7 Subgroup analysis

As described in Table 8, the SELECTION clinical programme protocol included four types of pre-planned subgroup analyses, based on: stratification factors, history of prior biologic use, demographic factors and disease baseline characteristics.

Detailed results for all subgroup analyses are presented in Appendix E. This section summarises subgroup data according to previous exposure to TNFα inhibitors.

In the cohort A induction study, subgroup analyses were based on stratification factors, but not on history of biologic agent use, therefore subgroup analysis according to prior TNFα inhibitor exposure is only presented below for the cohort B induction study and maintenance study, according to the following outcomes:

- EBS remission
- MCS response
- MCS remission
- Mucosal healing
- Six-month corticosteroid-free EBS remission (maintenance study only).

B.2.7.1 Cohort B induction study

In the cohort B induction study, 92.6% of patients had previously received treatment with a TNFα inhibitor.

EBS remission

In the cohort B induction study, at week 10, rates of EBS remission were higher in patients without prior exposure to TNFα inhibitors who had been treated with filgotinib 200mg and filgotinib 100mg. In the placebo group, patients without prior exposure to TNFα inhibitors did not achieve EBS remission, compared to [redacted] of patients with prior TNFα inhibitor exposure.

MCS response

At week 10, across all treatment arms, patients without prior exposure to TNFα inhibitors achieved higher rates of MCS response in the cohort B induction study. Both the filgotinib 200mg [redacted] and filgotinib 100mg [redacted] were found to be statistically significantly better than placebo [redacted] in achieving MCS response in patients who had prior TNFα inhibitor exposure.

MCS remission

Consistent with MCS response, at week 10, patients without prior exposure to TNFα inhibitors achieved higher rates of MCS remission across all treatment arms.

Mucosal healing

In the cohort B induction study, at week 10, rates of mucosal were higher in patients without prior exposure to TNFα inhibitors who had been treated with filgotinib 200mg and filgotinib 100mg. In the placebo group, [redacted] of patients without prior exposure to TNFα inhibitors achieved mucosal healing, compared to [redacted] of patients with prior TNFα inhibitor exposure.

Detailed results of the subgroup analyses by previous exposure to TNFα inhibitors are presented in Table 21.

Table 21. Cohort B induction study by previous exposure to TNFα inhibitors (non-responder imputation) at week 10

Endpoint	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)
Previous exposure to TNFα inhibitors (yes)	[redacted]	[redacted]	[redacted]
EBS remission n (%) [95%CI]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
MCS response n (%) [95%CI]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
Mucosal healing n (%) [95%CI]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
MCS remission n (%) [95%CI]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
Previous exposure to TNFα inhibitors (no)	[redacted]	[redacted]	[redacted]
EBS remission n (%) [95%CI]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
MCS response n (%) [95%CI]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
Mucosal healing n (%) [95%CI]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
MCS remission n (%) [95%CI]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable; mg, milligram; MCS, Mayo clinic score; TNFα, tumour necrosis factor-alpha.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107) and Gilead SELECTION HTA UK subgroup analysis, 2021 (data on file) (111).

B.2.7.2 Maintenance study

In the maintenance study, 37.3% of all patients had previously received treatment with a TNFα inhibitor.

EBS remission

At week 58, across all treatment arms, patients without prior exposure to TNFα inhibitors achieved higher rates of EBS remission in the maintenance study when compared to those with prior exposure to TNFα inhibitors. In patients with and without prior exposure to TNFα inhibitors, filgotinib 200mg was found to be statistically significantly better than placebo in achieving EBS remission.

MCS response

At week 58, across all treatment arms, patients without prior exposure to TNFα inhibitors achieved higher rates of MCS response in the maintenance study. Filgotinib 200mg [redacted] was found to be statistically significantly better than placebo [redacted] in achieving MCS response in patients who had prior TNFα inhibitor exposure.

MCS remission

Consistent with MCS response, at week 58, patients without prior exposure to TNFα inhibitors achieved higher rates of MCS remission across all treatment arms, when compared to those with prior exposure to TNFα inhibitors. In patients with and without prior exposure to TNFα inhibitors, filgotinib 200mg was found to be statistically significantly better than placebo in achieving MCS remission.

Mucosal healing

In the maintenance study, at week 58, across all treatment arms, patients without prior exposure to TNFα inhibitors achieved higher rates of mucosal healing, when compared to those with prior exposure to TNFα inhibitors. Filgotinib 200mg [redacted] was found to be statistically significantly better than placebo [redacted] in achieving mucosal healing at week 58, in patients who did not have prior exposure to TNFα inhibitors.

Results of the subgroup analyses by previous exposure to TNFα inhibitors are presented in Table 22.

Table 22. Maintenance study by previous exposure to TNFα inhibitors (non-responder imputation) at week 58

Subgroup	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 100mg (n=172)	Maintenance placebo (n=89)
Previous exposure to TNFα inhibitors (yes)	[redacted]	[redacted]	[redacted]	[redacted]
EBS remission n (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
MCS response n (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
Six-month corticosteroid-free EBS remission (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
Mucosal healing n (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
MCS remission n (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
Previous exposure to TNFα inhibitors (no)	[redacted]	[redacted]	[redacted]	[redacted]
EBS remission n (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
MCS response n (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
Six-month corticosteroid-free EBS remission (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
Mucosal healing n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 100mg (n=172)	Maintenance placebo (n=89)
[95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
MCS remission n (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable; mg, milligram; MCS, Mayo clinic score; TNFα, tumour necrosis factor-alpha.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107) and Gilead SELECTION HTA UK subgroup analysis, 2021 (data on file) (111).

B.2.8 Meta-analysis

One trial for filgotinib versus placebo has been completed, and no estimates for filgotinib versus other comparators are available. Therefore, in order to compare the efficacy of filgotinib to the comparators specified in the NICE scope, a network meta-analysis (NMA) was conducted. Performing a comprehensive NMA allows for the inclusion of all relevant evidence, and therefore a more precise estimation of relative treatment effects in the absence of head-to-head data. 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

An NMA was performed to inform the economic model for the assessment of the cost-effectiveness of filgotinib relative to the other treatments in UC. Studies for this were identified from an SLR using criteria in line with previous NICE appraisals in UC (TA342 (65), TA547 (66),TA329 (28) and TA633 (67)), 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 and the structure of SELECTION clinical programme, separate NMAs were conducted in biologic-naïve (cohort A) and biologic-experienced (cohort B), with MCS response and remission the primary outcomes considered.

B.2.9.1 Search strategy

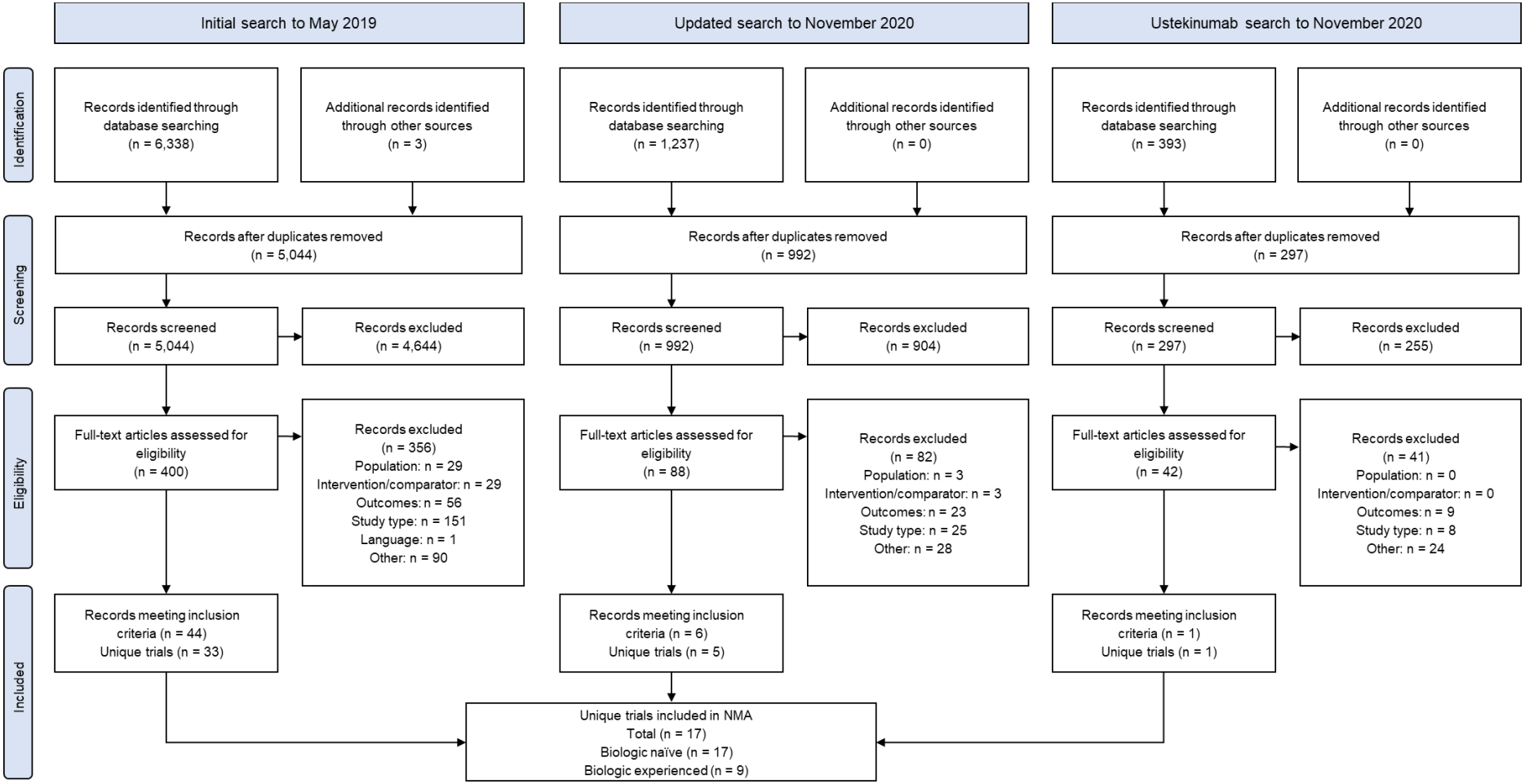
One SLR was conducted, for both biologic-naïve (cohort A) and biologic-experienced (cohort B) populations, across the following databases: MEDLINE, Embase, the Cochrane library, CDSR, the University of York CRD and the HTA database (please see Appendix D). The objectives of the SLR were to identify relevant clinical data from the published literature regarding the clinical effectiveness of filgotinib and other treatments for UC based on the clinical outcomes outlined by the NICE scope. The original review was conducted in May of 2019, with a subsequent update in November 2020.

Studies identified in the SLR were independently assessed by two reviewers 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 were designed to align with the following NICE appraisals: TA342 (65), TA547 (66) and TA329 (28), and are detailed in Appendix D.

B.2.9.2 Trials included in the SLR

Overall, a total of 51 records (39 unique studies) were eligible for inclusion across the original review and subsequent update (conducted on the 2nd November 2020). A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (Figure 7) shows the overall flow of studies across the original review and update.

Figure 7. PRISMA flow diagram for the clinical SLR



Abbreviations: n, number; NMA, network meta-analysis; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

B.2.9.3 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 the SLR were excluded in the two NMAs. The RCTs for inclusion in the NMA were restricted to phase II/III or phase III randomised controlled trials investigating currently European Medicines Agency (EMA) approved treatments for UC at the licenced dose, which reported either clinical response, clinical remission or mucosal healing for induction (6-16 weeks) or maintenance (48-56 weeks) phase. The list of studies excluded from each NMA along with associated reasons are available in Appendix D.

From the 51 records identified in the SLR (with 34 records excluded), 17 unique trials were included in the two NMAs overall:

- **Biologic-naïve** (cohort A): A total of 17 unique trials were included
- **Biologic-experienced** (cohort B): A total of 9 unique trials were included.

The outcomes included in the indirect comparison, MCS remission and response (primary endpoint) and mucosal healing (secondary endpoint), are presented in detail in Section B.2.9.5. A summary of the studies included in the evidence networks for each outcome is presented in Table 23 and Table 24 for the biologic-naïve population and the biologic-experienced population, respectively.

Table 23. Summary of studies included for each NMA outcome – biologic-naïve

Trials	Comparator	Induction				Maintenance				
		Time	Clinical remission	Clinical response	Mucosal healing	Length	Time	Clinical remission	Clinical response	Mucosal healing
ULTRA 1 (74)	ADA vs placebo	8	✓	✓	✓	NA	NA	×	×	×
ULTRA 2 (66, 112)		8	✓	✓	✓	44	52	✓	✓	✓
SELECTION	FIL vs placebo	10	✓	✓	✓	48	58	✓	✓	✓
PURSUIT-SC Induction (76)	GOL vs placebo	6	✓	✓	✓	NA	NA	×	×	×
PURSUIT-SC Maintenance (113)		6	×	×	×	54	60	✓	✓	×
ACT 1 (75)	IFX vs placebo	8	✓	✓	✓	54	54	✓	✓	✓
ACT 2 (75)		8	✓	✓	✓	NA	NA	×	×	×
Kobayashi 2016 (Japic) (114)		8	✓	✓	✓	NA	NA	×	×	×
Jiang 2015 (115)		8	✓	✓	✓	NA	NA	×	×	×
NCT01551290 (116)		8	✓	✓	✓	NA	NA	×	×	×
OCTAVE 1 (117)	TOF vs placebo	8	✓	×	✓	NA	NA	×	×	×
OCTAVE 2 (117)		8	✓	×	✓	NA	NA	×	×	×
OCTAVE SUSTAIN (118)		8	×	×	×	52	60	✓	✓	×
UNIFI (119)	UST vs. placebo	8	✓	✓	✓	44	52	✓	✓	✓
GEMINI 1 (120)	VDZ vs placebo	6	✓	✓	✓	46	52	✓	✓	✓
VISIBLE (121)		6	×	×	×	46	52	✓	×	×
VARSITY (122)*	VDZ vs ADA	14	✓	✓	×	52	52	✓	×	✓

Abbreviations: ADA, adalimumab; FIL, filgotinib; GOL, golimumab; IFX, infliximab; TOF, tofacitinib; UST, ustekinumab; VDZ, vedolizumab; NMA, network meta-analysis.
Notes: *The VARSITY study identified in the SLR was excluded from the maintenance phase remission/response analysis, as it lacked data for maintenance period responders by population (123). However, recently published data (122) were identified for this trial which allowed for estimation of the number of maintenance period responders based on published percentages of induction responders.

Table 24. Summary of studies included for each NMA outcome – biologic-experienced

Trials	Comparator	Induction				Maintenance				
		Time	Clinical remission	Clinical response	Mucosal healing	Length	Time	Clinical remission	Clinical response	Mucosal healing
ULTRA 2 (66, 112)	ADA vs placebo	8	✓	✓	✓	44	52	✓	✓	✓
SELECTION	FIL vs placebo	10	✓	✓	✓	48	58	✓	✓	✓
OCTAVE 1 (117)	TOF vs placebo	8	✓	×	×	NA	NA	×	×	×
OCTAVE 2 (117)		8	✓	×	×	NA	NA	×	×	×
OCTAVE SUSTAIN (118)		NA	×	×	×	52	60	✓	✓	×
UNIFI (119)	UST vs placebo	8	✓	✓	✓	44	52	✓	✓	✓
GEMINI 1 (120)	VDZ vs placebo	6	✓	✓	✓	46	52	✓	✓	✓
VISIBLE (121)		6	×	×	×	46	52	✓	×	×
VARSITY (122)*	VDZ vs ADA	14	✓	✓	×	52	52	✓	×	✓

Abbreviations: ADA, adalimumab; FIL, filgotinib; TOF, tofacitinib; UST, ustekinumab; VDZ, vedolizumab NMA, network meta-analysis.
Notes: *The VARSITY study identified in the SLR was excluded from the maintenance phase remission/response analysis, as it lacked data for maintenance period responders by population (123). However, recently published data (122) were identified for this trial which allowed for estimation of the number of maintenance period responders based on published percentages of induction responders.

B.2.9.4 Evidence networks

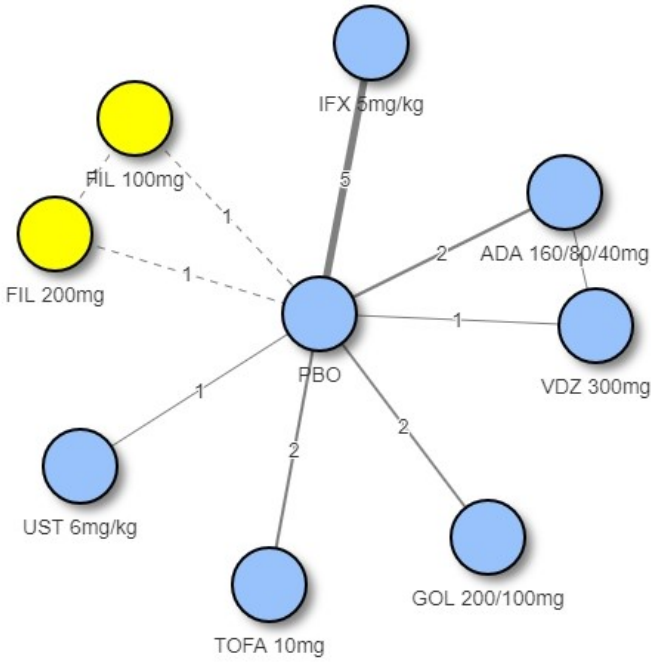
Evidence networks for the MCS response/remission outcome for the biologic-naïve and biologic-experienced populations are presented in the section below. The evidence networks for mucosal healing are provided in Appendix D.

Biologic-naïve

The evidence networks for MCS response and remission in biologic-naïve population are presented in Figure 8 and Figure 9 for the induction and maintenance phases, respectively.

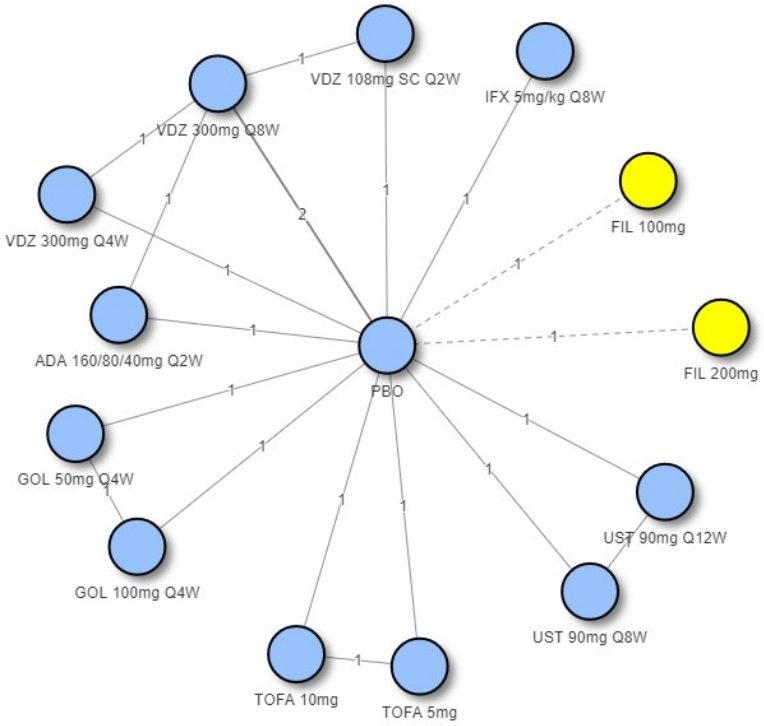
The analysis network for MCS response/remission in the biologic-naïve population after induction treatment included nine treatment groups across 13 studies.

Figure 8. MCS response/remission at induction in biologic-naïve patients – network of evidence



The analysis network for MCS response/remission in the biologic-naïve population during the maintenance phase included 14 treatment groups across nine studies.

Figure 9. MCS response/remission at maintenance in biologic-naïve patients – network of evidence

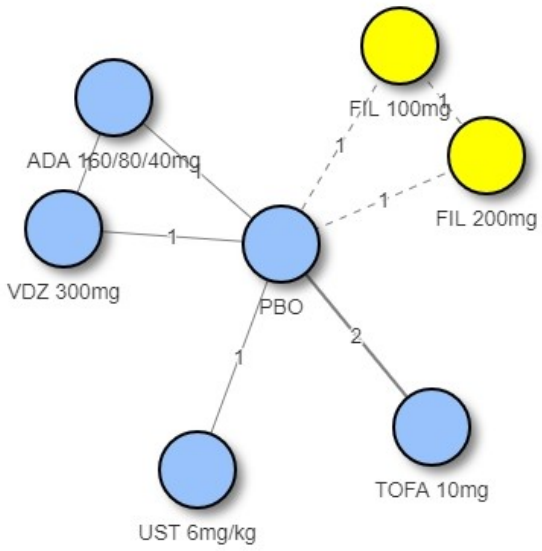


Biologic-experienced

The evidence networks for MCS response and remission in biologic-experienced population are presented in Figure 10 and Figure 11 for the induction and maintenance phases, respectively.

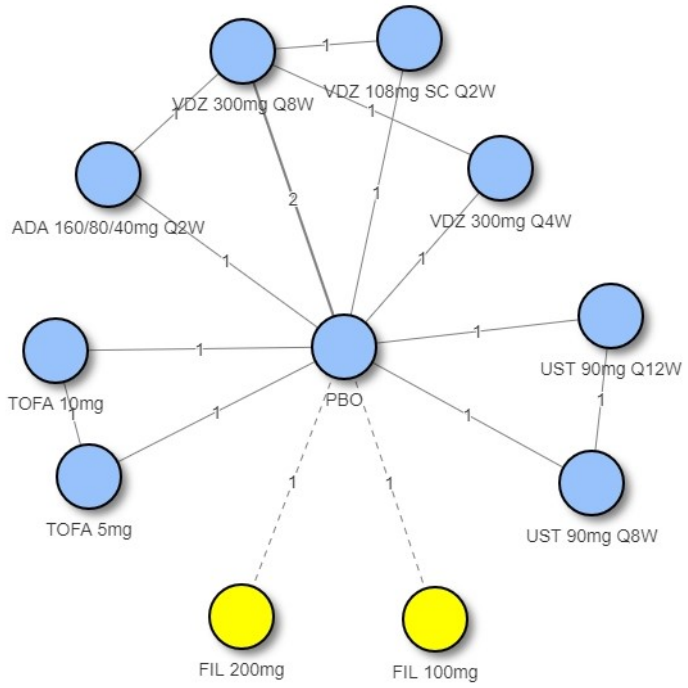
The analysis network for MCS response/remission in the biologic-experienced population after induction treatment included seven treatment groups across seven studies.

Figure 10. MCS response/remission at induction in biologic-experienced patients – network of evidence



The analysis network for MCS response/remission in the biologic-experienced population during maintenance phase included 11 treatment groups across six studies.

Figure 11. MCS response/remission at maintenance in biologic-experienced patients – network of evidence



B.2.9.5 Methods and outcomes of the included studies

Rationale for choice of outcome measure and scale

The outcomes included in the indirect comparison, MCS remission and response (primary endpoint) and mucosal healing (secondary endpoint), are among those which are most commonly reported in clinical trials in UC, including the SELECTION clinical programme of induction and maintenance trials, 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 UC (28, 65, 66), including TA329 (28).

MCS (primary indirect comparison outcome) is a key secondary outcome of the SELECTION clinical programme of induction and maintenance trials. MCS is frequently used to classify UC and has been previously used to derive main efficacy endpoints to inform economic analysis in previous HTA submissions in this area (28, 65, 66), including TA329 (28). Therefore, the following endpoints were considered as the primary endpoints for this analysis:

- **Remission**: defined as MCS of ≤ 2 points and no individual sub score > 1 point
- **Response**: defined as a decrease from baseline in the MCS ≥ 30% and ≥ 3 points, accompanied by a rectal bleeding sub score of 0 or 1 or a decrease from baseline in the rectal bleeding sub score ≥ 1.

Mucosal healing (secondary indirect comparison outcome) is also a key secondary outcome of the SELECTION clinical trial programme. Mucosal healing was considered as a secondary endpoint to provide a comprehensive analysis on the comparative effectiveness. Mucosal healing was defined as endoscopic sub score of 0–1, from the MCS.

B.2.9.6 Population included

The population included in the indirect comparison were those set out in the NICE scope, adults with moderately to severely active ulcerative colitis who have had an inadequate response, loss of response or were intolerant to conventional therapy (oral corticosteroids and/or immunomodulators), or a biologic agent (TNFα inhibitor or vedolizumab). In addition, in line with the NICE scope and given that the evidence of the SELECTION clinical programme allowed for these subgroups' analysis, the following two populations were included in the indirect comparison:

- **Biologic-naïve**: patients without prior use of any biologic (TNFα inhibitor or vedolizumab), which aligns to the SELECTION cohort A
- **Biologic-experienced**: patients who have previously demonstrated an inadequate clinical response, loss of response to, or intolerance to any biologic (TNFα inhibitor or vedolizumab), which aligns to the SELECTION cohort B.

As the biologic-naïve and biologic-experienced populations are considered to be clinically distinct groups of patients, they were analysed in separate networks.

B.2.9.7 Assessment of heterogeneity in trials included in the NMAs

A feasibility assessment was conducted to identify heterogeneity in patient characteristics, interventions and comparators, outcomes, and study designs of the

included studies. Detailed information on the feasibility assessment performed, and the conclusions, is provided in Appendix D.

Among the two populations, five major areas of heterogeneity were observed across the included trials: study designs across the maintenance period of trials, the time points for measuring trial outcomes, differences in inclusion criteria regarding the definition of biologic failure/exposure patients, different definitions of MCS response and remission, and variation in placebo response. Key sources of heterogeneity, and assumptions applied in the analysis are summarised below.

Trial design

The induction phases of the studies included in the NMA were consistent and were based on a treat-through design (i.e. patients continued to receive the treatment they were randomised to during the induction phase).

However, the studies included in the maintenance phase NMA were diverse in terms of the study design. Broadly, two study design types were included in the analysis: 're-randomised' design based on response (patients achieving a response during the induction phase are re-randomised for the maintenance phase), or 'treat-through' designs (patients continue receiving treatment according to the initial randomisation during the maintenance phase, irrespective of whether a response was achieved). In more recent trials (including SELECTION), the re-randomised design has been considered more ethical and clinically appropriate. As such, there is substantial heterogeneity in trial designs, and assuming equivalent design for the analysis would not be appropriate, as the populations entering the maintenance phases are different. E.g. the placebo arms are not comparable because some patients in the maintenance phase of re-randomised trials received active treatment during the induction phase.

In order to compare treatments across different trial types, an approach consistent with TA547 (66), TA633 (67) and Lohan et al. (2019) (124) was taken. This approach re-weights the results from the treat-through trials to mimic a re-randomised trial before the NMA. In particular, there are three treat-through trials included in the maintenance NMA: ACT 1, ULTRA 2, and VARSITY. The other six studies followed a

re-randomised design: SELECTION, PURSUIT-SC maintenance, GEMINI 1, UNIFI, OCTAVE SUSTAIN and VISIBLE.

Re-randomised trials were included in the NMA without imputation. The key assumptions applied for the treat-through trials imputations are the following:

- The number of responders at the end of the induction phase is used as a proxy for the total number of patients entering the maintenance phase.
- The number of patients achieving clinical response is the number of sustained responders (i.e. patients with response at both end of the induction and maintenance phases). This estimate is used to mitigate the risk of counting maintenance phase responders who were non-responders at the end of the induction phase, as all participants enrolled in re-randomised trials achieved at least a clinical response during the induction phase.
- Similarly, the number of patients achieving clinical remission is the number of patients who achieve clinical response at induction and at the end of the maintenance phase, applying the assumption that all maintenance remission patients were at least responders at induction.
- For ACT 1, the estimated reweighted placebo remission patients exceeded sustained response patients. This is not feasible in re-randomised trials. In this case, a proxy value was applied to the placebo arm based on the number of responders, calculated by applying the weighted average ratio of sustained clinical responders to clinical responders of all placebo arms reporting both outcomes

The imputed inputs for the maintenance phase NMA are available in Appendix D.

Sensitivity analyses were conducted with treat-through trials (ACT 1, ULTRA 2 and VARSITY) excluded (see Section B.2.9.12 Sensitivity analyses).

Assessment timepoints

The induction period in SELECTION was 10 weeks, and the maintenance period was 48 weeks from re-randomisation. The time point at which the outcomes are measured varied between the clinical trials, with induction periods ranging from 6–14

weeks and maintenance periods ranging from 44–54 weeks. For the maintenance phase NMA, these differences in trial length are unlikely to lead to biased estimates as response rates are not likely to vary considerably at the end of maintenance. For the induction period, it was considered clinically reasonable to assume that the induction phase outcomes were comparable, despite differences in the length of the induction phases. The timepoints in the approved posology reflect how treatments would be used in clinical practice for assessment of response/stopping treatment. To maximise the information included in each network, no restriction was imposed based on the exact week an outcome was observed. This is consistent with previous TAs (TA633 (67) and TA547 (66)).

Population definitions

The analysis populations included trials with differences in the definition of prior treatment with biologics:

- Biologic-experienced patients in SELECTION were those who had failed or were intolerant to prior biologics. Most trials used a similar definition, however, ULTRA 2 (adalimumab) and VARSITY (adalimumab vs vedolizumab) merely specified that patients be previously 'exposed' to biologics. OCTAVE 1 and 2 (tofacitinib) reported two different subgroup results: 'prior TNF exposure' and 'prior TNF failure'.
- Biologic-naïve patients in SELECTION were those who had never been exposed to a biologic therapy. Most trials took a similar approach, but UNIFI (ustekinumab) only specified that patients were 'non-failure' to biologics and OCTAVE 1 and 2 reported two subgroups (biologic-naïve and biologic non-failure).

Trials are not excluded based on population definitions in the base case. This approach is consistent with previous TAs (TA633 (67) and TA547 (66)). In a sensitivity analysis, ULTRA 2 and VARSITY were excluded from the biologic-experienced analysis, and UNIFI was excluded from the biologic-naïve analysis (see B.2.9.12 Sensitivity analyses).

Endpoint definitions

There are minor deviations from the definition of remission in the OCTAVE trial and other trials (full details are provided in Appendix D). However, this is unlikely to have a substantial impact on the number of patients who achieve remission. Additionally, the inclusion of this trial is consistent with previous TAs (TA633 (67) and TA547 (66)).

Placebo response

There are considerable differences in the placebo response between trials. For this analysis, it was assumed that placebo arms in re-randomised trials are similar, which could potentially introduce bias due to differences in carry-over effects between trials.

B.2.9.8 Risk of bias

A quality assessment of each trial in the biologic-naïve and biologic-experienced NMA was completed using the Cochrane Collaborations tool for assessing risk of bias (125) and is provided in Appendix D. A table summarising potential biases introduced in the analysis due to heterogeneity in study design and patient characteristics is also provided in Appendix D.

B.2.9.9 Methods of analysis

Methodology and primary endpoint

Based upon the clinical SLR and results from the SELECTION clinical programme, published outcomes from extracted studies were compared in two NMAs, allowing estimates of the comparative effectiveness of interventions which have not been compared directly in head-to-head studies, in accordance with published NICE Decision Support Unit (DSU) guidelines (126, 127). 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 SELECTION clinical programme.

The primary endpoints of response and remission are based on the MCS, a continuous score, with no response, response without remission and response with remission essentially ordered categories on a continuous scale. The analysis for these outcomes utilises a multinomial likelihood with a probit link (allowing for analysis of an ordered categorical variable and accounting for the correlation between response and remission outcomes). This approach was preferred by the ERG in TA547 (66). The secondary endpoint of mucosal healing is a single binary endpoint, and as such was analysed with a binomial likelihood with a logit link. In both cases, the credible interval for the treatment effects can be interpreted such that crossing 0 indicates that differences in treatment effects are not significant.

Data manipulation was undertaken in R Version 4.0.2, and WinBUGS version 1.4.3 was utilised for all NMAs. 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 baseline and nuisance parameters, as well as the between trial variance in the first instance, in line with NICE DSU guidelines (126). 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.

B.2.9.10 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, and models were compared using the deviance information criterion (DIC), in keeping with NICE DSU guidelines (126). The goodness of fit diagnostics for the random and fixed effects models for the base-case network in biologic-naïve and biologic-experienced populations is detailed in Appendix D.

As the analysis networks included limited data, fixed effect models were preferred for the analysis base case in the case of similar DIC for the two models. As detailed in the NICE DSU guidelines (126), there are difficulties associated with estimating heterogeneity in sparse networks, and for this analysis, the number of trials in the networks were considered too few to estimate the between-study standard deviation from the data alone. Results for both random and fixed effects models and details of model choice are presented in Appendix D.

B.2.9.11 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 are presented.

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 the estimated probability of achieving the first level of response (e.g. MCS response) in the reference treatment group. The posterior median was considered for the point estimates of relative effects of treatments within analysed networks based on NICE DSU guidelines (126).

A summary of the results for the base case analyses for MCS response and remission is presented below. Results for mucosal healing, as well as detailed results for both random and fixed effects models, and forest plots for relative effects are presented in Appendix D.

MCS response/remission

The results of the NMA for MCS response and remission at induction are presented in Table 25.

For the biologic-naïve population, all treatments were [redacted]. Filgotinib 200mg [redacted].

For the biologic-exposed population, [redacted]. Filgotinib 200mg was [redacted]

Table 25. Induction phase base-case NMA results - relative effects of treatments on the probit scale and probabilities of achieving response and remission

Treatment	Results on the probit scale vs placebo, median (95% CrI)	Results on the probit scale vs filgotinib 200mg, median (95% CrI)	Results on the probit scale vs filgotinib 100mg, median (95% CrI)	Modelled probability of response – posterior median (95% CrI)	
				MCS response	MCS remission
Biologic-naïve population					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIL 200mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIL 100mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80/40mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	Results on the probit scale vs placebo, median (95% CrI)	Results on the probit scale vs filgotinib 200mg, median (95% CrI)	Results on the probit scale vs filgotinib 100mg, median (95% CrI)	Modelled probability of response – posterior median (95% CrI)	
				MCS response	MCS remission
GOL 200/100mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX 5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF 10mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST 6mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ 300mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic-experienced population					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIL 200mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIL 100mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80/40mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF 10mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST 6mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	Results on the probit scale vs placebo, median (95% CrI)	Results on the probit scale vs filgotinib 200mg, median (95% CrI)	Results on the probit scale vs filgotinib 100mg, median (95% CrI)	Modelled probability of response – posterior median (95% CrI)	
				MCS response	MCS remission
VDZ 300mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CrI, credible interval; FIL, filgotinib; GOL, golimumab; IFX, infliximab; kg, kilogram; MCS, Mayo clinic score; mg, milligram; TOF, tofacitinib; UST, ustekinumab; VDZ, vedolizumab.
Notes: Positive values favour the first treatment. Negative values favour the second treatment.

The results of the NMA for MCS response and remission at maintenance are presented in Table 26.

For the biologic-naïve population, all treatments were [redacted]. Filgotinib 200mg [redacted] Filgotinib 200mg [redacted]

For the biologic-exposed population, [redacted]. Filgotinib 200mg was [redacted]

Table 26. Maintenance phase base-case NMA results - relative effects of treatments on the probit scale and probabilities of achieving response and remission

Treatment	Results on the probit scale vs placebo, median (95% CrI)	Results on the probit scale vs filgotinib 200mg, median (95% CrI)	Results on the probit scale vs filgotinib 100mg, median (95% CrI)	Modelled probability of response – posterior median (95% CrI)	
				MCS response	MCS remission

Treatment	Results on the probit scale vs placebo, median (95% CrI)	Results on the probit scale vs filgotinib 200mg, median (95% CrI)	Results on the probit scale vs filgotinib 100mg, median (95% CrI)	Modelled probability of response – posterior median (95% CrI)	
				MCS response	MCS remission
Biologic-naïve population					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIL 200mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIL 100mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80/40mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 50mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 100mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX 5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF 5mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF 10mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST 90mg Q12W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST 90mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	Results on the probit scale vs placebo, median (95% CrI)	Results on the probit scale vs filgotinib 200mg, median (95% CrI)	Results on the probit scale vs filgotinib 100mg, median (95% CrI)	Modelled probability of response – posterior median (95% CrI)	
				MCS response	MCS remission
VDZ 108mg SC Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ 300mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ 300mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic-experienced population					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIL 200mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIL 100mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80/40mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF 5mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF 10mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST 90mg Q12W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST 90mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	Results on the probit scale vs placebo, median (95% CrI)	Results on the probit scale vs filgotinib 200mg, median (95% CrI)	Results on the probit scale vs filgotinib 100mg, median (95% CrI)	Modelled probability of response – posterior median (95% CrI)	
				MCS response	MCS remission
VDZ 108mg SC Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ 300mg Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ 300mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; CrI, credible interval; FIL, filgotinib; GOL, golimumab; IFX, infliximab; kg, kilogram; MCS, Mayo clinic score; mg, milligram; q2w, once every two weeks; q4w, once every four weeks; q8w, once every eight weeks; q12w, once every twelve weeks; SC, subcutaneous; TOF, tofacitinib; UST, ustekinumab; VDZ, vedolizumab.

Notes: Positive values favour the first treatment. Negative values favour the second treatment.

B.2.9.12 Sensitivity analyses

The results of the sensitivity analyses are summarised in Appendix D. The following analyses were conducted:

- **Population definition:** in the base case, UNIFI was included in the induction networks despite having a different definition of biologic-naïve to the other studies (only requiring prior biologic non-failure). Similarly, VARSITY and ULTRA 2 were included in the induction networks despite having different definitions of biologic failure to other studies (only requiring prior biologic exposure). These trials were excluded in a sensitivity analysis.

- **Trial design:** in the base case VARSITY, ACT 1 and ULTRA 2 were included in maintenance networks despite having a different trial design to the other trials (treat-through compared to re-randomised). These trials were excluded in a sensitivity analysis.

- **Re-weighting methodology:** an alternative re-weighting methodology described in a published analysis of cost-effectiveness of vedolizumab, published by Hernandez et al. (128), was used. This methodology uses the same approach as in the base case for active arms, but aims to address a potential bias that favours placebo arms in treat-through trials. Full details of the methodology and imputations are provided in Appendix D.

[redacted]

B.2.9.13 Safety NMA – serious infections

In addition to the NMA assessing efficacy outcomes, a NMA of safety outcomes was conducted in order to compare the safety of filgotinib to other treatments. The studies identified in the clinical SLR were assessed for inclusion, and all studies reporting safety outcomes for subjects who received at least one dose of study drug from the

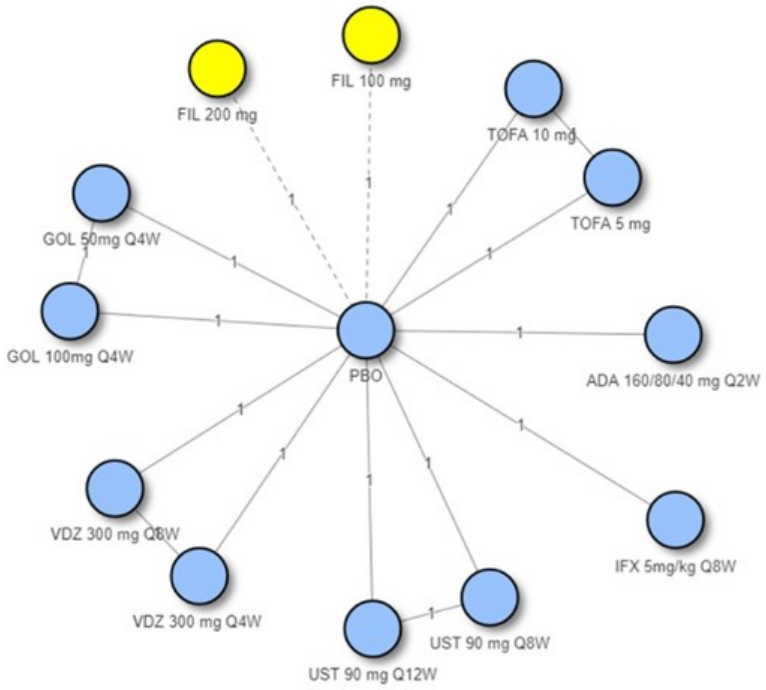
start of induction to the end of the maintenance follow-up were included. Studies reporting serious infections were of particular interest, as the probability of serious infections is included as an input in the cost-effectiveness analysis (see Section B.3.3.3). The studies included in the NMA of serious infections are summarised in Table 27, and the network of evidence is presented in Figure 12.

Table 27. Summary of studies included in the safety NMA

Trial	Comparator
ULTRA 2 (66, 112)	ADA vs placebo
SELECTION	FIL vs placebo
PURSUIT-SC Maintenance (113)	GOL vs placebo
ACT 1 (75)	IFX vs placebo
OCTAVE SUSTAIN (118)	TOF vs placebo
UNIFI (119)	UST vs. placebo
GEMINI 1 (120)	VDZ vs placebo
VARSITY (123)	VDZ vs ADA

Abbreviations: ADA, adalimumab; FIL, filgotinib; GOL, golimumab; IFX, infliximab; TOF, tofacitinib; UST, ustekinumab; VDZ, vedolizumab

Figure 12. Serious infections NMA – network of evidence



The timeframe over which study endpoints were assessed was identified as a source of heterogeneity. Treat-through trials reported safety outcomes from week 0 of induction phase through to the end of maintenance. These data were also available for the SELECTION trial. The re-randomised trials (GEMINI 1, VISIBLE 1, PURSUIT-M, OCTAVE Sustain and UNIFI) reported safety outcomes at maintenance, separately to those experienced in the induction phase. In studies reporting separate induction and maintenance phase safety outcomes, NMA inputs were imputed. Full details of the imputation are included in Appendix D.

This analysis considered both biologic-naïve and biologic-experienced populations combined in a single analysis, to maximise statistical power in light of rarity of analysed safety events. The probability of experiencing a serious infection is a single binary endpoint, and as such was analysed with a binomial likelihood with a logit link.

Consistent with the efficacy NMA, the fixed effects model was considered the most appropriate model given the limited data available for each network, and is therefore used in the base case analysis.

[redacted]. Filgotinib 200mg [redacted] Detailed results for both random and fixed effects models are presented in Appendix D.

B.2.10 Adverse reactions

Safety results from the SELECTION induction and maintenance studies are reported in the sections below. Additional details are provided in Appendix F.

B.2.10.1 Exposure data

The Safety Analysis Set for each of the induction or maintenance studies included all subjects who took at least one dose of study drug.

SELECTION trial induction study

In the induction study, cohort A, 659 out of 660 randomised subjects received at least one dose of filgotinib or placebo on day 1. In the induction study, cohort B, 689 out of 691 randomised subjects received at least one dose of filgotinib or placebo on day 1. The mean (SD) durations of study drug exposure are summarised in Table 28 for each treatment arm.

Table 28. Exposure data for inductions studies

	Filgotinib 200mg	Filgotinib 100mg	Placebo
SELECTION cohort A induction studies			
Duration of exposure, weeks, mean (SD)	[redacted]	[redacted]	[redacted]
Number of subjects	245	277	137
SELECTION cohort B induction study			
Duration of exposure, weeks, mean (SD)	[redacted]	[redacted]	[redacted]
Number of subjects	262	285	142

Abbreviations: SD, standard deviation.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107).

SELECTION trial maintenance study

In the maintenance study, 664 out of 664 re-randomised subjects received at least one dose of filgotinib or respective placebo at week 11. The mean (SD) durations of study drug exposure are presented in Table 29 for each treatment arm.

Table 29. Exposure data for maintenance study

	Filgotinib 200mg	Respective placebo	Filgotinib 100mg	Respective placebo
Duration of exposure, weeks, mean (SD)	39.4 (14.33)	28.8 (17.68)	34.5 (16.84)	29.2 (18.57)
Number of subjects	202	99	179	91

Abbreviations: SD, standard deviation.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107).

B.2.10.2 Common adverse events

The most common adverse events (4) affecting ≥5% of patients in the overall SELECTION study were nasopharyngitis, worsening ulcerative colitis, headache, anaemia, nausea, abdominal pain and upper respiratory tract infection, (Table 30 and Table 31). Slightly more AEs were observed in SELECTION induction cohort B compared to cohort A. In the SELECTION maintenance study, the frequencies of these events were generally similar across the filgotinib 200mg and filgotinib 100mg maintenance groups.

Full details of all treatment-emergent adverse events affecting ≥2% of patients in any group by system organ class and preferred term are shown in Appendix F.

B.2.10.3 Serious adverse events

Serious adverse events (SAEs) were defined as an event that, at any dose, resulted in any of the following outcomes:

- Death
- Life-threatening situation (immediate risk of death)
- Inpatient hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect

- Other medically significant events that based upon appropriate medical judgment may have jeopardised the subject or may have required medical or surgical intervention to prevent one of the outcomes listed above.

A full list of SAEs according to system organ class in the SELECTION trials is presented in Appendix F.

In SELECTION induction cohort A, SAEs were reported by treatment group as follows: [redacted] of patients in the filgotinib 200mg group, [redacted] of patients in the filgotinib 100mg group and [redacted] of patients in the placebo group.

In SELECTION induction cohort B, the corresponding SAEs were as follows: [redacted] of patients in the filgotinib 200mg group, [redacted] of patients in the filgotinib 100mg, and [redacted] of patients in the placebo group.

The most commonly occurring SAE was ulcerative colitis in the induction study.

In SELECTION maintenance study, SAEs were reported by treatment group as follows: 4.5% of patients in the filgotinib 200mg group, 0.0% of patients in respective placebo; 4.5% of patients in the filgotinib 100mg group and 7.7% of patients in respective placebo.

The most frequent SAE in the SELECTION clinical programme overall was ulcerative colitis, and most SAEs were related to ulcerative colitis. Serious adverse events reported for each arm are summarised in Table 30 for the induction studies and in Table 31 for the maintenance study.

B.2.10.4 Events leading to discontinuation

Across treatment groups, worsening of ulcerative colitis was the most commonly occurring adverse event (AE) leading to premature discontinuation of study drug. In the SELECTION maintenance study, rates of events leading to discontinuation were lower in the filgotinib 200mg treatment group (3.5%) than 100mg treatment group (5.6%), and lower in the respective placebo groups than the treatment groups.

A summary of adverse events in the SELECTION induction and maintenance studies are shown in Table 30 and Table 31, respectively.

Table 30. Summary of treatment-emergent adverse events in SELECTION, induction studies, cohorts A and B (Safety Analysis Set)

	Cohort A induction study			Cohort B induction study		
Safety assessment	**Filgotinib 200mg (n=245)**	**Filgotinib 100mg (n=277)**	**Placebo (n=137)**	**Filgotinib 200mg (n=262)**	**Filgotinib 100mg (n=285)**	**Placebo (n=142)**
Adverse events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any Grade 3 or higher adverse events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common Grade 3 or higher adverse events (≥2% of subjects), n (%)						
Colitis ulcerative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphatemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious adverse events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most frequent adverse events (≥5% of subjects), n (%)						
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Colitis ulcerative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Cohort A induction study			Cohort B induction study		
Safety assessment	**Filgotinib 200mg (n=245)**	**Filgotinib 100mg (n=277)**	**Placebo (n=137)**	**Filgotinib 200mg (n=262)**	**Filgotinib 100mg (n=285)**	**Placebo (n=142)**
Infections, n (%)						
Any infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event of special interest, n (%)						
Herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Opportunistic infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Malignancies (excluding non-melanoma skin cancers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-melanoma skin cancers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal perforation events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thromboembolic events ǂ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event leading to discontinuation of study drug, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abnormal laboratory results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Cohort A induction study			Cohort B induction study		
Safety assessment	**Filgotinib 200mg (n=245)**	**Filgotinib 100mg (n=277)**	**Placebo (n=137)**	**Filgotinib 200mg (n=262)**	**Filgotinib 100mg (n=285)**	**Placebo (n=142)**
(Grade 3 or 4), n (%)						
Abnormal laboratory results (Grade 4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: n, number.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107).
Notes: ǂ Thromboembolic events refers venous thrombosis, pulmonary embolism, arterial thrombosis, or cerebrovascular events.

Table 31. Summary of adverse events in SELECTION maintenance study (Safety Analysis Set)

Safety assessment	**Induction Filgotinib 200mg**		**Induction Filgotinib 100mg**		**Induction Placebo**
	Maintenance Filgotinib 200mg (n=202)	**Maintenance Placebo (n=99)**	**Maintenance Filgotinib 100mg (n=179)**	**Maintenance Placebo (n=91)**	**Maintenance Placebo (n=93)**
Adverse events, n (%)	135 (66.8%)	59 (59.6%)	108 (60.3%)	60 (65.9%)	57 (61.3%)
Any Grade 3 or higher adverse events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common Grade 3 or higher adverse events (≥2% of patients), n (%)					
Colitis ulcerative	2 (1.0%)	1 (1.0%)	3 (1.7%)	3 (3.3%)	3 (3.2%)
Serious adverse events, n (%)	9 (4.5%)	0	8 (4.5%)	7 (7.7%)	4 (4.3%)
Most frequent adverse events (≥5% of patients), n (%)					
Colitis ulcerative	21 (10.4%)	20 (20.2%)	19 (10.6%)	16 (17.6%)	11 (11.8%)

Safety assessment	Induction Filgotinib 200mg		Induction Filgotinib 100mg		Induction Placebo
	Maintenance Filgotinib 200mg (n=202)	Maintenance Placebo (n=99)	Maintenance Filgotinib 100mg (n=179)	Maintenance Placebo (n=91)	Maintenance Placebo (n=93)
Nasopharyngitis	22 (10.9%)	6 (6.1%)	12 (6.7%)	6 (6.6%)	5 (5.4%)
Arthralgia	8 (4.0%)	7 (7.1%)	6 (3.4%)	3 (3.3%)	4 (4.3%)
Headache	7 (3.5%)	0	11 (6.1%)	5 (5.5%)	5 (5.4%)
Abdominal pain	8 (4.0%)	6 (6.1%)	6 (3.4%)	2 (2.2%)	4 (4.3%)
Upper respiratory tract infection	11 (5.4%)	3 (3.0%)	6 (3.4%)	3 (3.3%)	3 (3.2%)
Infections, n (%)					
Any infection	71 (35.1%)	25 (25.3%)	46 (25.7%)	27 (29.7%)	21 (22.6%)
Serious infection	2 (1.0%)	0	3 (1.7%)	2 (2.2%)	1 (1.1%)
Adverse event of special interest, n (%)					
Herpes zoster	1 (0.5%)	0	0	1 (1.1%)	0
Malignancies (excluding non-melanoma skin cancers)	1 (0.5%)	0	1 (0.6%)	0	0
Non-melanoma skin cancers	0	0	1 (0.6%)	0	0
Gastrointestinal perforation events	0	0	0	0	0
Thromboembolic events ǂ	0	0	2 (1.1%)	0	2 (2.2%)
Death	2 (1.0%)	0	0	0	0
Adverse event leading to discontinuation of study drug, n (%)	7 (3.5%)	2 (2.0%)	10 (5.6%)	4 (4.4%)	3 (3.2%)
Abnormal laboratory results (Grade 3 or 4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Safety assessment	Induction Filgotinib 200mg		Induction Filgotinib 100mg		Induction Placebo
	Maintenance Filgotinib 200mg (n=202)	Maintenance Placebo (n=99)	Maintenance Filgotinib 100mg (n=179)	Maintenance Placebo (n=91)	Maintenance Placebo (n=93)
Abnormal laboratory results (Grade 4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: n, number.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107).
Notes: ǂ Thromboembolic events refers venous thrombosis, pulmonary embolism, arterial thrombosis, or cerebrovascular event.

B.2.10.5 Adverse events of special interest

Adverse events of special interest in the SELECTION clinical programme were infections, malignancies (excluding non-melanoma skin cancers), non-melanoma skin cancers, gastrointestinal perforation events and thromboembolic events (venous thrombosis, pulmonary embolism, arterial thrombosis, or cerebrovascular events). These adverse events are summarised in Table 30 and Table 31.

In the cohort A induction trial, overall infections were reported in [redacted] of the placebo group, [redacted] of the filgotinib 100mg group and [redacted] of the filgotinib 200mg group. In the cohort B induction trial, corresponding adverse event rates were [redacted], respectively. In the maintenance trial, infections were reported in 71 patients (35.1%) in the filgotinib 200mg group and 25 patients (25.3%) in the respective placebo group, 46 patients (25.7%) in the filgotinib 100mg group and 27 patients (29.7%) in the respective placebo group. Rates of serious infections for filgotinib 200mg and filgotinib 100mg were ≤3% across all arms [redacted] maintenance studies of the SELECTION clinical programme.

With the exception of overall infections, rates of adverse events of special interest were consistently low across the SELECTION clinical trial programme; [redacted] in all groups of the two induction studies, and ≤3% in all groups of the maintenance study. Full details of all adverse events of special interest for each of the induction and maintenance studies are presented in Appendix F.

B.2.10.6 Deaths

Two deaths occurred during the SELECTION maintenance study, both in the filgotinib 200mg treatment group.

- One death occurred on day 81. The subject was hospitalised for a glaucoma surgery and died the next day. The primary cause of death was determined to be left ventricular heart failure. The investigator assessed the left ventricular failure as not related to study drug
- One death was reported on day 302 attributed to asthma exacerbation. The investigator assessed the AE as not related to study drug.

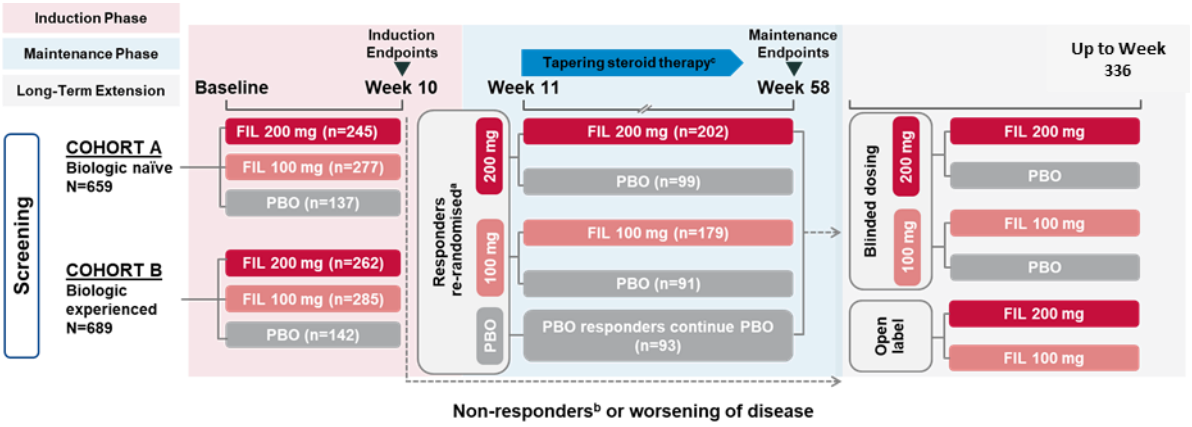
B.2.11 Ongoing studies

B.2.11.1 SELECTION LTE

SELECTION LTE (129) is an ongoing long-term extension study, to assess the long-term safety of filgotinib in patients who completed SELECTION or met protocol-specified efficacy discontinuation criteria.

SELECTION LTE is a non-randomised, double-blind, placebo-controlled, parallel assignment trial. The double-blind study is comprised of three treatment arms, in which patients receive filgotinib 200mg or filgotinib 100mg, and/or placebo for up to 336 weeks. The two open-label treatment arms receive filgotinib 200mg or filgotinib 100mg for up to 336 weeks, see Figure 13. The study is expected to complete in December 2023.

Figure 13. Trial design of SELECTIONLTE in patients with moderately to severely active UC



Abbreviations: mg, milligram; PBO, placebo; FIL, filgotinib; UC, ulcerative colitis.
References: Gilead SELECTION clinical study report, 2020 (data on file) (107); Gilead SELECTIONLTE clinical study protocol (data on file), 2020 (129).

The primary endpoints are the proportion of patients experiencing an AE and the proportion of patients experiencing clinically significant laboratory abnormalities during the follow-up period of 336 weeks. The secondary endpoint is the change from baseline in components of the Mayo Clinic Score (MCS) (129).

Exploratory endpoints for HRQoL that will be analysed are:

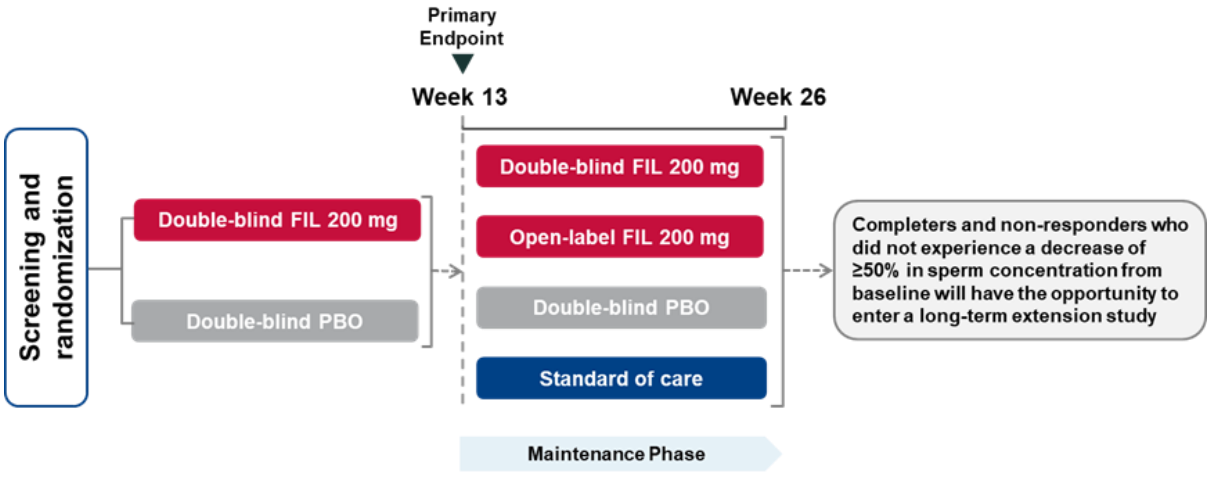
- Change from baseline in the 36-Item Short Form Health Survey (SF-36)
- Change in baseline in the EuroQol-5 Dimension Scale (EQ-5D)
- Change in baseline in the Inflammatory Bowel Disease Questionnaire (IBDQ)
- Change in baseline in percent impairment in the Work Productivity and Activity Impairment Questionnaire (WPAI).

B.2.11.2 MANTA

The MANTA study is an ongoing study conducted to evaluate the testicular safety of filgotinib in adult males with moderately to severely active UC or CD (130).

MANTA is a randomised, double-blind, placebo-controlled phase 2 study. In the double-blind phase of the trial, patients will receive a 200mg dose of filgotinib or placebo once-daily for 13 weeks. Patients will continue on blinded treatment for up to an additional 13 weeks, or commence open-label filgotinib, based on IBD response status and sperm parameters (130). In the long term extension phase, eligible patients will receive either open-label filgotinib or blinded study drug (filgotinib or placebo) for up to 195 weeks (130). An overview of the trial design of MANTA is presented in Figure 14. The estimated study completion date is October 2024.

Figure 14. Trial design of MANTA in male patients with moderately to severely active UC or CD



Abbreviations: CD, Crohn's disease; FIL, filgotinib; NR, non-responders; PBO, placebo; UC, ulcerative colitis.
References: Clinicaltrials.gov, 2021 (130)

The primary outcome measure is the proportion of patients with ≥50% decrease from baseline in sperm concentration at week 13 (130).

Current secondary outcome measures of the MANTA trial include:

- The proportion of subjects with a ≥ 50% decrease from baseline in sperm concentration at week 26
- At Weeks 13 and 26, change from baseline in:
    - percent motile sperm
    - total sperm count
    - sperm concentration
    - ejaculate volume
    - percent normal sperm morphology.

B.2.12 Innovation

Filgotinib is a second-generation JAK inhibitor that is a preferential and reversible inhibitor of JAK1. Cytokines that signal via JAK1 containing pairs are involved in the inflammatory signalling pathway that drives UC progression. Targeted inhibition of JAK1 could reduce inflammatory cytokine signalling involved in UC, whilst limiting impact on normal physiological function.

Oral administration means there are no additional costs associated with training for administering the treatment, unlike treatments given by intravenous infusion, or subcutaneously. Filgotinib also offers a more convenient option for patients when compared to SC treatment options, which may require refrigeration, and IV treatment options, which require hospital attendance.

In addition to the above, filgotinib is not a clinically relevant inhibitor or inducer of most enzymes or transporters commonly involved in interactions, such as cytochrome P450 enzymes and UDP-glucuronosyltransferases. Therefore, the potential for drug-drug interactions is low, which means filgotinib can be administered with commonly used UC drugs without the need for dose adjustments (9).

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 the UK, patients with moderately to severely active UC are treated with conventional therapy or biologics to induce remission. Where these patients fail to respond, or are intolerant to, their first-line biologic, they may be switched to another biologic or a targeted synthetic therapy. JAK inhibitors represent an important therapeutic option for these non-responder or intolerant patients. The response rates of patients treated with filgotinib demonstrate its clinical value, and supports that it has place in the treatment of patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to conventional therapy, biologics or targeted therapies.

B.2.13.1 Key findings from the SELECTION clinical trials

The efficacy and safety of filgotinib has been evaluated in the SELECTION clinical programme of induction and maintenance trials, which are randomised, double-blind, placebo-controlled in design. The two 10-week induction studies compared filgotinib with placebo, in biologic-naïve (cohort A induction study, detailed in Section B.2.6.1) and biologic-experienced (cohort B induction study, detailed in Section B.2.6.2) patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to conventional therapies, biologics or targeted therapies. Responders from the induction trials were re-randomised into the maintenance study comparing filgotinib with placebo up to week 58 (maintenance study detailed in Section B.2.6.3). 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 the UK.

Key findings from the SELECTION trials are summarised below:

Among biologic-naïve patients (cohort A induction study) with moderately to severely active UC

- Treatment for 10 weeks with filgotinib 200mg resulted in a significantly higher proportion of patients achieving EBS remission, MCS remission, an endoscopic sub score of 0, Geboes histologic remission, and MCS remission (alternative definition) compared with placebo.

Among biologic-experienced patients (cohort B induction study) with moderately to severely active UC

- Treatment for 10 weeks with filgotinib 200mg resulted in a significantly higher proportion of patients achieving EBS remission, compared with placebo.

Among biologic-naïve and biologic-experienced patients (maintenance study) with moderately to severely active UC who achieved a clinical response to induction treatment with filgotinib

- Treatment with filgotinib 200mg for 47 weeks resulted in a significantly higher proportion of patients achieving EBS remission, 6-month corticosteroid-free EBS remission, sustained EBS remission, MCS remission, an endoscopic sub score of 0, Geboes histologic remission, and MCS remission (alternative definition) at Week 58 compared with placebo
- Treatment with filgotinib 100mg for 47 weeks resulted in a significantly higher proportion of patients achieving EBS remission compared with placebo.

Among biologic-naïve and biologic-experienced patients with moderately to severely active UC

- Filgotinib 100mg and 200mg were generally well tolerated, as evidenced by low rates of study treatment discontinuation due to AEs, SAEs, Grade 3 or higher AEs, serious infections, herpes zoster infections, opportunistic infections, gastrointestinal perforations, malignancies excluding nonmelanoma skin cancers, nonmelanoma skin cancers, thromboembolic events, and laboratory abnormalities. Evidence for adverse events is detailed in Section B.2.10.

The SELECTION trials demonstrated that statistically significantly higher proportions of patients taking filgotinib 200mg achieved key efficacy endpoints compared to patients taking placebo in both the induction and the maintenance studies. Improvements in clinical outcomes were accompanied by reductions in inflammatory biomarkers and improvements in health-related quality of life measures (102).

A higher proportion of subjects achieved MCS response and/or EBS remission in the cohort A induction study compared with the cohort B induction study, and subjects from the cohort A induction study represented the majority of subjects entering the maintenance study. However, even among the highly refractory study population in the cohort B induction study, more than 50% of subjects who were treated with filgotinib 200mg achieved MCS response and were re-randomised into the maintenance study.

The key secondary endpoints assessed in the SELECTION trials include important treatment targets of UC such as endoscopic remission (Mayo endoscopic sub score of 0), histologic remission, 6-month corticosteroid-free clinical remission, and sustained clinical remission. Statistically significant treatment differences between filgotinib 200mg and placebo were observed for all key secondary endpoints in the cohort A induction study, as well as the maintenance study.

Post-hoc subgroup analysis (detailed in Section B.2.7) of patients with moderately to severely active UC compared filgotinib with placebo within the subgroup based on; stratification factors, demographic factors, baseline disease characteristics, and previous history of biologic agents. Overall, subgroup analyses in cohort A or cohort B induction studies and the maintenance study were consistent with those observed in the overall study population. Filgotinib demonstrated better efficacy in all subgroups investigated compared to the overall study population. The subgroup analyses in the maintenance study showed the consistent treatment effect of filgotinib 200mg across most subgroups, even among dual refractory subjects who had failed a TNFα antagonist and vedolizumab.

Finally, in addition to direct clinical evidence, a network meta-analysis of standard UC 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 biologic-naïve population indicated that filgotinib 200mg is an effective treatment in inducing MCS response/remission and mucosal healing in adult patients with moderate to severe ulcerative colitis. For MCS response/remission, filgotinib 200mg was [redacted]. Filgotinib 200mg was [redacted]. Filgotinib 200mg was [redacted].

In the biologic-experienced population, the NMA results indicated that filgotinib 200mg is an effective treatment in inducing MCS response/remission and mucosal healing in adult patients with moderate to severe ulcerative colitis. Filgotinib 200mg was [redacted] At maintenance, filgotinib 200mg was [redacted] in terms of inducing MCS response/remission, [redacted] Filgotinib 200mg [redacted]

Sensitivity analyses conducted indicated that the NMA was robust to excluding trials due to potential sources of heterogeneity.

B.2.13.2 Strengths and limitations of the clinical evidence base for filgotinib in UC

The SELECTION trials provided the clinical evidence base that demonstrates the efficacy and safety of filgotinib in the treatment of adult patients with moderately to severely active UC compared to placebo. The efficacy results for the induction and maintenance studies indicate that filgotinib reduces the clinical signs and symptoms of disease regardless of prior treatment history. In addition, the safety data suggest that filgotinib is well tolerated in patients with moderately to severely active UC and may offer advantages over currently available therapies.

Over time, the subject population enrolled in UC clinical trials has become increasingly refractory, reflecting that patients are failing treatment with additional and different classes of drugs available (131). While all patients in the infliximab ACT1 and ACT2 trials were biologic-naïve (75), approximately 50% of patients who participated in the ustekinumab UNIFI study had a history of treatment failure with at least one TNFα antagonist and about 20% of the patients failed two classes of biologic agents, TNFα antagonists, and vedolizumab (132).

A strength of the filgotinib SELECTION trials was that the patients enrolled in the induction studies had a high inflammatory burden at baseline compared to other registrational UC trials, yet patients receiving filgotinib 200mg achieved key efficacy endpoints, compared to patients taking placebo, in both the induction and the maintenance studies.

In the cohort A induction study, approximately 56% of the study subjects had a baseline Mayo endoscopic sub score of 3, and the mean faecal calprotectin level was significantly elevated at baseline. In the cohort B induction study, almost 80% of the study subjects had a Mayo endoscopic sub score of 3 at study entry. Median hs-CRP (filgotinib 200mg: 5.91mg/L; filgotinib 100mg: 5.92mg/L) and faecal calprotectin (filgotinib 200mg: 1,513µg/g; filgotinib 100mg 1,378µg/g) levels at baseline for subjects in the cohort B induction study were higher than median hs-CRP

(ustekinumab 6mg/kg: 4.8mg/L) and faecal calprotectin (ustekinumab 6mg/kg: 1,506.5mg/kg) values for subjects in the ustekinumab UNIFI study (132).

Additionally, more than 90% of the cohort B subjects had a prior treatment history of TNFα antagonist and approximately 45% of the subjects were treated with at least two different TNFα antagonists. Prior use of vedolizumab was reported for approximately 60% of subjects. About 51% of the cohort B induction study population had received both a TNFα antagonist and vedolizumab. These baseline characteristics indicate that among the trial populations in registrational UC trials, the cohort B induction study participants were the most refractory group of patients with the highest inflammatory burden to date with a substantial prior treatment history of biologic therapies and a high disease burden at baseline.

Another strength of the filgotinib SELECTION trials was that more stringent definitions were used for key secondary endpoints such as endoscopic efficacy endpoint (a Mayo endoscopic sub score of 0) and histologic remission (with the requirement of the absence of neutrophils in lamina propria) than in previous trials of treatments for UC, such as the tofacitinib OCTAVE trial (117) or the ustekinumab UNIFI study (132). In addition, 6-month corticosteroid-free EBS remission had a stringent definition requiring a minimum duration of 6 months of no corticosteroid use prior to Week 58 among subjects who were taking corticosteroids at maintenance baseline. Statistically significant treatment differences between filgotinib 200mg and placebo were observed for all key secondary endpoints in the Cohort A induction study as well as the maintenance study.

Limitations of the clinical evidence base for filgotinib include the limited interpretation of SAE results in the subgroup analysis due to low number of events across the studies. In general, no subgroup by age, sex, race, geographic region, or prior biologic failure was at increased risk of serious infections. Similarly, the incidence rates of serious infection were similar among study participants with or without concomitant immunomodulator and/or corticosteroid during the study.

Another limitation was the short duration of follow up in the induction phase, which limits the evaluation of induction of remission to 10 weeks. However, the

SELECTION trials provide data up to 58 weeks in patients with a clinical response at Week 10 re-randomised to the maintenance phase, and the double-blind long term extension study (SELECTION LTE) will provide data over a much longer period (up to 336 weeks) for responders. For non-responders at Week 10, patients could be randomised to the open-label filgotinib treatment arm of the SELECTION LTE study for long-term follow up.

As with other registrational clinical trials within UC, the SELECTION trials lack a direct comparison with active comparators (i.e. biologic therapies). This limitation has been addressed by conducting a network meta-analysis, taking into account past approaches considered by NICE and attempting to address heterogeneity across trials.

However, unlike other UC registrational trials, the SELECTION trials have a true placebo arm spanning the study duration, thus mitigating any carry-over effect of active induction therapy into the maintenance study (i.e. induction placebo patients will remain on placebo in the maintenance phase).

In summary, the robust study design of the SELECTION trials supports the clinical evidence base for filgotinib in the treatment of adult patients with moderately to severely active UC compared to placebo.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A SLR of cost-effectiveness studies in UC was conducted to identify published economic evaluations of interventions for the treatment of moderately to severely active UC, which could be used to address the decision problem and inform the economic model structure. The SLR identified 34 unique cost-effectiveness models in UC from 41 separate study references. Of these, 12 studies, addressing 9 models, were specific to the UK.

All models specific to the UK applied a Markov cohort model, in some cases combined with a decision tree (representing the induction phase) to create a hybrid approach. Of the 12 UK studies, 11 studies adopted a long-term perspective, i.e. between a 10-year and a lifetime time horizon. A summary of the published UK based cost-effectiveness studies identified in the SLR, including analyses developed to inform recent NICE technology appraisals is presented in Table 32.

Full details of the studies identified, the methodology to identify and select the relevant cost-effectiveness studies, including inclusion/exclusion criteria for review, PRISMA flow diagram, and study quality assessment are provided in Appendix G.

Table 32. Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (incremental)	Costs (incremental)	ICER (per QALY gained)
TA140 (Tsai et al. 2008 (133))	2008	Markov model Cycle time: Variable Time horizon: 10 years	Biologic-naïve (NR)	IFX vs ciclosporin and surgery: 0.753 for responders only analysis 0.387 for remission only analysis	IFX vs ciclosporin and surgery: £20,662 for responders only analysis £7,615 for remission only analysis	£27,424 for responders only analysis £19,696 for remission only analysis
TA140 (Hyde et al. 2009 (134))	2008	Markov model Cycle time: 8 weeks Time horizon: 10 years	Biologic-naïve (NR)	Not reported	Not reported	IFX vs ciclosporin and surgery: £33,866 for strategy A (modelled the continuation of infliximab in treatment responders who achieved and maintained remission) £25,044 for strategy B (narrower therapy continuation group defined as responders who achieve and maintain remission)

TA163 (Punekar et al. 2010 (135))	2008	Decision tree Markov model Cycle time: Variable Time horizon: lifetime	Biologic-naïve (NR)	IFX vs ciclosporin and SoC incl. surgery: 0.09	IFX vs ciclosporin and SoC incl. surgery: £1,725	£18,388
TA163 (Bryan et al. 2008 (134))	2008	Decision tree Markov model Cycle time: Variable Time horizon: lifetime	Biologic-naïve (NR)	Not reported	Not reported	IFX vs ciclosporin and SoC incl. surgery: £20,000
TA329 (28) (MSD submission)	2015	Markov model Cycle time: 2 months Time horizon: 10 years	Biologic-naïve (40)	IFX vs colectomy: 0.72 GOL vs colectomy: 0.55	IFX vs colectomy: £27,130 GOL vs colectomy: £15,100	IFX vs colectomy: £37,682 GOL vs colectomy: £27,322
TA329 (28) (AbbVie submission)	2015	Markov model Cycle time: 2 weeks Time horizon: 10 years	Biologic-naïve (NR)	ADA vs CT: 0.73	ADA vs CT: £25,335	£34,590
TA329 (28) (Assessment group model)	2015	Markov model Cycle time: Variable Time horizon: lifetime	Biologic-naïve (40)	Not reported	Not reported	IFX and GOL dominated by colectomy ADA vs colectomy £50,300
TA342 (65) (Essat et al.	2015	Decision tree Markov model	(1) Mixed ITT (2) Biologic-naïve	(1) VDZ vs CT: 0.15 VDZ vs surgery: 1.27	(1) VDZ vs CT: £5,131 VDZ vs surgery: -	(1) VDZ vs CT: £33,297 VDZ vs surgery: dominating

2016 (136))		Cycle time: Variable Time horizon: lifetime	(3) Biologic-experienced (NR)	(2) VDZ vs IFX: 0.08 VDZ vs GOL: 0.11 VDZ vs ADA: 0.14 VDZ vs CT: 0.34 VDZ vs surgery: 1.67 (3) VDZ vs CT: 0.09 VDZ vs surgery: 1.182	£30,775 (2) VDZ vs IFX: -£4,877 VDZ vs GOL: -£1,312 VDZ vs ADA: £918 VDZ vs CT: £1,669 VDZ vs surgery: -£38,756 (3) VDZ vs CT: £5,839 VDZ vs surgery: -£29,422	(2) VDZ vs IFX: dominating VDZ vs GOL: dominating VDZ vs ADA: £6,634 VDZ vs CT: £4,862 VDZ vs surgery: dominating (3) VDZ vs CT: £64,999 VDZ vs surgery: dominating
TA342 (65) (Wilson et al. 2018 (137))	2015	Decision tree Markov model Cycle time: Variable Time horizon: lifetime	Biologic-naïve (NR)	VDZ vs IFX: 0.29 VDZ vs GOL: 0.27 VDZ vs ADA: 0.21	VDZ vs IFX: -£6,635 VDZ vs GOL: -£587 VDZ vs ADA: £4,666	VDZ vs IFX: dominating VDZ vs GOL: dominating VDZ vs ADA: £22,775
TA547 (66) (Lohan et al. 2019 (124))	2018	Markov model Cycle time: 8 weeks Time horizon: lifetime	(1) Biologic-naïve (2) Biologic-experienced (41)	(1) ADA vs CT: 0.200 GOL vs CT: 0.294 IFX vs CT: 0.355 VDZ vs CT: 0.471 TOF vs CT: 0.544 (2) ADA vs CT: 0.148 IFX vs CT: 0.148 GOL vs CT: 0.148 VDZ vs CT: 0.242 TOF vs CT: 0.337	(1) ADA vs CT: £6,185 GOL vs CT: £9,012 IFX vs CT: £13,311 VDZ vs CT: £20,345 TOF vs CT: £11,615 (2) ADA vs CT: £4,324 IFX vs CT: £7,949 GOL vs CT: £5,376 VDZ vs CT: £12,668 TOF vs CT: £7,687	(1) ADA vs CT: £30,982 GOL vs CT: £30,602 IFX vs CT: £37,495 VDZ vs CT: £43,205 TOF vs CT: £21,388 (2) ADA vs CT: £29,284 IFX vs CT: £53,831 GOL vs CT: £36,403 VDZ vs CT: £52,275 TOF vs CT: £22,816
TA633 (67)	2020	Decision tree Markov model Cycle time: 2	(1) Biologic-naïve (2) Biologic-experienced	Not reported	Not reported	(1) UST vs CT: £23,446 UST vs ADA biosimilar: £19,146

		weeks Time horizon: lifetime	(NR)			UST vs ADA: £18,047 UST vs IFX biosimilar: £16,606 UST vs IFX: £14,710 UST vs GOL: £12,025 UST vs TOF: £13,465 UST vs VDZ: £1,762 (2) UST vs CT: £26,205 UST vs ADA biosimilar: £19,670 UST vs ADA: £18,210 UST vs TOF: £5,394 UST vs VDZ: dominant
Wilson et al. 2017 (138)	2017	Decision tree Markov model Cycle time: Variable Time horizon: 5 years	(1) Mixed ITT (2) Biologic-naïve (3) Biologic-experienced (40.25)	(1) VDZ vs CT: 0.335 (2) VDZ vs CT: 0.363 (3) VDZ vs CT: 0.266	(1) VDZ vs CT: £1,370 (2) VDZ vs CT: £1,604 (3) VDZ vs CT: £1,587	(1) £4,095 (2) £4,423 (3) £5,972

Abbreviations: ADA, adalimumab; CT, conventional therapy; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; ITT, intention to treat; NR, not reported; SoC, standard of care; TOF, tofacitinib; UST, ustekinumab; VDZ, vedolizumab; vs, versus; QALY, quality adjusted life-year

B.3.2 Economic analysis

The systematic literature review search of cost-effectiveness studies identified 34 unique economic evaluations in UC. No relevant economic evaluations able to provide estimates for the cost-effectiveness of filgotinib in UC were identified. Therefore, a de novo model was developed to assess cost-effectiveness of filgotinib compared to advanced and conventional therapeutic options for the treatments of adults with moderately to severely active UC.

The model was conceptualised based on an SLR of previous cost-effectiveness studies in UC, i.e. the model structure and inputs were based on the information described in Appendix G, including previous NICE technology appraisals.

B.3.2.1 Patient population

In accordance with the appraisal scope, the evidence base for filgotinib and its expected indication, the analysis considers patients with moderately to severely active ulcerative colitis who have had an inadequate response, loss of response or were intolerant to a previous biologic agent or conventional therapy. Within this population, two subgroups of patients are considered, based on prior exposure to biologic treatment. The efficacy results from the SELECTION trial, as presented in Section B.2.6, demonstrated comparable efficacy to other advanced therapies in both the biologic-naïve and biologic-experienced cohorts. Therefore, this submission is consistent with previous technology appraisals in moderately to severely active UC (28, 65-67) in which the analyses considered these two subgroups of patients separately.

The starting cohort age, proportion by sex, and weight are used as inputs in the model to account for variations due to demographic factors. The baseline characteristics applied in the model are based on the SELECTION trial induction study population (see Section B.2.2), and are summarised in Table 33.

Table 33. Patient subgroup baseline characteristics based on the SELECTION trial induction study cohort

Characteristic	Cohort A Biologic-naïve patients (N=659)		Cohort B Biologic-experienced patients (N=689)	
	Mean	SD	Mean	SD
Age (years)	42	13.1	43	14.4
Proportion male (%)	55.7	N/A	61.0	N/A
Weight (kg)	69.7	17.39	73.8	17.61

Abbreviations: kg, kilogram; SD, standard deviation
Reference: Gilead SELECTION clinical study report, 2020 (data on file) (107)

B.3.2.2 Perspective

In line with current NICE guidance, the perspective for this analysis is the NHS and Personal and Social services (PSS) in England and Wales. Therefore, patients' out of pocket expenses, carers' costs, and lost productivity are excluded.

B.3.2.3 Model structure

The cost effectiveness analysis is conducted using a Markov model structure, consistent with the approach taken by the assessment group (AG) in the multiple technology appraisal (TA) for infliximab, adalimumab, and golimumab as treatment for moderately to severely active UC (TA329), and subsequent TAs in UC for ustekinumab (TA633), tofacitinib (TA547), vedolizumab (TA342) (28, 65-67).

The model applies a fixed 10-week cycle length throughout the time horizon to allow for a continuous sequence of treatments, and a half-cycle correction was implemented, such that the number of patients in each health state per cycle were re-calculated as an average of the proportion of patients at the beginning and at the end of the cycle. The cycle length was chosen to align with the length of the induction period of the SELECTION trial. As such, when evidence was available for other timeframes, model inputs were adjusted to the 10-week cycle length.

In their respective clinical trials, the length of induction for treatments considered in the model varies between 6 and 10 weeks. Therefore, the cost of induction treatment for all comparators was calculated to ensure that for shorter induction durations, the respective treatment induction cost would not be overestimated. In addition, all patients are assumed to have active UC in the induction phase in the model, and

treatment benefits are accrued during the maintenance phase. Therefore, the impact of using a 10-weekly cycle length at induction was considered minimal. The model pathway is further described below.

As UC is a chronic, long-term condition for which patients may remain on treatment for long periods of time, a lifetime horizon was used for the base case analysis to capture the full impact of treatment with filgotinib on costs and patient outcomes. It was assumed that patients did not live past the age of 100.

Model schematic

A schematic illustrating the model pathway is outlined in Figure 15. The model comprises health states defined by the type of treatment (advanced treatment, conventional treatment, surgery, post-surgery), as well as disease control replicating the relapsing and remitting nature of UC (active UC, response without remission, remission). In the model base case, patients initiate advanced treatment, but following treatment failure, patients are assumed to initiate and remain on conventional treatment, unless they undergo surgery. This methodology is consistent with previous recent TAs. The model additionally includes an option to incorporate up to four lines of advanced treatment, with conventional therapy included as a fixed last line treatment.

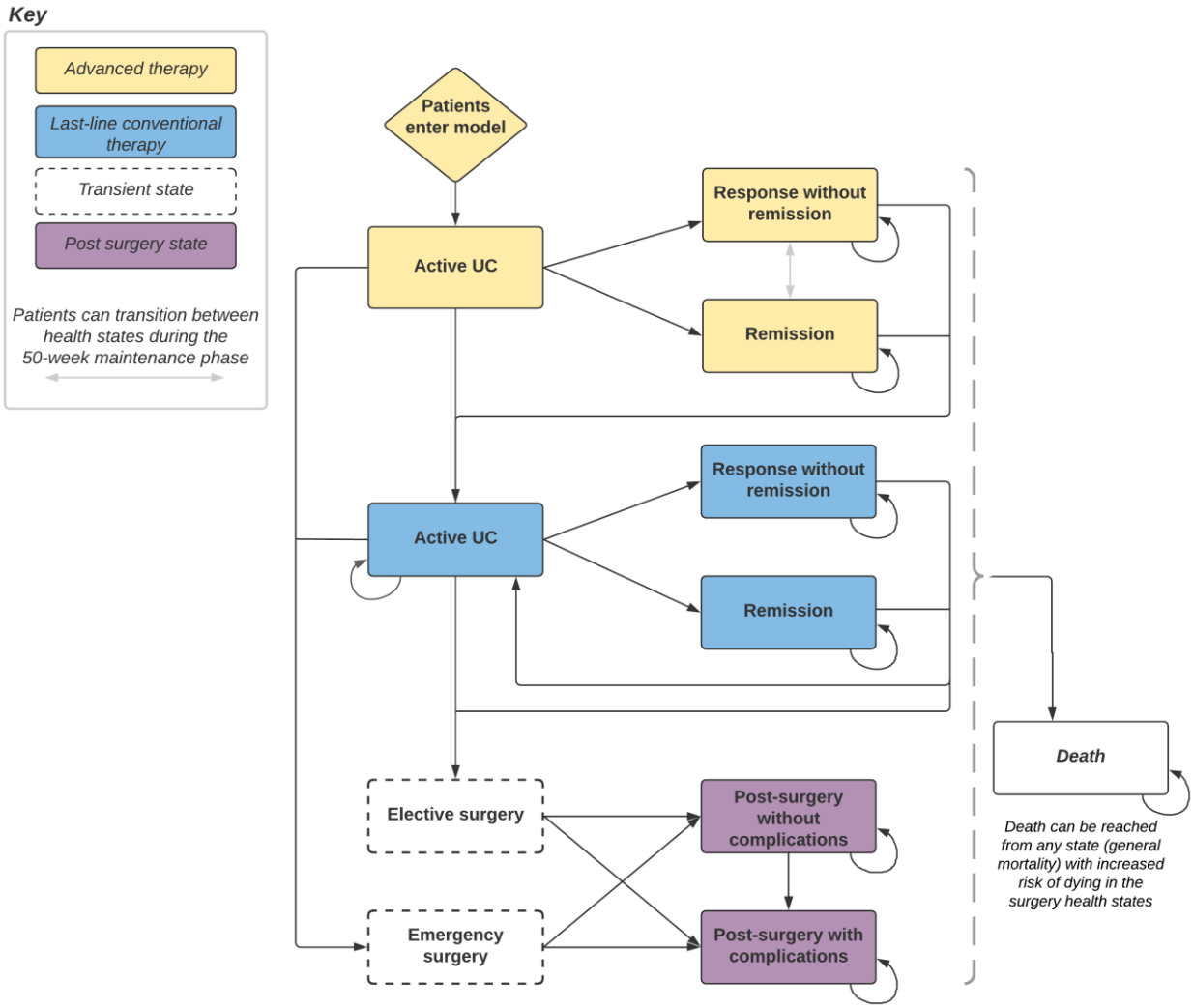
Two types of surgery are included in the model: emergency surgery and elective surgery. The operations are modelled as transient states, and patients who undergo surgery and survive move on to post-surgery states, where they are at risk of long-term complications arising. This is further detailed in the following sections.

In summary, the following health states are included:

- Active UC, response without remission, and remission states, for both advanced treatments as well as conventional treatment
- Two surgery states: elective or emergency surgery
- Post-surgery states: with or without long-term complications

- Death.

Figure 15. Schematic of the cost-effectiveness model



The health states were selected to reflect the natural history of the disease, and are consistent with previous published economic evaluations and technology appraisals (28, 65-67). The disease control health states (active UC, response without remission, and remission) were defined in line with the definitions used in the SELECTION trial programme. Descriptions of the model health states are provided in Table 34.

Table 34. Descriptions of the model health states

Health state	Definition
Remission	A Mayo score of ≤ 2 points and no individual sub score > 1 point
Response without remission	Not meeting remission definition, and a decrease from baseline in Mayo score of ≥ 30% and ≥ 3 points, accompanied by a decrease from baseline in the rectal bleeding sub score ≥ 1, or an absolute rectal bleeding sub score of 0 or 1
Active UC	Remission and response without remission not achieved. Patients are also assumed to enter the model with moderately to severely active UC, as determined by a total Mayo score between 6 and 12 and the following sub scores: endoscopy score and Physician's Global Assessment score ≥2, rectal bleeding score and stool frequency score ≥1
Emergency surgery	Emergency colectomy due to acute exacerbation
Elective surgery	Elective colectomy which can be undergone by patients with active UC
Post-surgery with complications	Chronic complications after undergoing surgery
Post-surgery without complications	No chronic complications after undergoing surgery

Abbreviations: UC, ulcerative colitis

Induction phase

Patients are assumed to enter the model with active UC, and initiate treatment induction. The length of the induction phase is 10 weeks (one model cycle), in line with the SELECTION trial induction phase.

At the end of the induction phase, patients are redistributed across model health states. At this timepoint, patients can experience the following:

- Remission, and remain on treatment
- Response, without remission, and remain on treatment
- No response, remain in active UC, discontinue treatment and transition to last-line conventional treatment
- Death.

The distribution of patients at the end of the induction phase is based on the NMA output (detailed in Section B.2.9). The use of the NMA in the model is detailed in Section B.3.3.1.

Maintenance phase

Patients who respond to treatment in the induction phase are moved through five tunnel states which represent a 50-week maintenance treatment phase, during which patients receive maintenance dosing of the same treatment they received in induction for the duration of their response. Patients in the maintenance phase are categorised as having response without remission, or remission. The proportion of patients in each category is informed by the results of the NMA of maintenance trials. During this time, patients have a constant probability of loss of treatment response (resulting in treatment discontinuation), or moving between the remission and response without remission health states. At the end of the 50-week maintenance phase, patients who have not stopped responding to treatment remain on the same maintenance treatment, and with the same level of response indefinitely, until loss of response or death.

Loss of treatment response over the time horizon was informed by the NMA. Patients that lose response to treatment are assumed to transition to conventional therapy, where a similar approach is taken, i.e. patients who do not respond to conventional therapy or lose response are assumed to remain with active UC. In line with TA329, conventional therapy is assumed to be the last line of therapy. Hence, patients remain on treatment indefinitely irrespective of whether they achieve response, unless they undergo surgery.

Details on how the NMA results are applied in the model are provided in Section B.3.3.1.

Surgery

Surgery is incorporated as two transient states: emergency surgery, and elective surgery. Patients who transition into the surgery states are assumed to stop all drug treatments for the remainder of the time horizon.

During the induction period, all patients are assumed to have active UC and are thus at risk of undergoing emergency (but not elective) surgery.

During the maintenance period, only patients with active UC are assumed to be at risk of undergoing surgery (emergency or elective). The model assumes that a proportion of patients undergo elective colectomy, aligned with the approach taken by the AG in TA329 (28). Additionally, in line with TA547, it is assumed that a proportion of patients with active UC suffer ulcerative colitis related acute exacerbation events, and require emergency surgery (66).

For both emergency and elective surgery, a perioperative risk of complications and mortality is assumed.

Post-surgery

Following colectomy, patients are allocated to post-surgery states, with or without complications, based on whether they experience long-term complications associated with the surgery. Additionally, patients have a constant risk of long-term complications arising every cycle after surgery. Long-term complications are assumed to be permanent.

Death

All-cause mortality is applied throughout the model. In addition, patients who undergo surgery have a risk of perioperative mortality.

Table 35. Features of the economic analysis

Factor	Previous appraisals				Current appraisal	
	TA329 (2015) (65)	TA342 (2015) (65)	TA547 (2018) (66)	TA633 (2020) (67)	Chosen values	Justification
Model framework	Markov model	Decision tree in induction phase, and Markov model in maintenance phase	Markov model	Decision tree in induction phase, and Markov model in maintenance phase	Markov model	Consistent with previous appraisals
Time horizon	Lifetime	10 years	Lifetime	Lifetime	Lifetime	Consistent with previous appraisals and the NICE reference case
Cycle length	8 weeks (induction) and 26 weeks (maintenance)	6 weeks (induction) and 8 weeks (maintenance)	8 weeks	2 weeks	10 weeks	Consistent with the length of the induction phase in the SELECTION trial
Discount for utilities and costs	3.5%	3.5%	3.5%	3.5%	3.5%	In line with the NICE reference case
Treatment waning effect and discontinuation	Treatment effect was assumed to be maintained with ongoing treatment. During the maintenance phase, patients were assumed to remain on the same advanced	Treatment effect was assumed to be maintained with ongoing treatment. Patients could discontinue advanced treatment due to lack of response or adverse events.	Treatment effect was assumed to be maintained with ongoing treatment. During the maintenance phase, patients were assumed to remain on the same advanced	Treatment effect was assumed to be maintained with ongoing treatment. During the maintenance phase, patients were assumed to remain on the same advanced	Treatment effect was assumed to be maintained with ongoing treatment. During the maintenance phase, patients were assumed to remain on the same advanced	Consistent with previous appraisals

	treatment until loss of response. If patients on advanced therapy lost response at any point, they transitioned to the active UC state.	Moreover, it was assumed that treatment with advanced therapy was at most one year, after which patients switched to conventional therapy.	treatment until loss of response. If patients on advanced therapy lost response at any point, they transitioned to the active UC state.	treatment until loss of response. If patients on advanced therapy lost response at any point, they transitioned to the active UC state.	treatment until loss of response. If patients on advanced therapy lost response at any point, they transitioned to the active UC state.	
Source of utilities	Utilities from Woehl et al. (139) were applied for all health states.	GEMINI 1 (vedolizumab trial) for pre-surgical states and. Post-surgical states from Punekar and Hawkins et al. (135)	Utilities from Woehl et al. (139) were applied for all health states. Utilities were adjusted for the age and sex of the population	Health state utilities for pre-surgical states from Woehl et al.(139) Post-surgical states from Arseneau et al. (140) Utilities were adjusted for the age and sex of the population	Health state utilities for pre-surgical states estimated from the SELECTION trial programme. Post-surgical states from Arseneau et al. (140) Utilities were adjusted for the age and sex of the population	There are limitations associated with the Woehl et al. publication. The SELECTION trial programme utilities is based on a large number of patients. A range of sensitivity analyses using different sources is provided.
Source of resource use	Tsai et al. (133)	Tsai et al. (133) Buchanan et al. (141)	Tsai et al. (133)	Tsai et al. (133)	Tsai et al. (133)	Consistent with previous appraisals
Source of costs	BNF for drug costs, and NHS reference costs 2012/13	BNF for drug costs, and NHS reference costs 2012/13	MIMS and eMIT for drug costs, NHS reference costs 2016/11, and PSSRU	BNF and MIMS for drug costs, previous submissions, published literature, NHS	MIMS for drug costs, NHS reference costs 2018/19	Consistent with the NICE reference case and previous appraisals

				reference costs 2017/18		
Adverse events	No AEs were considered	Serious infection, tuberculosis, lymphoma, hypersensitivity and injection site reaction	Serious infections only	Serious infections only	Serious infections only	Consistent with previous appraisals
Mortality	All-cause mortality and perioperative mortality associated with colectomy	All-cause mortality was adjusted for disease severity, surgery, post-surgery remission and complications	All-cause mortality and perioperative mortality associated with colectomy	All-cause mortality and perioperative mortality associated with colectomy	All-cause mortality and perioperative mortality associated with colectomy	Consistent with previous appraisals

Abbreviations: AE, adverse event; BNF, British National Formulary; eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialities; NHS, National Health System; NICE, National Institute for Health and Care Excellence; TA, technology appraisal; UC, ulcerative colitis

B.3.2.4 Intervention technology and comparators

Filgotinib is indicated for the treatment of moderately to severely active UC in adults who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent. The intervention considered in the model is filgotinib 200mg, administrated orally once daily. Filgotinib 100mg is not considered in the model, as this dosing is for a restrictive patient group with renal impairments (Table 2).

Comparators considered in the cost-effectiveness analysis are in line with NICE recommendations, and include the comparators in the final NICE scope for filgotinib:

- TNFα inhibitors (infliximab, adalimumab, and golimumab)
- Tofacitinib
- Ustekinumab
- Vedolizumab
- Conventional therapies.

A single dosing regimen is available for each advanced therapy during the induction phase. For the maintenance phase, two dosing regimens are considered in the analysis: standard dose and escalated dose. For the management of UC patients, clinicians are likely to consider dose escalation before considering surgery (based on clinician interviews, see Section B.3.10). In the base case, a proportion of patients are assumed to be treated with the escalated dose based on a literature review in Crohn's disease, which found that approximately 30% of patients on TNFα inhibitors had a dose escalation (142). It was assumed that the same percentage would apply to UC, as this is the same percentage used previously in TA633 (67). The same proportion is applied for other treatments. Dose escalation was only assumed to impact the cost of treatments, and not treatment response, as the added cost has a substantial impact on the results. The dosing regimens for advanced therapies are summarised in Table 36.

Table 36. Dosing regimen for the filgotinib and advanced comparators

Treatment	Route of administration	Dosing instruction	Standard dose (maintenance)	Escalated dose (maintenance)
Filgotinib	Orally	200mg daily	200mg qd	N/A
Adalimumab	SC	Initially 160mg, then 80mg at week 2, and 40mg every other week thereafter	40mg q2w	40mg qw
Golimumab	SC	Initially 200mg, then 100mg at week 2, and 50mg every 4 weeks thereafter	50mg q4w	100mg q4w
Infliximab	IV	Initially 5mg/kg, repeated at week 2 and 6, then every 8 weeks thereafter	5mg/kg q8w	5mg/kg q4w
Tofacitinib	Orally	10mg twice daily for 8 weeks, then 5mg twice daily	5mg bid	10mg bid
Ustekinumab	IV initially, then SC	Initial IV dose based on body weight: ≤ 55kg: 260mg >55kg to ≤ 85kg: 390mg > 85kg: 520mg Followed by a 90mg dose at week 8, then 90mg every 12 weeks thereafter	90mg q12w	90mg q8w
Vedolizumab IV	IV	300mg initially, repeated at week 2 and 6, then every 8 weeks thereafter	300mg q8w	300mg q4w
Vedolizumab	IV initially, then	300mg IV dose initially, repeated at	108mg q2w	N/A

SC	SC	week 2 and 6, then 108mg every 2 weeks thereafter		

Abbreviations: bid, twice per day; IV, intravenous; kg, kilogram; mg, milligram; qd, once daily; qw, once per week; q2w, once every two weeks; q4w, once every four weeks; q8w, once every eight weeks; q12w, once every twelve weeks; SC, subcutaneous

The assumed patient usage and dose regimens of treatments considered as conventional treatment are sourced from a recent national audit of the Royal College of Physicians (RCP) on inflammatory bowel diseases (IBD) (143). This is summarised in Table 37.

Table 37. Assumed patient usage for conventional treatment and dose regimens

Treatment	Route of administration	Dosing instruction	Patient usage
Amino salicylates			
Balsalazide	Orally	1.5mg twice daily adjusted according to response (maximum 6 g per day)	12.6%
Mesalazine	Orally	1.2 to 2.4g once daily	12.6%
Olsalazine	Orally	500mg twice daily	12.6%
Sulfasalazine	Suppository	0.5 to 1g twice daily	12.6%
Corticosteroids			
Budesonide*	Topically	1 metered application once daily on alternate days	3.8%
Prednisolone	Orally	Initially 20–40 mg daily until remission occurs, followed by reducing dose	44.1%
Immunomodulators			
Azathioprine	Orally	2.0 to 2.5mg/kg daily	46.4%

Abbreviations: g, gram; kg, kilogram; mg, milligram
Reference: RCP national audit on IBD (143)
*In a previous appraisal, TA547, hydrocortisone rectal foam was used. However, this product is no longer manufactured and budesonide rectal foam was considered the most appropriate replacement.

B.3.2.5 Treatment strategies in the model

For the biologic-naïve population, the model compared all strategies consisting of an advanced treatment in first-line, using all comparators available from the NMA, excluding ustekinumab which is not recommended for this population, followed by last-line conventional therapy. A treatment strategy considering conventional therapy alone, based on the placebo efficacy results from the NMA, was also included. Last-

line conventional therapy efficacy is based on assumed very low levels of efficacy (99% non-responders). Table 38 summarises the strategies considered for the biologic-naïve population.

Table 38. Treatment strategies considered for the biologic-naïve population

Sequence	First-line	Second-line
1	***Filgotinib***	***Conventional therapy***
2	Tofacitinib	Conventional therapy
3	Vedolizumab SC	Conventional therapy
4	Vedolizumab IV	Conventional therapy
5	Adalimumab	Conventional therapy
6	Golimumab	Conventional therapy
7	Infliximab	Conventional therapy
8	Conventional therapy	Conventional therapy

Abbreviations: IV, intravenous; SC, subcutaneous

For the biologic-experienced population, the model is assumed to start later in the treatment pathway (i.e. assuming all patients entering the model had previous exposure to a biologic treatment). Similar to the biologic-naïve population, all comparator therapies available from the NMA were considered. Table 39 summarises the strategies considered for the biologic-naïve population.

Table 39. Treatment strategies considered for the biologic-experienced population

Sequence	First-line	Second-line
1	***Filgotinib***	***Conventional therapy***
2	Tofacitinib	Conventional therapy
3	Ustekinumab	Conventional therapy
4	Vedolizumab SC	Conventional therapy
5	Vedolizumab IV	Conventional therapy
6	Adalimumab	Conventional therapy
7	Conventional therapy	Conventional therapy

Abbreviations: IV, intravenous; SC, subcutaneous

Due to the relapsing and remitting nature of UC, the treatment of UC is based on a patient by patient judgement, with the advice of changing medication promptly if no response or improvement is achieved. Thus, there is considerable uncertainty associated with defining a consistent sequence of treatments. Alternative treatment sequences, which consider multiple lines of advanced treatment, are explored in a scenario analysis. The treatment sequences are based on the NICE guidelines (Section B.1.3.4), clinician validation (Section B.3.10), and data from the IBD registry (144). These sources suggest that the majority of biologic-naïve patients are treated with vedolizumab or another TNFα inhibitor following failure of a TNFα inhibitor in first-line, with tofacitinib or ustekinumab commonly used as a third-line treatment. For comparisons, the same treatment sequences were applied for all comparators.

The results of the scenario analysis are presented in Section B.3.8.

B.3.3 Clinical parameters and variables

B.3.3.1 Treatment effectiveness: clinical response and remission

The model health states are defined in line with the SELECTION trial definitions.

Clinical remission in the SELECTION trial was defined as a Mayo score of 2 or less, and no single sub score higher than 1.

Clinical response in the SELECTION trial was defined as not meeting the remission definition, and a decrease from baseline Mayo score of at least 3 points and at least 30%, accompanied by a decrease from baseline in the rectal bleeding sub score of at least 1 point, or an absolute rectal bleeding sub score of 0 or 1.

Induction phase patient transitions

The distribution of patients in each health state at the end of the induction phase were informed by the NMA of the clinical trials for the induction period alone (Section B.2.9.4).

The absolute modelled probability of response for all treatments were calculated as part of the NMA results (presented in Section B.2.9) as follows:

- The modelled probabilities of response for placebo (the reference treatment in the NMA) were estimated.

- The modelled proportion of patients achieving overall response (overall response and remission) were derived by applying the relative treatment effect versus placebo, as estimated in the NMA.

The proportion of patients achieving response (i.e. without remission) was estimated as the difference of patients receiving overall response (including remission), and patients achieving remission. The proportion of patients that do not respond to treatment, and remain in active UC, was calculated as the proportion of patients not achieving response.

The induction phase treatment efficacy, i.e. the proportion of patients achieving remission, response without remission, and the proportion of patients who remain in active UC after the induction period, for both biologic-naïve and biologic-exposed subgroups, is summarised in Table 40.

Table 40. Estimated treatment efficacy based on NMA of trials at induction

Treatment	Active UC	Response without remission	Remission
Biologic-naïve			
Filgotinib	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]	[redacted]
Conventional therapy	[redacted]	[redacted]	[redacted]
Conventional therapy (last-line)*	[redacted]*	[redacted]*	[redacted]*
Biologic-exposed			

Filgotinib	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]	[redacted]
Conventional therapy	[redacted]	[redacted]	[redacted]
Conventional therapy (last-line)*	[redacted]*	[redacted]*	[redacted]*

Abbreviations: UC, ulcerative colitis
*Assumption

Maintenance phase patient transitions

Maintenance transition probabilities were converted from estimates of non-response, response (including remission), and remission in the maintenance NMA to 10-weekly probabilities, which were applied in the model over the 50-week maintenance phase period. After this, patients are assumed to remain at the same level of response and on the same treatment indefinitely, unless they lose response. In clinical practice, patients achieving long-term stable remission may discontinue treatment. A stopping rule is explored in a scenario analysis, assuming a proportion of patients in remission after the 50-week maintenance phase discontinue treatment. This is presented in Section B.3.8.4.

Upon loss of response in the model, patients discontinue current treatment. In line with previous technology appraisals in UC, the long-term loss of response over the model time horizon was estimated from the NMA results. The base case applies the results from the base case NMA (Section B.2.9). As highlighted in Section B.2.9.7, there is a considerable heterogeneity associated with different trial designs included in the NMA (treat-through and re-randomised trials). Therefore, two scenario analyses were also explored using results of sensitivity analyses from the NMA: excluding treat-through trials, and using an alternative methodology to re-weighting treat-through trial data (see Section B.2.9.12). This is presented in Section B.3.8.4.

Since the model applied the results from the NMA, the same duration was assumed for all comparator evidence, despite differences in trial lengths (see Section B.2.9.7. on outcome timepoint heterogeneity). The economic analysis therefore considered the SELECTION trial programme duration for both induction and maintenance phases (10 weeks and 48 weeks, respectively). As the model applies 10-weekly cycles, the length of the maintenance phase was assumed to be 50 weeks. Hence, the output of the maintenance phase NMA was assumed to reflect results over 60 weeks of treatment; 10 weeks in induction, and 50 weeks in maintenance.

Assuming a constant risk, the probability of no response was adjusted to a 10-weekly rate using

$$\text{10-weekly loss of response} = 1 - \exp(-\lambda)$$

where

$$\lambda = -\frac{\text{Cycle length}}{\text{Maintenance length}} \log(1 - \Pr(\text{no response at maintenance}))$$

The risk of loss of response was extrapolated beyond the trial periods, and assumed to be constant, i.e. the same rate was applied every cycle for the duration of treatment. The number of patients remaining on treatment was then estimated, i.e. those sustaining remission and response without remission, and patients were distributed according to the NMA maintenance results:

$$\text{Proportion remission} = \frac{\Pr(\text{remission at maintenance})}{\Pr(\text{overall response at maintenance})}$$

$$\text{Proportion response} = \frac{\Pr(\text{response without remission at maintenance})}{\Pr(\text{overall response at maintenance})}$$

Furthermore, it was assumed that the observed health state allocation for responders (remission, or response without remission) at the end of the maintenance phase remained the same in subsequent cycles.

The resulting maintenance phase transition probabilities are summarised in Table 41.

Table 41. Estimated long-term treatment efficacy based on NMA of trials at maintenance (per cycle probabilities)

Treatment	Loss of response (10-weekly rate)	Response without remission (proportion of patients)	Remission (proportion of patients)
Biologic-naïve			
Filgotinib	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]
Vedolizumab IV	[redacted]	[redacted]	[redacted]
Vedolizumab SC	[redacted]	[redacted]	[redacted]
Conventional therapy	[redacted]	[redacted]	[redacted]
Conventional therapy (last-line)*	[redacted]	[redacted]	[redacted]
Biologic-exposed			
Filgotinib	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]
Vedolizumab IV	[redacted]	[redacted]	[redacted]
Vedolizumab SC	[redacted]	[redacted]	[redacted]
Conventional therapy	[redacted]	[redacted]	[redacted]
Conventional therapy (last-line)*	[redacted]	[redacted]	[redacted]

Abbreviations: IV, intravenous; SC, subcutaneous.
*Assumption

B.3.3.2 Surgery and surgery complications

A proportion of patients with active UC were assumed to undergo colectomy, based on published literature as detailed below.

Colectomy rates

No updated literature informing colectomy rates was identified in the HRCU SLR (Appendix I), therefore, consistent with previous recent TAs (66, 67), the rates of elective and emergency surgery for patients with active UC were taken from Misra et al., a retrospective 15-year study of the UK Hospital Episode Statistics database (145). The study observed a total of 71,966 patients with UC admitted to hospital (excluding patients undergoing colectomy due to colorectal cancer). A total of 5,044 patients underwent colectomy, out of which 3,633 had elective, and 1,411 had emergency colectomy (145). Hence, the 15-year cumulative risk of elective and emergency colectomy were estimated to be 5.05% and 1.96%, respectively.

This resulted in an estimated 10-weekly probability of 0.066% for elective surgery, and 0.025% for emergency surgery.

Perioperative complications

The rates of short-term surgical complications were obtained from the UK 2014 national audit of inpatient care for adults with UC (146). The publication reported national- and hospital-level findings on the quality of care provided to people admitted between 1 January 2013 and 31 December 2013. Perioperative complications were reported for 32% and 35% of patients who underwent elective and non-elective surgery, respectively. This estimate was also applied in previous recent TAs in UC (66, 67).

Post-surgery complications

A proportion of patients are expected to experience long-term complications after undergoing colectomy. Consistent with TA547, the rates of long-term complications post-surgery were obtained from Ferrante et al. (147), a study which reported the rate of pouchitis in UC patients undergoing proctocolectomy over 6.5 years of follow-up as 46%, which resulted in an estimated 10-week probability of 1.81%.

B.3.3.3 Adverse events

In line with previous TAs (66, 67), only serious infections are included in the analysis due to substantial impact on costs and health-related quality of life (HRQoL).

The base case analysis applies the output from the NMA (Section B.2.9.13). The NMA results were converted to 10-weekly probabilities. The AE rates used for the base case are summarised in Table 42.

Table 42. Rates of adverse events (serious infections) applied the base case

Treatment	Probability of serious infection (from safety NMA)	10-weekly probability of serious infection
Filgotinib	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]
Conventional therapy	[redacted]	[redacted]

Abbreviations: NMA, network meta-analysis.

In a scenario analysis, the rates of serious infections applied in TA547 were used, obtained from a safety NMA as reported by Lohan et al. (124). As the NMA by Lohan et al. (124) did not include filgotinib or ustekinumab, conservative assumptions were applied. Filgotinib was assumed to have the same rate as tofacitinib (the only other JAK inhibitor included in the analysis), which had the highest infection rate. Ustekinumab was assumed to have the same rate as vedolizumab, which had the lowest infection rate. The AE rates used in a scenario are summarised in Table 43.

Table 43. Rates of adverse events (serious infections) applied in a scenario

Treatment	Probability of serious infection
Filgotinib	3.8%
Adalimumab	0.9%

Golimumab	0.1%
Infliximab	0.4%
Tofacitinib	3.8%
Ustekinumab	0.2%
Vedolizumab	0.2%
Conventional therapy	0.9%

B.3.3.4 Mortality risk

Age-dependent all-cause mortality was applied in the model. Using age- and sex-dependent mortality rates obtained from UK life tables, a weighted age-dependent mortality probability was calculated using the proportion of male and female patients in each subgroup (Section B.3.2.1, Table 33), to reflect the model patient population.

In the model, patients are assumed not to have an increased UC-specific mortality risk due to disease severity or treatment in the pre- and post-surgery states. A perioperative mortality is applied to all patients undergoing surgery using the rate of 2.84%, obtained from Archer et al (148).

B.3.4 Measurement and valuation of health effects

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

EQ-5D-5L data were collected alongside the SELECTION trial at week 10 (induction study), and week 58 (maintenance study). The utility data were analysed to predict the mean utility for each pre-surgical health state of the model (remission, response without remission, active UC). The health utilities were calculated and summarised using the crosswalk algorithm mapped to the EQ-5D-3L UK value set (149).

The mean utility scores across patients were then calculated to obtain estimates for the mean utilities by health state. The resulting utilities are summarised in Table 44.

Table 44. Estimated utility values from SELECTION in the induction and maintenance studies by health state

Outcome	Non responder/active UC	Response without remission	Remission
Baseline			
N	[redacted]	N/A	
Mean utility (SE)	[redacted]		
Week 10			
N	[redacted]	[redacted]	[redacted]
Mean utility (SE)	[redacted]	[redacted]	[redacted]
Week 58			
N	[redacted]	[redacted]	[redacted]
Mean utility (SE)	[redacted]	[redacted]	[redacted]

Abbreviations: SE, standard error; UC, ulcerative colitis

B.3.4.2 Mapping

No mapping was used to assess the health state utility values from the SELECTION trial, as EQ-5D data were collected in the trial programme.

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

A systematic literature review was conducted to assess published literature that characterises the impact of UC on HRQoL, the details of which are discussed in Appendix H. A summary of the utility data identified and used in the model is provided in Section B.3.4.5.

B.3.4.4 Adverse reactions

The only adverse events relating to pharmaceutical treatments considered for the analysis were serious infections (Section B.3.3.3). Experiencing an adverse reaction results in a fixed loss of HRQoL. The disutility for pneumonia (-0.52) was obtained from a cost-effectiveness study by Wilson et al. (137) This was then adjusted for the expected duration of the event (7 days, in line with TA547 (66)), resulting in a disutility of 0.052 applied over the 10-weekly cycle.

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

Each health state in the model is associated with utility values. For the base case, the utility values estimated from the SELECTION trial programme are used. The value at baseline is used for the active UC health state. For the remission and response without remission health states, the utility values calculated at the end of the induction phase (10 weeks) are used, as these estimates are based on a higher number of patients than the values at 58 weeks. A scenario analysis using the estimates at 58 weeks is also provided in Section B.3.8.4.

In order to characterise the surgery with complications and post-surgery states (as no appropriate values were reported in SELECTION) a study by Arsenau et al. (140) was used (140). The ratios between each state and remission were calculated using the values from Arsenau et al (140). These ratios were then applied to the remission utility value in SELECTION.

A summary of the base case utility inputs is provided in Table 45.

Table 45. Summary of utility values used for the cost-effectiveness analysis base case

State	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
Baseline	Dependent on age and sex	Section B.3.4.5	To reflect the natural decline of patients' quality of life associated with age
Remission	[redacted]	Section B.3.4.5	Estimated from the SELECTION clinical trial
Response without remission	[redacted]	Section B.3.4.5	
Active UC	[redacted]	Section B.3.4.5	
Surgery	[redacted]	Section B.3.4.5	Surgery and post-surgery states imputed using the rates in Arsenau et al. (140), as surgical health state utilities were not available from SELECTION
Surgery with complications	[redacted]	Section B.3.4.5	
Post-surgery without complications	[redacted]	Section B.3.4.5	
Post-surgery with complications	[redacted]	Section B.3.4.5	
Disutility due to serious infection	-0.052 (0.019)	Section B.3.4.4	Consistent with TA547

Abbreviations: TA, technology appraisal; UC, ulcerative colitis

There are some limitations associated with the use of the utility values estimated from the SELECTION trial. Firstly, there are no trial data that can be used to inform the surgery and post-surgical health states. Secondly, there is a potential for adaptation and selection bias. Since UC is a chronic disease, patients may overestimate their EQ-5D scores, e.g. report that they have no problems with their usual activities because they have adapted to living with their disease. There is also a general limitation with EQ-5D data collected in trials due to selection bias (i.e. patients who do not feel well do not fill in the questionnaire). In both cases, the utility for the more severe health states may be skewed upwards.

Notably, there is a lack of consistency between the estimated health utility values from SELECTION and from published literature, which is particularly true for the active UC health state. It should be noted that the active UC health state in the model includes patients where no further biologic treatment would be given, and patients remain in this health state until they receive surgery or die. This is not true

for patients entering the SELECTION trial. Therefore, it is likely that the utility value for the active UC state is overestimated in the base case, resulting in conservative estimates when comparing advanced therapies to conventional therapy.

Recent technology appraisals in UC, including TA329, have applied utility values sourced from Woehl et al. (139). This study used the EQ-5D questionnaire to collect utility scores from 180 patients with active UC in the UK and reported utility scores for patients in remission, mild disease, moderate to severe disease, and post-colectomy (without complications). This publication is only available as an abstract that includes limited information about the study methodology and the patient characteristics, and therefore, the use of this study has been noted as a source of uncertainty in previous appraisals due to methodological and reporting issues (67).

As there are a number of published studies reporting utility values in UC that have been noted as appropriate sources in previous technology appraisals, scenario analyses are provided using a range of utility inputs. Most studies did not report values for the surgery and post-surgery states, and therefore these values were imputed using the values from Arsenau et al. (140), as described for the base case.

A summary of the values used in scenario analyses is provided in Table 46.

Table 46. Summary of health state utility values used in a scenario analysis

State	SELECTION trial (58 weeks)	Woehl et al. 2008 (n=180, UK setting)	Swinburn et al. 2012 (n=230, UK setting)	Vaizey et al. 2013 (n=173, UK setting)	Arsenau et al. 2006 (n=48, US setting)
Remission	[redacted]	0.870	0.910	0.860	0.790
Response without remission	[redacted]	0.760	0.800	0.770	0.790[b]
Active UC	[redacted]	0.410	0.550	0.660	0.320
Surgery	[redacted]	0.720	0.660[a]	0.620[a]	0.570
Surgery with complications	[redacted]	0.540[a]	0.560[a]	0.530[a]	0.490
Post-surgery without complications	[redacted]	0.750[a]	0.780[a]	0.740[a]	0.680
Post-surgery with complications	[redacted]	0.440[a]	0.460[a]	0.440[a]	0.400

Abbreviations: UC, ulcerative colitis; UK, United Kingdom; US, United States
References: Woehl et al. (139), Swinburn et al. (150), Vaizey et al. (151), Arsenau et al. (140)
[a] Value not reported in study, imputed using estimates from Arsenau et al. (140)
[b] Value not reported in study, assumed equal to the remission utility value.

Adjusted baseline utility

An adjustment of health state utility values by age and sex was applied to all patients in the model to account for the natural decline of quality of life due to age and comorbidities.

Consistent with TA547 and TA633, the baseline utility values were adopted from a regression model by Ara and Brazier, which was based on data from the Health Survey for England in 2003 and 2006 (152). The following equation was used

$$\mathrm{U_{base}}(\mathrm{age}, \mathrm{sex}) = 0.9508566 + 0.0212126 * \mathrm{male} - 0.0002587 * \mathrm{age} - 0.0000332 * \mathrm{age}^2$$

For the age and sex values of $\mathrm{U_{base}}$, the analysis used the model population inputs (Table 33, Section 3.2.1). Utility weights for all health states were calculated by dividing their original utility values by the remission utility weight, and thereby adjusting the remission utility weight to 1. The utility value for a given health state at a specific age was then determined by multiplying $\mathrm{U_{base}}$ at that age by the utility weight of the given health state.

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

A systematic literature review was conducted to identify cost and resource use data associated with patients with UC from the published literature. Full details of the search are provided in Appendix I.

In line with NICE requirements, the model only considered direct medical costs. Cost and healthcare resource use inputs comprised drug acquisition, administration costs, costs associated with management of adverse events, and background disease management costs. Costs were obtained from published literature, 2018/19 NHS reference costs (published in 2020) (153), and the Monthly Index of Medical Specialties (MIMS) 2021 (154).

B.3.5.1 Intervention and comparators' costs and resource use

The model includes separate costs for drug acquisition and administration. Costs are applied per cycle and are separated for induction treatment (including any loading doses) and maintenance treatment.

Intervention and advanced treatment costs

Drug acquisition costs are based on UK costs and dosing regimens from MIMS 2021 (154). Treatment costs per 10-weekly cycle are based on the recommended posology for each treatment. Where more than one posology was available, dose escalation was considered and a weighted average cost was applied based on the number of patients estimated to have an escalated dose, based on a systematic review of the literature in Crohn's disease, which estimated that approximately 30% of patients had dose escalation on either adalimumab or infliximab (142). The same estimate was used previously in TA633 (67). This estimate was varied in a scenario analysis (Section B.3.8.3). It was assumed that the dose escalation was similar in UC, and that the same rate of escalation would also apply to vedolizumab, ustekinumab, golimumab and tofacitinib.

For drugs with weight-based dosing (infliximab and ustekinumab), doses for patients were computed based on a simulated baseline weight distribution, using a normal

distribution with mean and standard deviation based on the SELECTION trial, as detailed in Section B.3.2.1.

Simponi® (golimumab) has a non-confidential PAS scheme, where a higher dose is provided at a fixed price. Therefore, the cost of treatment with dose escalation is the same as for the standard dose. Confidential PAS prices were excluded for Xeljanz® (tofacitinib), Entyvio® (vedolizumab), and Stelara® (ustekinumab). Biosimilars are costed in the same way. Biosimilars for adalimumab and infliximab are included in the model. The model only considers the lowest priced biosimilars as comparators.

A summary of the pack costs, sizes and dosing regimens for treatments included in the model with the resultant ten-weekly medication costs (including a proportion of patients having dose escalation) is shown in Table 47.

Table 47. Summary of pack cost, sizes and dosing regimens for each treatment

Treatment		Pack cost	Pack size	Dosing regimen (maintenance)	Cost per cycle	
					Induction	Maintenance
FIL	Jyseleca® (brand)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	Amgevita™ (biosimilar)	£633.60	40mg x 2	40mg q2w, or dose escalated to qw	£2,851.20	£2,057.62
GOL	Simponi® (brand)	£762.97	162mg x 4	50mg q4w, or dose escalated to 100mg q4w	£2,659.71[c]	£1,907.43
IFX	Inflectra™ (biosimilar)	£377.00	100mg x 1	5mg/kg q8w	£3,941.54[a]/ £4,173.39[b]	£2,133.36[a]/ £2,258.85[b]
TOF	Xeljanz® (brand)	£690.03	5mg x 56	5mg bid, or dose escalated to 10mg bid	£3,208.29	£2,240.87
VDZ SC	Entyvio® (brand)	£1,025.00	108mg x 2	108mg q2w	£6,150.00	£2,562.50
VDZ IV	Entyvio® (brand)	£2,050.00	300mg x 1	300mg q8w, or dose escalated to 300mg q4w	£6,150.00	£3,328.69
UST	Stelara® (brand)	£2,147.00	13mg x 1 IV 90mg x 1 SC	90mg q12w, or dose escalated to 90mg q8w	£6,697.63[b]	£2,056.65

Abbreviations: bid, twice per day; kg, kilogram; mg, milligram; qd, once daily; qw, once per week; q2w, once every two weeks; q4w, once every four weeks; q8w, once every eight weeks; q12w, once every twelve weeks
[a] Based on the baseline weight for the biologic-naïve subgroup [b] Based on the baseline weight for the biologic-exposed subgroup [c] Induction dose is 2 doses (initially and at week 2) therefore not all patients may receive a third dose at week 6. Average price reflects the % of patients who are responders as estimated in the NMA (all assumed to receive the third dose), and assumes 0 % of non-responders would receive a third dose.

Conventional therapy costs

Drug acquisition costs provided in the model are based on UK costs obtained from MIMS 2021 (154). The usage of each treatment was sourced from TA547, both for conventional therapy alone, and as a concomitant therapy with advanced treatments (66). The resulting per cycle cost of conventional therapy alone was £83.08, and £65.96 as a concomitant therapy with biologics. The cost of concomitant treatment with JAK inhibitors (tofacitinib and filgotinib) differs from that of the biologics, as immunomodulators are not recommended for concomitant use with JAK inhibitors, and the estimated cost of concomitant therapy was £63.16. Unit drug costs and total costs per year for each concomitant treatment are summarised in Table 48. The calculated average annual costs of conventional therapy per patient are shown in Table 49.

Table 48. Summary of pack cost, sizes and dosing regimens for each conventional therapy

Treatment	Pack cost	Pack size	Dosing regimen	Cost per dose	Per cycle cost
Balsalazide (Colazide®)	£30.42	750mg x 130	1.5mg twice daily adjusted according to response (maximum 6g per day)[a]	£0.47	£65.52
Mesalazine (Asacol®)	£15.50	400mg x 120	1.2 to 2.4g once daily [a]	£0.39	£27.13
Olsalazine	£161.00	500mg x 60	500mg twice daily	£2.68	£375.67
Sulfasalazine	£3.30	500mg x 10	0.5 to 1g twice daily [a]	£0.33	£46.20
Prednisolone (Pevanti®)	£3.80	20mg x 30	Initially 20–40 mg daily until remission occurs, followed by reducing dose	£0.13	£8.87
Budesonide (Budenofalk®)	£57.11	2mg x 14	One actuation daily	£4.08	£285.55
Azathioprine	£3.10	50mg x 56	2.0 to 2.5mg/kg daily [a]	£0.15	£7.53

Abbreviations: g, gram; kg, kilogram; mg, milligram
[a] The lowest dose was used for the model

Table 49. Calculation of concomitant conventional therapy costs

Treatment	Total cost per cycle	Conventional therapy		Advanced therapy	
		Usage as conventional therapy alone[a]	Average cost per patient	Usage concomitant to advanced therapy[b]	Average cost per patient
Balsalazide (Colazide®)	£65.52	12.6%	£8.26	11.6%	£7.60
Mesalazine (Asacol®)	£27.13	12.6%	£3.42	11.6%	£3.15
Olsalazine	£375.67	12.6%	£47.33	11.6%	£43.58
Sulfasalazine	£46.20	12.6%	£5.82	11.6%	£5.36
Prednisolone (Pevanti®)	£8.87	44.1%	£3.91	19.9%	£1.76
Budesonide (Budenofalk®)	£285.55	3.8%	£10.85	0.6%	£1.71
Azathioprine	£7.53	46.4%	£3.49	37.2%/0%[c]	£2.80/£0.00[c]
Total cost of conventional therapy per cycle		**£83.08**		**£65.96/£63.16[c]**	

[a] Proportion of use of in conventional treatment as part of the conventional therapy mix, sourced from TA547 (66)
[b] Proportion of use of conventional treatments as concomitant therapy to advanced therapy, sourced from TA547 (66)
[c] Immunomodulators are not recommended in concomitant use with filgotinib and tofacitinib

Treatment administration costs

Costs of administration were dependent on mode of administration, i.e. IV, SC, or oral. Orally administered drugs (filgotinib and tofacitinib) were assumed to have no administration cost.

It was assumed that for subcutaneous injections, patients either self-inject their medication, or acquire no administration costs otherwise due to homecare and support schemes offered by the manufacturers.

Consistent with TA547 and TA633, the administration costs for IV drugs were assumed to be equal to the cost of an outpatient visit (66, 67). This was calculated using the weighted average of a consultant and a non-consultant led non-admitted face-to-face follow-up appointment. The unit costs and number of attendances were sourced from the 2018/19 NHS reference costs for gastroenterology service, and the

average cost of an outpatient visit was estimated to be £133.19 (153). Unit costs and inputs for the calculation are provided in Table 50.

Table 50. Treatment administration for IV therapies

Currency code and description	Number of attendances	National average unit cost
WF01A, Consultant led (CL), Non-Admitted Face-to-Face Attendance, Follow-up (Gastroenterology)	828,052	£137.88
WF01A, Non-consultant led (NCL), Non-Admitted Face-to-Face Attendance, Follow-up (Gastroenterology)	111,620	£98.38
Estimated cost of an IV administration (outpatient visit)	**£133.19**	

Abbreviations: IV, intravenous
Reference: NHS reference costs 2018/19 (153)

B.3.5.2 Health-state unit costs and resource use

The model includes disease management costs comprising regular outpatient visits, blood tests, endoscopy, and hospitalisations. In line with previous submissions, no additional treatment-related monitoring costs were assumed (28, 65-67).

Resource use inputs were based on a UK cost-effectiveness model, Tsai et al. (133). The estimates in this study have also been applied in previous TAs in UC (TA329, TA342, TA547, TA633 (28, 65-67)). No updated estimates were identified in the HCRU SLR (Appendix I), therefore, this study was considered the best available evidence due to lack of studies quantifying the resource use for patients with UC by disease severity or activity. The health state definitions for active UC, remission, and response without remission applied in Tsai et al. (133) align with the definitions in the cost-effectiveness model.

Tsai et al. (133) reported annual resource use for each of the model health states, which were estimated by a panel of UK gastroenterologists. However, consistent with TA547, the estimated annual hospitalisation episodes were increased to 1.20 for the response without remission health state, and 1.50 for the active UC health state. This adjustment is applied based on the notion that hospitalisation rates increase as

patient health worsens, based on clinical expert advice referenced in TA547 (66). All other resource use inputs were obtained directly from Tsai et al. (133), and are summarised in Table 51.

As Tsai et al. (133) reported no measures of variability for the estimated resource use, the range estimated in TA547 using adjacent health state values was used to calculate a standard error for model input (66). In TA547, for response without remission, the active UC resource use was used as the upper limit, and the remission resource use as the lower limit. For remission and post-surgery without complications the lower limit was assumed to be no resource use, and the upper limit was set to that of response without remission. The standard error applied in this analysis is then calculated using the upper and lower limits, assuming a normal distribution.

The cost of hospitalisation was calculated as the weighted average of all the attendances of the non-elective inpatient entries from the NHS reference costs (£3,289.00). All unit costs were taken from published NHS reference costs for 2018/19 (153).

Table 51. Health care resource use by model health state

Resource item	Unit cost	Resource use per health state per annum – number (SE)						
		Active UC	Response without remission	Remission	Surgery (without complications)	Surgery (with complications)	Post-surgery (without complications)	Post-surgery (with complications)
Outpatient visit	£133.19	6.5 (1.0)	4.5 (1.3)	2 (1.3)	0 (0.0)	0 (0.0)	1.5 (1.5)	1.75 (0.1)
Blood tests	£1.76	6.5 (1.3)	3.9 (1.3)	3.25 (1.7)	0 (0.0)	0 (0.0)	1.5 (1.2)	3.25 (0.9)
Endoscopy	£232.47	2 (0.8)	0.5 (0.8)	0.2 (0.2)	0 (0.0)	0 (0.0)	1.25 (0.6)	0.65 (0.3)
Hospitalisation episodes	£3,289.00	1.5 (0.2)	1.2 (0.5)	0.3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	3.25 (1.7)
Colectomy without complication	£6,622.91	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Colectomy with complication	£7,887.46	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)

Abbreviations: SE, standard error; UC, ulcerative colitis
Reference: Tsai et al. (133) and NHS reference costs 2018/19 (153)

The annual costs associated with each health state are summarised in Table 52.

Table 52. Total annual cost of resource use by health state

Health state	Annual cost
Active UC	£6,275.61
Response without remission	£4,669.25
Remission	£1,305.29
Surgery (without complications)	£6,622.91
Surgery (with complications)	£7,887.46
Post-surgery (without complications)	£493.01
Post-surgery (with complications)	£11,079.16

Abbreviations: UC, ulcerative colitis

The resource use estimates reported in Tsai et al. have been applied in previous NICE appraisals in UC (28, 65-67). However, the study by Tsai et al. (133) was published in 2008, and it has been highlighted in previous appraisals that these estimates may be higher than expected in current clinical practice in England and Wales (66). These inputs were also highlighted as a source of uncertainty as part of NICE Early Scientific Advice sought by the company (see Section B.3.10). The HCRU SLR conducted did not identify more recently published studies reporting updated resource use estimates (Appendix I), and, therefore, the estimates from Tsai et al. were applied in the economic analysis base case.

In the absence of more recently published evidence, interviews with five England-based gastroenterologists were conducted (see Section B.3.10) to elicit resource use estimates. Each clinician completed a survey and provided an estimation of the predicted annual resource use (i.e. outpatient visits, blood tests, endoscopy and hospitalisation episodes) by health state. The clinician estimates are broadly similar to the base case estimates for patients in remission, and post-surgery (without complications), but the average predicted resource use is somewhat lower for hospitalisations and outpatient visits in the more severe health states. It should be

noted, however, that these estimates are only based on five responses from separate clinician interviews, and the responses varied in some measure.

The average estimates, and the lowest and highest estimates provided, are presented in Table 53.

Table 53. Health care resource use by model health state based on clinician interviews – applied in a scenario analysis

Resource item	Resource use per health state per annum – Average (minimum - maximum)				
	Active UC	Response without remission	Remission	Post-surgery (without complications)	Post-surgery (with complications)
Outpatient visit	4.5 (4 - 6)	3.75 (3 - 4)	1.5 (1 - 2)	1.5 (1 - 2)	4.5 (2 - 10)
Blood tests	6 (4 - 12)	4.25 (3 - 6)	1.75 (0 - 4)	1.25 (0 - 2)	4.5 (2 - 10)
Endoscopy	1.5 (1 - 2)	1.25 (1 - 2)	0.25 (0 - 1)	0.25 (0 - 1)	0.25 (0 - 1)
Hospitalisation episodes	0.67 (0 - 1)	0 (0 - 0)	0 (0 - 0)	0 (0 - 0)	0.5 (0 - 1)

Abbreviations: UC, ulcerative colitis

B.3.5.3 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 B.3.4.4). Cost of serious infection was calculated based on the average of six types of serious infections: sepsis, tuberculosis, pneumonia, skin and soft tissue infection, bone and joint infection and urinary tract infection. The costs were estimated from the NHS reference costs 2018/19 by applying weight based on the number of finished consultant episodes reported for each event type (153). The cost of serious infections was estimated at £2,841.18. Unit costs and inputs for the calculation are provided in Table 54.

Table 54. Unit costs of treatment for adverse events

Adverse event type	Unit cost	Weights	Currency codes and description
Sepsis	£3,110.91	169,340	Weighted average of WJ06A to WJ06J (non-elective

			inpatient long-stay)
Tuberculosis	£4,203.68	2,288	Weighted average of DZ14F to DZ14J (non-elective inpatient long-stay)
Pneumonia	£2,706.96	308,228	Weighted average of DZ11K to DZ14V (non-elective inpatient long-stay)
Soft tissue infection	£2,358.13	15,445	Weighted average of HD21D to HD21H (non-elective inpatient long-stay)
Bone and joint infections	£4,934.37	12,257	Weighted average of HD21D to HD21H (non-elective inpatient long-stay)
Urinary tract infection	£2,652.37	135,683	Weighted average of LA04H to LA04S (non-elective inpatient long-stay)
Cost of an adverse event	**£2,841.18**		

Reference: NHS reference costs 2018/19 (153)

B.3.5.4 Miscellaneous unit costs and resource use

The costs associated with colectomy were obtained from the NHS reference costs 2018/19 using a weighted average of elective inpatient costs for proximal and distal colon procedures (153). This resulted in a cost of £7,887.46 and £6,622.91 for the surgery health states with and without complications, respectively. Unit costs and inputs for the calculations are provided in Table 55 and Reference: NHS reference costs 2018/19 (153)

Table 56.

Table 55. Costs of colectomy operation and perioperative complications

Currency code and description	Number of attendances	National average unit cost
FF32A, Elective inpatient (EL), Proximal Colon Procedures, 19 years and over, with CC Score 6+	655	£9,087.00

FF32B, Elective inpatient (EL), Proximal Colon Procedures, 19 years and over, with CC Score 3-5	1,896	£7,600.97
FF33A, Elective inpatient (EL), Distal Colon Procedures, 19 years and over, with CC Score 3+	727	£7,553.90
Estimated cost of a colectomy with complications	**£7,887.46**	

Reference: NHS reference costs 2018/19 (153)

Table 56. Costs of colectomy operation without perioperative complications

Currency code and description	Number of attendances	National average unit cost
FF32C, Elective inpatient (EL), Proximal Colon Procedures, 19 years and over, with CC Score 0-2	4,653	£6,823.30
FF33B, Elective inpatient (EL), Distal Colon Procedures, 19 years and over, with CC Score 0-2	2,228	£6,204.41
Estimated cost of a colectomy without complications	**£6,622.91**	

Reference: NHS reference costs 2018/19 (153)

B.3.6 Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

The inputs included in the base case analysis are summarised in Table 57.

Table 57. Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Standard error	Measurement of uncertainty and distribution	Reference to section in submission
Model parameters				
Discount rate (costs and effects	3.5%	Fixed	No sampling	B.3.2.3 Model structure
Age (biologic-naïve) (biologic-	 42 years 43 years	 0.510 0.549	Normal	B.3.2.1 Patient population

experienced)				
Weight (biologic-naïve) (biologic-experienced)	69.7 kg 73.8 kg	0.677 0.671	Normal	B.3.2.1 Patient population
Proportion male (biologic-naïve) (biologic-experienced)	55.7% 61.0%	0.0557 0.0610	Beta	B.3.2.1 Patient population
Transition probabilities				
Elective surgery (active UC)	0.00065	0.00103	Beta	B.3.3.2 Surgery and surgery complications
Emergency surgery (active UC)	0.00025	0.00122	Beta	B.3.3.2 Surgery and surgery complications
Immediate complications (elective surgery)	0.317	0.165	Beta	B.3.3.2 Surgery and surgery complications
Immediate complications (emergency surgery)	0.347	0.180	Beta	B.3.3.2 Surgery and surgery complications
Perioperative mortality	0.028	0.003	Beta	B.3.3.4 Mortality risk
Post-surgery long term complications	0.018	0.004	Beta	B.3.3.2 Surgery and surgery complications
Treatment specific efficacy (induction and maintenance response)	Based on NMA results (Table 40 and Table 41)	Estimated from the NMA	Dirichlet	B.3.3.1 Treatment effectiveness: clinical response and remission
Utilities				
Adverse event utility decrement (serious infections)	0.052	0.019	Beta	B.3.4.4 Adverse reactions
Active UC	[redacted]	[redacted]	Beta	B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Response	[redacted]	[redacted]	Beta	B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis
Remission	[redacted]	[redacted]	Beta	B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis
Surgery no complications	[redacted]	[redacted]	Beta	B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis
Surgery complications	[redacted]	[redacted]	Beta	B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis
Post-surgery no complications	[redacted]	[redacted]	Beta	B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis
Post-surgery complications	[redacted]	[redacted]	Beta	B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis
Costs				
Per cycle treatment costs (advanced therapies, induction)				
Filgotinib	[redacted]	Fixed	No sampling	B.3.5.1 Intervention and comparators' costs and resource use
Adalimumab	£2,851.20			
Golimumab	£2,659.71			
Infliximab (biologic-naïve) (biologic-experienced)	£3,941.54 £4,173.39			
Tofacitinib	£3,208.29			
Vedolizumab SC	£6,150.00			
Vedolizumab IV	£6,150.00			
Ustekinumab (biologic-experienced)	£6,697.63			

Per cycle treatment costs (advanced therapies, maintenance)				
Filgotinib	[redacted]	Fixed	No sampling	B.3.5.1 Intervention and comparators' costs and resource use
Adalimumab	£2,057.62			
Golimumab	£1,907.43			
Infliximab (biologic-naïve) (biologic-experienced)	£2,133.36 £2,258.85			
Tofacitinib	£2,240.87			
Vedolizumab SC	£2,562.50			
Vedolizumab IV	£3,328.69			
Ustekinumab	£2,056.65			
Per cycle conventional therapy costs				
Balsalazide	£65.52	Fixed	No sampling	B.3.5.1 Intervention and comparators' costs and resource use
Mesalazine	£27.13			
Olsalazine	£375.67			
Sulfasalazine	£46.20			
Prednisolone	£8.87			
Budesonide	£285.55			
Azathioprine	£7.53			
Health state unit costs				
Active UC	£6,275.61	£819.57	Gamma	B.3.5.2 Health-state unit costs and resource use
Response	£4,669.25	£1,860.38	Gamma	B.3.5.2 Health-state unit costs and resource use
Remission	£1,305.29	£1,718.64	Gamma	B.3.5.2 Health-state unit costs and resource use
Surgery without complications	£6,622.91	£662.29	Gamma	B.3.5.2 Health-state unit costs and resource use
Surgery with complications	£7,887.46	£788.75	Gamma	B.3.5.2 Health-state unit costs and resource use
Post-surgery without complications	£493.01	£354.27	Gamma	B.3.5.2 Health-state unit costs and resource use
Post-surgery with complications	£11,079.16	£5,549.35	Gamma	B.3.5.2 Health-state unit costs and resource use
Other costs				

IV administration costs	£133.19	Fixed	No sampling	B.3.5.1 Intervention and comparators' costs and resource use
Adverse event cost	£2,841.18	£395.77	Gamma	B.3.5.3 Adverse reaction unit costs and resource use

Abbreviations: AE, adverse event; HTA, health technology assessment; IV, intravenous; NMA, network meta-analysis; SC, subcutaneous; UC, ulcerative colitis

B.3.6.2 Assumptions

The inputs included in the base case analysis are summarised in Table 58.

Table 58. Summary of variables applied in the economic model

Parameter	Assumptions	Justification
Induction treatment	Responders to the induction treatment continue to receive maintenance therapy with the same treatment until loss of response.	This is consistent with previous HTA submissions
Conventional treatment	Once patients discontinue treatment, they are assumed to switch to conventional therapy. Once on conventional therapy, if treatment fails, patients remain in active UC, and on conventional treatment, unless they undergo surgery.	This is consistent with previous HTA submissions. There is a lack of data to characterise long term experience for patients after failing multiple biologic or JAK inhibitor therapies. In order to fairly assess treatments over the long term, conventional therapy is applied as the last drug in any sequence. Due to equivalence between arms this assumption is not expected to have a significant impact on model estimates.
Loss of treatment response	Loss of response rate is assumed to be constant over time, estimated based on rates from the maintenance periods NMA, assuming a constant risk of loss of response throughout the entirety of the model time horizon.	This is consistent with previous HTA submissions. Due to lack of long-term efficacy data, the calculated probability of loss of response from the NMA was extrapolated.
Adverse events	The only adverse events considered are serious infections.	This is consistent with previous HTA submissions. Only serious infections are included as the most impactful adverse events in terms of costs and disutilities.

Adverse events	The cost of AEs and associated disutility are assumed constant for all treatments.	This is consistent with previous HTA submissions. Most available data on AEs comes from clinical trials which are not powered to detect differences in AE rates between therapies.
Adverse events	AEs may only occur in the first 50 weeks of treatment.	AEs are most likely to occur early in treatment, so this assumption was made to avoid overestimating the rate of AEs in long-term maintenance
Adverse events	If a patient experiences an AE, they do not stop treatment.	This is consistent with previous HTA submissions. Discontinuation of advanced treatment is estimated using NMA results. Patients who lose response include those who discontinue due to AEs.
Mortality	UC was assumed not to have an effect on overall mortality	This is consistent with previous HTA submissions.
Risk of complications	Peri-operative surgical complications are a time-limited event which occur during the cycle of surgery (i.e. within 10 weeks of surgery) and then resolve	This is consistent with previous HTA submissions. This conservatively limits the additional mortality associated with surgery to the period immediately after surgery.
Risk of complications	Post-operative complications can occur at any time after surgery (i.e. from week 10 onwards) but are subsequently maintained and do not resolve	This is consistent with previous HTA submissions. There is a lack of data to characterise additional follow-up treatments or surgeries for patients with surgical complications. Due to the relatively low rates of surgeries in the model and equivalence between arms this assumption is not expected to have a significant impact on model estimates

Abbreviations: AE, adverse event; HTA, health technology assessment; NMA, network meta-analysis; UC, ulcerative colitis

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 using an annual price of [redacted] for filgotinib.

B.3.7.1 Base case incremental cost-effectiveness analysis results for the biologic-naïve population

The base case cost effectiveness results for the biologic-naïve population are presented in the Table 59. Filgotinib 200mg as a treatment for biologic-naïve patients was associated with quality adjusted life-year (QALY) gains, and decreased costs when compared to conventional therapy. Filgotinib 200mg was associated with lower costs than all other comparators and similar QALYs.

Table 59. Base case results for the biologic-naïve population

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	21.210	[redacted]	-	-	-	-	-
Conventional therapy	[redacted]	21.208	[redacted]	82.29	-0.002	-0.153	Dominated	Dominated
Golimumab	[redacted]	21.209	[redacted]	6,142.37	0.001	0.076	Dominated	81,199.75
Adalimumab	[redacted]	21.209	[redacted]	420.13	0.000	-0.003	Dominated	Dominated
Infliximab	[redacted]	21.210	[redacted]	4,625.55	0.001	0.074	Dominated	62,789.42
Tofacitinib	[redacted]	21.210	[redacted]	123.04	0.000	0.040	340,399.67 SW	3,069.36
Vedolizumab SC	[redacted]	21.210	[redacted]	4,144.06	0.000	0.011	351,564.50 SW	386,409.23
Vedolizumab IV	[redacted]	21.210	[redacted]	4,064.54	0.000	-0.032	1,666,942.24 SW	Dominated

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

B.3.7.2 Base case incremental cost-effectiveness analysis results for the biologic-experienced population

The base case cost effectiveness results for the biologic-experienced population are presented in the Table 60**.** Filgotinib 200mg as a treatment for biologic-experienced patients was associated with QALY gains (0.060) and increased costs (£279), generating an incremental cost-effectiveness ratio (ICER) of £4,637 per QALY. Filgotinib 200mg was associated with lower costs than all other comparators and similar QALYs.

Table 60. Base case results for the biologic-experienced population

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Conventional therapy	[redacted]	20.907	[redacted]	-	-	-	4,637.07	-
Filgotinib	[redacted]	20.908	[redacted]	278.99	0.001	0.060	-	4,637.07
Adalimumab	[redacted]	20.907	[redacted]	2,375.20	-0.001	-0.044	Dominated	Dominated
Tofacitinib	[redacted]	20.907	[redacted]	1,796.87	0.000	0.033	Dominated	53,927.89
Ustekinumab	[redacted]	20.907	[redacted]	853.65	0.000	-0.019	Dominated	Dominated
Vedolizumab SC	[redacted]	20.908	[redacted]	1,880.76	0.000	0.032	2,477,170.72 SW	58,087.87
Vedolizumab IV	[redacted]	20.907	[redacted]	1,018.23	0.000	-0.013	Dominated	Dominated

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

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. Results are based on 1,000 model runs. Probabilistic sensitivity analyses were conducted for both populations (biologic-naïve and biologic-experienced) included in the base case analysis. A full list of parameters included in the PSA is presented in Section B.3.6.1, Table 57.

B.3.8.1.1 Biologic-naïve population

The results of the PSA are presented in Table 61, with a cost-effectiveness acceptability curve in Figure 17 and a cost-effectiveness plane in Figure 16. Results in PSA are similar to the base case results.

At a WTP threshold of £20,000, filgotinib had a 100% probability of being the optimal treatment.

Table 61. Probabilistic sensitivity analysis results for the biologic-naïve population

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	21.190	[redacted]	-	-	-	-	-
Conventional therapy	[redacted]	21.188	[redacted]	129.04	-0.003	-0.161	Dominated	Dominated
Golimumab	[redacted]	21.189	[redacted]	6,245.65	0.001	0.081	Dominated	77,557.30
Adalimumab	[redacted]	21.189	[redacted]	351.39	-0.000	-0.005	Dominated	Dominated
Infliximab	[redacted]	21.190	[redacted]	4,723.40	0.001	0.078	Dominated	60,554.40
Tofacitinib	[redacted]	21.191	[redacted]	199.27	0.001	0.044	321,632.15 SW	4,532.86
Vedolizumab SC	[redacted]	21.191	[redacted]	4,142.96	0.000	0.009	346,825.95 SW	444,787.46
Vedolizumab IV	[redacted]	21.191	[redacted]	4,140.14	-0.001	-0.034	1,708,174.18 SW	Dominated

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Figure 16. PSA scatterplot on cost-effectiveness plane for the biologic-naïve population

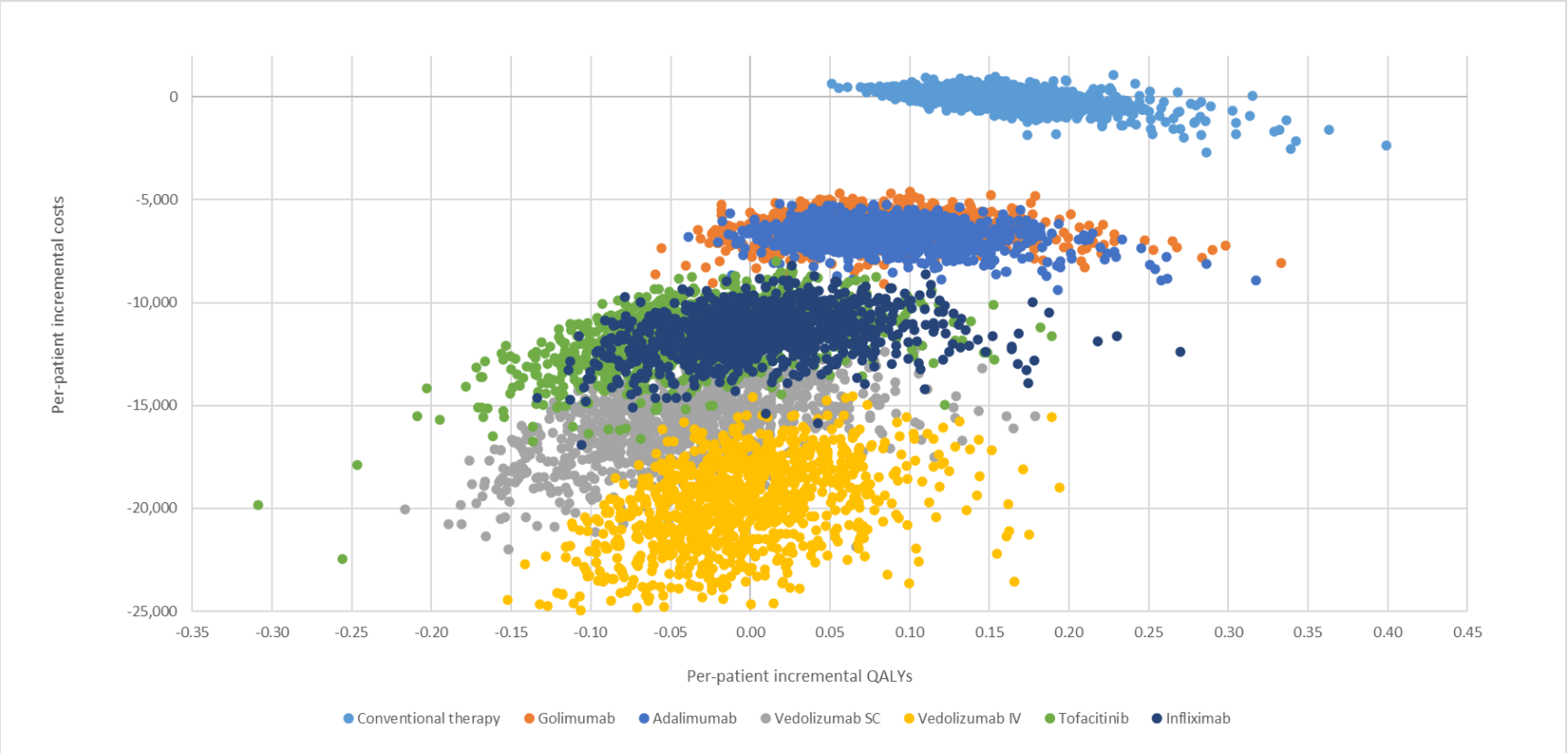
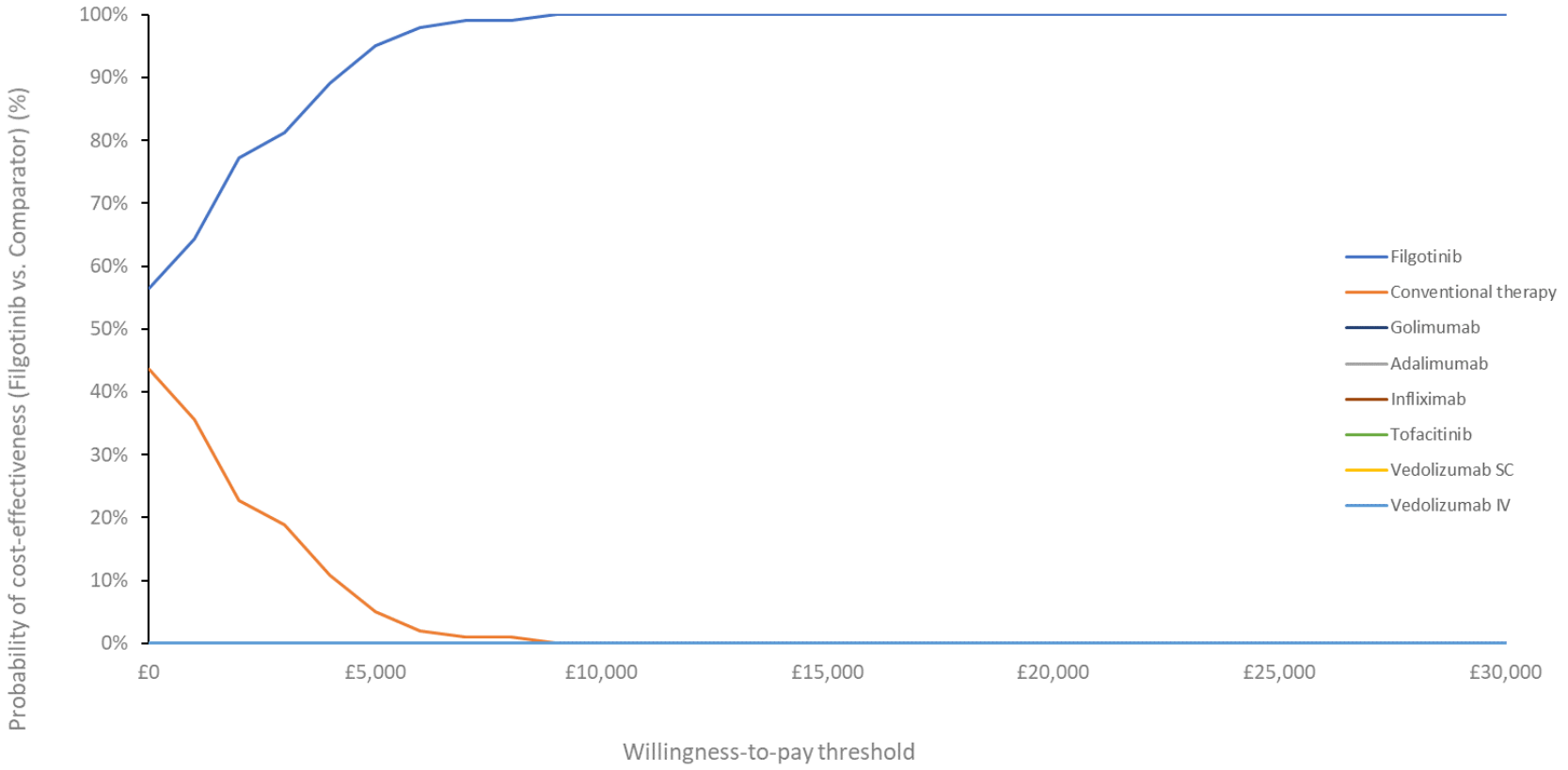


Figure 17. PSA cost-effectiveness acceptability curve for the biologic-naïve population



B.3.8.1.1 Biologic-experienced population

The results of the PSA are presented in Table 62**,** with a cost-effectiveness acceptability curve in Figure 19 and a cost-effectiveness plane in Figure 18. Results in PSA are in line with those from the base case results with an average ICER of £4,251.38 compared to the base case ICER of £4,637.07. At a WTP threshold of £20,000, filgotinib had a 100% probability of being the optimal treatment.

Table 62. Probabilistic sensitivity analysis results for the biologic-experienced population

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Conventional therapy	[redacted]	20.887	[redacted]	-	-	-	4,251.38	-
Filgotinib	[redacted]	20.888	[redacted]	266.43	0.001	0.063	-	4,251.38
Adalimumab	[redacted]	20.887	[redacted]	2,391.47	-0.001	-0.046	Dominated	Dominated
Tofacitinib	[redacted]	20.888	[redacted]	1,812.27	0.001	0.035	Dominated	52,304.54
Ustekinumab	[redacted]	20.887	[redacted]	851.88	-0.000	-0.020	Dominated	Dominated
Vedolizumab SC	[redacted]	20.888	[redacted]	1,909.18	0.001	0.034	2,489,071.29 SW	56,612.42
Vedolizumab IV	[redacted]	20.888	[redacted]	1,034.22	-0.000	-0.014	Dominated	Dominated

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Figure 18. PSA scatterplot on cost-effectiveness plane for the biologic-experienced population

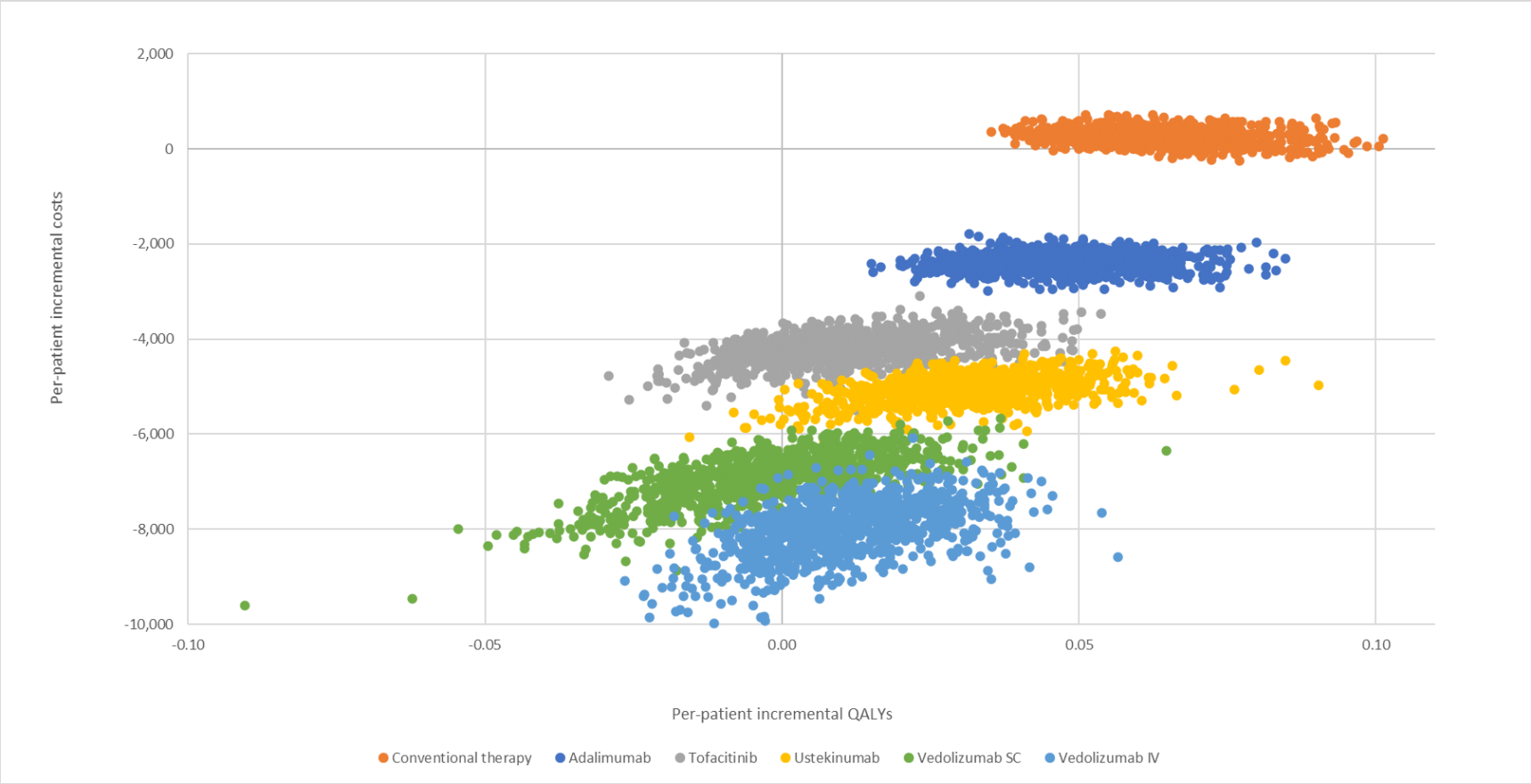


Figure 19. PSA cost-effectiveness acceptability curve for the biologic-experienced population

B.3.8.2 Deterministic sensitivity analysis

The robustness of the model was tested by a set of deterministic sensitivity analyses (DSAs). 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 20 and Figure 7). Table 63 summarises the list of parameters and assumptions tested in DSA. Two tornado diagrams comparing filgotinib to conventional therapy are presented in this section, one tornado for the biologic-naïve population (Figure 20) and the other for the biologic-experienced population (Figure 21) populations. As the ICERs were in many cases in the south-west quadrant, the tornado diagrams are based on net monetary benefit (NMB), using a WTP threshold of £20,000.

Table 63. Summary of parameters varied in DSA

Parameter	Base case	DSA input
Discount rate for costs and QALYs	3.5%	0% and 6%
Time horizon	Lifetime	10 and 80 years
Patient characteristics	Baseline characteristics from selection (Section B.3.2.1 Patient population)	Varied by ±20%
Treatment efficacy	Median point estimates from the NMA (Section B.3.3.1 Treatment effectiveness: clinical response and remission)	95% CI
Utility values	Utility values from SELECTION (Section B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis)	95% CI
AE utility decrement	Sourced from Wilson et al. (137) and TA547 (66) (Section B.3.4.4 Adverse reactions)	95%CI
Health state specific costs	Tsai et al. (133) and NHS reference costs (153) (Section B.3.5.2 Health-state unit costs and resource use, Section B.3.5.4 Miscellaneous unit costs and resource use)	95% CI
AE costs	NHS reference costs (153) (Section B.3.5.3 Adverse reaction unit costs and resource use)	95% CI

Surgery rates and complications	Sourced from Misra et al. (145), the UK 2014 national audit of inpatient care for adults with UC (146), Ferrante et al. (147) (Section B.3.3.2 Surgery and surgery complications)	95% CI
AE rates	Sourced from a safety NMA (Section B3.3.3 Adverse events)	95% CI

Abbreviations: AE, adverse event; CI, confidence interval; DSA, deterministic sensitivity analysis; NMA, network meta-analysis; QALY, quality adjusted life-year; TA, technology appraisal; UC, ulcerative colitis; UK, United Kingdom

B.3.8.3.1 Biologic-naïve population

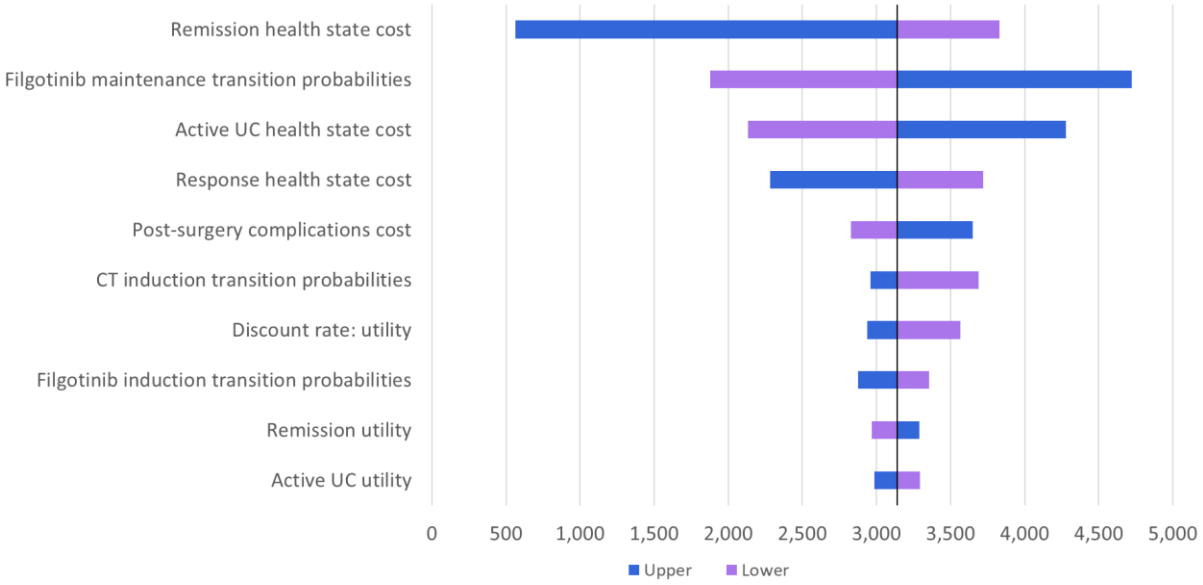
Deterministic sensitivity analysis results for the 10 most impactful parameters are presented in Table 64 and Figure 20. The NMB was most sensitive to changes in the health states costs, and the transition probabilities for filgotinib in the maintenance phase.

Table 64. One-way sensitivity analysis results for filgotinib vs conventional therapy in the biologic-naïve population

Parameter	NMB low (WTP of £20,000)	NMB high (WTP of £20,000)
Base case	£3,138.21	
Remission health state cost	£3,830.43	£565.45
Filgotinib maintenance transition probabilities	£1,876.17	£4,723.42
Active UC health state cost	£2,134.52	£4,277.15
Response health state cost	£3,718.11	£2,281.27
Post-surgery complications cost	£2,827.44	£3,647.75
CT induction transition probabilities	£3,690.92	£2,961.58
Discount rate: utility	£3,566.95	£2,939.23
Filgotinib induction transition probabilities	£3,353.74	£2,876.99
Remission utility	£2,970.07	£3,287.79
Active UC utility	£3,292.45	£2,985.17

Abbreviations: CT, conventional therapy; NMB, net monetary benefit; UC, ulcerative colitis; WTP, willingness-to-pay

Figure 20. Tornado diagram for filgotinib vs conventional therapy in the biologic-naïve population



B.3.8.3.1 Biologic-experienced

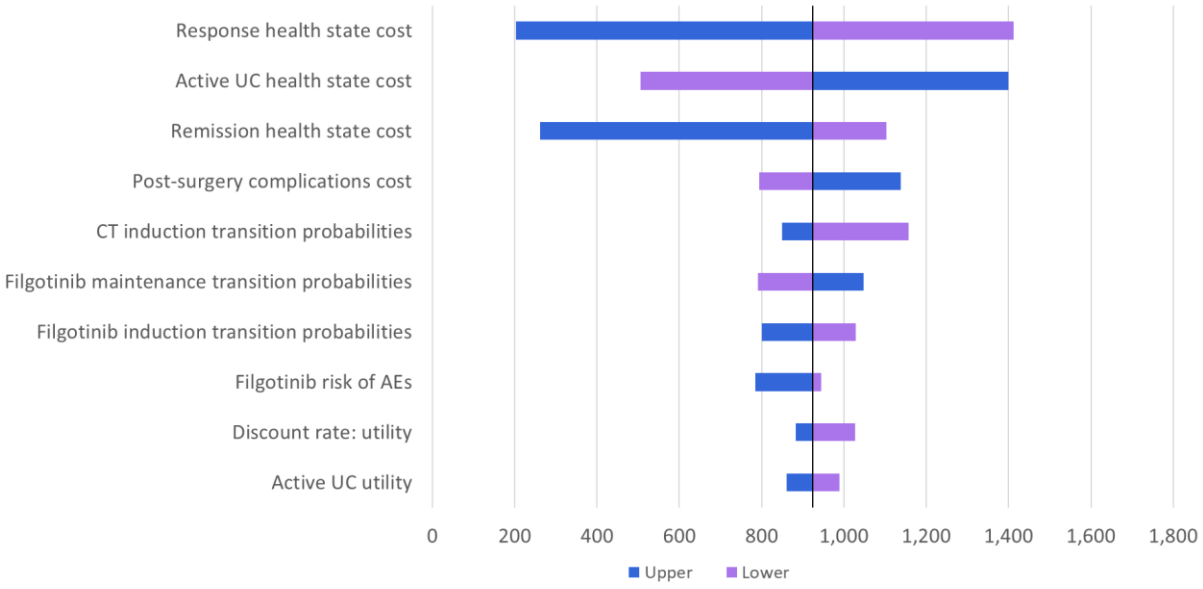
Deterministic sensitivity analysis results for the 10 most impactful parameters are presented in Table 65 and Figure 21. The NMB was most sensitive to changes in the health states costs.

Table 65. One-way sensitivity analysis results for filgotinib vs conventional therapy in the biologic-experienced population

Parameter	NMB low (WTP of £20,000)	NMB high (WTP of £20,000)
Base case	£924.32	
Response health state cost	£1,412.17	£203.40
Active UC health state cost	£506.14	£1,398.86
Remission health state cost	£1,102.46	£262.23
Post-surgery complications cost	£793.96	£1,138.07
CT induction transition probabilities	£1,157.50	£849.68
Filgotinib maintenance transition probabilities	£790.25	£1,048.30
Filgotinib induction transition probabilities	£ 1,028.57	£800.76
Filgotinib risk of AEs	£944.45	£785.16
Discount rate: utility	£1,027.74	£883.70
Active UC utility	£988.80	£860.35

Abbreviations: CT, conventional therapy; NMB, net monetary benefit; UC, ulcerative colitis; WTP, willingness-to-pay

Figure 21. Tornado diagram for filgotinib vs conventional therapy in the biologic-experienced population



B.3.8.3 Scenario analysis

Further scenario analyses were undertaken to assess the impact of key variables on the model outcomes (Table 66).

Table 66. Scenarios included in the cost-effectiveness analysis

Scenario		Base case	Scenario description
1	Treatment sequences	Upon loss of response, patients move on to last-line conventional therapy (Section B.3.2.5 Treatment strategies in the model)	Upon loss of response, a subsequent treatment is initiated for each comparator (except for conventional therapy). Biologic-naïve: • Second-line: vedolizumab, third-line: ustekinumab. • Second-line: adalimumab, third-line: vedolizumab. Biologic-experienced: • Third-line: ustekinumab. • Third-line: tofacitinib

Scenario		Base case	Scenario description
2	Treatment efficacy	Base case NMA used to estimate treatment efficacy in the maintenance phase (B.3.3.1 Treatment effectiveness: clinical response and remission)	Sensitivity analyses from the NMA used for treatment efficacy in the maintenance phase - Trials with different design (treat-through instead of re-randomised) excluded - Using an alternative methodology to re-weight treat-through trials
3	Adverse events	Adverse events from a safety NMA (Section B.3.3.3 Adverse events)	Using AE rates reported in Lohan et al. (124) (provided in Table 43, Section B.3.3.3)
4	Stopping rule	Patients in remission remain on treatment indefinitely, until loss of response (Section B.3.3.1 Treatment effectiveness: clinical response and remission)	Assumed 15% of patients in remission after one year of maintenance treatment discontinue treatment
5	Dose escalation	Dose escalation set to 30% (Section B.3.5.1 Intervention and comparators' costs and resource use)	Dose escalation set to 10% and 50% for all treatments
6	Utilities	SELECTION trial data (10 weeks) (Section B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis)	Alternative utility estimates (provided in Table 46, Section B.3.4.5) - SELECTION trial data at 58 weeks - Woehl et al. (139) - Swinburn et al. (150) - Vaizey et al. (151) - Arsenau et al. (140)
7	Resource use	Resource estimates sourced from Tsai et al. (133) (B.3.5.2 Health-state unit costs and resource use)	Alternative resource use estimates based on clinician interviews (provided in Table 53, B.3.5.2 Health-state unit costs and resource use)

Abbreviations: AE, adverse event; NMA, network meta-analysis

B.3.8.4.1 Biologic-naïve population

A summary of the results of the scenario analyses in the biologic-naïve population are presented Table 67. Overall, the results were consistent with the base case analysis. The model was most sensitive to the NMA sensitivity analyses results (scenario 2), and the various utility inputs (scenario 6). Full incremental results for key scenarios are presented in Appendix J.

Table 67. Scenario analyses: filgotinib vs comparator in the biologic-naïve population (ICER as cost per QALY)

Scenario	Description	CT	Golimumab	Adalimumab	Infliximab	Tofacitinib	Vedolizumab SC	Vedolizumab IV
Base case		***Dominated***	***Dominated***	***Dominated***	***Dominated***	***£340,400 SW***	***£351,565 SW***	***£1,666,942 SW***
Scenario 1: Treatment sequences	Subsequent treatments: vedolizumab and ustekinumab	Dominated	Dominated	Dominated	Dominated	£361,138 SW	£373,757 SW	NA
Scenario 1: Treatment sequences	Subsequent treatments: adalimumab and vedolizumab	Dominated	Dominated	NA	Dominated	£358,857 SW	£371,279 SW	NA
Scenario 2: Treatment efficacy	Using sensitivity analysis from the NMA (excluding treat-through trials)	Dominated	Dominated	NA	NA	£364,593 SW	£216,257 SW	£319,657 SW
Scenario 2: Treatment efficacy	Using sensitivity analysis from the NMA (alternative re-weighting for treat-through trials)	£206	Dominated	Dominated	£283,502 SW	£329,933 SW	£325,416 SW	£942,687 SW
Scenario 3: Adverse events	Rates from Lohan et al. (124)	£407	Dominated	Dominated	Dominated	£339,182 SW	£343,889 SW	£1,604,601 SW
Scenario 4:	15% of patients in	Dominated	Dominated	Dominated	Dominated	£318,707 SW	£332,586 SW	£1,589,070

Stopping rule	remission discontinue treatment							SW
Scenario 5: Dose escalation	Dose escalation set to 10%	Dominated	Dominated	Dominated	Dominated	£277,521 SW	£351,565 SW	£1,412,391 SW
Scenario 5: Dose escalation	Dose escalation set to 50%	Dominated	Dominated	Dominated	Dominated	£403,910 SW	£351,565 SW	£1,924,052 SW
Scenario 6: Utilities	Values from SELECTION (58 weeks)	Dominated	Dominated	Dominated	Dominated	£316,750 SW	£328,189 SW	£1,578,943 SW
Scenario 6: Utilities	Values from Woehl et al. (139)	Dominated	Dominated	Dominated	Dominated	£166,054 SW	£172,811 SW	£845,221 SW
Scenario 6: Utilities	Values from Swinburn et al. (150)	Dominated	Dominated	Dominated	Dominated	£230,804 SW	£242,098 SW	£1,235,044 SW
Scenario 6: Utilities	Values from Vaizey et al. (151)	Dominated	Dominated	Dominated	Dominated	£369,884 SW	£392,658 SW	£2,147,997 SW
Scenario 6: Utilities	Values from Arsenau et al. (140)	Dominated	Dominated	Dominated	Dominated	£139,471 SW	£141,429 SW	£613,707 SW
Scenario 7: Resource use	Estimates from clinician interviews	£6,622	Dominated	Dominated	Dominated	£347,868 SW	£357,808 SW	£1,667,441 SW

Abbreviations: ICER, incremental cost-effectiveness ratio; IV, intravenous; NMA, Network meta-analysis; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

B.3.8.4.2 Biologic-experienced population

A summary of the results of the scenario analyses in the biologic-experienced population are presented Table 68. Overall, the results were consistent with the base case analysis. The model was most sensitive to the NMA sensitivity analyses results (scenario 2), and the various utility inputs (scenario 6). Full incremental results for key scenarios are presented in Appendix J.

Table 68. Scenario analyses: filgotinib vs comparator in the biologic-experienced population (ICER as cost per QALY)

Scenario	Description	Conventional therapy	Adalimumab	Tofacitinib	Ustekinumab	Vedolizumab SC	Vedolizumab IV
Base case		***£4,637***	***Dominated***	***Dominated***	***Dominated***	***£2,477,171 SW***	***Dominated***
Scenario 1: Treatment sequences	Subsequent treatment: ustekinumab	£3,379	Dominated	Dominated	NA	£2,489,081 SW	Dominated
Scenario 1: Treatment sequences	Subsequent treatment: tofacitinib	£3,724	Dominated	NA	Dominated	£2,496,785 SW	Dominated
Scenario 2: Treatment efficacy	Using sensitivity analysis from the NMA (excluding treat-through trials)	£5,016	NA	Dominated	Dominated	£660,119 SW	Dominated
Scenario 2: Treatment efficacy	Using sensitivity analysis from the NMA (alternative re-weighting for treat-through trials)	£4,533	Dominated	Dominated	Dominated	£3,705,521 SW	Dominated
Scenario 3: Adverse events	Rates from Lohan et al. (124)	£6,806	Dominated	Dominated	Dominated	£2,256,431 SW	Dominated
Scenario 4: Stopping rule	15% of patients in remission discontinue treatment	£4,204	Dominated	Dominated	Dominated	£2,424,032 SW	Dominated
Scenario 5: Dose escalation	Dose escalation set to 10%	£4,637	Dominated	Dominated	Dominated	£2,477,171 SW	Dominated
Scenario 5: Dose escalation	Dose escalation set to 50%	£4,637	Dominated	Dominated	Dominated	£2,477,171 SW	Dominated
Scenario 6: Utilities	Values from SELECTION (58 weeks)	£4,356	Dominated	Dominated	Dominated	£2,216,262 SW	Dominated
Scenario 6: Utilities	Values from Woehl et al. (139)	£2,304	Dominated	Dominated	Dominated	£1,124,746 SW	Dominated
Scenario 6: Utilities	Values from Swinburn	£3,293	Dominated	Dominated	Dominated	£1,407,180	Dominated

	et al. (150)					SW	
Scenario 6: Utilities	Values from Vaizey et al. (151)	£5,520	Dominated	Dominated	Dominated	£1,950,783 SW	Dominated
Scenario 6: Utilities	Values from Arsenau et al. (140)	£1,783	Dominated	Dominated	Dominated	£1,431,858 SW	Dominated
Scenario 7: Resource use	Estimates from clinician interviews	£8,242	Dominated	Dominated	Dominated	£2,501,198 SW	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; IV, intravenous; NMA, Network meta-analysis; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

B.3.9 Subgroup analysis

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

B.3.10 Validation of cost-effectiveness analysis

B.3.10.1 Validation of the cost-effectiveness model

Early scientific advice

The company sought early scientific advice (ESA) with the purpose of validating the economic model structure, assumptions, and clinical evidence used in the model. The specialist advice was provided by a clinical expert, patient expert, HTA expert, and a health economics expert. Several key themes emerged from the discussion and the final advice report. A summary of the discussions and recommendations is presented below:

1) NMA methodology

The company requested advice regarding the proposed NMA methodology and studies for inclusion. The advice confirmed that the approach to include all available evidence in the network was appropriate, due to the low number of studies, and that potential sources of heterogeneity should be explored in sensitivity analyses. Heterogeneity due to trial design (treat-through versus re-randomised, see Section B.2.9.7) was highlighted as a source of uncertainty, and it was advised to explore scenarios in the economic model to assess the impact on the results. Therefore, two scenarios were explored using sensitivity analyses results from the NMA.

2) Model structure

The company enquired about the appropriateness of the model structure and cycle length. The advice confirmed that the Markov model structure was consistent with previous appraisals in UC, and appropriate for decision making. It was also confirmed that the cycle length was appropriate, and in particular that using a 10-weekly induction phase was reasonable, given that the bias is small for treatments with shorter induction phases.

3) Treatment pathway

The company enquired about the most appropriate choice of comparators for filgotinib, given the potential line of therapy. The comparators selected in the base case are aligned with the ESA advice. For patients who are biologic-naïve, it was confirmed that relevant comparators are the TNFα inhibitors adalimumab, infliximab, and golimumab. Tofacitinib and vedolizumab are also relevant comparators, although normally offered after failure of TNFα inhibitors. For patients who are biologic-experienced, it was confirmed that vedolizumab, ustekinumab and tofacitinib are relevant comparators for filgotinib, but treatment with a second TNFα inhibitor would be an option for some patients. Therefore, adalimumab was included as a comparator in the biologic-experienced population, as there were efficacy inputs available from the NMA.

4) Surgery

The company enquired about the appropriate assumptions for modelling surgery as a one-cycle transient state with one-off costs and disutilities, followed by post-surgery states either with or without long-term complications. The advice confirmed that this approach is in line with previous appraisals, but also that this approach does not allow for modelling of the range of procedures undertaken, including surgical revision in cases with complications. The HTA expert noted that simplifying assumptions are appropriate for decision making.

5) Resource use inputs

The company enquired about the appropriate inputs for resource use, given the lack of recent sources. It was recommended that the company should validate the resource use inputs with UK clinicians, in order to align these with current practice. Clinician input was therefore sought (see Section B.3.10.2 below).

6) Utility inputs

The company sought advice about the appropriate utility source for the model, given the range of sources and lack of consistency. It was noted that there are limitations associated with published utility estimates from Woehl et al. (139), and that sensitivity analyses using a range of utility estimates should be provided. It was also highlighted that the SELECTION data is considered appropriate for decision making. The company therefore applied results from the large patient cohort from the

SELECTION trial programme in the base case, as well as a range of scenario analyses testing various published sources.

Internal validation

Internal quality assurance measures were undertaken throughout the model development. The model was validated through use of extreme values and formula auditing to ensure the consistency of model estimates. Systematic variation of the model input parameters was conducted to establish whether changes in inputs resulted in predictable changes in the model outputs. Accuracy of input data was checked by comparing the model inputs against the data sources referenced. Overall, the validation identified no issues with the computational accuracy of the model. Any errors or discrepancies identified were rectified.

Comparison of model output to previously published CEM costs and QALYs

The model was validated against the published cost-effectiveness analysis for tofacitinib by Lohan et al. (124). The model was adapted using the reported model parameters (summarised in Appendix J). It was possible to achieve similar estimates of modelled costs and QALYs for all comparators which were all within 3% of the published results (see Table 69). The validation exercise confirmed that the model is operating similarly to the published cost-effectiveness model.

Table 69. Comparison of the results of the validation model with the results published by Lohan et al.

	Lohan et al. published model results		Validation model results		Comparison (validation model results as % of Lohan model results)	
Strategy	**QALYs**	**Costs**	**QALYs**	**Costs**	**QALYs**	**Costs**
TNF naïve						
CT	8.99	£132,349	8.84	£135,781	98%	103%
Adalimumab	9.19	£138,534	9.10	£138,680	99%	100%
Golimumab	9.29	£141,360	9.19	£140,511	99%	99%
Infliximab	9.35	£145,660	9.25	£143,483	99%	99%
Vedolizumab	9.46	£152,694	9.35	£148,268	99%	97%
Tofacitinib	9.54	£143,963	9.43	£141,301	99%	98%
TNF exposed						
CT	8.90	£132,712	8.84	£135,781	99%	102%
Adalimumab	9.05	£137,035	8.98	£138,008	99%	101%
Vedolizumab	9.15	£145,360	9.07	£143,340	99%	99%

Tofacitinib	9.24	£141,500	9.43	£141,301	102%	100%

Abbreviations: CT, conventional therapy; QALY: quality adjusted life-year
Reference: Lohan et al. (124)

B.3.10.2 Validation of the assumptions applied in the cost-effectiveness model

Early scientific advice

In addition to the model structure and inputs, various model assumptions were validated in ESA:

1) NMA methodology

The company requested advice regarding the proposed NMA methodology and the approach to include the evidence in the economic model. The advice confirmed that comparing evidence for different outcome timepoints across the trials included, for both induction and maintenance outcomes, was clinically reasonable and appropriate for model input.

2) Dose escalation

The company enquired about the inclusion of dose escalation in the economic model, and sources that can inform this. It was noted by the clinical expert that dose escalation is frequent in clinical practice, and therefore recommended that the company would explore dose escalation for the model. Dose escalation was implemented in the model, and the proportion of patients with dose escalation was validated with UK clinicians (detailed below).

3) Adverse events.

The company enquired about the appropriateness of including adverse events due to serious infections for the first year in the model. The advice confirmed that the approach to modelling AEs was reasonable. The clinical expert agreed that serious infections are the most frequently occurring AE in clinical practice with considerable impact on patient outcomes and cost to the NHS.

4) Stopping rule

The company enquired about the assumption that patients discontinue treatment after achieving long-term, stable remission. This assumption was confirmed as appropriate, and in line with clinical practice. It was noted, however, that there is uncertainty around the proportion of patients discontinuing treatment in remission.

The company therefore applied a stopping rule in a scenario analysis, based on clinician validation (detailed below).

Clinical validation

Various model inputs and assumptions were validated during interviews with five England-based gastroenterologists, which were conducted between February and March 2021.

The clinicians confirmed that dose escalation is common in clinical practice, and provided estimates for the percentage of patients treated with an escalated dose for each treatment included in the model. The estimates provided by the five clinicians varied considerably, and therefore, the proportion applied in the model base case was sourced from published literature, and scenario analyses were conducted varying this estimate. Additionally, the clinicians provided estimates for the annual resource use in moderate to severe patients according to the model health states, as applied in the model base case. These estimates varied somewhat from the values used in the model base case, sourced from Tsai et al. (133), particularly for the more severe health states. A scenario using the average estimates based on the clinician interviews was therefore conducted. The clinician discussions also confirmed that the assumptions applied for the stopping rule and treatment sequences used in a scenario analysis were plausible.

B.3.11 Interpretation and conclusions of economic evidence

The cost-effectiveness of filgotinib has been evaluated across different points 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 ulcerative colitis.

Filgotinib has been priced to be cost-effective in both biologic-naïve and biologic-experienced populations. For both populations, filgotinib generated a cost-effective ICER compared to conventional therapy. In the biologic-naïve population, the filgotinib treatment sequence was less costly than conventional treatment, and associated with increased QALYs, and in the biologic-exposed population, filgotinib

was associated with an ICER of £5,423.17 per QALY gained compared to conventional therapy. Compared to advanced therapies, filgotinib was associated with similar QALYs but significantly lower costs than all comparators across both populations.

The robustness of the 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. Cost-effectiveness conclusions remain largely unchanged across scenario and sensitivity analyses. This strengthens the conclusions drawn from the base case analyses. Across both populations, probabilistic sensitivity analyses estimated that filgotinib had a 100% probability of being the optimal treatment at a WTP threshold of £20,000. In one-way sensitivity analyses, the economic model was found to be most sensitive to varying the health state specific costs, and treatment efficacy during the maintenance phase. A range of scenarios were presented, including the possibility of treatment sequencing in the model, and a stopping rule for patients achieving long-term stable remission. Although used in practice, the exact treatment sequences and estimates for proportion of patients discontinuing treatment in remission are uncertain, due to the relapsing and remitting nature of UC. The plausible inputs for both scenarios were validated by England-based clinicians, and the results further demonstrated the robustness of the results and the benefit of treatment with filgotinib.

Based on feedback from early scientific advice, various sources of utility inputs were tested, as well as alternative efficacy inputs estimated from NMA sensitivity analyses, which were found to be the most impactful scenarios. A lack of robust utility estimates and inconsistency in published sources is a key limitation in UC modelling. The base case analysis used estimates from the SELECTION trial programme, which were based on a large number of patients. Key limitations are that no estimates were available for the surgery and post-surgery health states, and that the utility estimate for patients with active UC is potentially overestimated. This potential overestimation is due to selection bias in the clinical trial, as well as the fact that the active UC state in the model represent patients that have exhausted their treatment options, which is not the case for the patients participating in SELECTION. However, it should be noted the potential overestimation of the active UC state utility is

conservative for patients on advanced therapies, compared to conventional therapy. Scenario analyses demonstrated that the results for filgotinib were robust when utility estimates were varied.

The inputs and methodologies employed in developing the economic model are well established in UC modelling and consistent with methods described for the economic model developed by the assessment group in TA329 (28), as well as subsequent NICE submissions (TA342, TA547 and TA633 (65-67)). Validation work confirmed similar outputs between the manufacturers model and the published model for tofacitinib, allowing for comparability of model outputs. The model assumptions and inputs were validated through clinical expert advice to ensure applicability to clinical practice in England and Wales.

In conclusion, filgotinib has been shown to be a cost-effective treatment option in moderate and severe disease activity across the treatment pathway. The results have been shown to be both robust and generalisable to the England and Wales population.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Filgotinib for treating moderately to severely active ulcerative colitis [ID3736]

Clarification questions

September 2021

File name	Version	Contains confidential information	Date
[ID3736] Filgotinib clarification letter 070921_Responses_vF	**1.0**	**Yes**	**23/09/2021**

Section A: Clarification on effectiveness data

Literature Searches

A1. Priority question: Please justify why budesonide multimatrix (cortiment) has not been included as an intervention as per NHS Clinical pathways for mild to moderate ulcerative colitis (UC) (https://pathways.nice.org.uk/pathways/ulcerative-colitis)?

A1. Response: Budesonide multimatrix (Cortiment) was not identified as a comparator for filgotinib within the NICE scope. As budesonide multimatrix is only licensed for use within a mild to moderate UC population, and filgotinib is positioned within a moderate to severe population it was considered inappropriate to make comparisons across these populations.

A2. Please explain how non-randomised and non-controlled studies were identified.

A2. Response: The systematic literature review inclusion/exclusion criteria was limited to randomised controlled trials; therefore, the search strategy was designed to exclude non-randomised or non-controlled studies from the results. During the screening stages, studies describing a non-randomised trial design or where a randomisation step was not mentioned were considered as non-randomised by the reviewers. Non-controlled studies were identified by reviewers if a study described only one-treatment arm (i.e. there was no comparator for the intervention); comparators can include the same intervention with different doses. Decisions regarding inclusion/exclusion required consensus between the two reviewers. If there was ambiguity in the publication, reviewers would use study protocols, or trial registries such as clinicaltrials.gov, to clarify details regarding the trial design.

A3. Please confirm if adverse events were identified only through SELECTION or if they were identified through other means also.

A3. Response: The most relevant adverse events were decided by clinical experts from the most common adverse events (> 2%) in the SELECTION trial and from adverse events of interest in treating UC recognised by clinicians.

A4. 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 6-21 of the Embase search (page 3 and 4), lines 6-21 of the PubMed search (page 7) and lines 9-24 of the Cochrane Library search (page 10 and 11).

A4. Response: It was considered that including search terms for comparators, including generic, brand names and early development names as title and abstract terms was an appropriate approach to identifying all relevant publications.

A5. Please explain the use of an English language limit in Embase and PubMed searches. Please describe what steps were taken to mitigate for potential language bias as a consequence.

A5. Response: It was decided that the systematic literature review was limited to English language for a number of reasons; due to the complexity of the disease area and the associated trial designs, it was considered that extracting data from translated publications may be more likely to introduce errors into the data. Additionally, including non-English language studies add to increase resource use and logistics of the review. Limiting searches to English language, has been shown not to introduce systematic bias (1). However, we aimed to limit the impact of the English language limit by reviewing the International Clinical Trials Registry to identify any trial data from geographical regions where results are less likely to be published in English language journals. An English language limit was used in the tofacitinib NICE submission (TA547 (2)) which the ERG considered to be appropriate for a submission to NICE.

A6. Please clarify which controlled trials study design filter was used and, if possible, provide a reference to that filter.

A6. Response: The controlled trials study filter used in the review was a modified version of the SIGN filter for randomised controlled trials (3).

A7. Please provide a rationale for including a clinical studies methodological filter in the Cochrane Library.

A7. Response: A methodological filter was used in the Cochrane Library search terms as the search terms were translated from the Embase and Medline, we

recognise that such a filter may be redundant for this database; however, we believe it did not have a significant impact on the results.

A8. Please explain the further limitation to "Trials" only (line 55, page 11) in Cochrane Library searches when a clinical studies methodological filter has already been applied.

A8. Response: The trials limit was used in the Cochrane Library searches in addition to the clinical trials filter to remove any publications not identified using the clinical trials filter, that were categorised as trials in the database. It was expected that the majority of non-clinical trial publications would already have been identified with the filter.

A9. The CS states "recent reviews (published in the last two years) were searched to ensure all relevant studies were identified" (Appendix D, page 13). How were recent reviews identified as CDSR searches had a clinical trials filter applied and DARE has not been updated since 2015?

A9. Response: Relevant reviews were identified through free-text searches and included any studies identified via the systematic literature review searches. It was considered to be an appropriate approach as including reviews in the search strategy considerably increased the number of hits, adding additional complexity to the review process.

A10. Please explain why editorials, letters, case studies, reviews, comments, guidelines and case reports were 'NOT'-d out of the Cochrane Library search.

A10. Response: This filter was used in the Cochrane Library search terms as the search terms were translated from the Embase and Medline, we recognise that such a filter may be redundant for this database; however, we believe it did not have a significant impact on the results.

A11. Please provide URLs, search terms used and the number of results for each of the conference proceedings searches reported in Appendix D (page 13).

A11. Response:

Table 1. Conference searches Appendix D

Conference	Search term	URL	Number of Includes
American College of Gastroenterology (ACG)	"Ulcerative colitis"	https://journals.lww.com/ajg/toc/2020/10001 https://journals.lww.com/ajg/toc/2019/10001 https://journals.lww.com/ajg/toc/2019/10001 https://journals.lww.com/ajg/toc/2018/10001 https://journals.lww.com/ajg/toc/2017/10001 https://journals.lww.com/ajg/toc/2016/10001	First pass: 14 Second pass: 0
British Society of Gastroenterology	"Ulcerative colitis"	https://gut.bmj.com/content/68/Suppl_2 https://gut.bmj.com/content/67/Suppl_1/A282 https://gut.bmj.com/content/66/Suppl_2 https://gut.bmj.com/content/65/Suppl_1	First Pass: 10 Second pass: 0
European Crohn's and Colitis Organisation (ECCO)	"Ulcerative colitis"	https://academic.oup.com/ecco-jcc/issue/13/Supplement_1 https://academic.oup.com/ecco-jcc/issue/12/supplement_1 https://academic.oup.com/ecco-jcc/issue/11/suppl_1 https://academic.oup.com/ecco-jcc/issue/10/suppl_1	First Pass: 18 Second Pass: 1
Crohn's and Colitis UK	NA	NA	NA

A12. Please provide search terms and results for searches of clinical registry trials also reported on page 13 of Appendix D.

A12. Response:

Table 2. Trial registry searches Appendix D

Trial Registry	Search term	Number of results
Clinicaltrials.gov	Ulcerative Colitis Interventional Studies Adult, Older Adult Phase 2, 3, 4	427
International clinical trials registry	"Ulcerative Colitis" Phase 2, 3, 4	751 records (674 trials)
EU Clinical trials register	"Ulcerative colitis" Phase 2, 3, 4	355
Klinische Prüfungen PharmNet.Bund	Ulcerative Colitis Adult, Elderly Phase 2, 3, 4	113

Decision Problem

A8. Priority question: Given that the 100mg dose of filgotinib is not considered in the cost effectiveness analysis, would the company agree that the

intervention in the decision problem be updated to 200mg only? Is it also the case that, because the reason for not including 100 mg is 'this dosing is for a restrictive patient group with renal impairments (Table 2).' (Section B.3.2.4), that the population in the decision problem should also be amended to exclude those with renal impairments?

A8. Response: The decision problem should retain filgotinib 100mg and 200mg doses. Filgotinib 100mg is recommended only for patients who have moderate or severe renal impairment. Although filgotinib 100mg was studied in SELECTION (and is included in the NMA), patients within this treatment arm who are classified as having moderate or severe renal impairment are limited. As such, filgotinib 100mg was not included in the economic analysis due to a paucity of data for both filgotinib and comparators in this subgroup of patients.

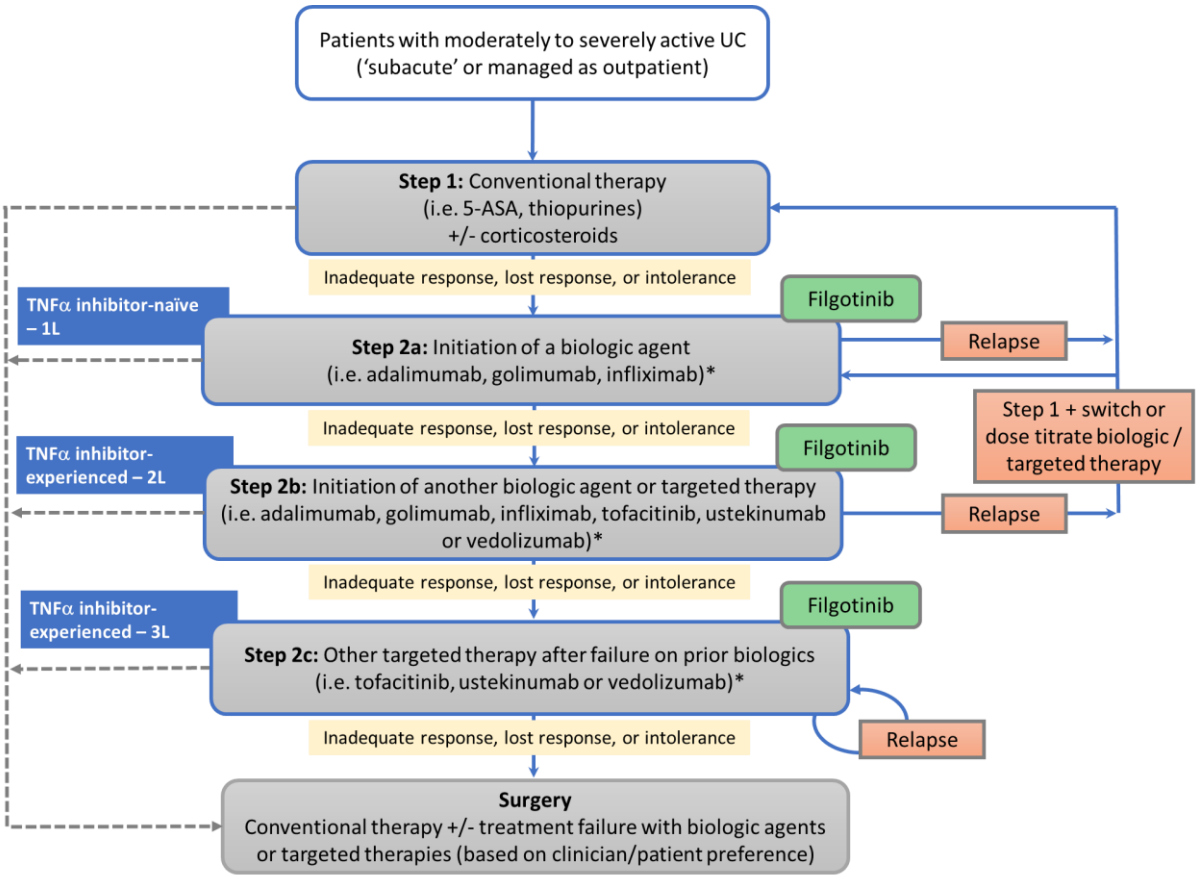
A9. Priority question: Figure1 shows that filgotinib can be positioned at more than one place in the biologic experienced population, specifically 2L or 3L. However, the biologic experienced subgroup is treated as a single population i.e. not subdivided by line.

a. **Precisely which lines of therapy do the company intend are included in the biologic experienced subgroup? Do they include 3L? Do they include lines later than 3L?**
b. **Please discuss the implications of this lack of discrimination between treatment lines in the biologic experienced subgroup in terms of potential differences in efficacy**
c. **Please indicate if the results of the NMA and from the trials included for the biologic experienced subgroup are more applicable to one line than another**
d. **Given that lines later than 2L would imply the experience of biologics pre-filgotinib, if the company does intend that the biologic subgroup includes, could the cost effectiveness model be amended to remove those biologics already experiences from the sequence subsequent to filgotinib?**
e. **Does the company consider that the line immediately pre-surgery be included in the biologic subgroup? If so, then could the company amend the model accordingly and include the possibility of dose escalation for filgotinib?**

A9. Response:

a. In line with Figure 1 of the company submission, filgotinib is intended for inclusion as an option at all lines of advanced therapy i.e. as a first advanced therapy following the failure of conventional therapy, as well as second- and third-line advanced therapy, immediately prior to surgery.

Figure 1. Proposed positioning of filgotinib within NICE treatment pathway



*Patients in response/remission remain on therapy with 12-month review

b. Prior treatment is considered likely to be a treatment effect modifier in UC, since patients who have already tried and failed on a drug with one mechanism of action e.g. TNFα inhibitors, may be considered less likely to respond to a drug with the same mechanism of action in future lines of therapy. There may also be an effect modifier on drugs with other mechanisms of action, although the direction is unclear (failing one mechanism of action may either indicate an increased chance of responding to a drug with a different mechanism of action, or indicate that the patient is

generally harder to treat regardless of mechanism of action). Heterogeneity of prior treatment was observed in the included trials of the company NMA; therefore, this was considered an important effect modifier in the current analysis. Therefore, separate analyses were run for trials conducted in biologic experienced patients or biologic naïve patients. In summary, although it is likely that lack of distinction between treatment lines in the biologic-experience NMA is likely to impact efficacy, it is difficult to determine the direction of this impact.

c. With respect to the biologic experienced subgroup of the NMA, of the nine trials included in this analysis, two (ULTRA 2 and VARSITY) specified that patients be previously 'exposed' to biologics. In addition, OCTAVE 1 and 2 (tofacitinib) reported two different subgroup results: 'prior TNF exposure' and 'prior TNF failure'. The remaining studies included patients with biologic failure. Therefore, it is likely that results from the biologic-experienced NMA are most applicable to the second-line of advanced therapy.

d. To account for potential differences in efficacy in treatment lines, the base case has been updated to include treatment sequences (See response to Question B12).

e. The company has presented below a scenario analysis looking at filgotinib as third line advanced treatment (Table 4). However, dose escalation is not applicable for filgotinib and such this has not been included.

Table 3. Biologic-experienced treatment sequences used in scenario A9e

First line	Second line
Adalimumab	Filgotinib
Adalimumab	Tofacitinib
Adalimumab	Ustekinumab
Adalimumab	Vedolizumab SC
Adalimumab	Vedolizumab IV

Table 4. Scenario analysis supporting A9e – Biologic-experienced subgroup

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	20.910	[redacted]	-	-	-	-	-
Tofacitinib	[redacted]	20.909	[redacted]	-5,470.77	0.00012	0.010	Dominated	Dominated
Ustekinumab	[redacted]	20.909	[redacted]	-8,126.35	0.00033	0.029	Dominated	Dominated
Vedolizumab SC	[redacted]	20.910	[redacted]	-9,838.04	-0.00002	-0.003	3,630,604.35 SW	53,806.97
Vedolizumab IV	[redacted]	20.909	[redacted]	-10,847.41	0.00013	0.010	Dominated	Dominated

Filgotinib Trials*A10. Please provide the number of UK study centres and UK patients included in the SELECTION trial by treatment arm and study phase.*

A10. Response: The number of UK study centres and UK patients included in the SELECTION trial by treatment arm and by study phase are provided in Table 5 and Table 6.

Table 5. Region of enrolment, cohort A and B induction study (all randomised analysis)

Study	Cohort A Induction Study				Cohort B Induction Study			
Arm	Filgotinib 200 mg	Filgotinib 100 mg	Placebo	Total	Filgotinib 200 mg	Filgotinib 100 mg	Placebo	Total
Baseline patients, n	245	278	137	660	262	286	143	1348
United Kingdom								
Patients, n	7	3	0	10	12	11	7	30
Centres, n	5	2	0	6	7	7	5	11

Abbreviations: mg, milligram; n, number.

Source: Gilead SELECTION clinical study report, 2020 (data on file) (4).

Table 6. Region of enrolment, maintenance study (all randomised analysis)

Study	Induction filgotinib 200mg			Induction filgotinib 100mg			Induction placebo
Arm	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Total	Maintenance filgotinib (n=172)	Maintenance placebo (n=89)	Total	Maintenance placebo
Baseline patients, n	202	99	301	179	91	270	93
United Kingdom							
Patients, n	8	1	9	3	3	6	2
Centres, n	6	1	7	3	2	3	2

Abbreviations: mg, milligram; n, number.

Source: Gilead SELECTION clinical study report, 2020 (data on file) (4).

A11. Please describe the randomisation methods in the SELECTION trial, both for the induction phase and the maintenance phase. Please also provide the final protocol for the SECETION trial.

A11. Response: Based on protocol eligibility criteria, patients were screened within 30 days before randomisation to determine eligibility for participation in either the cohort A induction study or the cohort B induction study. It was the responsibility of

the investigator to ensure that the patient was eligible for the study prior to enrolment. Patients were assigned a screening number at the time of consent. Patients were assigned to study drug, using the Interactive Web Response System (IWRS) using a stratified randomisation schedule.

Treatment assignment

Patients who met protocol eligibility criteria were assigned to the respective induction study and subsequently randomised in a blinded fashion in a 2:2:1 ratio to one of three treatments as follows:

Treatment Groups (Induction Studies)

- Filgotinib 200 mg: filgotinib 200 mg and placebo-to-match (PTM) filgotinib 100 mg, once daily
- Filgotinib 100 mg: filgotinib 100 mg and PTM filgotinib 200 mg, once daily
- Placebo: PTM filgotinib 200 mg and PTM filgotinib 100 mg, once daily

Stratification

Within each induction study, treatment assignments were stratified according to the following factors in the induction studies and Maintenance Study:

- ***Stratification Factors (Cohort A Induction Study)***
  - Concomitant use of oral, systemic corticosteroids (e.g., prednisone) at Day 1 (Yes or No)
  - Concomitant use of immunomodulators (e.g., 6-mercaptopurine [6-MP], azathioprine, methotrexate [MTX]) at Day 1 (Yes or No)

- ***Stratification Factors (Cohort B Induction Study)***
  - Exposure to one biologic agent versus more than one biologic agent
  - Concomitant use of oral, systemic corticosteroids (e.g., prednisone) at Day 1 (Yes or No)
  - Concomitant use of immunomodulators (e.g., 6-MP, azathioprine, MTX) at Day 1 Yes or No)

- ***Stratification Factors (Maintenance Study)***
  - Participation in the Cohort A Induction Study or the Cohort B Induction Study
  - Concomitant use of oral, systemic corticosteroids (e.g., prednisone) at Day 1 (Yes or No)

- Concomitant use of immunomodulators (e.g., 6-MP, azathioprine, MTX) at Day 1 (Yes or No)

Patients from the induction studies who were eligible for the Maintenance Study were re-randomised to treatment as shown in Table 7. Patients receiving filgotinib 200mg or 100mg in the induction studies were randomised in a 2:1 manner to either continue on the assigned filgotinib regimen or to placebo for the duration of the Maintenance Study.

Table 7. Re-randomisation for maintenance study

Treatment Assignment: Cohort A Induction Study and Cohort B Induction Study	Re-randomisation: Maintenance Study
Treatment 1: Filgotinib 200mg	Treatment 1: Filgotinib 200mg
	Treatment 3: Placebo
Treatment 2: Filgotinib 100mg	Treatment 2: Filgotinib 100mg
	Treatment 3: Placebo
Treatment 3: Placebo	Treatment 3: Placebo

Abbreviations: mg, milligram.

Note: Patients receiving Treatment 1 or 2 in the Induction study will be randomised in a 2:1 manner to either continue on the assigned filgotinib regimen or to placebo for the duration of the Maintenance study.

Source: Gilead SELECTION clinical study report, 2020 (data on file) (4).

In the event of a medical emergency where breaking the blind was required to provide medical care to the patient, the investigator obtained treatment assignment directly from the IWRS for that patient. Gilead recommended but did not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment remained blinded unless that knowledge was necessary to determine patient emergency medical care. The rationale for unblinding was to be clearly explained in source documentation and on the electronic case report form (eCRF), along with the date on which the treatment assignment was obtained. 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 this clinical trial; therefore, if a patient's treatment assignment was disclosed to the investigator, the patient had his or her study treatment discontinued. All patients were followed until study completion unless consent to do so was specifically withdrawn by the patient.

Gilead Pharmacovigilance and Epidemiology (PVE) could independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

A12. It is stated in the company submission that mortality was not assessed in the SELECTION trial (CS, page 13). Please confirm that only 2 deaths occurred during the SELECTION trial, both in the filgotinib 200mg treatment group. Please also provide any further follow-up data related to mortality in the SELECTION trial, if available.

A12. Response: Deaths were reported for two patients (1.0%) in the filgotinib 200mg treatment group in the Maintenance Study. The primary cause of death for the two patients were left ventricular failure and asthma exacerbation (Table 8), respectively. Investigators assessed that the two deaths were not related to study drug. No further follow-up data related to mortality in the SELECTION trial is available.

Table 8. Number of deaths, maintenance study (all randomised analysis set)

Patient number	Treatment group	Age/sex/race/ ethnicity	Death study day, n	Days to death after last dose, n	Primary cause of death
1	Filgotinib 200mg → Filgotinib 200mg	66/Male/White/not Hispanic	81	0	Left ventricular heart failure
2	Filgotinib 200mg → Filgotinib 200mg	65/ Male/White/not Hispanic	302	0	Asthma exacerbation

Abbreviations: mg, milligram; n, number.

Notes: a Day was the number of days relative to the date of first Maintenance study drug dosing (Day 1).

Age (in years) was calculated from the date of first study drug dosing if dosed, randomization if not dosed, or informed consent if not enrolled.

Source: Gilead SELECTION clinical study report, 2020 (data on file) (4).

A13. Baseline characteristics are not evenly distributed across treatment arms. For instance, in the induction study - cohort A, the Filgotinib 200 group has relatively more women (49.8%) than the placebo group (36.5%); and the Filgotinib 200 group

has relatively more non-US patients (94.3%) than the placebo group (86.1%) (CS, Table 9). Please discuss how this might have affected results.

A13. Response: Pre-specified sub-group analyses (Table 9 for Cohort A, Table 10 for Cohort B and Table 11 for the maintenance phase) showed consistent treatment effect of both filgotinib 200mg and filgotinib 100mg for EBS remission across most subgroups by demographic factors, indicating that minor baseline imbalances did not significantly impact the overall treatment effects and conclusions for the comparison between filgotinib and placebo.

EBS remission by demographic factors

Table 9. Difference in EBS remission between filgotinib and placebo at week 10 by demographics characteristics, induction study cohort A (Full Analysis Set)

Characteristic	Filgotinib 200mg (N=245)	Filgotinib 100mg (N=277)	Placebo (N=137)
Age <65 years, n	234	261	129
EBS remission n (%) [95% CI]	61 (26.1%) [20.2% to 31.9%]	49 (18.8%) [13.8% to 23.7%]	20 (15.5%) [8.9% to 22.1%]
Non-stratified risk differences in proportions versus placebo % [95% CI]	10.6% [1.6% to 19.6%]	3.3% [-5.1% to 11.7%]	NA
p-value	0.0248	0.4821	NA
Age >65 years, n	11	16	8
EBS remission n (%) [95% CI]	3 (27.3%) [0.0% to 58.1%]	4 (25.0%) [0.7% to 49.3%]	1 (12.5%) [0.0% to 41.7%]
Non-stratified risk differences in proportions versus placebo % [95% CI]	14.8% [-30.9% to 60.5%]	12.5% [-28.1% to 53.1%]	NA
p-value	0.6027	0.6311	NA
Sex at birth, Female, n	122	120	50
EBS remission n (%) [95% CI]	39 (32.0%) [23.3% to 40.7%]	27 (22.5%) [14.6% to 30.4%]	11 (22.0%) [9.5% to 34.5%]
Non-stratified risk differences in proportions versus placebo % [95% CI]	10.0% [−5.6% to 25.5%]	0.5% [-14.6% to 15.6%]	NA
p-value	0.2670	1.0000	NA
American Indian or Alaska Native, n	1	0	0
Asian, n	77	79	38
EBS remission n (%) [95% CI]	14 (18.2%) [8.9% to 27.4%]	6 (7.6%) [1.1% to 14.1%]	5 (13.2%) [1.1% to 25.2%]
Non-stratified risk differences in proportions versus placebo % (95% CI)	5.0% [-10.7% to 20.8%]	-5.6% [-19.7% to 8.6%]	NA

Characteristic	Filgotinib 200mg (N=245)	Filgotinib 100mg (N=277)	Placebo (N=137)
p-value	0.5995	0.3330	NA
Black or African American, n	2	3	1
EBS remission n (%) [95% CI]	0	0	0
Non-stratified risk differences in proportions versus placebo % (95% CI)	NA	NA	NA
p-value	NA	NA	NA
White, n	165	192	95
EBS remission n (%) [95% CI]	0 (30.3%) [23.0% to 37.6%]	47 (24.5%) [18.1% to 30.8%]	16 (16.8%) [8.8% to 24.9%]
Non-stratified risk differences in proportions versus placebo % (95% CI)	13.5% [2.3% to 24.6%]	7.6% [-2.8% to 18.1%]	NA
p-value	0.0180	0.1728	NA
United States, n	14	33	19
EBS remission n (%) [95% CI]	4 (28.6%) [1.3% to 55.8%]	9 (27.3%) [10.6% to 44.0%]	2 (10.5%) [0.0% to 27.0%]
Difference in proportions% (95% CI)	18.0% [-15.6% to 51.6%]	16.7% [-7.9% to 41.4%]	NA
p-value	0.3631	0.2899	NA
Non-US, n	231	244	118
EBS remission n (%) [95% CI]	60 (26.0%) [20.1% to 31.8%]	44 (18.0%) [13.0% to 23.1%]	19 (16.1%) [9.0% to 23.2%]
Difference in proportions% (95% CI)	9.9% [0.5% to 19.2%]	1.9%, [−6.9% to 10.8%]	NA
p-value	0.0425	0.7676	NA

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable; mg, milligram.

References: Gilead SELECTION clinical study report, 2020 (data on file) (4).

Table 10. Difference in EBS remission between filgotinib and placebo at week 10 by demographics characteristics, induction study cohort B (Full Analysis Set)

Characteristic	Filgotinib 200mg (N=245)	Filgotinib 100mg (N=277)	Placebo (N=137)
Age <65 years, n	234	264	128
EBS remission n (%) [95% CI]	28 (11.5%) [7.3% to 15.7%]	27 (10.2%) [6.4% to 14.1%]	5 (3.9%) [0.2% to 7.7%]
Non-stratified risk differences in proportions versus placebo % [95% CI]	7.6% [1.8% to 13.4%]	6.3% [0.8% to 11.9%]	NA
p-value	0.0129	0.0316	NA

Characteristic	Filgotinib 200mg (N=245)	Filgotinib 100mg (N=277)	Placebo (N=137)
Age >65 years, n	19	21	14
EBS remission n (%) [95% CI]	2 (10.5%) [0.0% to 27.0%]	0 NA	1 (7.1%) [0.0% to 24.2%]
Non-stratified risk differences in proportions versus placebo % [95% CI]	3.4% [-22.1% to 28.9%]	-7.1% [-26.6% to 12.3%]	NA
p-value	1.0000	0.4000	NA
Sex at birth, Female, n	114	99	56
EBS remission n (%) [95% CI]	21 (18.4%) [10.9% to 26.0%]	13 (13.1%) [6.0% to 20.3%]	3 (5.4%) [0.0% to 12.1%]
Non-stratified risk differences in proportions versus placebo % [95% CI]	13.1% [2.5% to 23.6%]	7.8% [-2.5% to 18.1%]	NA
p-value	0.0205	0.1718	NA
Asian, n	50	51	27
EBS remission n (%) [95% CI]	3 (6.0%) [0.0% to 13.6%]	4 (7.8%) [0.0% to 16.2%]	1 (3.7%) [0.0% to 12.7%]
Non-stratified risk differences in proportions versus placebo % (95% CI)	2.3% [-10.3% to 14.8%]	4.1% [-8.9% to 17.2%]	NA
p-value	1.0000	0.6538	NA
Black or African American, n	4	6	3
EBS remission n (%) [95% CI]	1 (25.0%) [0.0% to 79.9%]	0	0
Non-stratified risk differences in proportions versus placebo % (95% CI)	25.0% [-46.6% to 96.6%]	NA	NA
p-value	1.0000	NA	NA
White, n	190	212	98
EBS remission n (%) [95% CI]	25 (13.2%) [8.1% to 18.2%]	22 (10.4%) [6.0% to 14.7%]	5 (5.1%) [0.2% to 10.0%]
Non-stratified risk differences in proportions versus placebo % (95% CI)	8.1% [0.8% to 15.3%]	5.3% [-1.5% to 12.0%]	NA
p-value	0.0409	0.1922	NA
United States, n	36	58	21
EBS remission n (%) [95% CI]	7 (19.4%) [5.1% to 33.8%]	7 (12.1%) [2.8% to 21.3%]	0 [NA]
Difference in proportions% (95% CI)	19.4% [2.7% to 36.1%]	12.1% [0.4% to 23.7%]	NA
p-value	0.0394	0.1802	NA
Non-US, n (%)	226	227	121

Characteristic	Filgotinib 200mg (N=245)	Filgotinib 100mg (N=277)	Placebo (N=137)
EBS remission n (%) [95% CI]	23 (10.2%) [6.0% to 14.3%]	20 (8.8%) [4.9% to 12.7%]	6 (5.0%) [0.7% to 9.2%]
Difference in proportions% (95% CI)	5.2% [-0.9% to 11.4%]	3.9%, [−2.1% to 9.8%]	NA
p-value	0.1064	0.2839	NA

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable; mg, milligram.

References: Gilead SELECTION clinical study report, 2020 (data on file) (4).

Table 11. Difference in EBS remission between filgotinib and placebo at week 10 by demographics characteristics, Maintenance study (Full Analysis Set)

Endpoint	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib (n=172)	Maintenance placebo (n=89)
Age <65 years, n	184	94	168	82
EBS remission n (%) [95% CI]	67 (36.4%) [29.2% to 43.6%]	11 (11.7%) [4.7% to 18.7%]	39 (23.2%) [16.5% to 29.9%]	12 (14.6%) [6.4% to 22.9%]
Non-stratified risk differences in proportions versus placebo % [95% CI]	24.7% [14.4% to 35.0%]	NA	8.6% [-2.3% to 19.5%]	NA
p-value	<0.0001	NA	0.1336	NA
Age >65 years, n	15	4	4	7
EBS remission n (%) [95% CI]	7 (46.7%) [18.1% to 75.2%]	0 NA	2 (50.0%) [0.0% to 100.0%]	0 NA
Non-stratified risk differences in proportions versus placebo % [95% CI]	46.7% [5.6% to 87.7%]	NA	50.0% [-18.6% to 100.0%]	NA
p-value	0.2451	NA	0.1091	NA
Sex at birth: Female, n	106	50	77	41
EBS remission n (%) [95% CI]	43 (40.6%) [30.7% to 50.4%]	5 (10.0%) [0.7% to 19.3%]	17 (22.1%) [12.2% to 32.0%]	8 (19.5%) [6.2% to 32.9%]
Non-stratified risk differences in proportions versus placebo % [95% CI]	30.6% [16.6% to 44.5%]	NA	2.6% [-14.6% to 19.7%]	NA
p-value	<0.0001	NA	0.8166	NA
Asian, n	56	29	41	19
EBS remission n (%) [95% CI]	21 (37.5%) [23.9% 51.1%]	3 (10.3%) [0.0% to 23.2%]	12 (29.3%) [14.1% to 44.4%]	1 (5.3%) [0.0% to 17.9%]
Non-stratified risk differences in proportions versus placebo % (95% CI)	27.2% [7.7% to 46.6%]	NA	24.0% [3.0% to 45.0%]	NA

Endpoint	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib (n=172)	Maintenance placebo (n=89)
p-value	0.0104	NA	0.0454	NA
Black or African American, n	4	0	4	0
EBS remission n (%) [95% CI]	0	0	1 (25.0%) [0.0% to 79.9%]	0
Non-stratified risk differences in proportions versus placebo % (95% CI)	NA	NA	NA	NA
p-value	NA	NA	NA	NA
White, n	135	67	123	69
EBS remission n (%) [95% CI]	50 (37.0%) [28.5% to 45.6%]	8 (11.9%) [3.4% to 20.5%]	27 (22.0%) [14.2% to 29.7%]	11 (15.9%) [6.6% to 25.3%]
Non-stratified risk differences in proportions versus placebo % (95% CI)	25.1% [12.7% to 37.5%]	NA	6.0% [-6.4% to 18.5%]	NA
p-value	0.0001	NA	0.3508	NA
United States, n	19	11	28	11
EBS remission n (%) [95% CI]	8 (2.1%) [17.3% to 66.9%]	3 (27.3%) [0.0% to 58.1%]	7 (25.0%) [7.2% to 42.8%]	1 (9.1%) [0.0% to 30.6%]
Difference in proportions% (95% CI)	14.8% [-26.8% to 56.4%]	NA	15.9% [-13.8% to 45.6%]	NA
p-value	0.4661	NA	0.3996	NA
Non-US, n (%)	180	87	144	78
EBS remission n (%) [95% CI]	66 (36.7%) [29.3% to 44.0%]	8 (9.2%) [2.5% to 15.8%]	34 (23.6%) [16.3% to 30.9%]	11 (14.1%) [5.7% to 22.5%]
Difference in proportions% (95% CI)	27.5% [17.3% to 37.6%]	NA	9.5% [-1.9% to 20.9%]	NA
p-value	<0.0001	NA	0.1156	NA

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable; mg, milligram.

References: Gilead SELECTION clinical study report, 2020 (data on file) (4).

A14. Priority question: All results in Section 2.6 of the CS are presented per arm only. Please provide all effect estimates (odds ratios, relative risks, hazard ratios or mean differences as applicable) with 95% CI for all outcomes reported in Section 2.6 and 2.7 of the CS, for filgotinib 200mg vs placebo and for filgotinib 100mg vs placebo.

A14. Response:

Cohort A induction study

Table 12. Summary of main efficacy outcomes for cohort A induction study, week 10 (Non-responders' imputation; Full Analysis Set)

Endpoint	Filgotinib 200mg (n=245)	Filgotinib 100mg (n=277)	Placebo (n=137)
EBS remission n (%) [95%CI]	64 (26.1%) [20.4% to 31.8%]	53 (19.1%) [14.3% to 23.9%]	21 (15.3%) [8.9% to 21.7%]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	10.8% [2.1% to 19.5%]	3.8 [-4.3% to 12.0%]	NA
p-value	0.0157[a]	0.3379	NA
MCS response n (%) [95%CI]	163 (66.5%) [60.4% to 72.6%]	164 (59.2%) [53.2% to 65.2%]	64 (46.7%) [38.0% to 55.4%]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	19.8% [9.0% to 30.6%]	12.5% [1.8% to 23.2%]	NA
p-value	0.0002[a]	0.0173	NA
MCS remission n (%) [95%CI]	60 (24.5%) [18.9% to 30.1%]	47 (17.0%) [12.4% to 21.6%]	17 (12.4%) [6.5% to 18.3%]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	12.1% [3.8% to 20.4%]	4.6%, 95% [−3.1% to 12.2%]	
p-value	0.0053[a]	0.2295	NA
Mucosal healing[b] n (%) [95%CI]	83 (33.9%) [27.7% to 40.0%]	73 (26.4%) [21.0% to 31.7%]	28 (20.4%) [13.3% to 27.6%]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	13.4% [3.9%, 23.0%]	5.9% [−3.1%, 15.0%]	NA
p-value	0.0055[a]	0.1760	NA
Endoscopic sub score of 0, n (%) [95%CI]	30 (12.2%) [7.9% to 16.6%]	16 (5.8%) [2.8% to 8.7%]	5 (3.6%) [0.1% to 7.2%]
Comparison with placebo			

Endpoint	Filgotinib 200mg (n=245)	Filgotinib 100mg (n=277)	Placebo (n=137)
Non-stratified risk difference in proportions % (95% CI)	8.6% [2.9% to 14.3%]	2.2% [−2.6% to 6.8%]	NA
p-value	0.0047[a]	0.3495	NA
Geboes Histologic remission, n (%) [95%CI]	86 (35.1%) [28.9% to 41.3%]	66 (23.8%) [18.6% to 29.0%]	22 (16.1%) [9.5% to 22.6%]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	19.0% [9.9% to 28.2%]	7.8% [−0.7% to 16.2%]	NA
p-value	<0.0001[a]	0.0672	NA
MCS remission (alternative definition) n (%) [95%CI]	30 (12.2%) [7.9% to 16.6%]	24 (8.7%) [5.2% to 12.2%]	6 (4.4%) [0.6% to 8.2%]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	7.9% [1.9% to 13.8%]	4.3% [−1.0% to 9.6%]	NA
p-value	0.0105[a]	0.1062	NA

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; MCS, Mayo Clinic Score; n, number; NA, not applicable.

References: Gilead SELECTION clinical study report, 2020 (data on file) (4).

Notes: [a]Statistically significant P-value.

The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1.

Table 13. Summary of health-related quality of life results for cohort A induction study, week 10

Endpoint	Filgotinib 200mg (n=245)	Filgotinib 100mg (n=277)	Placebo (n=137)
IBDQ total score, mean (SD)			
Baseline	119 (30.5)	117 (34.2)	114 (32.4)
Change from baseline	52 (37.8)	49 (40.2)	34 (40.5)
Change from baseline (LOCF imputed) LS mean (SE) [95% CI]	51 (2.4) [46% to 56%]	45 (2.3) [41% to 50%]	30 (3.1) [24% to 36%]

Endpoint	Filgotinib 200mg (n=245)	Filgotinib 100mg (n=277)	Placebo (n=137)
LS mean treatment difference n (SE) [95% CI]	21 (3.7) [13% to 28%]	15 (3.6) [8% to 22%]	NA
p-value	<0.0001	<0.0001	NA
SF-36, mean (SD)			
Baseline physical component	42.22 (6.804)	42.25 (7.037)	42.49 (6.908)
Change from baseline n (SD)	6.78 (6.850)	5.69 (7.430)	3.10 (7.309)
Change from baseline (LOCF imputed) LS mean (SE) [95% CI]	6.31 (0.437) [5.45% to 7.17%]	5.13 (0.416) [4.32% to 5.95%]	2.80 (0.565) [1.69% to 3.91%]
LS mean treatment difference n (SE) [95% CI]	3.52 (0.678) [2.19% to 4.85%]	2.34 (0.664) [1.02% to 3.64%]	NA
p-value	<0.0001	0.0005	NA
Baseline mental component mean (SD)	39.50 (9.467)	39.50 (10.640)	37.65 (9.546)
Change from baseline mental component mean (SD)	8.04 (10.178)	6.81 (10.613)	6.12 (9.319)
Change from baseline (LOCF imputed) LS mean (SE) [95% CI]	7.87 (0.600) [6.69% to 9.05%]	6.52 (0.574) [5.40% to 7.64%]	4.85 (0.778) [3.33% to 6.38%]
LS mean treatment difference n (SE) [95% CI]	3.02 (0.933) [1.18% to 4.85%]	1.66 (0.914) [-0.13% to 3.46%]	NA
p-value	0.0013	0.0693	NA
EQ-5D VAS, mean (SD)			
Baseline	54 (18.9)	54 (19.3)	52 (19.1)
Change from Baseline	17 (21.5)	16 (21.4)	9 (21.3)
Change from baseline (LOCF imputed) LS mean (SE) [95% CI]	17 (1.2) [15% to 19%]	16 (1.1) [13% to 18%]	7 (1.5) [4% to 10%]
LS mean treatment difference n (SE) [95% CI]	9 (1.8) [6% to 13%]	8 (1.8) [5% to 12%]	NA

Endpoint	Filgotinib 200mg (n=245)	Filgotinib 100mg (n=277)	Placebo (n=137)
p-value	<0.0001	<0.0001	NA

Abbreviations: CI, confidence interval; EQ-5D, European quality of life 5 dimensions; IBDQ, inflammatory bowel disease questionnaire; LS, least square; LOCF, last observation carried forward; NA, not applicable; SD, standard deviation; SE, standard error; SF-36, 36 item short form survey; VAS, visual analogue scale.

References: Gilead SELECTION clinical study report, 2020 (data on file) (4).

Notes: *p-values from Stratified Cochran-Mantel-Haenszel Test.

Cohort B induction study

Table 14. Summary of efficacy outcomes for cohort B induction study (Non-responders' imputation; Full Analysis Set)

Endpoint	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)
EBS remission n (%) [95%CI]	30 (11.5%) [7.4% to 15.5%]	27 (9.5%) [5.9% to 13.0%]	6 (4.2%) [0.6% to 7.9%]
Comparison with placebo			
Non-stratified risk difference in proportions % [95% CI)	7.2% [1.6% to 12.8%]	5.2% [-0.0% to 10.5%]	NA
p-value	0.0103[a]	0.0645	NA
MCS response n (%) [95%CI]	139 (53.1%) [46.8% to 59.3%]	102 (35.8%) [30.0% to 41.5%]	25 (17.6%) [11.0% to 24.2%]
Comparison with placebo			
Non-stratified risk difference in proportions % [95% CI)	35.4% [26.2% to 44.7%]	18.2% [9.3% to 27.1%]	NA
p-value	<0.0001	0.0001	NA
MCS remission n (%) [95%CI]	25 (9.5%) [5.8% to 13.3%]	17 (6.0%) [3.0% to 8.9%]	6 (4.2%) [0.6% to 7.9%]
Comparison with placebo			
Non-stratified risk difference in proportions % [95% CI)	5.3% [-0.1% to 10.7%]	1.7% [-3.1% to 6.6%]	NA
p-value	0.0393	0.5308	NA
Mucosal healing n (%) [95%CI]	45 (17.2%) [12.4% to 21.9%]	37 (13.0%) [8.9% to 17.1%]	11 (7.7%) [3.0% to 12.5%]
Comparison with placebo			
Non-stratified risk difference in proportions % [95% CI)	9.4% [2.5% to 16.3%]	5.2% [-1.2% to 11.6%]	NA
p-value	0.0053	0.1138	NA

Endpoint	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)
Endoscopic sub score 0 n (%) [95%CI]	9 (3.4%) [1.0% to 5.8%]	6 (2.1%) [0.3% to 3.9%]	3 (2.1%) [0.0% to 4.8%]
Comparison with placebo			
Non-stratified risk difference in proportions % [95% CI)	1.3% [-2.5% to 5.1%]	-0.0% [-3.4% to 3.4%]	NA
p-value	0.4269	0.9987	NA
Geboes Histologic remission n (%) [95%CI]	52 (19.8%) [14.8% to 24.9%]	39 (13.7%) [9.5% to 17.8%]	12 (8.5%) [3.5% to 13.4%]
Comparison with placebo			
Non-stratified risk difference in proportions % [95% CI)	11.4% [4.2% to 18.6%]	5.2% [-1.4% to 11.8%]	NA
p-value	0.0019	0.1286	NA
MCS remission (alternative definition) n (%) [95%CI]	10 (3.8%) [1.3% to 6.3%]	6 (2.1%) [0.3% to 3.9%]	3 (2.1%) [0.0% to 4.8%]
Comparison with placebo			
Non-stratified risk difference in proportions % [95% CI)	1.7% [-2.2% to 5.6%]	-0.0% [-3.4% to 3.4%]	NA
p-value	0.3084	0.9109	NA

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; MCS, Mayo Clinic Score; n, number; NA, not applicable.

References: Gilead SELECTION clinical study report, 2020 (data on file) (4).

Notes: *p-values from Stratified Cochran-Mantel-Haenszel Test.[a] Statistically significant p-value.

Table 15. Summary of Health-related Quality of Life results for cohort B induction study, week 10

Endpoint	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)
IBDQ total score, mean (SD)			
Baseline	112 (32.1)	118 (30.9)	118 (33.1)
Change from baseline	46 (37.7)	29 (36.9)	13 (35.2)
Change from baseline (LOCF imputed) LS mean (SE) [95% CI]	43 (2.3) [38% to 47%]	30 (2.3) [25% to 34%]	14 (3.1) [8% to 20%]
LS mean treatment difference n (SE) [95% CI]	28 (3.6) [21% to 35%]	15 (3.6) [0% to 22%]	NA

Endpoint	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)
p-value	<0.0001	<0.0001	NA
SF-36, mean (SD)			
Baseline physical component	40.55 (7.768)	41.85 (7.376)	40.10 (8.134)
Change from baseline physical component	6.61 (7.278)	4.16 (6.622)	2.44 (8.062)
Change from baseline (LOCF imputed) LS mean (SE) [95% CI]	6.31 (0.444) [5.44% to 7.18%]	4.53 (0.431) [3.69% to 5.38%]	2.29 (0.585) [1.14% to 3.44%]
LS mean treatment difference n (SE) [95% CI]	4.02 (0.691) [2.66, 5.37]	2.24 (0.682) [0.90% to 3.58%]	NA
p-value	<0.0001	0.0011	NA
Baseline mental component	37.93 (10.895)	40.55 (9.943)	39.94 (10.341)
Change from baseline mental component	7.92 (10.409)	3.85 (9.512)	1.66 (9.540)
Change from baseline (LOCF imputed) LS mean (SE) [95% CI]	6.99 (0.588) [5.83% to 8.14%]	4.30 (0.567) [3.19% to 5.41%]	2.02 (0.772) [0.51% to 3.54%]
LS mean treatment difference n (SE) [95% CI]	4.97 (0.913) [3.17% to 6.76%]	2.28 (0.896) [0.52% to 4.04%]	NA
p-value	<0.0001	0.0113	NA
EQ-5D VAS, mean (SD)			
Baseline	48 (20.5)	51 (19.8)	49 (18.9)
Change from baseline	19 (22.2)	10 (21.2)	6 (20.2)
Change from baseline (LOCF imputed) LS mean (SE) [95% CI]	17 (1.3) [15% to 20%]	11 (1.2) [9% to 13%]	6 (1.6) [2% to 9%]
LS mean treatment difference n (SE) [95% CI]	12 (1.9) [8% to 15%]	5 (1.9) [2% to 9%]	NA
p-value	<0.0001	0.0051	NA

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; EQ-5D, European quality of life 5 dimensions; IBDQ, inflammatory bowel disease questionnaire; LS, least square; LOCF, last observation carried

forward; NA, not applicable; SD, standard deviation; SE, standard error; SF-36, 36 item short form survey; VAS, visual analogue scale.

References: Gilead SELECTION clinical study report, 2020 (data on file) (4).

Notes: *p-values from Stratified Cochran-Mantel-Haenszel Test.

Maintenance study

Table 16. Summary of efficacy outcomes for maintenance study, week 58 (Non-responders' imputation; Full Analysis Set)

Endpoint	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib (n=172)	Maintenance placebo (n=89)
EBS remission n (%) [95%CI]	74 (37.2%) [30.2% to 4.2%]	11 (11.2%) [4.5% to 18.0%]	41 (23.8%) [17.2% to 0.5%]	12 (13.5%) [5.8% to 21.1%]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	26.0% [16.0% to 5.9%]	NA	10.4% [−0.0% to 0.7%]	NA
p-value	<0.0001[a]	NA	0.0420[a]	NA
Sustained EBS remission n (%) [95%CI]	36 (18.1%) [12.5% to 3.7%]	5 (5.1%) [0.2% to 0.0%]	15 (8.7%) [4.2% to 13.2%]	7 (7.9%) [1.7% to 14.0%]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	13.0% [5.3% to 20.6%]	NA	0.9% [−7.0% to 8.7%]	NA
p-value	0.0024[a]	NA	0.7951	NA
MCS response n (%) [95%CI]	133 (66.8%) [60.0% to 73.6%]	32 (32.7%) [22.9% to 42.4%]	87 (50.6%) [42.8% to 58.3%]	35 (39.3%) [28.6% to 50.0%]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	34.2% [22.1% to 46.3%]	NA	11.3% [−2.2% to 24.7%]	NA
p-value	<0.0001[a]	NA	0.0703	NA

Endpoint	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib (n=172)	Maintenance placebo (n=89)
MCS remission n (%) [95%CI]	69 (34.7%) 27.8% to 41.5%]	9 (9.2%) [3.0% to 15.4%]	39 (22.7%) [16.1% to 29.2%]	12 (13.5%) [5.8% to 21.1%]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	25.5%, [16.0% to 35.0%]	NA	9.2%, [−1.1% to 19.5%]	NA
p-value	<0.0001[a]	NA	0.0658	NA
Mucosal healing n (%) [95%CI]	81 (40.7%) [33.6% to 47.8%]	15 (15.3%) [7.7% to 22.9%]	46 (26.7%) [19.8% to 33.6%]	17 (19.1%) [10.4% to 27.8%]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	25.4% [14.8% to 36.0%]	NA	7.6% [−3.7% to 19.0%]	NA
p-value	<0.0001	NA	0.1625	NA
Endoscopic sub score 0 n (%) [95%CI]	31 (15.6%) [10.3% to 20.9%]	6 (6.1%) [0.9% to 11.4%]	23 (13.4%) [8.0% to 18.7%]	7 (7.9%) [1.7% to 14.0%]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	9.5% [1.8% to 17.1%]	NA	5.5% [-2.9% to 13.9%]	NA
p-value	0.0157[a]	NA	0.1808	NA
Geboes Histologic remission n (%) [95%CI]	76 (38.2%) [31.2% to 45.2%]	13 (13.3%) [6.0% to 20.5%]	48 (27.9%) [20.9% to 34.9%]	16 (18.0%) [9.4% to 26.5%]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	24.9% [14.6% to 35.2%]	NA	9.9% [-1.3% to 21.2%]	NA
p-value	<0.0001[a]	NA	0.0521	NA

Endpoint	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib (n=172)	Maintenance placebo (n=89)
MCS remission (alternative definition) n (%) [95%CI]	44 (22.1%) [16.1% to 28.1%]	6 (6.1%) [0.9% to 11.4%]	21 (12.2%) [7.0% to 17.4%]	7 (7.9%) [1.7% to 14.0%]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	16.0% [7.8% to 24.2%]	NA	4.3% [-3.9% to 12.6%]	NA
p-value	0.0005[a]	NA	0.2946	NA
6-months corticosteroid-free remission** n (%) [95%CI]	25 (27.2%) [17.5% to 36.8%]	3 (6.4%) [0.0% to 14.4%]	11 (13.6%) [5.5% to 21.7%]	2 (5.4%) [0.0% to 14.0%]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	20.8% [7.7% to 33.9%]	NA	8.2% [-4.2% to 20.6%]	NA
p-value	0.0055[a]	NA	0.1265	NA

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; MCS, Mayo Clinic Score; NA, not applicable.

References: Gilead SELECTION clinical study report, 2020 (data on file) (4).

Notes: *p-values from Stratified Cochran-Mantel-Haenszel Test.

**Denominator of percentage is the number of Full Analysis Set subjects who were on corticosteroid at maintenance baseline.

Table 17. Summary of Health-related Quality of Life endpoints for maintenance study, week 47

Endpoint	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 200mg (n=172)	Maintenance placebo (n=89)
IBDQ total score, mean (SD)				
Baseline	178 (28.4)	182 (25.6)	176 (30.8)	176 (27.0)

Endpoint	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 200mg (n=172)	Maintenance placebo (n=89)
Change from baseline	9 (27.3)	-5 (26.5)	8 (26.0)	5 (21.5)
Change from baseline (LOCF imputed) LS mean (SE) [95% CI]	5 (2.0) [1% to 9%]	-9 (2.7) [-14.0% to -3.0%]	2 (2.2) [-3.0% to 6.0%]	-4 (2.9) [-10.0% to 2.0%]
LS mean treatment difference n (SE) [95% CI]	13 (3.2) [7% to 20%]	NA	6 (3.3) [-1.0% to 12.0%]	NA
p-value	<0.0001	NA	0.0834	NA
SF-36, mean (SD)				
Baseline physical component	49.99 (7.393)	49.51 (6.652)	49.30 (7.596)	48.57 (6.658)
Change from baseline physical component	2.45 (5.745)	1.90 (5.506)	1.45 (6.536)	1.68 (5.437)
Change from baseline (LOCF imputed) LS mean (SE) [95% CI]	1.65 (0.425) [0.81% to 2.48%]	-0.37 (0.572) [-1.49% to 0.76%]	0.84 (0.460) [-0.06% to 1.75%]	0.12 (0.604) [-1.07% to 1.31%]
LS mean treatment difference n (SE) [95% CI]	2.01 (0.665) [0.71% to 3.32%]	NA	0.72 (0.697) [-0.65% to 2.09%]	NA
p-value	0.0027	NA	0.3037	NA
Baseline mental component	48.67 (9.451)	49.52 (8.124)	48.54 (9.219)	47.88 (8.621)
Change from baseline mental component	1.45 (8.980)	-0.99 (8.572)	1.44 (6.973)	1.86 (7.769)

Endpoint	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 200mg (n=172)	Maintenance placebo (n=89)
Change from baseline (LOCF imputed) LS mean (SE) [95% CI]	0.91 (0.600) [-0.27% to 2.09%]	-1.71 (0.809) [-3.30% to -0.11%]	-0.42 (0.584) [-1.57% to 0.73%]	-0.46 (0.767) [-1.97% to 1.05%]
LS mean treatment difference n (SE) [95% CI]	2.62 (0.941) [0.77% to 4.47%]	NA	0.04 (0.884) [-1.70% to 1.78%]	NA
p-value	0.0057	NA	0.9623	NA
EQ-5D VAS, mean (SD)				
Baseline mean	73 (17.8)	75 (13.2)	74 (15.1)	73 (15.3)
Change from baseline	5 (17.0)	1 (12.5)	2 (15.9)	4 (14.6)
Change from baseline (LOCF imputed) LS mean (SE) [95% CI]	3 (1.2) [0% to 5%]	-3 (1.6) [-6% to 0%]	-1 (1.2) [-3% to 2%]	-2 (1.6) [-5% to 1%]
LS mean treatment difference n (SE) [95% CI]	5 (1.8) [2% to 9%]	NA	1 (1.8) [-2% to 5%]	NA
p-value	0.0030	NA	0.4235	NA

Abbreviations: CI, confidence interval; EQ-5D, European quality of life 5 dimensions; IBDQ, inflammatory bowel disease questionnaire; LS, least square; LOCF, last observation carried forward; NA, not applicable; SD, standard deviation; SE, standard error; SF-36, 36 item short form survey; VAS, visual analogue scale.

References: Gilead SELECTION clinical study report, 2020 (data on file) (4).

Notes: *p-values from Stratified Cochran-Mantel-Haenszel Test.

Subgroup analysis

Cohort B induction study

Table 18. Cohort B induction study by previous exposure to TNFα inhibitors (non-responder imputation) at week 10

Endpoint	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)
Previous exposure to TNFα inhibitors (yes)	[redacted]	[redacted]	[redacted]
EBS remission n (%) [95%CI]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
MCS response n (%) [95%CI]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
Mucosal healing n (%) [95%CI]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
MCS remission n (%) [95%CI]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
Previous exposure to TNFα inhibitors (no)	[redacted]	[redacted]	[redacted]

Endpoint	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)
EBS remission n (%) [95%CI]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
MCS response n (%) [95%CI]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
Mucosal healing n (%) [95%CI]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
MCS remission n (%) [95%CI]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable; mg, milligram; MCS, Mayo clinic score; TNFα, tumour necrosis factor-alpha.

References: Gilead SELECTION clinical study report, 2020 (data on file)(4) and Gilead SELECTION HTA UK subgroup analysis, 2021 (data on file) (5).

Maintenance study

Table 19. Maintenance study by previous exposure to TNFα inhibitors (non-responder imputation) at week 58

Subgroup	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 100mg (n=172)	Maintenance placebo (n=89)
Previous exposure to TNFα inhibitors (yes)	[redacted]	[redacted]	[redacted]	[redacted]
EBS remission n (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
MCS response n (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
Six-month corticosteroid-free EBS remission (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 100mg (n=172)	Maintenance placebo (n=89)
Mucosal healing n (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
MCS remission n (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
Previous exposure to TNFα inhibitors (no)	[redacted]	[redacted]	[redacted]	[redacted]
EBS remission n (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
MCS response n (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 100mg (n=172)	Maintenance placebo (n=89)
Six-month corticosteroid-free EBS remission (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
Mucosal healing n (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
MCS remission n (%) [95%CI]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; MCS, Mayo clinic score; n, number; NA, not applicable; mg, milligram; TNFα, tumour necrosis factor-alpha.

References: Gilead SELECTION clinical study report, 2020 (data on file)(4) and Gilead SELECTION HTA UK subgroup analysis, 2021 (data on file) (5).

A15. Priority question: In several tables (CS, Tables 15-22) you report 'non-responder's imputation' results. Please clarify what that means and why these have been reported. This imputation approach is not listed in Table 12 - Summary of statistical analyses in SELECTION. Please provide results using each of the imputation methods listed in Table 12 (Observed cases only;

Missing=Success; Missing=Success for the placebo and Missing=Failure for the filgotinib groups; Multiple imputation).

A15. Response: The 'non-responder's imputation' (NRI) analysis (Missing = Failure for all groups) was specified as the primary method to handle missing efficacy data as per the protocol:

- Patients who do not have sufficient measurements to determine efficacy endpoints will be considered failures (i.e., failing to reach the primary time point of interest or to measure it could be seen as a failure of the treatment regimen and hence the endpoints are considered not met ("failure")).

The imputation methods described in Table 12 in Document B were specifically planned for sensitivity analyses of the primary endpoint (EBS remission rates at week 10) but not planned for any other endpoint.

Implementation of those missing data imputation rules on endpoints other than the primary is not recommended due to the fact that those analyses were not pre-planned and because of the questionable clinical relevance of the effects being estimated:

- Missing=Success:
    - favours active if more dropouts in active (e.g. for safety reasons)
    - favours placebo if more dropouts in placebo (e.g. dropouts on placebo for lack of efficacy)
- Missing=Success for placebo and failure for filgotinib:
    - Penalises filgotinib without clinical rationale
- Multiple imputation:
    - Relies on unverifiable assumptions regarding the missing data pattern (that the missing data can be explained (predicted) by other observed variables). In some instances, this assumption makes clinical sense, in particular when patients are gradually getting worse until the dropout occurs.

The proportion of patients who achieve EBS remission in Cohort A, Cohort B and Maintenance studies are summarised by treatment group from Table 20 to Table 22 using the observed cases only imputation, from Table 23 to Table 25 using the missing = success imputation, from Table 26 to Table 28 using the missing = success for the

placebo and missing = failure for the filgotinib groups and from Table 29 to Table 31 using multiple imputation.

Observed cases only imputation - Cohort A induction study

Table 20. Sensitivity analysis: Summary of EBS remission for cohort A induction study, week 10 (Observed cases only; Full Analysis Set)

Endpoint	Filgotinib 200mg (n=236)	Filgotinib 100mg (n=261)	Placebo (n=128)
EBS remission n (%) [95%CI for the proportion]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
EBS remission not achieved n (%)	[redacted]	[redacted]	[redacted]
Observed non-responders n (%)	[redacted]	[redacted]	[redacted]
Non-responders due to treatment failure	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable.
References: Gilead SELECTION clinical study report, 2020 (data on file)(4).
Notes: The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. Treatment failure refers to commencement or dose escalation of potentially effective non-study treatment for UC. Patients with insufficient data due to reasons other than treatment failure are excluded.

Observed cases only imputation - Cohort B induction study

Table 21. Sensitivity analysis: Summary of EBS remission for cohort B induction study, week 10 (Observed cases only; Full Analysis Set)

Endpoint	Filgotinib 200mg (n=239)	Filgotinib 100mg (n=258)	Placebo (n=129)
EBS remission n (%) [95%CI for the proportion]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
EBS remission not achieved n (%)	[redacted]	[redacted]	[redacted]
Observed non-responders n (%)	[redacted]	[redacted]	[redacted]
Non-responders due to treatment failure	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable. **References**: Gilead SELECTION clinical study report, 2020 (data on file)(4). **Notes:** The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. Treatment failure refers to commencement or dose escalation of potentially effective non-study treatment for UC. Patients with insufficient data due to reasons other than treatment failure are excluded.

Observed cases only imputation - Maintenance study

Table 22. Sensitivity analysis: Summary of EBS remission for Maintenance study, week 58 (Observed cases only; Full Analysis Set)

Subgroup	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=182)	Maintenance placebo (n=89)	Maintenance filgotinib 100mg (n=153)	Maintenance placebo (n=78)
EBS remission n (%) [95%CI for the proportion]	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=182)	Maintenance placebo (n=89)	Maintenance filgotinib 100mg (n=153)	Maintenance placebo (n=78)
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
EBS remission not achieved n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Observed non-responders n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Non-responders due to treatment failure	[redacted]	[redacted]	[redacted]	[redacted]
Protocol specified disease worsening (PSDW)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable.
References: Gilead SELECTION clinical study report, 2020 (data on file)(4).
Notes: The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. Treatment failure refers to commencement or dose escalation of potentially effective non-study treatment for UC. Patients with insufficient data due to reasons other than treatment failure or protocol specified disease worsening are excluded.

Missing = Success imputation - Cohort A induction study

Table 23. Sensitivity analysis: Summary of EBS remission for cohort A induction study, week 10 (Missing = Success; Full Analysis Set)

Endpoint	Filgotinib 200mg (n=245)	Filgotinib 100mg (n=277)	Placebo (n=137)
EBS remission n (%) [95%CI for the proportion]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in	[redacted]	[redacted]	[redacted]

Endpoint	Filgotinib 200mg (n=245)	Filgotinib 100mg (n=277)	Placebo (n=137)
proportions % (95% CI)			
p-value	[redacted]	[redacted]	[redacted]
EBS remission not achieved n (%)	[redacted]	[redacted]	[redacted]
Observed non-responders n (%)	[redacted]	[redacted]	[redacted]
Non-responders due to treatment failure	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable.

References: Gilead SELECTION clinical study report, 2020 (data on file)(4).

Notes: The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. Treatment failure refers to commencement or dose escalation of potentially effective non-study treatment for UC. Patients with insufficient data due to reasons other than treatment failure are excluded.

Missing = Success imputation - Cohort B induction study

Table 24. Sensitivity analysis: Summary of EBS remission for cohort B induction study, week 10 (Missing = Success; Full Analysis Set)

Endpoint	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=258285	Placebo (n=142)
EBS remission n (%) [95%CI for the proportion]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
EBS remission not achieved n (%)	[redacted]	[redacted]	[redacted]
Observed non-responders n (%)	[redacted]	[redacted]	[redacted]

Endpoint	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=258285	Placebo (n=142)
Non-responders due to treatment failure	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable.

References: Gilead SELECTION clinical study report, 2020 (data on file)(4).

Notes: The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. Treatment failure refers to commencement or dose escalation of potentially effective non-study treatment for UC. Patients with insufficient data due to reasons other than treatment failure are excluded.

Missing = Success imputation - Maintenance study

Table 25. Sensitivity analysis: Summary of EBS remission for Maintenance study, week 58 (Missing = Success; Full Analysis Set)

Subgroup	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 100mg (n=172)	Maintenance placebo (n=89)
EBS remission n (%) [95%CI for the proportion]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
EBS remission not achieved n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Observed non-responders n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Non-responders due to treatment failure	[redacted]	[redacted]	[redacted]	[redacted]
Protocol specified disease worsening (PSDW)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable.

References: Gilead SELECTION clinical study report, 2020 (data on file)(4).

Notes: The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. Treatment failure refers to commencement or dose escalation of potentially effective non-study treatment for UC. Patients with insufficient data due to reasons other than treatment failure or protocol specified disease worsening are excluded.

Missing = success for placebo and = failure for filgotinib imputation - Cohort A induction study

Table 26. Sensitivity analysis: Summary of EBS remission for cohort A induction study, week 10 (Missing = Success for placebo and = failure for filgotinib; Full Analysis Set)

Endpoint	Filgotinib 200mg (n=245)	Filgotinib 100mg (n=277)	Placebo (n=137)
EBS remission n (%) [95%CI for the proportion]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
EBS remission not achieved n (%)	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable.
References: Gilead SELECTION clinical study report, 2020 (data on file)(4).
Notes: The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. Treatment failure refers to commencement or dose escalation of potentially effective non-study treatment for UC.

Missing = success for placebo and = failure for filgotinib imputation - Cohort B induction study

Table 27. Sensitivity analysis: Summary of EBS remission for cohort B induction study, week 10 (Missing = Success for placebo and = failure for filgotinib; Full Analysis Set)

Endpoint	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)
EBS remission n (%) [95%CI for the proportion]	[redacted]	[redacted]	[redacted]
Comparison with placebo			

Endpoint	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
EBS remission not achieved n (%)	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable.

References: Gilead SELECTION clinical study report, 2020 (data on file)(4).

Notes: The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. Treatment failure refers to commencement or dose escalation of potentially effective non-study treatment for UC.

Missing = success for placebo and = failure for filgotinib imputation - Maintenance study

Table 28. Sensitivity analysis: Summary of EBS remission for Maintenance study, week 58 (Missing = Success for placebo and = failure for filgotinib; Full Analysis Set)

Subgroup	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 100mg (n=172)	Maintenance placebo (n=89)
EBS remission n (%) [95%CI for the proportion]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]
EBS remission not achieved n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable.

References: Gilead SELECTION clinical study report, 2020 (data on file)(4).

Notes: The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. Treatment failure refers to commencement or dose escalation of

potentially effective non-study treatment for UC.

Multiple imputation - Cohort A induction study

Table 29. Sensitivity analysis: Summary of EBS remission for cohort A induction study, week 10 (Multiple imputation; Full Analysis Set)

Endpoint	Filgotinib 200mg (n=245)	Filgotinib 100mg (n=277)	Placebo (n=137)
EBS remission n (%) [95%CI for the proportion]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable.

References: Gilead SELECTION clinical study report, 2020 (data on file)(4).

Notes: The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. The baseline value of EBS subscores and stratification factors were included as covariates in the logistic regression model for imputation.

Multiple imputation - Cohort B induction study

Table 30. Sensitivity analysis: Summary of EBS remission for cohort B induction study, week 10 (Multiple imputation; Full Analysis Set)

Endpoint	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)
EBS remission n (%) [95% CI for the proportion]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable.

References: Gilead SELECTION clinical study report, 2020 (data on file)(4).

Notes: The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. The baseline value of EBS subscores and stratification factors were included as covariates in the logistic regression model for imputation.

Multiple imputation - Maintenance study

Table 31. Sensitivity analysis: Summary of EBS remission for Maintenance study, week 58 (Multiple imputation; Full Analysis Set)

Subgroup	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 100mg (n=172)	Maintenance placebo (n=89)
EBS remission n (%) [95%CI for the proportion]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EBS, endoscopy/bleeding/stool frequency; n, number; NA, not applicable.
References: Gilead SELECTION clinical study report, 2020 (data on file)(4).
Notes: The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. The baseline value of EBS subscores and stratification factors were included as covariates in the logistic regression model for imputation.

A16. Please state whether quality assessment of the relevant clinical effectiveness evidence was done by two or more independent assessors.

A16. Response: Each study that met criteria for inclusion was critically appraised by a single reviewer and reviewed by a second reviewer using the Cochrane Collaboration's tool for assessing the risk of bias (6) in line with NICE requirements (7).

Indirect comparisons

A17. Priority question: Please provide separate files for all embedded files in the company submission (For instance, Appendix D, pages 46 and 104; but there may be others). Please provide all analysis code for all analyses, including the WinBugs code and input data for the NMAs.

A17. Response: Please see the .zip file 'ID3736_FIL_UC_NICE_CQ_A17' accompanying this file.

A18. Priority question: None of the trials that inform the effectiveness of treatment during the maintenance phase include patients who had responded to induction with a treatment that was not examined in the maintenance phase e.g. the patients analysed in the maintenance phase of the SELECTION trial are only those that entered the same trial during the induction phase. In effect this would imply that the population of patients studied in the maintenance phase is those largely those who had achieved response on that particular treatment (with a smaller number who had originally received placebo). This would imply that the effectiveness of obtaining remission or loss of response in those who had responded or were already in remission at the end of the induction period is most or only applicable to those who had achieved response on the same treatment. In terms of and NMA it would bring into question the degree of comparability of trials of different treatments.

a. **Please comment on this issue and provide justification for pooling studies that assess the effectiveness of treatments during the maintenance phase?**
b. **Please conduct a scenario analysis where the estimates of effectiveness for each treatment from the maintenance phase NMA are replaced with ones taken only from trials where the treatment analysed in the maintenance phase was that studied in the induction phase of the same trial.**

A18. Response:

a. We have interpreted this question to mean, maintenance phase treatments should only be pooled if the induction phase treatment was the same for all sources of data for the pooled treatments (i.e. the patients have had the same treatment experience).

The majority of maintenance phase treatments only have one source of evidence, so are unaffected by this request. Excluding placebo, only adalimumab 160/80/40mg Q2W and vedolizumab 300mg Q8W use pooled evidence, see Table 32.

Evidence for adalimumab 16/80/40 mg Q2W was taken from ULTRA 2 and VARSITY; both trials use the same induction phase treatment.

Evidence for vedolizumab 300mg Q8W was taken from GEMINI, VARSITY and VISIBLE, all three trials used the same induction phase treatment.

Therefore, the NMA doesn't pool any maintenance phase treatments where patients enter the maintenance phase with different induction phase treatment experiences.

Table 32. Maintenance phase data sources

Maintenance treatment	Data sources (# trials)
Placebo	9
Adalimumab 160/80/40mg Q2W	2
Filgotinib 100mg QD	1
Filgotinib 200mg QD	1
Golimumab 100mg Q4W	1
Golimumab 50mg Q4W	1
Infliximab 5mg/kg Q8W	1
Tofacitinib 10mg	1
Tofacitinib 5mg	1
Ustekinumab 90mg Q12W	1
Ustekinumab 90mg Q8W	1
Vedolizumab 108mg SC Q2W	1

Abbreviations: kg, kilogram; mg, milligram; Q2W, every two weeks; Q8W, every eight weeks; Q12W, every 12 weeks; QD, once daily; SC, subcutaneous.

b. Please see response to part a. The company does not believe that the suggested approach is appropriate, and have not provided the requested scenario analysis.

A19. Please confirm whether all outcomes described in the NICE final scope were included in the NMA, and if not, provide a justification.

A19. Response:

The following outcomes were described in the NICE final scope:

- mortality
- measures of disease activity
- rates of and duration of response, relapse and remission
- rates of hospitalisation (including readmission)
- rates of surgical intervention
- endoscopic healing
- mucosal healing (combines endoscopic and histological healing)
- corticosteroid-free remission
- achieving mucosal healing
- adverse effects of treatment
- health-related quality of life

In line with prior technology assessments in moderate to severe UC, outcomes included in the company NMA include MCS remission, MCS response and endoscopic mucosal healing (2, 8, 9). In addition to analysis of efficacy outcomes, a NMA of safety outcomes was also conducted in order to compare the safety of filgotinib to other treatments.

Health related quality of life (HRQoL) measures, whilst important for technology assessment were not considered for inclusion in the NMA. HRQoL is included in an overall assessment of cost-effectiveness via inclusion in the cost-effectiveness model. The economic model does not require evidence of comparative HRQoL since comparative efficacy drive state membership and HRQoL is state specific. Therefore, HRQoL measures included in the economic model are derived from SELECTION data.

MCS is frequently used to classify UC and has been previously used to derive the main efficacy endpoints to inform economic analyses in previous HTA submissions in this area (2, 8, 9). Therefore, the current NMA is believed to provide sufficient evidence to inform the comparison of the efficacy and safety of filgotinib and its comparators.

A20. The company notes a number of “key assumptions applied for the treat-through trials imputations”.

a. Can the company please provide a justification for claiming that these are an exhaustive list of relevant key assumptions?
b. Can the company please provide a rationale to support the claim that a complete list of assumptions were met?

A20. Response (Parts a. & b.): The company submission notes a number of assumptions that were applied to treat-through trials incorporated into the NMA. These assumptions were provided in order to transparently detail the actions taken in order to include these trials in the maintenance phase NMA.

NICE Early Scientific Advice sought prior to submission stated that the approach taken is a reasonable compromise, given the evidence base, the requirement of the decision problem and the economic model structure.

A21. Please state whether risk of bias assessments for the NMA were conducted by two or more independent reviewers.

A21. Response: The risk of bias assessments of studies included in the NMA were conducted by two independent reviewers.

A22. Priority question: The CS states that ‘The RCTs for inclusion in the NMA were restricted to phase II/III or phase III randomised controlled trials’ (Section B.2.9.3) Also, the following studies were included in previous STAs, but excluded in this submission: Sandborn WJ, Ghosh S, Panes J, Vranic I, Su C, Rousell S, et al. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. New England Journal of Medicine. 2012;367(7):616-24; Probert CS, Hearing SD, Schreiber S, Kuhbacher T, Ghosh S, Arnott ID, et al. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. Gut. 2003;52(7):998-1002; Suzuki Y, Motoya S, Hanai H, Matsumoto T, Hibi T, Robinson AM, et al. Efficacy and safety of adalimumab in Japanese patients with moderately to severely active ulcerative colitis. J Gastroenterol. 2014;49(2):283-94; Motoya S, Watanabe K, Ogata H, Kanai T, Matsui T, Suzuki Y, et al. Vedolizumab in Japanese patients with ulcerative colitis: A Phase 3, randomized, double-blind, placebo-controlled study. PLoS

One. 2019;14(2):e0212989; Mshimesh 2017, REF 113=113. Mshimesh BAR. Efficacy and safety of adalimumab versus infliximab in patients suffered from moderate to severe active ulcerative colitis. Asian Journal of Pharmaceutical and Clinical Research. 2017;10(3):300-7.

a. **Please justify why each of the above studies was excluded.**
b. **Please clarify whether any RCTs were excluded because they were not 'Phase II/III or phase III'. Specifically, please justify why phase II studies were excluded.**
c. **Please redo the NMAs including all RCTs regardless of phase.**

A22. Response:

a.

Table 33. Justification for exclusion of studies listed from NMA

Study name	Justification for exclusion
Sandborn (2012)	No outcome data for NMA*
Probert (2003)	Inappropriate measure of remission†
Motoya (2019)	Population; included patients < 18 years
Mshimesh (2017)	Study was retracted by Author
*In population of interest only response outcomes were reported; in the response/remission single model approach both response and remission data is required. †Remission was measured by ulcerative colitis symptom score (UCSS), the NMA was based on mayo clinic score (MCS), so it was inappropriate to use this remission data.	

b. Although, the NMA inclusion/exclusion criteria described excluding phase II trials, in practice no trials were excluded exclusively for this reason.

c. There are no additional studies to be included in the described alternative scenario.

A23. Priority question: The CS states that 'For the induction period, it was considered clinically reasonable to assume that the induction phase outcomes were comparable, despite differences in the length of the induction phases.' (Section B.2.9.7). Please clarify whether any trials provided efficacy results for more than one time point for the same comparator. If this is the case then

show those results and conduct sensitivity analyses to show the variation in time point.

A23. Response: All publications identified, via the SLR, of trials included in the NMA were reviewed, no outcomes were identified at additional timepoints within the induction phase. Therefore, no additional sensitivity analyses were needed to be conducted. As part of the NICE Scientific Advice, the clinical expert noted of the approach to include trials of 6 to 8 weeks induction duration "It would be clinically reasonable to assume that the induction phase outcomes were comparable, despite differences in the length of induction phase".

Section B: Clarification on cost-effectiveness data

Literature searches

B1. Please justify the use of the "$" symbol in lines 17, 19, 20 and 22 of PubMed searches for health-related quality-of-life (Appendix H, page 5) and if any evidence may have been missed with the use of this symbol instead of the recommended "*" for truncation in PubMed.

B1. Response: The inclusion of the "$" appears to an error carried through from the Embase search strategy. This was noticed and corrected in the updated searches conducted in November 2020. The searches have been re-run in PubMed replacing "$" with "*", to assess the sensitivity to this error. In total, only two additional studies were identified when "$" was replaced with "*"; therefore, we believe this not to have had a significant impact on the SLR results.

B2. Please explain why editorials, letters, case studies, reviews and case reports were 'NOT'-d out of the Cochrane Library searches in Appendices G, H and I.

B2. Response: This filter was used in the Cochrane Library search terms as the search terms were translated from the Embase and Medline, we recognise that such a filter may be redundant for this database; however, we believe it did not have a significant impact on the results.

B3. Please provide URLs, search terms used and the number of results for each of the conference proceedings searches reported in Appendix G (page 7), Appendix H (page 7) and Appendix I (page 8).

B3. Response:

Table 34. Conference searches Appendix G

Conference	Search term	URL	Number of Includes
American College of Gastroenterology (ACG)	"Ulcerative colitis"	https://journals.lww.com/ajg/toc/2020/10001 https://journals.lww.com/ajg/toc/2019/10001 https://journals.lww.com/ajg/toc/2018/10001 https://journals.lww.com/ajg/toc/2017/10001 https://journals.lww.com/ajg/toc/2016/10001	First pass: 6 Second pass: 2
British Society of Gastroenterology	"Ulcerative colitis"	https://gut.bmj.com/content/68/Suppl_2 https://gut.bmj.com/content/67/Suppl_1/A282 https://gut.bmj.com/content/66/Suppl_2 https://gut.bmj.com/content/65/Suppl_1	First Pass: 9 Second Pass: 4
European Crohn's and Colitis Organisation (ECCO)	"Ulcerative colitis"	https://academic.oup.com/ecco-jcc/issue/14/Supplement_1 https://academic.oup.com/ecco-jcc/issue/13/Supplement_1 https://academic.oup.com/ecco-jcc/issue/12/supplement_1 https://academic.oup.com/ecco-jcc/issue/11/suppl_1 https://academic.oup.com/ecco-jcc/issue/10/suppl_1	First Pass: 7 Second Pass: 6
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	"Ulcerative colitis"	https://www.valueinhealthjournal.com/issue/S1098-3015(20)X0015-5 https://www.valueinhealthjournal.com/issue/S1098-3015(19)X0015-7 https://www.valueinhealthjournal.com/issue/S1098-3015(18)X0007-2	First Pass: 20 Second Pass: 14
United European Gastroenterology Weeks (UEG)	"Ulcerative colitis"	https://ueg.eu/library#stq=*&stp=1&sts=Default&stc=All&stcf=UEG%20Week%202019&stf=Abstract&stms=All&sty=All https://ueg.eu/library#stq=*&stp=1&sts=Default&stc=All&stcf	First Pass: 0 Second Pass: 0

Conference	Search term	URL	Number of Includes
		=UEG%20Week%202018&stf=Abstract&stms=All&sty=All https://ueg.eu/library#stq=*&stp=1&sts=Default&stc=All&stcf=UEG%20Week%202016&stf=Abstract&stms=All&sty=All	
Crohn's and Colitis UK	NA	NA	NA

Table 35. Conference searches Appendix H

Conference	Search term	URL	Number of Includes
American College of Gastroenterology (ACG)	"Ulcerative colitis"	https://journals.lww.com/ajg/toc/2020/10001 https://journals.lww.com/ajg/toc/2019/10001 https://journals.lww.com/ajg/toc/2018/10001 https://journals.lww.com/ajg/toc/2017/10001 https://journals.lww.com/ajg/toc/2016/10001	First pass: 3 Second pass: 1
British Society of Gastroenterology	"Ulcerative colitis"	https://gut.bmj.com/content/68/Suppl_2 https://gut.bmj.com/content/67/Suppl_1/A282 https://gut.bmj.com/content/66/Suppl_2 https://gut.bmj.com/content/65/Suppl_1	First Pass: 5 Second Pass: 1
European Crohn's and Colitis Organisation (ECCO)	"Ulcerative colitis"	https://academic.oup.com/ecco-jcc/issue/14/Supplement_1 https://academic.oup.com/ecco-jcc/issue/13/Supplement_1 https://academic.oup.com/ecco-jcc/issue/12/supplement_1 https://academic.oup.com/ecco-jcc/issue/11/suppl_1 https://academic.oup.com/ecco-jcc/issue/10/suppl_1	First Pass: 24 Second Pass: 10
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	"Ulcerative colitis"	https://www.valueinhealthjournal.com/issue/S1098-3015(20)X0015-5 https://www.valueinhealthjournal.com/issue/S1098-3015(19)X0015-7 https://www.valueinhealthjournal.com/issue/S1098-3015(18)X0007-2	First Pass: 1 Second Pass: 1

Conference	Search term	URL	Number of Includes
United European Gastroenterology Weeks (UEG)	"Ulcerative colitis"	https://ueg.eu/library#stq=*&stp=1&sts=Default&stc=All&stcf=UEG%20Week%202019&stf=Abstract&stms=All&sty=All https://ueg.eu/library#stq=*&stp=1&sts=Default&stc=All&stcf=UEG%20Week%202018&stf=Abstract&stms=All&sty=All https://ueg.eu/library#stq=*&stp=1&sts=Default&stc=All&stcf=UEG%20Week%202016&stf=Abstract&stms=All&sty=All	First Pass: 10 Second Pass: 5
Crohn's and Colitis UK	NA	NA	NA

Table 36. Conference searches Appendix I

Conference	Search term	URL	Number of Includes
American College of Gastroenterology (ACG)	"Ulcerative colitis"	https://journals.lww.com/ajg/toc/2020/10001 https://journals.lww.com/ajg/toc/2019/10001 https://journals.lww.com/ajg/toc/2018/10001 https://journals.lww.com/ajg/toc/2017/10001 https://journals.lww.com/ajg/toc/2016/10001	First pass: 9 Second pass: 0
British Society of Gastroenterology	"Ulcerative colitis"	https://gut.bmj.com/content/68/Suppl_2 https://gut.bmj.com/content/67/Suppl_1/A282 https://gut.bmj.com/content/66/Suppl_2 https://gut.bmj.com/content/65/Suppl_1	First Pass: 4 Second Pass: 0
European Crohn's and Colitis Organisation (ECCO)	"Ulcerative colitis"	https://academic.oup.com/ecco-jcc/issue/14/Supplement_1 https://academic.oup.com/ecco-jcc/issue/13/Supplement_1 https://academic.oup.com/ecco-jcc/issue/12/supplement_1 https://academic.oup.com/ecco-jcc/issue/11/suppl_1 https://academic.oup.com/ecco-jcc/issue/10/suppl_1	First Pass: 14 Second Pass: 0

International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	"Ulcerative colitis"	https://www.valueinhealthjournal.com/issue/S1098-3015(20)X0015-5 https://www.valueinhealthjournal.com/issue/S1098-3015(19)X0015-7 https://www.valueinhealthjournal.com/issue/S1098-3015(18)X0007-2	First Pass: 15 Second Pass: 0
United European Gastroenterology Weeks (UEG)	"Ulcerative colitis"	https://ueg.eu/library#stq=*&stp=1&sts=Default&stc=All&stcf=UEG%20Week%202019&stf=Abstract&stms=All&sty=All https://ueg.eu/library#stq=*&stp=1&sts=Default&stc=All&stcf=UEG%20Week%202018&stf=Abstract&stms=All&sty=All https://ueg.eu/library#stq=*&stp=1&sts=Default&stc=All&stcf=UEG%20Week%202016&stf=Abstract&stms=All&sty=All	First Pass: 6 Second Pass: 0
Crohn's and Colitis UK	NA	NA	NA

B4. Please provide details of the search terms and results for searches of Econpapers listed as a resource searched in Appendices G (page 2), H (page 2) and I (page 2).

B4. Response: This is an error in reporting, Econpapers was only used for free-text searches and was not part of the database search strategy for these reviews.

B5. Some inconsistencies have been noted in the review.

a. In Appendix G, Published Cost-effectiveness studies, the inclusion/exclusion criteria for the identification of studies on health economic models are given. The title of Table 6 says "patients with moderate-severe RA" (also in the text announcing the table). Please confirm that these criteria are for UC.
b. In the inclusion criteria, conventional therapy is defined as: "† Conventional therapy considered to include topical or oral aminosalicylate, corticosteroids, mercaptopurine, azathioprine or prednisolone." It is unclear why two specific immunomodulators (mercaptopurine, azathioprine) are mentioned as opposed to using the more generic immunomodulators? As it is, cyclosporine would be excluded. Please provide justification and discuss implications of this potential oversight.

c. Prednisolone was mentioned separately from corticosteroids. Please justify why this was the case and discuss any potential implications.

B5. Response:

a. This is an editorial error and the information in Appendix G Table 6 relate to UC.

b. The footnote referring to conventional therapy was intended as clarification for reviewers to highlight some of the key conventional therapies, and was not exhaustive or exclusive; however, this could be clearer. The wording "Conventional therapy considered to include…" would read more accurately as "Conventional therapy considered including but not limited to...".

c. Prednisolone was included separately as one of the most frequently prescribed corticosteroids. We recognise mentioning only one corticosteroid may cause confusion; however, this footnote was not an exhaustive or exclusive list. Additionally, we believe the specification of corticosteroids clarifies that other corticosteroid treatments for UC were accepted and not limited to prednisolone.

Model structure & time horizon

B6. The model structure does not account for the relapse-remitting nature of the disease.

a. Although this is in line with previous TAs, can you please explain why no relapses are included in the model and discuss the potential impact of this assumption on model outcomes?

B6. Response: Relapse is modelled in the economic analysis as loss of response and relapse to active disease during the maintenance phase, in line with previous TAs (TA342 (8), TA547 (2),TA329 (9) and TA633 (10)), i.e. patients with no relapse maintain remission. It was noted by the ERG in TA633 (10) that there is no consensus in the literature about how secondary loss of response is defined (loss of response during maintenance treatment), but commonly an assessment of this is based on Mayo scores in UC: if patients experience substantial improvements in these scores but then experience clinical relapse, they would be classified as having

had a secondary loss of response to treatment. Based on this, the ERG suggested that loss of response may adequately reflect relapse.

The relapsing/remitting nature of UC may also be better reflected with the update to the model base case to include treatment sequences (see question B24).

B7. A Markov model was constructed. Some of the previous TAs ([TA342] and [TA329]) used hybrid models with a decision tree and Markov part.

a. Please elaborate on why a Markov model was preferred over a hybrid model.
b. Are any differences in outcomes expected when a hybrid model is used, and if so, which ones?

B7. Response:

a. The use of a Markov model is in line with both TA329 (9) and TA547 (2). The model framework was developed in line with these models, as this structure has been accepted in previous NICE submissions. The Markov model structure was also found to be widely used based on the literature review of cost-effectiveness analyses, which is summarised in Appendix G and Section B3.1 of the CS.

b. As described in the CS, the length of induction for treatments considered in the model varies between 6 and 10 weeks. Therefore, the cost of induction treatment for all comparators was calculated to ensure that for shorter induction durations, the respective treatment induction cost would not be overestimated (see response to B8). Outcomes in the model impacted are therefore the quality-adjusted life-years accrued over the first cycle (i.e. the induction phase), however all patients are assumed to have active UC in the induction phase in the model, and treatment benefits are accrued during the maintenance phase. Therefore, the impact of applying a Markov model structure instead of a decision tree at induction is considered minimal.

B8. A cycle length of 10 weeks was used in the model. Some of the induction therapies only have a six weeks duration. Costs were recalculated to fit the cycle length of 10 weeks.

a. Please explain why a cycle length of 10 weeks was chosen and not a shorter cycle length (e.g. 2 weeks) to better fit the induction phase of other therapies.
b. Would a shorter time horizon change the outcomes for the other therapies (e.g. because of the impact of side effects of therapy in the induction phase)?

B8. Response:

a. The model applies a fixed 10-week cycle length throughout the time horizon in line with the induction period in the SELECTION trial and to allow modelling of a 50-week (5-cycle) maintenance period. The 10-week cycle length was chosen to allow inclusion of induction periods of different lengths among comparators, which varied between 6 and 8 weeks. A two-week Markov cycle was applied in the previous appraisal TA633 (10). However, the ERG criticised that it is unlikely to be feasible to identify loss of response in routine NHS practice within two weeks and noted that the short cycle length may underestimate the costs if symptom recurrence is not always detected, and treatment discontinued, within two weeks.

b. The cost of induction treatment for all comparators was calculated to ensure that for shorter induction durations, the respective treatment induction cost would not be overestimated. In addition, all patients are assumed to have active UC in the induction phase of the model, and treatment benefits are accrued during the maintenance phase. Therefore, the impact of using a 10-week cycle length at induction was considered minimal.

   Moreover, in NICE Early Scientific Advice, the experts were also confirmed that the 10-week cycle length was appropriate, and in particular that using a 10-weekly cycle was reasonable, given that the bias is small for treatments with shorter induction phases.

B9. It was assumed that patients did not live above 100 years old. Please explain why this assumption was made and whether including a higher maximum age could have resulted in different outcomes.

B9. Response: Age-dependent all-cause mortality obtained from UK life tables (11) was applied in the model to reflect the modelled patient population. The UK life tables provide life expectancy statistics for 0 to 100 years of age. The model assumes that patients do not live beyond 100 years of age due to the lack of mortality data for patients beyond this. Moreover, only 1.1% of patients are still alive at 100 years of age in the model, thus the impact of considering patients beyond 100 years of age would be minimal. Therefore, the assumption that patients do not live beyond 100 years of age can be considered sufficient to reflect all important differences in costs and patient outcomes between filgotinib and its comparators.

Population, intervention and comparators

B10. Priority question: The baseline characteristics applied in the model are based on the SELECTION trial induction study population. In Table 33 mean age and SD are given for Cohort A and Cohort B, as well as a (comparable) proportion male/female. The given SD's cover an acceptable range. However, modelling based on mean age and SD would not reflect the bimodal incidence of UC as in the general population with the peak incidence between 15 and 25 years and a small secondary peak between 55 and 65 years. Also, men have a significantly higher incidence after age of 45.

a. **Please comment on whether differentiation of the population in the model based on the bimodal peak in incidence and/or a higher incidence of UC in men in higher age could have an impact on the results of the model.**
b. **Please consider using a distribution for age based on SELECTION in the model, rather than just mean age, or explain whether this is already done.**
c. **Also, is there any evidence on response to treatment conditional on sex/age? Is there any evidence on this?**

B10. Response:

a. The modelled population were aligned to the eligibility criteria of the SELECTION trial, namely adults with moderate or severely active UC

who are biologic-naïve (SELECTION Cohort A) or biologic-experienced (SELECTION Cohort B). All the modelled patients had UC at the baseline. Thus, the different incidences of UC between male and female, or between age groups would not impact the model results.

b. In the model, the mean age was used for background mortality and age-specific utility adjustment only. In the submission, the baseline age was tested in the DSA (varied by ±20%) and the DSA results showed that this parameter is not a key model driver. To further understand the impact of specific age groups on the model results, two scenario analyses are provided to model two specific age groups: 20 years old and 60 years old groups.
c. Subgroup analyses on age group (<65 and ≥65 years) and sex (female and male) have been performed using the SELECTION trial data in Table 41

Table 37. Scenario analysis supporting B10 - biologic-naïve, 20 years old

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	24.645	[redacted]	-	-	-	-	57,562.25
Conventional therapy	[redacted]	24.641	[redacted]	15,969.61	0.003	0.277	57,562.25	-
Golimumab	[redacted]	24.644	[redacted]	-10,947.05	0.001	0.061	Dominated	Dominated
Adalimumab	[redacted]	24.644	[redacted]	-11,378.05	0.001	0.064	Dominated	Dominated
Infliximab	[redacted]	24.645	[redacted]	-15,738.81	0.000	-0.013	1,213,728 SW	56,346.90
Tofacitinib	[redacted]	24.645	[redacted]	-11,319.50	0.000	-0.035	319,253 SW	3,853.26
Vedolizumab SC	[redacted]	24.647	[redacted]	-19,054.38	-0.003	-0.228	83,635 SW	15,431.33
Vedolizumab IV	[redacted]	24.647	[redacted]	-23,238.93	-0.002	-0.194	119,509 SW	Dominated

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 38. Scenario analysis supporting B10 - biologic-experienced, 20 years old

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	24.622	[redacted]	-	-	-	-	88,622.03
Conventional therapy	[redacted]	24.621	[redacted]	11,466.33	0.002	0.129	88,622.03	-
Adalimumab	[redacted]	24.622	[redacted]	-2,462.08	0.001	0.047	Dominated	Dominated

Tofacitinib	[redacted]	24.622	[redacted]	-4,195.21	0.0001	0.011	Dominated	48,843.98
Ustekinumab	[redacted]	24.622	[redacted]	-5,090.96	0.0004	0.032	Dominated	Dominated
Vedolizumab SC	[redacted]	24.622	[redacted]	-4,203.38	0.0002	0.017	Dominated	Dominated
Vedolizumab IV	[redacted]	24.622	[redacted]	-5,244.45	0.0004	0.031	Dominated	756,071.85

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 39. Scenario analysis supporting B10 - biologic-naïve, 60 years old

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	15.624	[redacted]	-	-	-	-	69655.03
Conventional therapy	[redacted]	15.622	[redacted]	15,923.25	0.002	0.229	69,655.03	-
Golimumab	[redacted]	15.624	[redacted]	-10,904.54	0.0004	0.049	Dominated	Dominated
Adalimumab	[redacted]	15.624	[redacted]	-11,329.10	0.0004	0.052	Dominated	Dominated
Infliximab	[redacted]	15.624	[redacted]	-15,638.24	-0.0002	-0.012	1,321,863 SW	67,455.67
Tofacitinib	[redacted]	15.625	[redacted]	-11,177.59	-0.0003	-0.029	387,130 SW	3,495.06
Vedolizumab SC	[redacted]	15.626	[redacted]	-18,816.93	-0.002	-0.185	101,564 SW	18,327.24
Vedolizumab IV	[redacted]	15.626	[redacted]	-22,997.30	-0.001	-0.159	144,934 SW	Dominated

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 40. Scenario analysis supporting B10 - biologic-experienced, 60 years old

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	15.561	[redacted]	-	-	-	-	106,151.76
Conventional therapy	[redacted]	15.560	[redacted]	11,492.77	0.001	0.108	106,151.76	-
Adalimumab	[redacted]	15.560	[redacted]	-2,446.08	0.000	0.039	Dominated	Dominated
Tofacitinib	[redacted]	15.561	[redacted]	-4,183.50	0.0001	0.009	Dominated	58,497.28
Ustekinumab	[redacted]	15.561	[redacted]	-5,082.33	0.0002	0.026	Dominated	Dominated
Vedolizumab SC	[redacted]	15.561	[redacted]	-4,197.67	0.0001	0.014	Dominated	Dominated
Vedolizumab IV	[redacted]	15.561	[redacted]	-5,237.22	0.0002	0.026	Dominated	713,284.86

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 41. SELECTION trial data response to treatment conditional on sex and age subgroups

Efficacy	Cohort	Subgroup	Filgotinib 200mg	Placebo	Difference	Filgotinib 100mg	Placebo	Difference
Remission at week 10	Cohort A	Age <65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Age ≥65	[redacted]	[redacted]		[redacted]	[redacted]	
		Male	[redacted]	[redacted]		[redacted]	[redacted]	
		Female	[redacted]	[redacted]		[redacted]	[redacted]	
	Cohort B	Age <65	[redacted]	[redacted]		[redacted]	[redacted]	
		Age ≥65	[redacted]	[redacted]		[redacted]	[redacted]	
		Male	[redacted]	[redacted]		[redacted]	[redacted]	
		Female	[redacted]	[redacted]		[redacted]	[redacted]	
Remission at week 58		Age <65	[redacted]	[redacted]		[redacted]	[redacted]	
		Age ≥65	[redacted]	[redacted]		[redacted]	[redacted]	
		Male	[redacted]	[redacted]		[redacted]	[redacted]	
		Female	[redacted]	[redacted]		[redacted]	[redacted]	

B11. Priority question: Two subgroups of patients were considered in the model: Biologic-naïve patients and biologic-experienced patients. NICE guideline [NG130] as shown in Figure 4 (Document B page 28) suggests there may be three relevant subgroups: first-line advanced (first biologic), second-line advanced (after failed first biologic) and third-line advanced (after failed second biologic or targeted therapy).

a. **Please explain why two subgroups were defined instead of three subgroups.**
b. **Is it correct that filgotinib is not intended to be used as a third-line advanced therapy?**
c. **Please also provide analyses with filgotinib as a third-line advanced therapy, if possible using subgroup data from the SELECTION trials (see also next question on treatment sequences).**

B11. Response:

a. The two subgroups applied in the economic analysis (biologic-naïve and biologic-experienced) were defined as specified in the final decision problem scope issued by NICE. This is also in line with previous submissions in UC (TA633 (10), TA547 (2), TA342(8)). Moreover, efficacy results for comparators identified in the SLR were not further split by line of therapy.
b. Filgotinib is intended to be used as third-line advanced therapy. The proposed positioning of filgotinib within the NICE treatment pathway is as follows (Figure 1 in the CS):
    a. First-line treatment for biologic-naïve patients (no previous exposure to biologic therapy TNFα inhibitor or vedolizumab)
    b. Treatment for biologic-experienced patients (previous exposure to biologic therapy TNFα inhibitor or vedolizumab), regardless of line of therapy.
c. As noted in response to B11a, the treatment efficacy inputs were available for the two subgroups included in the submission (biologic-naïve and biologic-experienced), but not by treatment line. To account for differences in treatment lines, the base case has been updated to include treatment sequences (See response to Question B12).

B12. Priority question: No treatment sequences are modelled in the base-case. Given the treatment pathway, the company base-case does not represent clinical practice. Please include treatment sequences for intervention and comparators in the base-case. Uncertainty about the appropriate treatments

can be explored through scenarios with alternative treatment sequences or weighted averages of subsequent treatments, which can be informed using expert opinion. Please also provide detail on how treatment sequences were incorporated (e.g. directly upon loss of response and whether these were also included after conventional care).

B12. Response:

Up to four lines of active therapy followed by conventional therapy may be included in the model. All sequences must end with conventional therapy as the final line. Patients can discontinue advanced treatment due to loss of effect, but patients only discontinue last-line conventional treatment by transitioning to surgery. To account for potential differences in efficacy in treatment lines, the base case has been updated to include treatment sequences. Upon loss of response, a subsequent treatment is initiated for each comparator (except for conventional therapy). The base case treatment sequences for filgotinib and comparators are presented in the Table 42. In the biologic-naïve population, the NMA results for the biologic-experienced population are used for later lines after patients fail on their first advanced therapy. These treatment sequences are informed by clinical opinion.

Table 42. Treatment sequence setting in the base case

First line	Second line	Third line
Biologic-naïve population		
Filgotinib	Adalimumab	Vedolizumab IV
Conventional therapy	-	-
Golimumab	Vedolizumab IV	Ustekinumab
Adalimumab	Vedolizumab IV	Ustekinumab
Infliximab	Vedolizumab IV	Ustekinumab
Tofacitinib	Adalimumab	Vedolizumab IV
Vedolizumab SC	Tofacitinib	Ustekinumab
Vedolizumab IV	Tofacitinib	Ustekinumab
Biologic-experienced population		
Filgotinib	Vedolizumab IV	-
Conventional therapy	-	-
Adalimumab	Vedolizumab IV	-
Tofacitinib	Vedolizumab IV	-
Ustekinumab	Vedolizumab IV	-
Vedolizumab SC	Ustekinumab	-
Vedolizumab IV	Ustekinumab	-

Abbreviations: IV, intravenous; SC, subcutaneous.

B13. Priority question: infliximab and golimumab were not included for the biologic-experienced population because data was unavailable from the NMA. Please elaborate whether any information is available for infliximab and golimumab in a biologic-experienced population and whether any estimation could be possible for the treatment effectiveness of these medications in this group, for example assuming equal effectiveness as in the biologic-naïve population. Please provide results of such a scenario analysis.

B13. Response: Studies included in the NMA were identified from an SLR using criteria in line with previous NICE appraisals in UC (TA342 (8), TA547 (2),TA329 (9) and TA633 (10)). Five studies for infliximab (12-15) and two studies (16, 17) for golimumab were identified in the SLR, all of which only reported results for the biologic naïve population. Therefore, it was not feasible to include these treatments in the biologic-experienced population NMA.

In order to estimate the treatment effectiveness of infliximab and golimumab in a biologic-experienced population, a scenario analysis is provided by assuming the clinical efficacy in the biologic-experienced population is equal to the efficacy in the biologic-naïve population. This assumption is considered to be conservative as it is likely that biologic-experienced patients would have a lower response than the biologic-naïve population

Table 43. Scenario analysis supporting B13

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	20.910	[redacted]	-	-	-	-	96,056.10
Conventional therapy	[redacted]	20.909	[redacted]	11,489.68	0.001	0.120	96,056.10	-
Adalimumab	[redacted]	20.909	[redacted]	-2,452.30	0.001	0.043	Dominated	Dominated
Tofacitinib	[redacted]	20.910	[redacted]	-4,191.25	0.0001	0.010	Dominated	53,006.51
Ustekinumab	[redacted]	20.910	[redacted]	-5,084.88	0.0003	0.029	Dominated	Dominated
Vedolizumab SC	[redacted]	20.910	[redacted]	-4,199.83	0.0002	0.016	Dominated	Dominated
Vedolizumab IV	[redacted]	20.910	[redacted]	-5,238.67	0.0003	0.029	Dominated	Dominated
Infliximab	[redacted]	20.911	[redacted]	-10,757.79	-0.0014	-0.123	87,369.77	36,292.20
Golimumab	[redacted]	20.911	[redacted]	-5,094.82	-0.0006	-0.054	94,575.26	119.68

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

B14. Priority question: Conventional therapy is one of the comparators in the model and is also used as a last-line therapy. Please explain:

a. **The exact definitions of conventional therapy used as a comparator and as a last-line therapy, as well as an overview and justification of all therapies included.**
b. **The percentages presented in Table 37 are said to be taken from a recent National Audit but the ERG could not reproduce the values in the Table from the reference provided. Were they UC specific or merely IBD specific?**
c. **Whether, in addition to azathioprine, other immunomodulators, such as Cyclosporine, 6-mercaptopurine should be included? If not, please provide justification.**
d. **how this 'package' of conventional therapies used for the comparator matches the placebo arm as included in the model.**
e. **the assumption of last-line conventional therapy to have a 99% risk of loss of response.**

B14. Response:

a. Conventional therapy is made up of a mix of therapies with usage rates informed by the Royal College of Physicians national audit report (18). Conventional therapy includes balsalazide, mesalazine, olsalazine, sulfasalazine, prednisolone, hydrocortisone, and azathioprine, which is aligned with TA547, with the exception of hydrocortisone rectal foam, as this product is no longer manufactured and thus, budesonide rectal foam was considered the most appropriate replacement.

   The assumption of conventional therapy to be the last line of therapy irrespective of whether patients achieve response to that conventional therapy was applied in previous appraisals (TA329 (9), TA342 (8) and TA547(2)). Patients that lose response to treatment are assumed to transition to conventional therapy, where a similar approach is taken, i.e. patients who do not respond to conventional therapy or lose response are assumed to remain in active UC.

b. The percentages presented in Table 37 were sourced from the concomitant medication for ulcerative colitis treatment reported by the Royal College of

Physicians National Audit (18), which is in line with the previously appraisal TA547 (2) (Table 53 in TA547 CS section 3.5.1.2).

c. Conventional therapy usage in the company submission was informed by the Royal College of Physicians national audit report (18), in line with TA547. Cyclosporine was not included in this audit. However, it is noted that cyclosporine may be used for severe acute UC refractory to corticosteroid treatment. That said, the impact of the inclusion of cyclosporine to conventional therapy in the model is expected to be minimal.

   When thiopurines are used, 6-mercaptopurine is used less often than azathioprine in the UK because it was only considered as an option to use in UC when patients are unable to tolerate azathioprine (19). The literature review shows the efficacy between 6-mercaptopurine and azathioprine is similar (20). Thus, including only azathioprine appropriately represents this treatment option.

d. In the SELECTION trial, subjects entering either of the two induction studies may have been on a stable dose of the following as background treatment:

   - Oral 5-aminosalicylate (5-ASA) compounds
   - Azathioprine
   - 6-mercaptopurine (6-MP)
   - Methotrexate
   - Oral corticosteroid therapy (prednisolone and budesonide)

   Thus, the efficacy data collected from the placebo arm can be considered representative of the efficacy of conventional treatments in clinical practice. This approach was widely used in the previously appraisals (TA342 (8), TA547 (2), and TA633 (10)).

e. When used in last line of treatment, conventional therapy is assumed to have very low efficacy since at this point in the pathway patients are likely to have failed both conventional and advanced therapies and may be considered particularly hard to treat. These low levels of efficacy are in line with approaches used in previous appraisals (TA329 (9)).

Treatment effectiveness

B15. Priority question: The results from the maintenance phase NMA (as shown in Table 41) are potentially biased (see question A18). Please submit a new model file with effectiveness estimates as per the analyses requested in A18.

B15. Response: Please refer to response to question A18.

B16. Priority question: Loss of response is assumed to be constant over time, and so is the observed health state allocation for responders.

a. **Please justify the assumption that the probability of loss of response would remain constant over time, also considering that this means that after approximately 10 years, virtually zero modelled patients are still treated with biologics.**
b. **Please implement in the model the option for scenarios in which loss of response follows different patterns (for example increasing / decreasing probability over time) and please provide expert opinion on possible loss of response patterns over time.**
c. **Please also provide a scenario where loss of response is equal for all comparators.**
d. **Please comment on the plausibility of the assumption that the observed health state allocation for responders (remission, or response without remission) at the end of the maintenance phase informed transition probabilities in subsequent cycles (page 145 of CS). Please consider whether transition probabilities depend on the health state (e.g. would probability of loss of response differ between patients in the response but not remission state and remission state). Please justify your response with expert opinion. Please also provide alternative scenarios, for example assigning different loss of response probabilities per health state.**

B16. Response:

a. The assumption that probability of loss of response is constant over time is likely an overestimation. Extrapolation of these rates from the maintenance trials is therefore likely to underestimate the average duration of treatment. This assumption was made in the absence of evidence, specifically, there is

no publicly available data to inform the estimates of response and remission rates in the second and subsequent years for patients receiving the modelled treatments in the first year. This was noted by the ERG in TA633 (10) and TA547 (2), who additionally also accepted the use of a constant rate due to lack of available data. Scenarios using alternative assumptions are considered in b, c and d.

b. It was noted by the ERG in TA547 (2) that clinical experience indicates the risk of relapse is greatest in the first 6-12 months; and falls thereafter. Additionally, the ERG in TA633 (10) noted that Ferrante et al. (2008) (21) reported longer follow-up in 81 people with refractory UC treated with infliximab. The results suggested an increasing risk in the first year, but the ERG noted that rate appears relatively constant after that. In TA633 (10), the company provided a scenario assuming 25% reduction in the loss of response rate after the first year of maintenance treatment. Due to lack of robust long-term data for the treatments considered in the model, a similar assumption was made, assuming that the loss of response rate is reduced after the first year. The results are provided below. Additionally, the model has been updated such that a custom reduction on risk of relapse can be applied after the first year.

Table 44. Scenario analysis supporting B16b - biologic-naïve

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	21.213	[redacted]	-	-	-	-	55,157.40
Conventional therapy	[redacted]	21.210	[redacted]	16,707.44	0.003	0.303	55,157.40	-
Golimumab	[redacted]	21.213	[redacted]	-11,825.43	0.001	0.074	Dominated	Dominated
Adalimumab	[redacted]	21.213	[redacted]	-12,336.26	0.001	0.077	Dominated	Dominated
Infliximab	[redacted]	21.213	[redacted]	-17,315.25	-0.0002	-0.008	2,291,283 SW	Dominated
Tofacitinib	[redacted]	21.214	[redacted]	-13,168.02	-0.0004	-0.039	333,641 SW	7,152.66
Vedolizumab SC	[redacted]	21.216	[redacted]	-22,005.96	-0.003	-0.247	89,142 SW	19,601.08
Vedolizumab IV	[redacted]	21.216	[redacted]	-26,810.59	-0.002	-0.209	128,282 SW	Dominated

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 45. Scenario analysis supporting B16b - biologic-experienced

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	20.910	[redacted]	-	-	-	-	89,924.35
Conventional therapy	[redacted]	20.909	[redacted]	11,968.97	0.002	0.133	89,924.35	-
Adalimumab	[redacted]	20.910	[redacted]	-2,595.55	0.001	0.048	Dominated	Dominated

Vedolizumab SC	[redacted]	20.910	[redacted]	-4,291.52	0.0002	0.018	Dominated	56,538.49
Tofacitinib	[redacted]	20.910	[redacted]	-4,474.65	0.0001	0.012	Dominated	30,953.89
Ustekinumab	[redacted]	20.910	[redacted]	-5,211.40	0.0004	0.034	Dominated	Dominated
Vedolizumab IV	[redacted]	20.910	[redacted]	-5,365.84	0.0004	0.034	Dominated	622,083.78

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

c. A scenario is provided using a discontinuation rate estimated based on a study by Maillard et al. (22). This study reported that 36.6% of the patients followed-up in a TNF registry stopped therapy. The 10-weekly probability of discontinuation was estimated as 3.74% during the long-term maintenance phase, and the same rate was assumed for other treatments. The results are provided below.

Table 46. Scenario analysis supporting B16c - biologic-naïve

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	21.216	[redacted]	-	-	-	-	64,040.51
Conventional therapy	[redacted]	21.212	[redacted]	21,936.18	0.004	0.343	64,040.51	-
Golimumab	[redacted]	21.216	[redacted]	-21,215.44	0.000	-0.027	782,505.34	Dominated
Adalimumab	[redacted]	21.216	[redacted]	-21,519.51	0.000	0.013	Dominated	Dominated
Infliximab	[redacted]	21.217	[redacted]	-30,488.19	-0.002	-0.131	232,122 SW	62,195.67

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Tofacitinib	[redacted]	21.216	[redacted]	-20,781.67	0.000	-0.039	538,694 SW	538,694.11
Vedolizumab SC	[redacted]	21.220	[redacted]	-35,820.76	-0.004	-0.398	89,895 SW	19,962.64
Vedolizumab IV	[redacted]	21.220	[redacted]	-49,018.47	-0.004	-0.396	123,791 SW	Dominated

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 47. Scenario analysis supporting B16c - biologic-experienced

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	20.915	[redacted]	-	-	-	-	55,205.35
Conventional therapy	[redacted]	20.910	[redacted]	25,851.99	0.005	0.468	55,205.35	-
Adalimumab	[redacted]	20.913	[redacted]	-7,919.29	0.002	0.187	Dominated	Dominated
Tofacitinib	[redacted]	20.914	[redacted]	-14,846.03	0.0004	0.037	Dominated	Dominated
Ustekinumab	[redacted]	20.915	[redacted]	-15,823.78	0.0004	0.039	Dominated	Dominated
Vedolizumab SC	[redacted]	20.915	[redacted]	-9,540.71	0.0004	0.036	Dominated	10728.23
Vedolizumab IV	[redacted]	20.915	[redacted]	-16,618.72	0.0004	0.039	Dominated	4467527.18

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

d. In the base case, the long-term loss of response over the model time horizon was estimated from the NMA results and the rates did not differ by health state (e.g. the response but not remission state vs. remission state). Clinical experts agree that if a patient is considered to be in response or remission, their response to treatment would not wane over time. Thus, the loss of response is assumed to be constant over time could be considered as appropriate in the base case.

B17. Colectomy rates were estimated from a retrospective 15-year study of the UK Hospital Episode Statistics database. On inspection it was found that these data were collected between 1 April 1997 and 31 March 2012. Please validate these rates providing clinical expert opinion and comment on developments in colectomy practice.

B17. Response:

A targeted literature review (TLR) was conducted to identify more up to date UK epidemiology studies reported the colectomy rate in UC. A UK study based on the Hospital Episode Statistics database was identified, however, this study only reported the colectomy rate for emergency surgery (Worley et al., 2020) (23). Another observational study based on the 4,281 UC patients in Scotland was identified from this TLR and it reported the colectomy rate for both elective surgery and emergency surgery (Jenkinson et al., 2020) (24). In 2018, the prevalent population was 3,876 and six patients went through elective colectomy, while 11 patients went through emergency colectomy. This resulted in an estimated 10-weekly probability of 0.03% for elective and 0.055% for emergency surgery. This updated colectomy rate was applied in the updated base case analysis, which is presented in the response to question B27.

B18. Post-surgery complications were modelled with an estimated 10-week probability of 1.81%. Please comment on the likelihood of patients developing post-surgery complications multiple decades after they had the surgery. The ERG requests an updated analysis in which the probability of developing post-surgery

complications is limited to a certain timeframe after colectomy (for instance the same timeframe as in the source used for the probability, which is 6 years).

B18. Response: Clinical experts have stated that post-surgical complications can be short- and long-term in nature. For those considered to be long term, these can be experienced multiple decades after surgery e.g. pouch failure. The approach taken in the submission is in line with the previous appraisal TA547 (2). Thus, assuming patients who are allocated to post-surgery states with complications have a risk of long-term complications is considered to be appropriate.

Health-related quality of life

B19. Priority question: In the model, constant health state utilities are used throughout the time horizon (although they are adjusted by age) and irrespective of treatment or whether patients were biologic-experienced or -naïve.

a. **Please discuss the clinical plausibility of no deterioration in utilities due to disease progression, apart from that induced by aging.**
b. **Could the company kindly discuss whether utilities in SELECTION differed by treatment arm? Were treatment-dependent utilities explored and what were the reasons for not including them?**
c. **Please provide utility values by biologic-experienced / -naïve subgroup and provide results of scenario analyses using these.**

B19. Response:

a. The adjustment of health state utility values by age and sex were included in the model to account for the natural decline in quality of life due to age and other co-morbidities. This methodology is consistent with TA547 (2) and TA633 (10).

b&c. A summary of utility values by treatment and study cohort is provided in Table 48 and Table 49. In general, utility scores were higher in responders than non-responders, irrespective of the type of treatment. With more response and remission records in the filgotinib arm, the utilities generated are relatively more robust. Moreover, from the statistical point of view, the differences of the utility values between the two arms are not statistically different (Table 55 to Table 57).

Table 48: Health utilities by MCS status and treatment in Cohort A

Outcome	Filgotinib 200mg			Placebo		
	Non responder/active UC Baseline (total cohort)	Response without remission (Week 10)	Remission (Week 10)	Non responder/active UC Baseline (total cohort)	Response without remission (Week 10)	Remission (Week 10)
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean utility (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 49: Health utilities by MCS status and treatment in Cohort B

Outcome	Filgotinib 200mg			Placebo		
	Non responder/active UC Baseline (total cohort)	Response without remission (Week 10)	Remission (Week 10)	Non responder/active UC Baseline (total cohort)	Response without remission (Week 10)	Remission (Week 10)
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean utility (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For the model base case, utilities from the full analysis set, split by MCS response status, were applied, irrespective of treatment arm, which is in line with previous TAs (TA633 (10), TA547 (2), TA329 (9)). This resulted in a higher sample size to assign utility value per health state. Additionally, utility values by treatment are only available for filgotinib and placebo. A scenario analysis using the utility values from the patients treated with filgotinib 200mg formulation is provided in B20a. A scenario using utility values for cohort A and cohort B is provided below.

Table 50. Scenario analysis supporting B19 - biologic-naïve, cohort A

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	21.213	[redacted]	-	-	-	-	65,119.56
Conventional therapy	[redacted]	21.210	[redacted]	15,997.73	0.003	0.246	65,119.56	-
Golimumab	[redacted]	21.212	[redacted]	-10,931.16	0.001	0.055	Dominated	Dominated
Adalimumab	[redacted]	21.212	[redacted]	-11,360.53	0.001	0.058	Dominated	Dominated
Infliximab	[redacted]	21.213	[redacted]	-15,721.69	0.000	-0.011	1,472,978 SW	63282.14
Tofacitinib	[redacted]	21.213	[redacted]	-11,297.56	0.000	-0.032	357,348 SW	4206.17
Vedolizumab SC	[redacted]	21.215	[redacted]	-19,040.43	-0.002	-0.202	94,072 SW	17309.47
Vedolizumab IV	[redacted]	21.215	[redacted]	-23,219.62	-0.002	-0.173	134,467 SW	Dominated

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 51. Scenario analysis supporting B19 - biologic- experienced, cohort B

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	20.910	[redacted]	-	-	-	-	81,471.84
Conventional therapy	[redacted]	20.909	[redacted]	11,489.68	0.001	0.141	81,471.84	-
Adalimumab	[redacted]	20.909	[redacted]	-2,452.30	0.001	0.051	Dominated	Dominated

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Tofacitinib	[redacted]	20.910	[redacted]	-4,191.25	0.0001	0.012	Dominated	44,832.45
Ustekinumab	[redacted]	20.910	[redacted]	-5,084.88	0.0003	0.034	Dominated	Dominated
Vedolizumab SC	[redacted]	20.910	[redacted]	-4,199.83	0.0002	0.019	Dominated	Dominated
Vedolizumab IV	[redacted]	20.910	[redacted]	-5,238.67	0.0003	0.034	Dominated	680,409.69

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

B20. Priority question: Utility values are sourced from SELECTION.

a. **Please provide all analyses using utility values from the patients treated with filgotinib 200mg formulation.**
b. **There appears to be a lot of missing data, particularly at the 58 week measurement point. Please provide for each measuring point the total number of EQ-5D-5L responses, the extent of missing data observed.**
c. **Please explain, with appropriate justifications, how missing data were handled and the implications of the chosen approach.**
d. **Please compare patient characteristics of patients which were included and patients excluded from utility values calculations.**
e. **Please clarify what the likely causes of missing data were and what the potential impact of these missing data on the estimation of the utility scores would be.**
f. **Please comment on the potential implications of using week 10 utility values for the whole model time horizon.**

B20. Response:

a. Table 52 details the utility values requested and utilised in the scenario analysis shown in

b. Table 53.

Table 52: Filgotinib 200mg utilities by MCS status in SELECTION

Outcome	Non responder/active UC Baseline (total cohort)	Response without remission (Week 10)	Remission (Week 10)
N	[redacted]	[redacted]	[redacted]
Mean utility (SE)	[redacted]	[redacted]	[redacted]

Table 53. Scenario analysis supporting B20a - biologic-naïve

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	21.213	[redacted]	-	-	-	-	62,205.47
Conventional therapy	[redacted]	21.210	[redacted]	15,997.73	0.003	0.257	62,205.47	-
Golimumab	[redacted]	21.212	[redacted]	-10,931.16	0.001	0.056	Dominated	Dominated
Tofacitinib	[redacted]	21.213	[redacted]	-11,297.56	0.000	-0.033	344,853 SW	4,111.07
Adalimumab	[redacted]	21.212	[redacted]	-11,360.53	0.001	0.059	Dominated	Dominated
Infliximab	[redacted]	21.213	[redacted]	-15,721.69	0.000	-0.012	1,269,750 SW	60,758.85
Vedolizumab SC	[redacted]	21.215	[redacted]	-19,040.43	-0.002	-0.210	90,489 SW	16,758.32
Vedolizumab IV	[redacted]	21.215	[redacted]	-23,219.62	-0.002	-0.180	129,168 SW	Dominated

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 54. Scenario analysis supporting B20a - biologic-naïve

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	20.910	[redacted]	-	-	-	-	95,824.90
Conventional therapy	[redacted]	20.909	[redacted]	11,489.68	0.001	0.120	95,824.90	-

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Adalimumab	[redacted]	20.909	[redacted]	-2,452.30	0.001	0.043	Dominated	Dominated
Tofacitinib	[redacted]	20.910	[redacted]	-4,191.25	0.0001	0.010	Dominated	52,878.19
Vedolizumab SC	[redacted]	20.910	[redacted]	-4,199.83	0.0002	0.016	Dominated	Dominated
Ustekinumab	[redacted]	20.910	[redacted]	-5,084.88	0.0003	0.029	Dominated	Dominated
Vedolizumab IV	[redacted]	20.910	[redacted]	-5,238.67	0.0003	0.029	Dominated	750,281.90

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

c. Change from baseline at Week 10 for the Cohort A Induction Study (Table 55) and Cohort B Induction Study (Table 56) and change from re-baseline at Weeks 26 and 58 for the Maintenance Study (Table 57) were analysed using an ANCOVA model. The model included treatment, stratification factors and baseline/re-baseline score as covariates. The last observation carried forward (LOCF) approach was used to impute missing values. Estimated means of treatment effects and estimated differences in treatment effects between each filgotinib treatment group and the placebo group were presented with 95% CIs and nominal p-values. Descriptive statistics were used to summarise the absolute values and change from baseline (or re-baseline) values for each domain as well as each component by treatment group and analysis visit.

Missing data per timepoint is presented in the tables below for Cohort A Induction Study (Table 55), Cohort B Induction Study (Table 56) and change from re-baseline at Weeks 26 and 58 for the Maintenance Study (Table 57).

Table 55. Summary of EQ-5D UK utility score and change from baseline results for cohort A induction study (FAS)

EQ-5D utility score for UK	Filgotinib 200mg (n=245)	Filgotinib 100mg (n=277)	Placebo (n=137)
Baseline			
N	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 10			
N	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline at Week 10			
N	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline at Week 10 (LOCF imputed)			
LS mean	[redacted]	[redacted]	[redacted]
SE of LS mean	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
LS mean of treatment difference			
LS mean of treatment difference	[redacted]	[redacted]	[redacted]
SE of LS mean of treatment difference	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]

EQ-5D utility score for UK	Filgotinib 200mg (n=245)	Filgotinib 100mg (n=277)	Placebo (n=137)
P value	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EQ-5D, European quality of life 5 dimensions; FAS, full analysis set; LS mean, least squares means; LOCF, last observation carried forward; NA, not applicable; SD, standard deviation; SE, standard error; UK, United Kingdom.
Reference: Gilead SELECTION clinical study report, 2020 (data on file)(4).
Notes: LS-Mean, 95% CI and P-value were provided from ANCOVA.

Table 56. Summary of EQ-5D UK utility score and change from baseline results for cohort B induction study (FAS)

EQ-5D utility score for UK	Filgotinib 200mg (n=262)	Filgotinib 100mg (n=285)	Placebo (n=142)
Baseline			
N	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Week 10			
N	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline at Week 10			
N	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline at Week 10 (LOCF imputed)			
LS mean	[redacted]	[redacted]	[redacted]
SE of LS mean	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
LS mean of treatment difference			
LS mean of treatment difference	[redacted]	[redacted]	[redacted]
SE of LS mean of treatment difference	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EQ-5D, European quality of life 5 dimensions; FAS, full analysis set; LS mean, least squares means; LOCF, last observation carried forward; NA, not applicable; SD, standard deviation; SE, standard error; UK, United Kingdom.
Reference: Gilead SELECTION clinical study report, 2020 (data on file)(4).
Notes: LS-Mean, 95% CI and P-value were provided from ANCOVA.

Table 57. Summary of EQ-5D UK utility score and change from baseline results for Maintenance Study (FAS)

EQ-5D utility score for UK	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib (n=172)	Maintenance placebo (n=89)
Baseline				
N	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance Week 15				
N	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at Week 15				
N	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at Week 15 (LOCF imputed)				
LS mean	[redacted]	[redacted]	[redacted]	[redacted]
SE of LS mean	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
LS mean of treatment difference				
LS mean	[redacted]	[redacted]	[redacted]	[redacted]
SE of LS mean	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance Week 47				
N	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at Week 47				
N	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at Week 47 (LOCF imputed)				
LS mean	[redacted]	[redacted]	[redacted]	[redacted]
SE of LS mean	[redacted]	[redacted]	[redacted]	[redacted]

EQ-5D utility score for UK	Induction filgotinib 200mg		Induction filgotinib 100mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib (n=172)	Maintenance placebo (n=89)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
LS mean of treatment difference				
LS mean	[redacted]	[redacted]	[redacted]	[redacted]
SE of LS mean	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; EQ-5D, European quality of life 5 dimensions; FAS, full analysis set; LS mean, least squares means; LOCF, last observation carried forward; NA, not applicable; SD, standard deviation; SE, standard error; UK, United Kingdom.
Reference: Gilead SELECTION clinical study report, 2020 (data on file)(4).
Notes: LS-Mean, 95% CI and P-value were provided from ANCOVA.
"Week 15" correspond to the 15th week from the start of maintenance (at the end of Week 11) i.e. the 26th week from start of induction and "Week 47" correspond to the 47th week from the start of maintenance (at the end of Week 11) i.e. the 58th week from start of induction.

d. In general, missing data were not imputed unless methods for handling missing data were specified. Only observed cases were used for analysis without any imputation. Only subjects in the FAS with both baseline and week 10 (or week 58) data were included for analysis.

e. A minimal number of patients were excluded from the utility values calculations in the Cohort A and Cohort B studies (see Table 55 and Table 56). In the Maintenance Study a higher proportion of patients were excluded from the utility values calculations (Table 57). These figures were expected based on both the study design of the induction studies and the Maintenance Study entry criteria of either EBS remission or MCS response at Week 10. In addition, filgotinib patients re-randomised to placebo in the Maintenance Study were more likely

to drop out prior to the Week 58 assessment as treatment expectations were not met.

f. The number of patients excluded from the utility values calculations were expected based on both the study design of the induction studies and the Maintenance Study entry criteria of either EBS remission or MCS response at Week 10. In addition, filgotinib patients re-randomised to placebo in the Maintenance Study were more likely to drop out prior to the Week 58 assessment as treatment expectations were not met. In the filgotinib 200mg to filgotinib 200mg re-randomisation arm versus the filgotinib 200mg to placebo re-randomisation arm there was 25% versus 59% missing data. Similarly, in the filgotinib 100mg to filgotinib 100mg re-randomisation arm versus the filgotinib 100mg to placebo re-randomisation arm there was 42% versus 55% missing data. The trial design (randomised withdrawal design in the Maintenance Study) resulted in an expected imbalance in missing data between arms.

   The impact of missing data can be assessed by looking at treatment comparisons using observed case versus last observation carried forward (LOCF) approaches. For example, the difference between filgotinib 200mg to filgotinib 200mg re-randomisation arm and the filgotinib 200mg to placebo re-randomisation arm at Week 58 is 0.035 using observed case versus 0.041 using LOCF. The small difference between the two approaches suggest that the patients who dropped off potentially had lower utility values than those who completed the Maintenance Study and hence non-completers were penalised by carrying forward a low value. However, given the fact that the difference between the two approaches is small, the missing values in the utility data would have limited impact on the estimated utility scores.

g. The utility values applied in the model base case were based on trial data at week 10 from SELECTION, as the sample size was larger at this timepoint than at the end of the maintenance phase. Although these values may not reflect the long-term utility of treatment, there are some limitations associated with the available utility data sources from published literature in UC, as noted by the committee in TA633 (9). Therefore, a number of scenario analyses

were provided as a part of the CS, including using SELECTION trial data at 58 weeks. The full incremental cost-effectiveness analysis results are provided in Appendix J. Using 58 week data resulted in higher total QALYs for all treatments, but the incremental QALYs were similar to the base case, resulting in similar ICERs.

B21. The company state that utilities used for surgery and post-surgery states are taken from Arseneau et al.

a. Please explain why utilities differ in Tables 45 and 46, when both are taken from Arseneau et al?
b. Please justify the use of the same utility values for elective and emergency surgery.
c. Please discuss whether it is clinically plausible that the post-surgery complications disutility is applied until death.

B21. Response:

a. No utility values characterising the surgery with complications and post-surgery states were reported in SELECTION. Therefore, the study by Arseneau et al. (25) was used to impute appropriate values. The ratios between each state and remission were calculated using the values from Arseneau et al. (25). These ratios were then applied to the remission utility value in SELECTION. The calculation is shown in Table 58.

Table 58. Calculated utility values for surgery and post-surgery states

State	Values from Arseneau et al. 2006	Arseneau et al. ratio to remission (health state utility/remission utility)	Resulting base case utilities (Arseneau et al. ratio multiplied by SELECTION remission utility value of [redacted])
Remission	0.790	-	-
Surgery	0.570	0.722	[redacted]
Surgery with complications	0.490	0.620	[redacted]
Post-surgery without complications	0.680	0.861	[redacted]
Post-surgery with complications	0.400	0.506	[redacted]

b. There is no evidence available in the current literature that provides utility values for elective and emergency surgery separately. The identical utility value was applied to all types of surgery in the previous TA547 (2) and TA633 (10). Moreover, based on the deterministic sensitivity analysis results, the utility value for surgeries were not identified as a main driving factor in the model. Thus, the impact of applying different utility values can be considered minimal.

c. As discussed in question B18, clinical experts have stated that post-surgical complications can occur for many years after surgery has taken place. Thus, it is clinically plausible to assume that the post-surgery complications disutility is applied until death.

B22. Priority question: The company adjust utility values used in the model by age and gender. This adjustment is already applied to baseline utility values in cycle 1 of the model. The ERG considers that this approach is likely flawed as these baseline utility values are obtained directly from SELECTION and should not be adjusted. Furthermore, the ERG considers that the company's age and gender adjustment may be incorrect. To illustrate this: the company's estimated utility values from SELECTION from week 10 are [redacted], [redacted], [redacted] for active UC, response without remission and remission respectively. In cycle 1 of the model the age and gender adjusted values are [redacted], [redacted], [redacted] respectively. The ERG considers that utility values in cycle 1 of the model should equal the ones in the SELECTION trial. Apart from that the ERG was surprised to see that utilities were adjusted upwards. Can the company please implement a correct age and gender adjustment, for example by applying the ratio of future period age adjustment to baseline as a factor to the SELECTION utility values?

B22. Response: The utility adjustment approach applied in the submission model was aligned with TA547 (2). The baseline utility value U_{Base} (0.893 in our case) was adopted from a regression model by Ara and Brazier (26). A utility decrement, or multiplier (φ), was estimated based on the difference between the general population utility U_{GenPop}(Age, Gender) and the utility of the health state or event U_{HS}:

$$\varphi_{HS} = U_{HS}/U_{GenPop}$$

To calculate the general population utility from Woehl et al. (27), using the model by Ara and Brazier would result in a lower utility (0.84) than the value for remission obtained from the trial data at week 10 (0.866). To ensure internal consistency with the data presented by Woehl et al., the remission utility was assumed to be the same as the general population. In the model the utility decrements were then multiplied at each cycle with the baseline utility, based on the proportions of patients and their state membership: $U_{Base} * \varphi_{HS}$. Thus, when the $U_{Base} > U_{GenPop}$ (as in our case), the utilities would be adjusted upwards in the first few cycles.

To avoid adjusting the utilities upwards, the model has been updated as suggested. As described in section B3.4.5 in the CS, baseline utility values were adopted from a regression model by Ara and Brazier (26). The following equation was used to calculate a value for U_t at each timepoint in the model, where age_t is the cohort age at timepoint t:

$$U_t(age_t, sex) = 0.9508566 + 0.0212126 * male - 0.0002587 * age - 0.0000332 * age^2$$

Using the proportion of male patients, and the baseline age as shown in Table 33 in the CS, a value for U_{base} was calculated and applied throughout the model. The health state utilities at each timepoint were adjusted by multiplying the utility value and the ratio U_t/U_{base}. This ensured that the SELECTION utility values are applied after cycle 1 (as the ratio U_t/U_{base} is equal to 1), and that utilities are not adjusted upwards, but deteriorate with increasing age.

Two scenarios around the utility values are provided below:

1) applying fixed utility values from the SELECTION trial without any adjustment: results are shown in Table 59 and Table 60;

2) an alternative age-specific adjustment as described above so that the utilities are adjusted downwards over time: results are shown in Table 61 and Table 62.

Table 59. Scenario analysis supporting B22 applying fixed utility values - biologic-naïve

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	21.213	[redacted]	-	-	-	-	64,311.59
Conventional therapy	[redacted]	21.210	[redacted]	15,997.73	0.003	0.252	63,471.33	-
Golimumab	[redacted]	21.212	[redacted]	-10,931.16	0.001	0.056	Dominated	Dominated
Tofacitinib	[redacted]	21.213	[redacted]	-11,297.56	0.000	-0.032	350,699 SW	4,249.55
Adalimumab	[redacted]	21.212	[redacted]	-11,360.53	0.001	0.059	Dominated	Dominated
Infliximab	[redacted]	21.213	[redacted]	-15,721.69	0.000	-0.012	1,336,906 SW	62,813.59
Vedolizumab SC	[redacted]	21.215	[redacted]	-19,040.43	-0.002	-0.207	91,991 SW	17,324.07
Vedolizumab IV	[redacted]	21.215	[redacted]	-23,219.62	-0.002	0.749	Dominated	Dominated

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 60. Scenario analysis supporting B22 applying fixed utility values - biologic-experienced

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	20.910	[redacted]	-	-	-	-	98,860.74
Conventional therapy	[redacted]	20.909	[redacted]	11,489.68	0.001	0.117	98,020.84	-
Adalimumab	[redacted]	20.909	[redacted]	-2,452.30	0.001	0.042	Dominated	Dominated

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Tofacitinib	[redacted]	20.910	[redacted]	-4,191.25	0.000	0.010	Dominated	54,554.19
Vedolizumab SC	[redacted]	20.910	[redacted]	-4,199.83	0.000	0.015	Dominated	Dominated
Ustekinumab	[redacted]	20.910	[redacted]	-5,084.88	0.000	0.029	Dominated	Dominated
Vedolizumab IV	[redacted]	20.910	[redacted]	-5,238.67	0.000	0.028	Dominated	773,797.02

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 61. Scenario analysis supporting B22 applying alternative utility adjustment - biologic-naïve

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	21.213	[redacted]	-	-	-	-	64,311.59
Conventional therapy	[redacted]	21.210	[redacted]	15,997.73	0.003	0.249	64,311.59	-
Golimumab	[redacted]	21.212	[redacted]	-10,931.16	0.001	0.055	Dominated	Dominated
Tofacitinib	[redacted]	21.213	[redacted]	-11,297.56	0.000	-0.032	356,504 SW	4,249.55
Adalimumab	[redacted]	21.212	[redacted]	-11,360.53	0.001	0.057	Dominated	Dominated
Infliximab	[redacted]	21.213	[redacted]	-15,721.69	0.000	-0.012	1,313,661 SW	62,813.59
Vedolizumab SC	[redacted]	21.215	[redacted]	-19,040.43	-0.002	-0.204	93,548 SW	17,324.07
Vedolizumab IV	[redacted]	21.215	[redacted]	-23,219.62	-0.002	-0.174	133,536 SW	Dominated

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 62. Scenario analysis supporting B22 applying alternative utility adjustment - biologic-experienced

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	20.910	[redacted]	-	-	-	-	98,860.74
Conventional therapy	[redacted]	20.909	[redacted]	11,489.68	0.001	0.116	98,860.74	-
Adalimumab	[redacted]	20.909	[redacted]	-2,452.30	0.001	0.042	Dominated	Dominated

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Tofacitinib	[redacted]	20.910	[redacted]	-4,191.25	0.000	0.010	Dominated	54,554.19
Vedolizumab SC	[redacted]	20.910	[redacted]	-4,199.83	0.000	0.015	Dominated	Dominated
Ustekinumab	[redacted]	20.910	[redacted]	-5,084.88	0.000	0.028	Dominated	Dominated
Vedolizumab IV	[redacted]	20.910	[redacted]	-5,238.67	0.000	0.028	Dominated	773,797.02

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Resource use and costs

B23. Priority question: Dose escalation was assumed for all comparators but not for filgotinib.

a. **Please provide expert opinion on the probability of dose escalation per treatment and implement a scenario using these expert estimates.**
b. **It was assumed that 30% of patients had dose escalation. In scenario analyses 10% and 50% was included. Please provide a scenario analyses in which 0% dose escalation is included.**

B23. Response:

a&b. As described in Section B.3.10. of the CS, the company sought clinical validation of the model assumptions. Interviews with five England-based gastroenterologists were conducted between February and March 2021.The clinicians confirmed that dose escalation is common in clinical practice, and provided estimates for the percentage of patients treated with an escalated dose for each treatment included in the model.

The clinician estimates are provided in Table 63. Notably, the estimates provided by the five clinicians varied considerably, and therefore, the proportion applied in the model base case was sourced from published literature was considered appropriate. A scenario analysis applying these estimates in the economic analysis is provided.

Table 63. Estimated proportion of patients with dose escalation for advanced therapies reported in clinician interviews

Therapy	Average value (n=5)	Lowest estimate	Highest estimate
Infliximab dose escalation to 10mg/kg every 8 weeks	[redacted]	[redacted]	[redacted]
Infliximab dose escalation to 5mg/kg every 4 weeks	[redacted]	[redacted]	[redacted]
Adalimumab dose escalation to 40mg weekly	[redacted]	[redacted]	[redacted]
Golimumab dose escalation to 100mg every 4 weeks	[redacted]	[redacted]	[redacted]
Tofacitinib dose escalation to 10mg twice daily	[redacted]	[redacted]	[redacted]
Ustekinumab dose escalation to 90mg every 8 weeks	[redacted]	[redacted]	[redacted]
Vedolizumab dose escalation to 300mg every 4 weeks	[redacted]	[redacted]	[redacted]

Table 64. Scenario analysis supporting B23 - biologic-naive, clinicians' opinion average dose escalation

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	21.213	[redacted]	-	-	-	-	60,178.68
Conventional therapy	[redacted]	21.210	[redacted]	15,440.56	0.003	0.257	60,178.68	-
Tofacitinib	[redacted]	21.213	[redacted]	-8,984.93	-0.0004	-0.033	274,880 SW	274,880.02
Golimumab	[redacted]	21.212	[redacted]	-11,042.51	0.001	0.056	Dominated	Dominated
Adalimumab	[redacted]	21.212	[redacted]	-11,556.30	0.001	0.059	Dominated	Dominated
Infliximab	[redacted]	21.213	[redacted]	-13,628.27	-0.0002	-0.012	1,104,012 SW	28,932.43
Vedolizumab SC	[redacted]	21.215	[redacted]	-17,490.73	-0.002	-0.210	83,314 SW	19,547.40
Vedolizumab IV	[redacted]	21.215	[redacted]	-20,017.87	-0.002	-0.179	111,612 SW	Dominated

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 65. Scenario analysis supporting B23 - biologic-experienced, clinicians' opinion average dose escalation

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	20.910	[redacted]	-	-	-	-	92,075.35
Conventional therapy	[redacted]	20.909	[redacted]	11,013.53	0.001	0.120	92,075.35	-
Adalimumab	[redacted]	20.909	[redacted]	-2,472.94	0.001	0.043	Dominated	Dominated

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Tofacitinib	[redacted]	20.910	[redacted]	-3,534.19	0.0001	0.010	Dominated	32,348.88
Vedolizumab SC	[redacted]	20.910	[redacted]	-4,787.95	0.0002	0.016	Dominated	Dominated
Ustekinumab	[redacted]	20.910	[redacted]	-5,196.30	0.0003	0.029	Dominated	Dominated
Vedolizumab IV	[redacted]	20.910	[redacted]	-5,341.38	0.0003	0.029	Dominated	709284.07

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 66. Scenario analysis supporting B23 - biologic-naïve, 0% dose escalation

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	21.213	[redacted]	-	-	-	-	54,586.42
Conventional therapy	[redacted]	21.210	[redacted]	14,005.70	0.003	0.257	54,586.42	-
Tofacitinib	[redacted]	21.213	[redacted]	-8,147.75	-0.0004	-0.033	249,268 SW	249,267.77
Adalimumab	[redacted]	21.212	[redacted]	-9,829.91	0.001	0.059	Dominated	Dominated
Golimumab	[redacted]	21.212	[redacted]	-10,915.47	0.001	0.056	Dominated	358,954.27
Infliximab	[redacted]	21.213	[redacted]	-12,993.10	-0.0002	-0.012	1,052,557 SW	30,290.54
Vedolizumab IV	[redacted]	21.215	[redacted]	-17,302.75	-0.002	-0.179	96,473 SW	25,804.93
Vedolizumab SC	[redacted]	21.215	[redacted]	-17,641.17	-0.002	-0.210	84,030 SW	11,064.77

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 67. Scenario analysis supporting B23 - biologic-experienced, 0% dose escalation

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	20.910	[redacted]	-	-	-	-	85,136.42
Conventional therapy	[redacted]	20.909	[redacted]	10,183.53	0.001	0.120	85,136.42	-
Adalimumab	[redacted]	20.909	[redacted]	-2,089.10	0.001	0.043	Dominated	Dominated
Tofacitinib	[redacted]	20.910	[redacted]	-3,292.82	0.0001	0.010	Dominated	36,691.96
Ustekinumab	[redacted]	20.910	[redacted]	-4,770.20	0.0003	0.029	Dominated	Dominated
Vedolizumab IV	[redacted]	20.910	[redacted]	-4,910.20	0.0003	0.029	Dominated	684,417.11
Vedolizumab SC	[redacted]	20.910	[redacted]	-5,204.38	0.0002	0.016	Dominated	22,390.44

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

B24. Please elaborate on the method used to calculate cost of induction treatment for all comparators to ensure that for shorter induction durations, the respective treatment induction cost would not be overestimated, as this was alluded to in the model structure section (page 129 of CS) but not further described in resource use and costs.

B24. Response: A summary of the pack costs, sizes and dosing regimens used to calculate the cost of induction treatment for all comparators is shown in Table 68. Only golimumab was amended such that a percentage of patients received the third dose during the induction phase. Other comparators had the same number of administrations over 10 weeks as their induction phase period. Induction dosing for golimumab is two doses (at week 0 and week 2). Therefore, not all patients may receive a third dose at week 6. The average price reflects the percentage of patients who are responders (all assumed to get third dose) and conservatively assumes 0% of non-responders would receive a third dose.

Table 68. Summary of pack cost, sizes and dosing regimens for each treatment in induction phase

Treatment		Pack cost	Pack size	Dosing regimen (induction)	Cost per cycle - Induction
FIL	Jyseleca® (brand)	[redacted]	[redacted]	200mg once daily	[redacted]
ADA	Amgevita™ (biosimilar)	£633.60	40mg x 2	160mg at 0 weeks, 80mg at 2 weeks	£2,851.20
GOL	Simponi® (brand)	£762.97	162mg x 4	200mg at 0 weeks, 100mg at 2 weeks. Maintenance dose 50mg q4w at week 6, or dose escalated to 100mg q4w	£2,659.71[c]
IFX	Inflectra™ (biosimilar)	£377.00	100mg x 1	5mg/kg at 0,2,6 weeks	£3,941.54[a]/ £4,173.39[b]
TOF	Xeljanz® (brand)	£690.03	5mg x 56	10mg twice daily for 8 weeks	£3,208.29
VDZ SC	Entyvio® (brand)	£2,050.00	300mg x 1	300mg IV at 0,2,6 weeks	£6,150.00
VDZ IV	Entyvio® (brand)	£2,050.00	300mg x 1	300mg IV at 0,2,6 weeks	£6,150.00
UST	Stelara® (brand)	£2,147.00	13mg x 1 IV 90mg x 1 SC	Loading dose: Patients <55kg: 260mg IV Patients <=85kg: 390mg IV Patents >85kg: 520mg IV Then 90mg at week 8	£6,697.63[b]

Abbreviations: kg, kilogram; mg, milligram
[a] Based on the baseline weight for the biologic-naïve subgroup [b] Based on the baseline weight for the biologic-exposed subgroup [c] Induction dose is 2 doses (initially and at week 2) therefore not all patients may receive a third

dose at week 6. Average price reflects the % of patients who are responders as estimated in the NMA (all assumed to receive the third dose), and assumes 0 % of non-responders would receive a third dose

B25. The unit costs for serious infection (AE) were based on a weighted average of 6 different types of infections. Please clarify:

a. whether the weights used were based on, or representative of, a UC population
b. why for costing of AEs 6 types of infections were used, while for disutilities only pneumonia was considered.

B25. Response:

a. The weights are based on the total number of activities for each infection that was provided by the National Schedule of NHS costs in year 2018-2019 (28). Although UC specific data is not available, the method of calculating the average unit cost is consistent with TA547 (2) and TA633 (10).

b. The cost of serious infection was calculated based on the average of six types of serious infections: sepsis, tuberculosis, pneumonia, skin and soft tissue infection, bone and joint infection and urinary tract infection. The choice of the infections aligns with previous appraisal TA547 (2). The disutility of infection without hospitalisation (-0.52) was used as the disutility value for serious infections, which was obtained from a cost-effectiveness study by Wilson et al., (29). This was then adjusted for the expected duration of the event, resulting in a disutility of 0.052 applied over the 10-weekly cycle.

B26. Resource use for model health states was aligned with Tsai et al. However, for annual hospitalizations in active UC and response without remission, the hospitalizations were increased compared to Tsai et al. [ref 133 in CS] from 0.3 for both health states to 1.5 and 1.2, respectively. This seems to be in contrast with the statement in the CS that the Tsai et al (2008) estimates may be higher than expected in current clinical practice, and with the estimates from clinicians consulted by the company which expected 0.67 and 0 hospitalization episodes, respectively.

Please justify the use of the increased hospitalization rates, other than that it is in line with TA547.

B26. Response:

In the TA547, the company justified these inputs as follows: '*A clinical expert advised that hospitalisation would increase as the patient health state worsens. The estimated annual 0.3 hospitalisation for standard care was increased to 1.20 for the response without remission health state and to 1.50 for the active UC state… For remission and post-surgery without complications the low limit was assumed to be no resource (0%) and the high limit was set to that of response-no remission.'*

In this submission, we have aligned with the rates used in TA547 (2), as well as providing a scenario analysis using rates provided by clinicians consulted i.e. 0.67 and 0 hospitalisations in active UC and response without remission, respectively. To further test the impact of these inputs, a scenario analysis is provided below using the inputs sourced from Tsai et al. (30) i.e. 0.3 for both health states.

Table 69. Scenario analysis supporting B26 - biologic-naïve

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	21.213	[redacted]	-	-	-	-	74,339.59
Conventional therapy	[redacted]	21.210	[redacted]	19,073.94	0.003	0.257	74,339.59	-
Golimumab	[redacted]	21.212	[redacted]	-9,937.88	0.001	0.056	Dominated	Dominated
Adalimumab	[redacted]	21.212	[redacted]	-10,359.78	0.001	0.059	Dominated	Dominated
Tofacitinib	[redacted]	21.213	[redacted]	-11,753.41	-0.0004	-0.033	359,578 SW	15,155.29
Infliximab	[redacted]	21.213	[redacted]	-15,643.90	-0.0002	-0.012	1,267,296 SW	Dominated
Vedolizumab SC	[redacted]	21.215	[redacted]	-21,842.40	-0.002	-0.210	104,042 SW	31,369.84
Vedolizumab IV	[redacted]	21.215	[redacted]	-25,564.89	-0.002	-0.179	142,540 SW	Dominated

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 70. Scenario analysis supporting B26 - biologic-experienced

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	20.910	[redacted]	-	-	-	-	105,967.74
Conventional therapy	[redacted]	20.909	[redacted]	12,675.26	0.001	0.120	105,967.74	-
Adalimumab	[redacted]	20.909	[redacted]	-2,027.40	0.001	0.043	Dominated	Dominated

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Vedolizumab SC	[redacted]	20.910	[redacted]	-4,040.41	0.0002	0.016	Dominated	73,336.69
Tofacitinib	[redacted]	20.910	[redacted]	-4,082.47	0.0001	0.010	Dominated	7,850.52
Ustekinumab	[redacted]	20.910	[redacted]	-4,746.11	0.0003	0.029	Dominated	Dominated
Vedolizumab IV	[redacted]	20.910	[redacted]	-4,902.83	0.0003	0.029	Dominated	766,189.13

Cost-effectiveness results

B27. Base case results were presented with ICERS. Please include Net Health Benefits

B27. Response:

Table 71. Base case results – biologic naïve group

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)	Net Health Benefit
Filgotinib	[redacted]	21.213	[redacted]	-	-	-	-	62,350.24	-
Conventional therapy	[redacted]	21.210	[redacted]	15,997.73	0.003	0.257	62,350.24	-	-0.98
Golimumab	[redacted]	21.212	[redacted]	-10,931.16	0.001	0.056	Dominated	Dominated	0.90
Tofacitinib	[redacted]	21.213	[redacted]	-11,297.56	0.000	-0.033	345,631 SW	4,119.95	0.84
Adalimumab	[redacted]	21.212	[redacted]	-11,360.53	0.001	0.059	Dominated	Dominated	0.94
Infliximab	[redacted]	21.213	[redacted]	-15,721.69	0.000	-0.012	1,273,598 SW	60,897.92	1.20
Vedolizumab SC	[redacted]	21.215	[redacted]	-19,040.43	-0.002	-0.210	90,695 SW	16,795.73	1.26
Vedolizumab IV	[redacted]	21.215	[redacted]	-23,219.62	-0.002	-0.179	129,463 SW	Dominated	1.62

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 72. Base case results – biologic experienced group

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)	Net Health Benefit
Filgotinib	[redacted]	20.910	[redacted]	-	-	-	-	96,056.10	-
Conventional therapy	[redacted]	20.909	[redacted]	11,489.68	0.001	0.120	96,056.10	-	-0.77

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)	Net Health Benefit
Adalimumab	[redacted]	20.909	[redacted]	-2,452.30	0.001	0.043	Dominated	Dominated	0.23
Tofacitinib	[redacted]	20.910	[redacted]	-4,191.25	0.0001	0.010	Dominated	53,006.51	0.33
Vedolizumab SC	[redacted]	20.910	[redacted]	-4,199.83	0.0002	0.016	Dominated	Dominated	0.34
Ustekinumab	[redacted]	20.910	[redacted]	-5,084.88	0.0003	0.029	Dominated	Dominated	0.42
Vedolizumab IV	[redacted]	20.910	[redacted]	-5,238.67	0.0003	0.029	Dominated	751,844.73	0.43

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

B28. Probabilistic sensitivity analyses:

a. It appears that results from the NMA are not included in the PSA and uncertainty about relative effectiveness is therefore not appropriately accounted for. Please include these in the PSA by including the CODA.
b. Gamma distributions were included for treatment effectiveness Please explain why Gamma distributions were preferred over other distributions (Beta distributions)
c. Sex and Weight were included in the PSA. However, these are factors of heterogeneity and do not result in uncertainty around (mean) parameter values. Please exclude these factors from the PSA
d. The PSA results were based on 1,000 model runs. Please explain why this was deemed appropriate, considering convergence plots showing stability of results?

B28. Response: PSA has been conducted based on the new base case and is presented below. As requested by the ERG, the CODA was included and the sex and weight were excluded from the PSA. The Gamma distributions were used to obtain Dirichlet distribution (i.e. we have a categorial variable, active UC, response, remission), however, this has been superseded in the model with the use of the CODA. The convergence plots indicate 1,000 model runs tend to be sufficient to investigate the robustness of the model.

Biologic-naïve population

The results of the PSA are presented in Table 73, with a cost-effectiveness acceptability plane in Figure 2 and a cost-effectiveness acceptability curve in Figure 3. Results of PSA are similar to the base case results. At a WTP threshold of £20,000, filgotinib had a 1.98% probability of being the optimal treatment. The convergence plot is provided in Figure 4.

Table 73. Probabilistic sensitivity analysis results for the biologic-naïve population

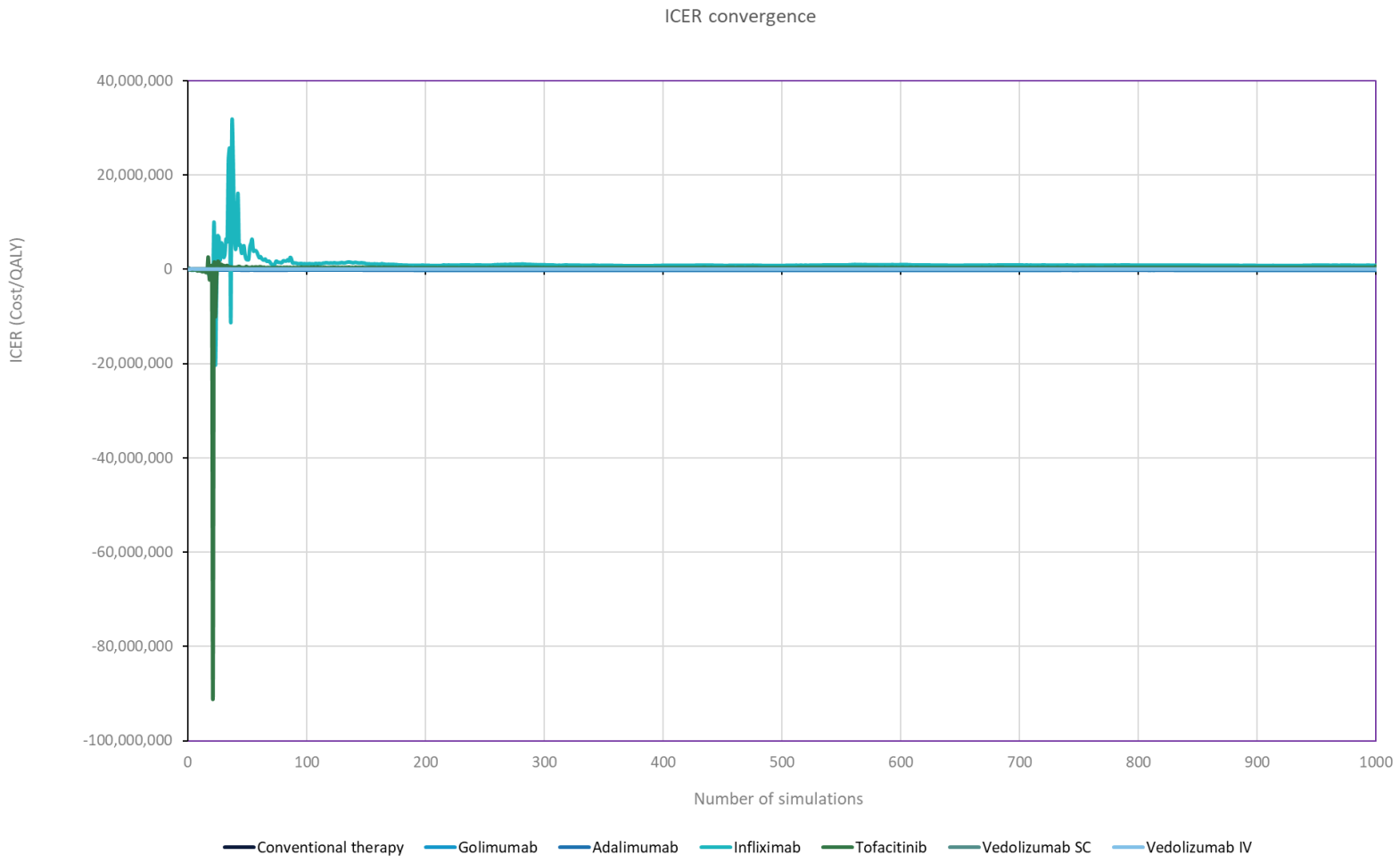
First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	21.211	[redacted]	-	-	-	-	57,199.83
Conventional therapy	[redacted]	21.207	[redacted]	15,982.03	0.003	0.279	57,199.83	-
Golimumab	[redacted]	21.210	[redacted]	-11,328.98	0.001	0.069	Dominated	Dominated
Adalimumab	[redacted]	21.210	[redacted]	-11,885.68	0.001	0.069	Dominated	1,028,718.21
Infliximab	[redacted]	21.211	[redacted]	-16,808.13	-0.0003	-0.019	878,941.42 SW	Dominated
Tofacitinib	[redacted]	21.211	[redacted]	-12,056.59	-0.0004	-0.032	381,668.07 SW	1,701.30
Vedolizumab SC	[redacted]	21.213	[redacted]	-20,551.07	-0.003	-0.230	89,522.40 SW	17,786.22
Vedolizumab IV	[redacted]	21.213	[redacted]	-24,549.16	-0.002	-0.186	132,284.19 SW	Dominated

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Figure 2. PSA scatterplot on cost-effectiveness plane for the biologic-naïve population

Figure 3. PSA cost-effectiveness acceptability curve for the biologic-naïve population

Figure 4. PSA ICER convergence for the biologic-naïve population



Biologic-experienced population

The results of the PSA are presented in Table 74, with a cost-effectiveness acceptability curve in Figure 6 and a cost-effectiveness plane in Figure 5. Results of PSA are similar to the base case results. At a WTP threshold of £20,000, filgotinib had a 0% probability of being the optimal treatment. The convergence plot is provided in Figure 7.

Table 74. Probabilistic sensitivity analysis results for the biologic-experienced population

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	20.908	[redacted]	-	-	-	-	91,268.67
Conventional therapy	[redacted]	20.906	[redacted]	11,764.13	0.002	0.129	91,268.67	-
Adalimumab	[redacted]	20.907	[redacted]	-2,587.15	0.001	0.045	Dominated	Dominated
Tofacitinib	[redacted]	20.908	[redacted]	-4,424.73	0.000	0.009	Dominated	52,142.42
Ustekinumab	[redacted]	20.907	[redacted]	-5,195.96	0.0004	0.032	Dominated	Dominated
Vedolizumab SC	[redacted]	20.908	[redacted]	-4,456.96	0.0001	0.011	Dominated	Dominated
Vedolizumab IV	[redacted]	20.907	[redacted]	-5,351.44	0.000	0.031	Dominated	649,603.48

Figure 5. PSA scatterplot on cost-effectiveness plane for the biologic-experienced population

Figure 6. PSA cost-effectiveness acceptability curve for the biologic-experienced population

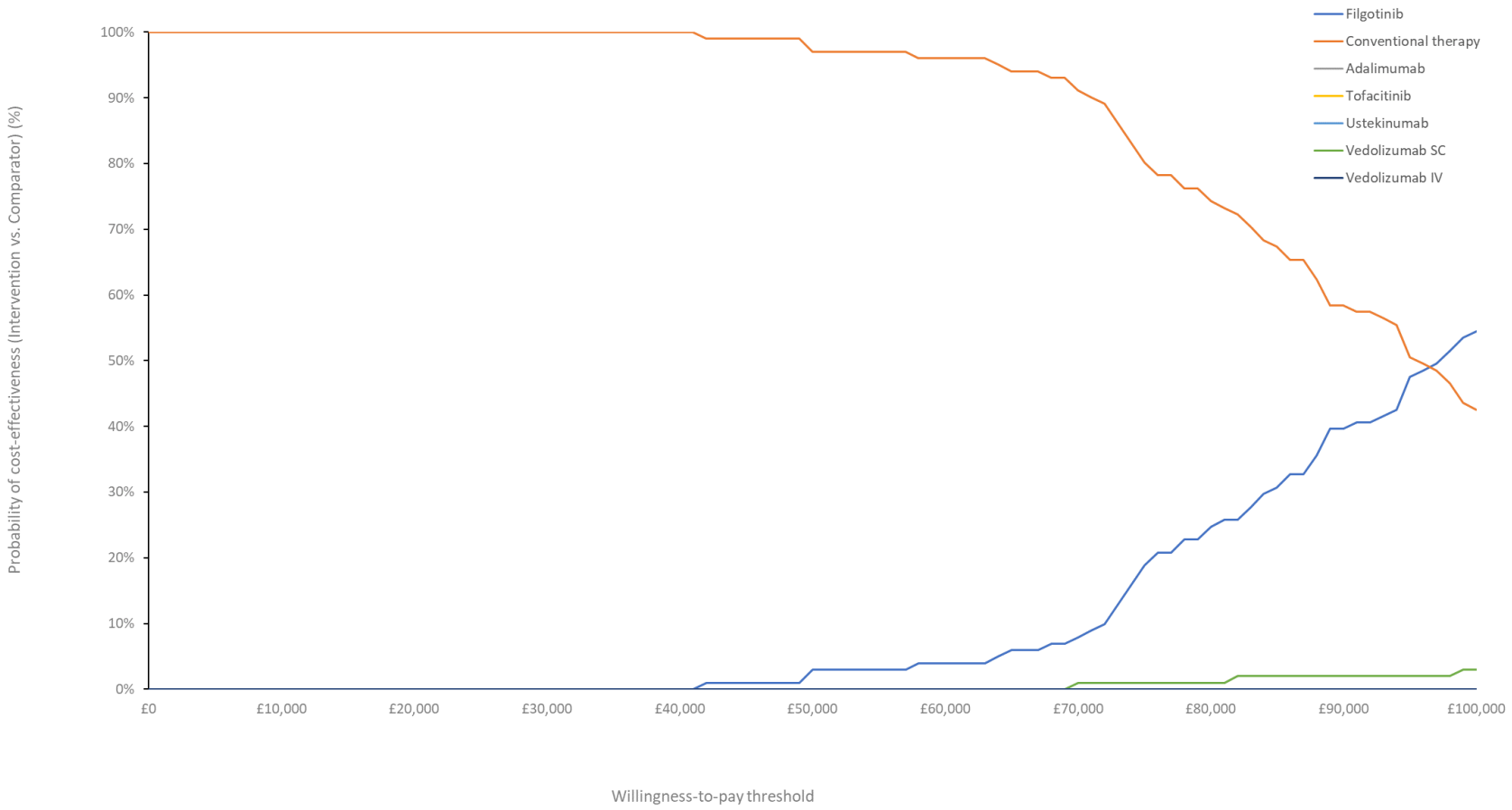
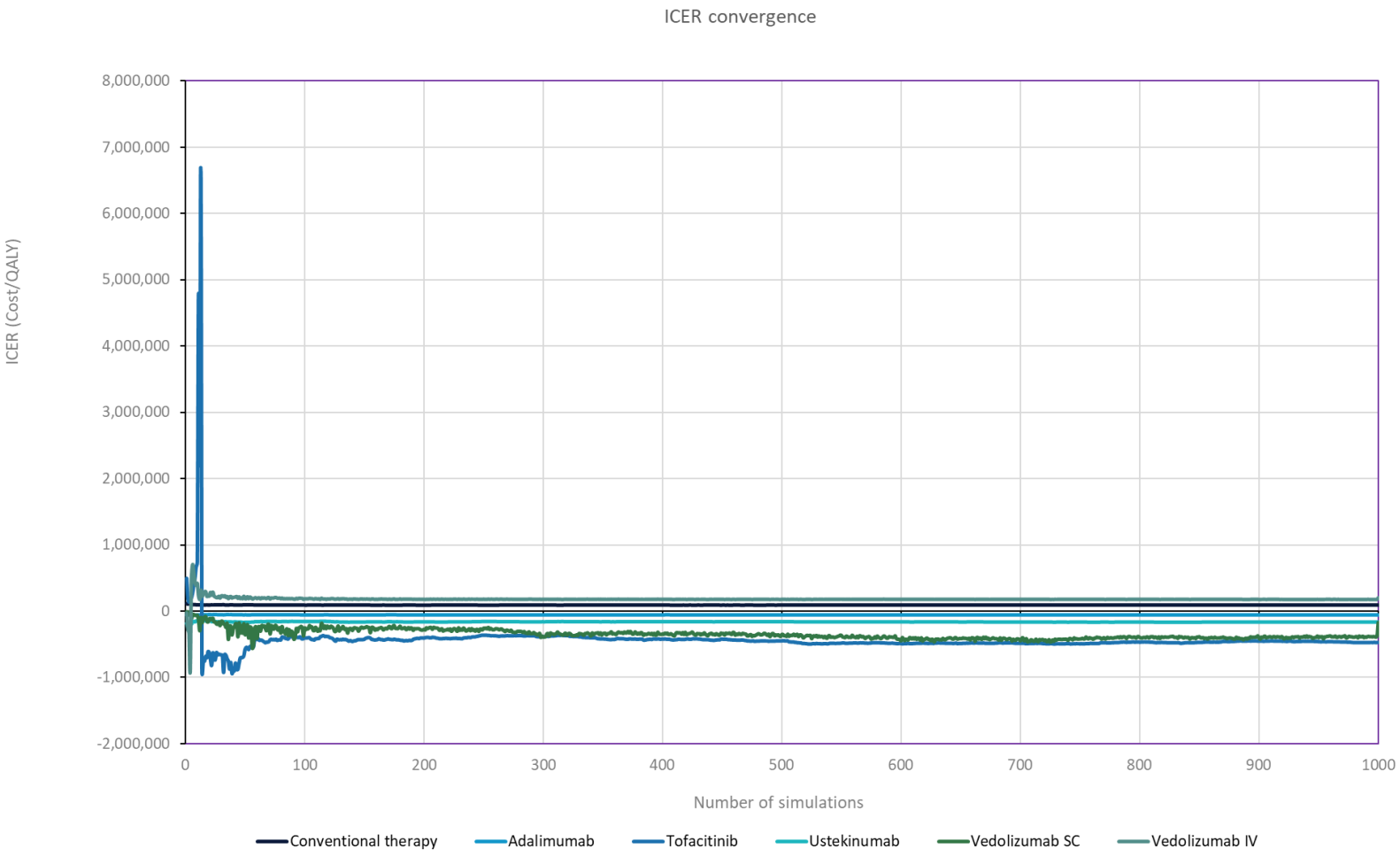


Figure 7. PSA ICER convergence for the biologic-experienced population



B29. Please provide any detail on internal validation exercises performed, for example by completing the TECH-VER checklist (Büyükkaramikli et al, 2019 (https://pubmed.ncbi.nlm.nih.gov/31705406/)

B29. Response: Please see the Excel file 'ID3736_FIL_UC_NICE_CQ_B29' accompanying this file.

B30. Priority question: Please assess the external validity of the estimated (intermediate) outcomes with data used to develop the model and also other data not used to develop the model, where available.

B30. Response: Details of external validation of the cost-effectiveness model are provided in section B.3.10.1 of the company submission. The model was validated against the published cost-effectiveness analysis for tofacitinib by Lohan et al. (31) The model was adapted using the reported model parameters (summarized in Appendix J of the company submission). It was possible to achieve similar estimates of modelled costs and QALYs for all comparators which were all within 3% of the published results (see Table 75). The validation exercise confirmed that the model is operating similarly to the published cost-effectiveness model.

Table 75. Comparison of the results of the validation model with the results published by Lohan et al.

	Lohan et al. published model results		Validation model results		Comparison (validation model results as % of Lohan model results)	
Strategy	**QALYs**	**Costs**	**QALYs**	**Costs**	**QALYs**	**Costs**
TNF naïve						
CT	8.99	£132,349	8.84	£135,781	98%	103%
Adalimumab	9.19	£138,534	9.10	£138,680	99%	100%
Golimumab	9.29	£141,360	9.19	£140,511	99%	99%
Infliximab	9.35	£145,660	9.25	£143,483	99%	99%
Vedolizumab	9.46	£152,694	9.35	£148,268	99%	97%
Tofacitinib	9.54	£143,963	9.43	£141,301	99%	98%
TNF exposed						
CT	8.90	£132,712	8.84	£135,781	99%	102%
Adalimumab	9.05	£137,035	8.98	£138,008	99%	101%
Vedolizumab	9.15	£145,360	9.07	£143,340	99%	99%
Tofacitinib	9.24	£141,500	9.43	£141,301	102%	100%

Abbreviations: CT, conventional therapy; QALY: quality adjusted life-year
Reference: Lohan et al. (31)

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Appendix A. Deterministic sensitivity analysis

The deterministic sensitivity analyses (DSAs) were conducted based on the new base case for both biologic-naïve population and biologic-experienced population.

Biologic-naïve population

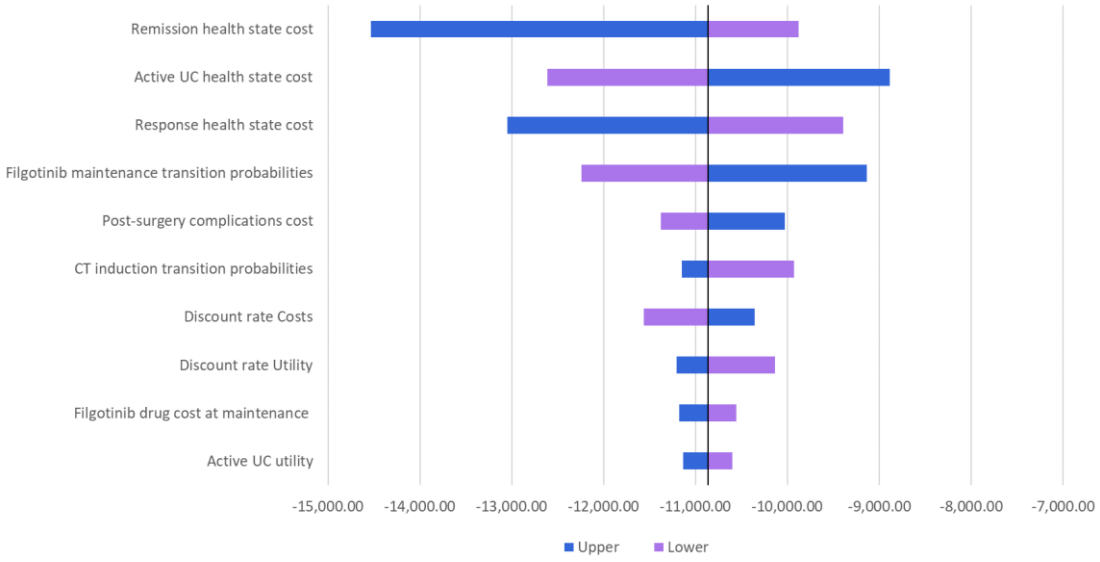
DSA results for the ten most impactful parameters are presented in Table 76 and Figure 8. The net monetary benefit was most sensitive to changes in the health states costs, and the transition probabilities for filgotinib in the maintenance phase.

Table 76. One-way sensitivity analysis results for filgotinib vs conventional therapy in the biologic-naïve population

Parameter	NMB low (WTP of £20,000)	NMB high (WTP of £20,000)
Base case	**-10,866**	
Remission health state cost	-9,880.16	-14,530.80
Active UC health state cost	-12,610.18	-8,887.12
Response health state cost	-9,390.40	-13,046.95
Filgotinib maintenance transition probabilities	-12,242.40	-9,137.63
Post-surgery complications cost	-11,379.86	-10,023.87
CT induction transition probabilities	-9,927.32	-11,150.87
Discount rate Costs	-11,561.32	-10,355.31
Discount rate Utility	-10,134.03	-11,206.79
Filgotinib drug cost at maintenance	-10,553.88	-11,178.44
Active UC utility	-10,598.29	-11,131.93

Abbreviations: CT, conventional therapy; NMB, net monetary benefit; UC, ulcerative colitis; WTP, willingness-to-pay

Figure 8. Tornado diagram for filgotinib vs conventional therapy in the biologic-naïve population



Biologic-experienced population

Deterministic sensitivity analysis results for the ten most impactful parameters are presented in Table 77 and Figure 9. The NMB was most sensitive to changes in the health states costs.

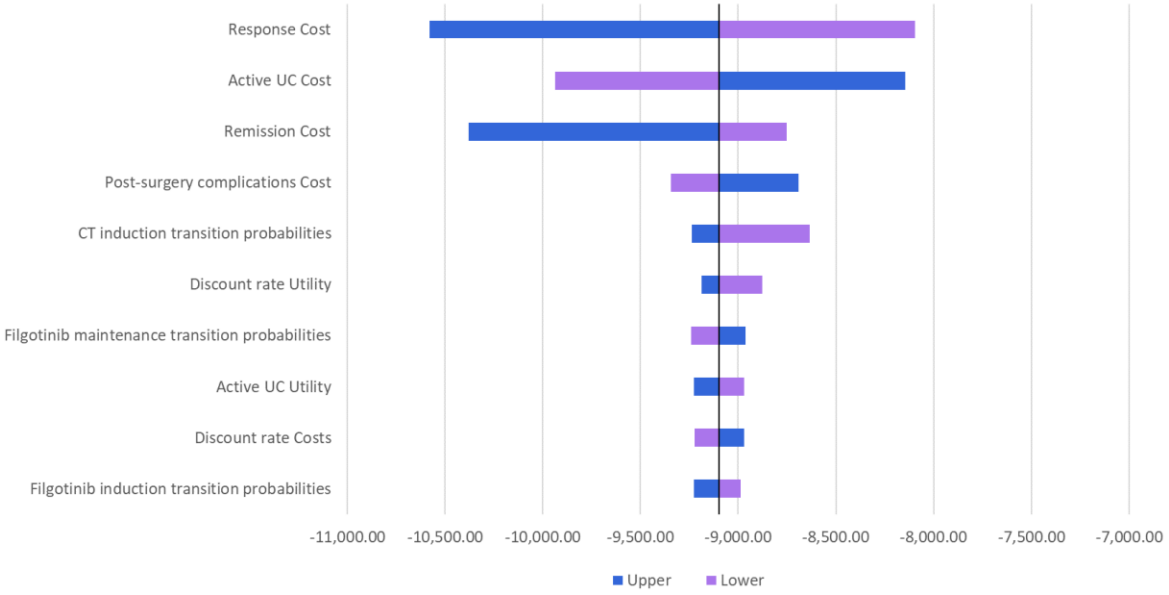
Table 77. One-way sensitivity analysis results for filgotinib vs conventional therapy in the biologic-experienced population

Parameter	NMB low (WTP of £20,000)	NMB high (WTP of £20,000)
Base case	**- 9,097**	
Response Cost	-8,094.38	-10,579.59
Active UC Cost	-9,938.09	-8,143.41

Parameter	NMB low (WTP of £20,000)	NMB high (WTP of £20,000)
Remission Cost	-8,752.78	-10,378.23
Post-surgery complications Cost	-9,345.71	-8,690.25
CT induction transition probabilities	-8,634.94	-9,237.90
Discount rate Utility	-8,877.03	-9,189.03
Filgotinib maintenance transition probabilities	-9,242.72	-8,963.00
Active UC Utility	-8,967.93	-9,225.85
Discount rate Costs	-9,224.88	-8,969.57
Filgotinib induction transition probabilities	-8,986.91	-9,228.42

Abbreviations: CT, conventional therapy; NMB, net monetary benefit; UC, ulcerative colitis; WTP, willingness-to-pay

Figure 9. Tornado diagram for filgotinib vs conventional therapy in the biologic-experienced population



Appendix B. Scenario analysis

Further scenario analyses were undertaken to assess the impact of key variables on the model outcomes (Table 78).

Table 78. Scenarios included in the cost-effectiveness analysis

Scenario		Base case	Scenario description
1	Treatment efficacy	Base case NMA used to estimate treatment efficacy in the maintenance phase (B.3.3.1 Treatment effectiveness: clinical response and remission	Sensitivity analyses from the NMA used for treatment efficacy in the maintenance phase - Using an alternative methodology to re-weight treat-through trials
2	Adverse events	Adverse events from a safety NMA (Section B.3.3.3 Adverse events)	Using AE rates reported in Lohan et al. (31) (provided in Section B.3.3.3)
3	Stopping rule	Patients in remission remain on treatment indefinitely, until loss of response (Section B.3.3.1 Treatment effectiveness: clinical response and remission)	Assumed 15% of patients in remission after one year of maintenance treatment discontinue treatment
4	Dose escalation	Dose escalation set to 30% (Section B.3.5.1 Intervention and comparators' costs and resource use)	Dose escalation set to 10% and 50% for all treatments
5	Utilities	SELECTION trial data (10 weeks) (Section B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis)	Alternative utility estimates (provided in Section B.3.4.5) - SELECTION trial data at 58 weeks - Woehl et al. (27) - Swinburn et al. (32) - Vaizey et al. (33) - Arseneau et al. (34)
6	Resource use	Resource estimates sourced from Tsai et al. (30) (B.3.5.2 Health-state unit costs and resource use)	Alternative resource use estimates based on clinician interviews (provided in B.3.5.2 Health-state unit costs and resource use)

Abbreviations: AE, adverse event; NMA, network meta-analysis

Biologic-naïve population

A summary of the results of the scenario analyses in the biologic-naïve population are presented Table 79. Overall, the results were consistent with the base case analysis. The model was most sensitive to the NMA sensitivity analyses results (scenario 1), and the various utility inputs (scenario 5).

Table 79. Scenario analyses: filgotinib vs comparator in the biologic-naïve population (ICER as cost per QALY)

Scenario	Description	CT	Golimumab	Adalimumab	Infliximab	Tofacitinib	Vedolizumab SC	Vedolizumab IV
Base case		***62,350***	***Dominated***	***Dominated***	***1,273,598 SW***	***345,631 SW***	***90,695 SW***	***129,463 SW***
Scenario 1: Treatment efficacy	Using sensitivity analysis from the NMA (alternative re-weighting for treat-through trials)	68,282	Dominated	Dominated	272,949 SW	334,698 SW	91,271 SW	128,746 SW
Scenario 2: Adverse events	Rates from Lohan et al. (31)	62,837	Dominated	Dominated	1,223,764 SW	344,415 SW	90,159 SW	128,797 SW
Scenario 3: Stopping rule	15% of patients in remission discontinue treatment	60,410	Dominated	Dominated	1,240,150 SW	323,475 SW	83,724 SW	120,844 SW
Scenario 4: Dose escalation	Dose escalation set to 10%	57,183	Dominated	Dominated	1,126,484 SW	281,496 SW	86,259 SW	107,507 SW
Scenario 4: Dose escalation	Dose escalation set to 50%	67,569	Dominated	Dominated	1,422,190 SW	410,411 SW	95,176 SW	151,641 SW
Scenario 5: Utilities	Values from SELECTION (58 weeks)	58,263	Dominated	Dominated	1,247,089 SW	321,373 SW	84,464 SW	120,648 SW
Scenario 5: Utilities	Values from Woehl et al. (27)	62,350	Dominated	Dominated	1,273,598 SW	345,631 SW	90,695 SW	129,463 SW

Scenario	Description	CT	Golimumab	Adalimumab	Infliximab	Tofacitinib	Vedolizumab SC	Vedolizumab IV
Scenario 5: Utilities	Values from Swinburn et al. (32)	43,156	Dominated	Dominated	1,136,441 SW	233,533 SW	61,751 SW	88,430 SW
Scenario 5: Utilities	Values from Vaizey et al. (33)	70,784	Dominated	Dominated	2,595,913 SW	374,899 SW	99,785 SW	143,317 SW
Scenario 5: Utilities	Values from Arseneau et al. (34)	24,682	Dominated	Dominated	385,125 SW	141,265 SW	36,694 SW	52,148 SW
Scenario 6: Resource use	Estimates from clinician interviews	67,892	Dominated	Dominated	1,260,417 SW	353,162 SW	97,592 SW	136,093 SW

Abbreviations: ICER, incremental cost-effectiveness ratio; IV, intravenous; NMA, Network meta-analysis; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Biologic-experienced population

A summary of the results of the scenario analyses in the biologic-naïve population are presented Table 80. Overall, the results were consistent with the base case analysis. The model was most sensitive to the NMA sensitivity analyses results (scenario 1), and the various utility inputs (scenario 4).

Table 80. Scenario analyses: filgotinib vs comparator in the biologic-experienced population (ICER as cost per QALY)

Scenario	Description	Conventional therapy	Adalimumab	Tofacitinib	Ustekinumab	Vedolizumab SC	Vedolizumab IV
Base case		**96,056**	**Dominated**	**Dominated**	**Dominated**	**Dominated**	**Dominated**
Scenario 1: Treatment efficacy	Using sensitivity analysis from the NMA (alternative re-weighting for treat-through trials)	95,667	Dominated	Dominated	Dominated	Dominated	Dominated

Scenario	Description	Conventional therapy	Adalimumab	Tofacitinib	Ustekinumab	Vedolizumab SC	Vedolizumab IV
Scenario 2: Adverse events	Rates from Lohan et al. (31)	96,914	Dominated	Dominated	Dominated	Dominated	Dominated
Scenario 3: Stopping rule	15% of patients in remission discontinue treatment	94,615	Dominated	Dominated	Dominated	Dominated	Dominated
Scenario 4: Dose escalation	Dose escalation set to 10%	88,788	Dominated	Dominated	Dominated	Dominated	Dominated
Scenario 4: Dose escalation	Dose escalation set to 50%	103,397	Dominated	Dominated	Dominated	Dominated	Dominated
Scenario 5: Utilities	Values from SELECTION (58 weeks)	90,227	Dominated	Dominated	Dominated	Dominated	Dominated
Scenario 5: Utilities	Values from Woehl et al. (27)	96,056	Dominated	Dominated	Dominated	Dominated	Dominated
Scenario 5: Utilities	Values from Swinburn et al. (32)	68,226	Dominated	Dominated	Dominated	Dominated	Dominated
Scenario 5: Utilities	Values from Vaizey et al. (33)	114,983	Dominated	Dominated	Dominated	Dominated	Dominated
Scenario 5: Utilities	Values from Arseneau et al. (34)	36,671	Dominated	Dominated	Dominated	Dominated	Dominated
Scenario 6: Resource use	Estimates from clinician interviews	99,417	Dominated	Dominated	Dominated	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; IV, intravenous; NMA, Network meta-analysis; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

NICE National Institute for Health and Care Excellence

Patient organisation submission

Filgotinib for treating moderately to severely active ulcerative colitis [ID3736]

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	Crohn's & Colitis UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Crohn's & Colitis UK is the UK's leading charity for everyone affected by Crohn's and Colitis. We're working to improve diagnosis and treatment, and to fund research into a cure; to raise awareness and to give people hope, comfort, and confidence to live freer, fuller lives. We want: • To drive world-class research that improves lives today and brings us closer to a world free from Crohn's and Colitis tomorrow • Everyone to understand Crohn's and Colitis • To support and empower everyone to manage their conditions • To drive high-quality and sustainable clinical care • Early and accurate diagnosis for all. Founded as a patients' association in 1979, we now have 40,000 members across the UK. Our members include people living with the conditions, their families and friends, health professionals and others who support our work. We have 50 Local Networks which arrange educational meetings, generate publicity and organise fundraising.[1] Funding is through membership subscriptions and a wide range of fundraising activities, including events, grants, legacies and corporate partnerships. Full details are available in our annual accounts. https://www.crohnsandcolitis.org.uk/about-us/annual-accounts
4b. Has the organisation received any funding from the	Yes

[1] About Us | Crohn's & Colitis UK (crohnsandcolitis.org.uk)

manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	A list of our funders can be read on our website.
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?	We gather information about the experience of patients, carers and families through: • the Crohn's & Colitis UK helpline • local networks • calls for evidence via our website and social media • one to one discussion with people with IBD, clinicians, and the wider IBD community; and

	• research - our own and that of external organisations. For this submission, we did a call for evidence via our website and social media which gathered a small number of written responses. One of the patients that contacted us agreed to be nominated as an Expert Patient.
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?	The symptoms of ulcerative colitis, and their unpredictable nature, can have a profound and devastating impact on all aspects of a person's life. Frequent diarrhoea, abdominal pain and fatigue, anaemia, extra-intestinal manifestations such as joint, skin and eye problems, and the side effects of medications, all affect an individual's ability to work, study, socialise, participate in leisure activities or have intimate relationships. (IBD Quality of Life Survey, 2018; IBD Standards, 2013 and 2019). *"Life with UC has been difficult, as I was constantly ill over a period of years, I had my relationship break down. I have been lucky that my previous line manager at work had a daughter of his own who suffered from UC, so any hospital stays weren't a problem and he allowed me to work from home on particularly bad days."* Given that disease severity is wide-ranging, and while each person has their own individual experience, we would like to take this opportunity to describe the impact and experience of the specific cohort of patients this guidance is targeting moderate to severe ulcerative colitis. This cohort is likely to comprise of patients with Ulcerative Colitis who experience more severe flares, weight loss, fever and constitutional symptoms, and whose disease has not responded to or are unable to tolerate other treatments, and/or can benefit from this treatment in particular

	Truelove and Witts define severe Ulcerative Colitis as six or more stools a day plus at least one of the features of systemic upset (marked with an *): visible blood; pyrexia*; pulse rate greater than 90 BPM*; erythrocyte sedimentation rate (mm/hour) * and anaemia.2 The Mayo Score defines severe Colitis as more than five stools a day, blood passed without stool, obvious blood with stools in most cases and severe disease (spontaneous bleeding, ulceration).3 For this subgroup of patients with moderate to severe Ulcerative Colitis, the condition is more than challenging, but frequently overwhelming and detrimentally life-altering, as described below: *"I had 3 blood transfusions, multiple steroids, sleepless drained nights, cannula paracetamol, Iron deficiency, stomach ulcers and multiple drugs and many blood tests, not being able to eat and losing a Hugh amount of weight over 2 and a half stone in just 2 weeks wasn't expected out the blue in my life."* ***Person with Ulcerative Colitis, treated with Filgotinib.*** **Mortality** There are risks and mortality associated with untreated and uncontrolled disease. NICE Guideline on Ulcerative Colitis 130 states: 'Ulcerative colitis is a lifelong disease that is associated with significant morbidity. It can also affect a person's social and psychological wellbeing, particularly if poorly controlled'.[4] This is echoed by BSG Guidelines that state that 'acute severe colitis is a potentially life-threatening condition'.[5]

[2] NICE (2019) NICE Guideline on Ulcerative Colitis: Management (NG130) https://www.nice.org.uk/guidance/ng130/chapter/Recommendations

[3] Dignass, A,. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 1: Definitions and diagnosis. Journal of Crohn's and Colitis Vol 6. Issue 10 https://www.sciencedirect.com/science/article/pii/S1873994612004047#t0020

[4] NICE Guideline on Ulcerative Colitis: Management: Overview | Ulcerative colitis: management | Guidance | NICE

[5] BSG (2011) British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. https://gut.bmj.com/content/60/5/571.long

	Acute severe colitis has a 1% mortality risk and a 29% chance of requiring emergency surgery to remove the inflamed bowel (colectomy).[6] Between 15-25% of patients with Ulcerative Colitis will need to be hospitalised due to an acute severe flare-up at some stage. Often this will be the first presentation of their disease.[7] When a flare occurs in acute severe colitis, deterioration can occur rapidly. Patients will require close monitoring and review by appropriate specialists. It's also vitally important to make decisions quickly to avoid severe complications. The very real risks associated with acute severe colitis include: • Life-threatening haemorrhage • Toxic megacolon - can occur in up to 1 in 40 people with Colitis[8] • Perforation of the bowel[9] Additional complications of chronic, uncontrolled, active ulcerative colitis also include: • Both osteoporosis and vitamin D deficiency are common in IBD. The major risk factors for osteoporosis complicating IBD are age, steroid use and disease activity[10] • Anaemia is a common complication of IBD. Iron deficiency and anaemia of chronic disease are the commonest causes of anaemia in IBD[11] • Increased risk of cancer[12] **Impact on emotional and mental health**

[6] BSG (2011) British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. https://gut.bmj.com/content/60/5/571.long
[7] BSG (2011) British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. https://gut.bmj.com/content/60/5/571.long
[8] Parray, F. Q. et al. Ulcerative colitis: a challenge to surgeons. Int. J. Prev. Med. 3, 749–63 (2012)
[9] IBDUK (2019) IBD Standards 2019 www.ibduk.org
[10] Mowat C, Cole A, Windsor A et al. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011; 60:571-607.
[11] Ibid
[12] BSG guideline (2019)

	Emotional wellbeing can be significantly affected by difficulty in coping with personal lives and feelings of anger, embarrassment, frustration, sadness and fears of needing surgery or developing cancer (Cosnes et al, 2011). Stigma and lack of wider understanding of the condition exacerbate the impact. Anxiety and depression are higher in people with IBD, with mood disorders at least in part a consequence of the IBD itself (Graff, 2009) and its medical treatment (e.g., corticosteroid therapy), surgery, including specifically colectomy and stoma formation. Additionally, most reports indicate that stress may be involved in triggering relapse. "*The last 9 months have been really quite horrible for me dealing with my UC and I went through a really low point in my life, feeling very anxious and depressed. I took 5 months off work and only recently started a new job. My UC really affected my social life and confidence especially with getting out of the house and carrying out simple tasks."* "*The isolation I have felt has been overwhelming. I can't take my children to the park, for a walk or play date or any of the other simple things that I used to take for granted. I do not have any kind of social life myself as it is simply not possible for me to go out when I may need to open my bowels with no warning."* "*He was struggling to maintain a healthy weight, was constantly feeling sick, rushing to the toilet and in pain and missing a great deal of his work at a stage in his career that was very important to him. He was unable to continue his sport and his social life was negligible*." **Social functioning** Social functioning can be impaired - leading to an inability to work, attend school, participate in leisure activities, or have intimate relationships. Research shows that young people aged 16-25 with IBD who have not yet entered full-time employment often feel that their condition has compromised their education and significantly limited their career aspirations. There is a clear associated "productivity loss" by health

	state, whereby the lowest score for health state (Visual Analogue Score 0-2.5) corresponds with a 71% productivity loss.[13] More recent research supports this.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There is unmet need amongst people with moderate to severe Ulcerative Colitis. Patients express dissatisfaction with many of the current treatment options. Many experience lack of response (primary or secondary) and/or adverse reactions. The effects of steroids are extremely unpleasant and long-term safety profile of other treatments, including biologics, of some concern. "*When I am unwell, I struggle with extreme tiredness and extended periods in the bathroom which makes my working life very difficult. I work in construction so spend a lot of time away from toilets. Vedolizumab, when I first started, it was my wonder drug. It was difficult spending so much time in hospital but worth it to be completely symptom free. I was in remission for nearly 4 months.* *I was then given Golimumab which was a lot more convenient, and I liked having the control of self-administering. This however never gave me remission and my CRP worsened over the period I was taking it. I am now being offered Tofacitinib but have been told this is my final option*." "*I have suffered with UC for 13 years. It's always been moderate to severe. I have tried all drugs including all biologics. All failed after a while. The best was Infliximab, I had my first ever remission for 2 years. However, it came to an end in Aug 2017. I had 18 months of pain and blood, countless hospital admissions, yet I was still pushed to try yet another biologic, Vedolizumab then Golimumab. None of it worked. 6 weeks later I had an emergency op and my colon was removed. My recovery is slow as I was ill for quite some time before and I'm building up my stamina now."* **Steroids**

[13] Gay M et al. Crohn's, Colitis and Employment – from Career Aspirations to Reality. Crohn's and Colitis UK, 2011

	"Corticosteroids have no proven efficacy in maintaining remission in IBD and should not be used for this purpose."[14] The BSG guidelines set out clear stipulations on the best practice of prescribing steroid therapies given their diminishing returns, harsh side effects and risk of dependency.[15] **Surgery** For many patients with ulcerative colitis, the prospect of surgery is one they face with considerable anxiety, and it can bring with it a range of potential complications, which may require further treatment and ongoing management. There can also be an associated profound psychological and social impact, for example, in terms of body image and self-esteem. For those who are facing this at an age when they have just begun to form relationships and do not yet have a family, this can be especially difficult, as it can for those of some religious faiths and cultures. Clinical outcomes after pouch surgery remain variable and fertility in women can be significantly affected by any pelvic surgery. *"I had severe Pan Ulcerative Colitis. I started my journey with an emergency admission in a very poor state (…). I spent 2 weeks in hospital while they tried to stop the frequency and bleeding, I came out on steroids, cyclosporine and Asacol. I was better for a little while but soon became very ill again and was off work. I was put on azathioprine but could not tolerate this, so I was switched to mercaptopurine. This put me in remission for 3 years, when this no longer worked I was put on Simponi. The initial double dose showed some promising results, but the single dose didn't keep me in remission. Following this I became dependent on steroids.* *My life was terrible quality. I missed out on opportunities at work, very rarely went anywhere and people would comment on my features from the steroids, and they said I looked a strange green-yellow colour.* *Finally, I had enough of being ill and hospital admissions and blood transfusions and requested surgery to remove my colon. My consultant told me if I was in any other country, they'd have taken it out much*

[14] Barrett, K. (2018) Using corticosteroids appropriately in inflammatory bowel disease: a guide for primary care, British Journal of General Practice. 68 (675): 497-498. https://bjgp.org/content/68/675/497

[15] BSG (2019) British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. https://www.bsg.org.uk/resource/bsg-consensus-guidelines-ibd-in-adults.html

	sooner. The surgeon said it disintegrated as he was taking it out it was in such a bad state. I now have a j-pouch and while life is a lot better it isn't the cure that was promised and it impacts on my life considerably." Surgery has significant associated long- and short-term risks which include: - general anaesthetic complications - infections. - anastomosis - adhesions - pouchitis, - pouch leakage, - pelvic abscesses - pouch fistulae - small bowel obstruction, - post-operative bleeding - sexual dysfunction - delayed wound healing - nerve damage[16,17] A 2011 research study found severe postoperative complications were experienced for 27% of surgeries.[18] Additionally, a meta-analysis has shown 'an approximate threefold increase (from 15% to 48%) in the risk of infertility in women with Ulcerative Colitis as a result of ileal pouch anal anastomosis (IPAA) (Waljee et al. 2006). Johnson et al. reported the infertility rate in females who had pelvic pouch surgery was significantly higher compared to females who were managed medically (38.1 % compared with 13.3 %; $p < 0.001$).'[19]

[16] Ibid

[17] Brown C, Gibson PR, Hart A, et al. Long-term outcomes of colectomy surgery among patients with ulcerative colitis. *Springerplus*. 2015; 4:573. Published 2015 Oct 5. doi:10.1186/s40064-015-1350-7

[18] Ibid

19 Johnson et al. 2004 in Ibid

	We would also urge the Committee to consider the 'persistent quality of life issues that impact multiple domains, including psychological and sexual functioning'.[20] A 2015 study found 81% experienced problems in at least one of the following areas: depression, work productivity, restrictions in diet, body image, and sexual function. In the same study, amongst moderate to severe Ulcerative Colitis patients, post-colectomy, 27% of men and 28% of women reported that their sexual life was worse now than before surgery.[21]
8. Is there an unmet need for patients with this condition?	The range of options available for treating ulcerative colitis remain far from optimal for patients, a substantial number of whom experience lack of response (primary or secondary) and/or adverse reactions to biologic as well as conventional therapies. There are significant short and long-term side effects with corticosteroids, including opportunistic infections, steroid-induced psychosis, steroid dependence, diabetes and osteoporosis. Their use is also limited to induction of remission. Up to one third of patients with IBD are intolerant to thiopurines and a further 10% are unresponsive to them. In the majority of patients who do respond, the benefits take three to six months to appear. Significant risks of thiopurines including non-Hodgkin's lymphoma (as high as 4-5-fold compared with unexposed IBD patients and further increased when used in combination with anti-TNFs). Other side effects include early hypersensitivity reactions such as fever and pancreatitis, bone marrow suppression and hepatotoxicity requiring frequent lab monitoring during treatment. Anti-TNFs are increasingly being used earlier in the treatment pathway and can have a significant and positive effect on quality of life for patients. However, up to 40% of patients treated with anti-TNF therapy

[20] Ibid
[21] Ibid

	do not respond to induction therapy. In the approximately one-third of patients who do achieve remission with anti-TNF therapy, between 10%-50% lose response over time.[22] Overall, there is a pressing need for additional treatment options which offer a different mode of action and the potential for people with ulcerative colitis to resume their lives and restore their quality of life.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients most likely to benefit from this drug are those for whom currently available therapies are ineffective, contraindicative or they develop an intolerance. In this group, it is likely that individuals, without further choice, will return to treatment/s which have already been established to be inadequate. This may include highly undesirable long-term steroid use or unproven unconventional therapy. It is also likely that patients in this group who exhaust all other treatment options would be forced to have a colectomy, either elective or as an emergency. *"I am well aware that these drugs have a very significant cost but without them, the last 12 years would have been very different for me. Even with them I have had to have 2 lots of surgery to remove scarred bowel but without them I think I would have had to have more extensive surgery and possibly not even be here to send this email. I am also well aware that I am on my last chance here with current available drugs having taken everything the NHS has to offer; if the vedo stops working then I have nowhere else to go with medication. New drugs and options for medication will be vital for my health going forward."* ***Person with IBD, in which drug treatments have not been effective.*** *I am a very active person and would consider myself a fitness fanatic but at my lowest point I struggled to get myself out of bed or off the couch. The stomach pains and associated cramps, the lethargy and constant trips to the toilet both day and night were draining both physically and mentally. I hated giving in but at times I just had to stop my usual routines and was often scared to leave the house. I cancelled plans and my social and family life suffered. The constant worry of where the nearest toilet was whenever I was out soon took over my mind. Then in 2019 I started the Filgotinib trial. To be honest I wasn't sure*

[22] Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management (nih.gov)

	what to expect but at that point I had been feeling so ill that I was willing to give it a try to see if it helped. Within 5 or 6 weeks of taking the tablets pretty much all of my symptoms had started to disappear and I was feeling as good as I had for a long time. ***Person with Ulcerative Colitis, treated with Filgotinib*** Another patient population that might benefit more from this treatment would be women of child-bearing age with moderate to severe ulcerative colitis who wish to avoid or delay surgery to preserve their fertility and start or complete their family.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The main potential disadvantage to patients would be in terms of prescription cost (in England) which can impact adherence and lead to complications and increased cancer risk and cost to the NHS (York Health Economics Consortium, 2018). However, this is outweighed by the value of an additional treatment option, which has a different mode of action, reduced likelihood of loss of response, and a convenient delivery method. There should also be an associated reduction in NHS costs due to reduced infusions.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who have had little or no success with currently available medical treatment options, and wish to avoid or delay surgery, are likely to benefit. This would include young people wishing to complete studies or start a family and those for whom surgery would be considered unacceptable due to cultural or religious factors.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	For certain religious groups, the impact of active disease and the effects of surgery may interfere with religious practices and cause distress, which could be alleviated by an additional medical therapeutic option. As noted above, women who have not yet had any children and wish to do so would have a reduced chance of conceiving naturally following colectomy or pouch surgery. This technology would offer another option to delay or avoid surgical intervention.
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

15. In up to 5 bullet points, please summarise the key messages of your submission:

- The symptoms of Ulcerative Colitis, and their unpredictable nature, together with the side effects of medications, can have a profound and devastating impact on all aspects of a person's life. Filgotinib is clinically effective within its indication for people with moderate to severe ulcerative colitis
- There is significant unmet need within the moderate to severe cohort. Current treatments remain far from optimal for patients, a substantial number of whom experience a lack of response (primary or secondary) and/or adverse reactions to medical treatments and may face the prospect of surgery with considerable anxiety.

- It offers a novel and effective treatment option and increases choice for both clinicians and patients (in the context of shared decision making).
- It gives greater personalised treatment options. This is particularly relevant given how individual a person's condition can be and consequently how personalised treatments are required to be.
- It has the potential to significantly improve the lives of patients with uncontrolled and unresponsive refractory disease, who are likely to be experiencing extremely low quality of life.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Filgotinib for treating moderately to severely active ulcerative colitis [ID3736]

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 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 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 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	UKCPA

3. Job title or position	St Mark's Pharmacy Manager and IBD Pharmacist
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):
5a. Brief description of the organisation (including who funds it).	The UK Clinical Pharmacy Association (UKCPA) is a member association providing education and training for clinical pharmacy practitioners. The UKCPA actively develops clinical pharmacy practice and individual practitioners. Activities include establishing professional curricula, developing professional recognition (credentialing) processes, and developing professional tools and frameworks for practitioners. The UKCPA Gastroenterology Interest Group provides a network for information exchange and training for any pharmacist working within the speciality of gastroenterology. In 2016 the UKCPA was awarded Royal Pharmaceutical Society accreditation as a Foundation Training Provider and a Faculty Training Provider.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	No

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	"Induce & maintain steroid-free remission (clinical/ endoscopic) for 12 months or longer & prevent need for surgical intervention. Improve quality of life for patient suffering with UC having failed conventional therapy without introducing additional risk factors (ie cancer risk, ADRs)" + histological response (Robart's)
7. What do you consider a clinically significant treatment response? (For example, a	"Mayo score ≤ 2 Sustained remission for 12 months

reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement in Quality of life to near equal of healthy individuals Steroid free periods for ≥ 12 months" - SCCAI score reduction of 2 or more
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, - will be useful to have another oral option available, especially if better tolerated than Tofacitinib and with less monitoring
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	PO/PR 5 ASA, steroids, immunomodulators, biologics (anti-TNF infliximab/adalimumab/golimumab), vedolizumab, ustekinumab, Tofacitinib, dietary interventions unlikely to be effective, surgery
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE: TA163 acute UC, TA329 maintenance UC NICE: TA329 acute and maintenance of UC NICE TA329 acute and maintenance of UC NICE: TA342 UC NICE: TA456 UC NICE: TA547 UC British Society of Gastroenterology https://www.bsg.org.uk , Management of IBD guideline ECCO Ulcerative Colitis (UC) Consensus Update (2017) – Part 1 & 2

• 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.)	Certainly variation, especially since COVID-19 pandemic - Definitions of what a patient may or may not tolerate vary (ie now a reluctance to use infliximab + immunosuppressant for any patient due to infection risk) - Choice of first line biologics may vary nationally - Locally defined treatment pathways - commissioners /secondary care - Interpretation of NICE guidance varies by commissioners resulting in variability of access in England
• What impact would the technology have on the current pathway of care?	Alternative to injectable biologics and Tofacitinib Higher Patient acceptability as oral Alternative mode of action if other treatment targets fail Less chance of immunogenicity developing Short half life
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	The costs would be similar to therapies currently in use

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics - under the supervision of specialist gastroenterologist with interest in IBD
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Staff Education Homecare contracts management Monitoring clinics for outcomes and adverse effects
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes and higher patient acceptability Rapid onset of action, may be used instead of steroid in acute management of UC, less side effects than tofacitinib
• Do you expect the technology to increase length of life more than current care?	Potentially yes as low immunogenicity, but longterm effectiveness needs to be evaluated
• Do you expect the technology to increase health-related quality of life more than current care?	Potentially yes; delay need for surgery, increased steroid free periods and quality of life improvement Replacing steroids in management of acute flares

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	"Appropriate: Needle phobic *Failed/intolerant to other biologics* *Less appropriate:* Compliance concerns" - Less appropriate for patients with certain comorbidities (DVT risk) and potential for pharmacokinetic interactions
The use of the technology	
13. 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	Higher patient acceptability Easier to use lower hospital resource requirements (oral vs injections), less nursing time required

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Expect as per TA approval criteria for other biologics and small molecules
15. 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?	Potentially: no need to attend infusion clinics (time) higher acceptability of treatment lower psychological barriers to treatment
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	Yes

benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	No
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Patients will have to undergo pre-treatment screening Monitoring of lipid profiles and cardiovascular risk – many need additional clinics and follow ups (time and blood sample extraction)
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• If not, how could the results be extrapolated to the UK setting?	Yes
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

20. How do data on real-world experience compare with the trial data?	Unsure
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Another oral small molecule therapy
- Hope it will be better tolerated than Tofacitinib
- Concerns about pregnancy and family planning
- Additional monitoring required for adverse side effects

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Erasmus School of Health Policy & Management

Maastricht University

Filgotinib for moderately to severely active ulcerative colitis [ID3736]

Produced by Kleijnen Systematic Reviews (KSR) Ltd, United Kingdom (UK) in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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None.

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink 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 Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Nigel Armstrong acted as project lead and health economist on this assessment, critiqued the clinical effectiveness methods and evidence, the company's economic model 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. Thea van Asselt, Merel Kimman, Andrea Peeters, Tim Govers, and Charlotte Ahmadu acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Jeremy Howick, Kevin McDermott and Rob Riemsma acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Shelley de Kock and Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore critiqued the company's economic evaluation, contributed to the writing of the report, and provided general health economic 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

2L	Second-line
3L	Third-line
5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
ACG	American College of Gastroenterology
ADA	Adalimumab
AE	Adverse event
AIFA	Agenzia Italiana del Farmaco
AWMSG	All Wales Medicines Strategy Group
bid	Twice daily
CCA	Cochrane Clinical Answers
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CrCl	Creatinine clearance
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CRP	C-reactive protein
CS	Company submission
DARE	Database of Abstracts of Reviews of Effects
DIC	Deviance information criterion
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EBS	Endoscopy/bleeding/stool frequency
ECCO	European Crohn's and Colitis Organisation
EED	Economic Evaluation Database
EMA	European Medicines Agency
EQ-5D	EuroQoL-5 Dimensions Health Survey
EQ-5D-3L	EuroQoL-5 Dimensions-3 Levels Health Survey
EQ-5D-5L	EuroQoL-5 Dimensions-5 Levels Health Survey
ERG	Evidence Review Group
EU	European Union
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FE	Fixing errors
FIL	Filgotinib
FV	Fixing violations
FWER	Family-wise type I error rate
GOL	Golimumab
HAS	Haute Autorité de Santé
HRQoL	Health-related quality of life
hs-CRP	High sensitivity C-reactive protein
HTA	Health technology assessment
IBDQ	Inflammatory Bowel Disease Questionnaire
ICER	Incremental cost effectiveness ratio
IFX	Infliximab
IM	Intramuscular
IQWiG	Institute for Quality and Efficiency in Healthcare
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IV	Intravenous

JAK	Janus kinase
KSR	Kleijnen Systematic Reviews
LOCF	Last observation carried forward
LS	Least square
LTE	Long-term extension
LYG	Life years gained
MCS	Mayo clinic score/Mental component summary
MECIR	Methodological Expectations of Cochrane Intervention Reviews
MIMS	Monthly Index of Medical Specialties
MJ	Matters of judgement
MTX	Methotrexate
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
NMB	Net monetary benefit
NRI	Non-responder's imputation
PAS	Patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PBO	Placebo
PCS	Physical component summary
PGA	Physician's Global Assessment
PICOS	Population, intervention, comparator, outcomes and study design
PK	Pharmacokinetics
PP	Per-protocol
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSA	Probability sensitivity analysis
PSDW	Protocol specified disease worsening
PSS	Personal Social Services
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
Q8W	Once every 8 weeks
Q12W	Once every 12 weeks
QALY	Quality-adjusted life year
QD	Once daily
RB	Rectal bleeding
RCT	Randomised controlled trial
SAP	Statistical analysis plan
SAS	Safety analysis set
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF	Stool frequency
SF-36	Short form-36 items
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SW	South-Western
TA	Technology appraisal
TB	Tuberculosis
TNF	Tumour necrosis factor
TOF	Tofacitinib
TTP	Time to progression
UC	Ulcerative colitis

UEG	United European Gastroenterology
UK	United Kingdom
UMC+	University Medical Center+
US	United States
UST	Ustekinumab
VAS	Visual analogue scale
VDZ	Vedolizumab
WPAI	Work Productivity and Activity Impairment
WTP	Willingness-to-pay

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. If possible, it also includes the ERG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem. Sections 1.4 and 1.5 discuss issues related to the clinical effectiveness and cost effectiveness, respectively. Other key issues are discussed in Section 1.6 while a summary is presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main ERG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1: Summary of key issues

#	Summary of issue	Report Section
1	Potential lack of clarity in the precise line of therapy where filgotinib would be indicated	2.1
2	Lack of data and analyses for the 100 mg dose	2.1
3	Lack of evidence of effectiveness of a sequence of biologics	3.2
4	Questionable validity of the maintenance phase NMA	3.4, 3.5
5	Conventional care not appropriate as comparator	4.2.4
6	Inclusion of and uncertainty about appropriate treatment sequences	4.2.4
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10	Probability of pouchitis not aligned with utility	4.2.6
11	Uncertainty about HRQoL impact	4.2.8
12	Use of baseline utility values likely inappropriate	4.2.9
13	Application of dose escalation in model questionable	4.2.9
14	Fully incremental results not provided in the model	5.1

HRQoL = health-related quality of life; NMA = network meta-analysis

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival (OS)) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Difference in percentage of patients with response (with and without remission) impacting quality of life
- Difference in percentage of patients with response (with and without remission) resulting in a different proportion of patients who end up with surgery impacting both mortality and quality of life
- Difference in adverse events (AEs) (serious infections) of treatment impacting quality of life

Overall, the technology is modelled to affect costs by:

- Difference in costs of medication
- Difference in percentage of patients with response (with and without remission)
- Difference in percentage of patients with response (with and without remission resulting) in a different proportion of patients with last-line conventional therapy
- Difference in percentage of patients with response (with and without remission resulting) in a different proportion of patients who end up with surgery

The modelling assumptions that have the greatest effect on the ICER are:

- Assumptions about long-term effectiveness
- Assumptions about utility estimates used in the model
- Assumptions about dose escalation

1.3 The decision problem: summary of the ERG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there is a potential lack of clarity in the precise line of therapy where filgotinib would be indicated and, given the lack of analyses for the 100 mg dose of filgotinib, there is a question as to whether patients with moderate or severe renal impairment should be included.

Table 1.2: Key issue 1. Potential lack of clarity in the precise line of therapy where filgotinib would be indicated

Report Section	**2.1**
Description of issue and why the ERG has identified it as important	The company clarified that filgotinib could be included at any line in the biologic experienced population. However, the biologic experienced NMA and CEA were line agnostic. Also, dose escalation was applied to some comparators even though dose escalation was not recommended in the SmPCs or the NICE guideline NG130 for ulcerative colitis. The company did, however, suggest that 'second-line advanced' therapy, which the ERG interpret as first-line in the biologic experienced (2L), was the most relevant population.
What alternative approach has the ERG suggested?	Given the lack of specification of later line of therapy in the trial data and in accordance with the company suggestion, the Decision Problem could be restricted to 2L in the biologic experienced. Otherwise, treatment sequences that include other biologics following filgotinib could be included in the CEA. Also, if 3L is included then dose escalation should probably not be applied to any comparators in the base case.

Report Section	2.1
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	A decision as to which are the relevant lines of therapy and the CEA amended accordingly.
2L = second-line; 3L = third-line; CEA = cost effectiveness analysis; ERG = Evidence Review Group; NMA = network meta-analysis	

Table 1.3: Key issue 2. Lack of data and analyses for the 100 mg dose

Report Section	2.1
Description of issue and why the ERG has identified it as important	The company did not present any CEA for the 100 mg dose of filgotinib or patients with moderate or severe renal impairment where 100 mg is recommended.
What alternative approach has the ERG suggested?	Restrict decision problem to 200 mg dose and exclude patients with moderate or severe renal impairment.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	If the 100 mg dose is retained in the decision problem, both, NMA and CEA, in those patients with moderate or severe renal impairment would be warranted.
CEA = cost effectiveness analysis; ERG = Evidence Review Group; NMA = network meta-analysis	

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Table 1.4: Key issue 3. Lack of evidence of effectiveness of a sequence of biologics

Report Section	3.2
Description of issue and why the ERG has identified it as important	Re-randomisation precludes an unbiased estimate of the long-term effectiveness of a treatment sequence.
What alternative approach has the ERG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	An analysis of the effectiveness of biologic therapy at 3L (second-line biologic) would be helpful. Ideally, this would be based on an RCT, but observational data appropriately adjusted for confounding might also be valuable.
3L = third-line; ERG = Evidence Review Group; RCT = randomised controlled trial	

Table 1.5: Key issue 4. Questionable validity of the maintenance phase NMA

Report Section	3.4, 3.5
Description of issue and why the ERG has identified it as important	The maintenance phase NMA implies that all treatments are comparators in this phase when actually the only valid comparator, according to expected clinical practice, is no treatment or the curtailment of the intervention on which

Report Section	3.4, 3.5
	induction was achieved. The NMA could also be considered to have questionable validity in terms of heterogeneity. This is because the population on entry to the maintenance phase is those patients who have responded on the induction treatment (e.g., in SELECTION, n=297 out of 507 patients on filgotinib 200 mg in the induction phase), which, of course, varies between trials of different treatments.
What alternative approach has the ERG suggested?	The ERG calculated values for 50-week probabilities of no response, response (no remission) and remission conditional on response at 10-weeks to replace the values from the maintenance phase NMA based on the individual RCT values at the end of the maintenance period.
What is the expected effect on the cost effectiveness estimates?	Filgotinib also dominates infliximab and tofacitinib with the change towards individual trial data, as opposed to only golimumab and adalimumab with the NMA results.
What additional evidence or analyses might help to resolve this key issue?	The ERG has no further suggestions.
ERG = Evidence Review Group; n = number; NMA = network meta-analysis; RCT = randomised controlled trial	

1.5 The cost effectiveness evidence: summary of the ERG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the ERG's summary and detailed critique are in Section 4, and the ERG's amendments to the company's model and results are presented in Section 6. The main ERG results are reproduced using confidential Patient Access Schemes (PASs) in a confidential Appendix. The key issues in the cost effectiveness evidence are discussed in Tables 1.6 to 1.15.

Table 1.6: Key issue 5. Conventional care not appropriate as comparator

Report Section	4.2.4
Description of issue and why the ERG has identified it as important	Conventional care cannot be a comparator based on the NICE treatment pathway.
What alternative approach has the ERG suggested?	Exclude conventional care as comparator.
What is the expected effect on the cost effectiveness estimates?	Filgotinib continues to be compared with the other appropriate comparators – no effect on cost effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	None required.
ERG = Evidence Review Group; NICE = National Institute for Health and Care Excellence	

Table 1.7: Key issue 6. Inclusion of and uncertainty about appropriate treatment sequences

Report Section	4.2.4
Description of issue and why the ERG has identified it as important	Originally, treatment sequences were only included in scenarios. This does not reflect clinical practice. The company did update their base-case to include treatment sequences informed by expert opinion. There is uncertainty about the most appropriate treatment sequences.
What alternative approach has the ERG suggested?	Include treatment sequence in base-case and explore in scenarios.
What is the expected effect on the cost effectiveness estimates?	Depends on comparison.
What additional evidence or analyses might help to resolve this key issue?	Potentially, if available, further scenarios informed by expert opinion.
ERG = Evidence Review Group	

Table 1.8: Key issue 7. Third-line population not modelled

Report Section	4.2.4
Description of issue and why the ERG has identified it as important	The company did not provide analyses of filgotinib vs. its comparators in the third-line (i.e., 3L biologic-experienced population).
What alternative approach has the ERG suggested?	Provide a scenario in this line using effectiveness estimates for the overall population.
What is the expected effect on the cost effectiveness estimates?	Depends on comparison.
What additional evidence or analyses might help to resolve this key issue?	As above.
3L = third-line; ERG = Evidence Review Group; vs. = versus	

Table 1.9: Key issue 8. Loss of response likely differential for response without remission and remission health states

Report Section	4.2.6
Description of issue and why the ERG has identified it as important	Loss of response is assumed to be equal for those in remission and those in only response (without remission), implying that if at the end of the maintenance phase there are fewer patients in remission than in response, this cannot turn around anymore. The ERG questions the clinical plausibility of this assumption. Remission may be more difficult to attain than response, but once in remission, patients may be more stable, and stay in remission longer before they lose response than patients in response without remission. Unfortunately, the model does not allow for this to happen, nor did the company provide means to explore the impact of this assumption via a scenario.
What alternative approach has the ERG suggested?	Estimate of loss of response per health state. The model needs structural adjustments.

Report Section	4.2.6
What is the expected effect on the cost effectiveness estimates?	Unclear, but the impact may be substantial.
What additional evidence or analyses might help to resolve this key issue?	Data or expert opinion to inform (long-term) transition probabilities to active UC stratified for those in response (but no remission) and those in remission.
ERG = Evidence Review Group; UC = ulcerative colitis	

Table 1.10: Key issue 9. Assumption of constant loss of response not likely to hold

Report Section	4.2.6
Description of issue and why the ERG has identified it as important	Loss of response rates are assumed to be constant over lifetime based on the proportion of non-responders at the end of the maintenance phase. In reality, loss of response will probably decrease over time, but there is no evidence to say exactly how (as stated by the company and confirmed by the ERG's clinical expert), and whether the rate of decrease would be similar between treatments.
What alternative approach has the ERG suggested?	The ERG included the company's scenario of 25% reduction in loss of response rate after the first year of maintenance as a scenario in the ERG analyses as well. This does however not address uncertainty as to the true reduction and potential differences between treatments.
What is the expected effect on the cost effectiveness estimates?	The scenario has mixed effects on NMB for the various comparators, because loss of response impacts both treatment duration and effectiveness (distribution over health states).
What additional evidence or analyses might help to resolve this key issue?	Evidence on treatment-specific long-term loss of response, or expert opinion on loss of response over time.
ERG = Evidence Review Group; NMB = net monetary benefit	

Table 1.11: Key issue 10. Probability of pouchitis not aligned with utility

Report Section	4.2.6
Description of issue and why the ERG has identified it as important	The probability of pouchitis used in the model was related to incidence of all pouchitis events, but the utility related to chronic pouchitis. Given that chronic pouchitis has a greater impact on HRQoL, the probability of chronic pouchitis is likely more appropriate.
What alternative approach has the ERG suggested?	Use probability of chronic pouchitis.
What is the expected effect on the cost effectiveness estimates?	The change will favour treatments with higher number of patients in the active UC state.
What additional evidence or analyses might help to resolve this key issue?	None.
ERG = Evidence Review Group; HRQoL = health-related quality of life; UC = ulcerative colitis	

Table 1.12: Key issue 11. Uncertainty about health-related quality of life impact

Report Section	4.2.8
Description of issue and why the ERG has identified it as important	The ERG believes that there is considerable uncertainty about the most appropriate utility estimates to be used in the model. Using biologic-naïve and biologic-experienced values for the respective models is likely to lead to more reliable results. Moreover, the impact of including utilities using the 10- and 26-weeks EQ-5D SELECTION trial data, and differential utilities for the induction and maintenance phase is unknown.
What alternative approach has the ERG suggested?	The ERG prefers the use of biologic-naïve and biologic-experienced specific values and the 10-weeks data for the active UC health state in the base-case analysis. Additionally, a scenario analysis using the 26-weeks data for the response without remission and remission states should be conducted. Another scenario analysis should explore the impact of using differential utilities for the induction and maintenance phase.
What is the expected effect on the cost effectiveness estimates?	It is unknown how the ICER is affected by these changes.
What additional evidence or analyses might help to resolve this key issue?	• An analysis using biologic-naïve and biologic-experienced specific utility values applied to the new base-case analysis where 10-weeks data are used for all pre-surgery health states. • An analysis using the 26-weeks data for the pre-surgery health states 'response without remission' and 'remission' (and 10-weeks value for active UC/non-responder). • An analysis using differential utilities for the induction and maintenance phase.
EQ-5D = EuroQoL-5 Dimensions Health Survey; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; UC = ulcerative colitis	

Table 1.13: Key issue 12. Use of baseline utility values likely inappropriate

Report Section	4.2.9
Description of issue and why the ERG has identified it as important	Baseline utility values for the active UC states are likely biased as they include non-responders and responders and do not include any improvement from treatment.
What alternative approach has the ERG suggested?	Use 10-week active UC utility values.
What is the expected effect on the cost effectiveness estimates?	Use of 10-week active UC utility value improves QALYs for all active treatment comparators.
What additional evidence or analyses might help to resolve this key issue?	Utility data that are appropriate for the actual 'active UC' health state.
ERG = Evidence Review Group; QALY = quality-adjusted life year; UC = ulcerative colitis	

Table 1.14: Key issue 13. Application of dose escalation in model questionable

Report Section	4.2.9
Description of issue and why the ERG has identified it as important	Dose escalation was applied to most comparators but not to filgotinib without adequate justification for why this was the case. However, the FAC made it clear that the justification was the stipulations of the various summary of product characteristics (SmPCs).
What alternative approach has the ERG suggested?	The ERG had disabled dose escalation for all treatments in the ERG base case, but in the light of the justification provided in the FAC, this has now been amended to include dose escalation per CS.
What is the expected effect on the cost effectiveness estimates?	Disabling dose escalation reduces the costs of all comparators.
What additional evidence or analyses might help to resolve this key issue?	Evidence as to the use of dose escalation in NHS clinical practice and, in particular, at the line prior to surgery.
ERG = Evidence Review Group	

Table 1.15: Key issue 14. Fully incremental results not provided in the model

Report Section	5.1
Description of issue and why the ERG has identified it as important	The company's model does not enable the generation of fully incremental results.
What alternative approach has the ERG suggested?	Update the model file to enable generating fully incremental results.
What is the expected effect on the cost effectiveness estimates?	Not applicable.
What additional evidence or analyses might help to resolve this key issue?	As above.
ERG = Evidence Review Group	

1.6 Other key issues: summary of the ERG's view

There are no other key issues.

1.7 Summary of the ERG's view

Table 1.16: Biologic-naive base-case (deterministic)

Technologies	NMB (threshold £20,000 / QALY)	Incremental QALYs FIL vs. X	Incremental costs (£) FIL vs. X	ICER (£/QALY) pairwise FIL vs. X	ICER (£/QALY) fully incremental
Company base-case (biologic-naïve), without conventional care, with company's treatment sequences					
Filgotinib	£115,860	0.000	£0	0	
Golimumab	£103,804	0.056	-£10,931	FIL dominates	Dominated
Tofacitinib	£105,216	-0.033	-£11,298	345,631 SW	345,631
Adalimumab	£103,314	0.059	-£11,361	FIL dominates	Dominated
Infliximab	£100,385	-0.012	-£15,722	1,273,598 SW	Dominated
Vedolizumab SC	£101,019	-0.210	-£19,040	90,695 SW	43,683
Vedolizumab IV	£96,228	-0.179	-£23,220	129,463 SW	Dominated
ERG change 1: Do not use NMA results for maintenance					
Filgotinib	£114,280	0.000	£0	0	
Tofacitinib	£102,135	0.109	-£9,964	FIL dominates	Dominated
Golimumab	£99,118	0.021	-£14,750	FIL dominates	Dominated
Adalimumab	£98,782	0.024	-£15,008	FIL dominates	Dominated
Infliximab	£96,761	0.002	-£17,472	FIL dominates	Dominated
Vedolizumab SC	£98,154	-0.076	-£17,648	231,845 SW	231,845
Vedolizumab IV	£90,376	-0.149	-£26,894	179,898 SW	126,007
ERG change 2: Use of 10-week active UC utilities					
Filgotinib	£129,555	0.000	£0	0	
Golimumab	£117,684	0.047	-£10,931	FIL dominates	Dominated
Tofacitinib	£118,796	-0.027	-£11,298	419,503 SW	419,503
Adalimumab	£117,207	0.049	-£11,361	FIL dominates	Dominated
Infliximab	£114,022	-0.009	-£15,722	1,667,830 SW	Dominated

Technologies	NMB (threshold £20,000 / QALY)	Incremental QALYs FIL vs. X	Incremental costs (£) FIL vs. X	ICER (£/QALY) pairwise FIL vs. X	ICER (£/QALY) fully incremental
Vedolizumab SC	£113,967	-0.173	-£19,040	110,306 SW	53,148
Vedolizumab IV	£109,282	-0.147	-£23,220	157,601 SW	Dominated
ERG change 3: Use probability of chronic pouchitis					
Filgotinib	£121,132	0.000	£0	0	
Golimumab	£109,166	0.055	-£10,873	FIL dominates	Dominated
Adalimumab	£108,683	0.058	-£11,298	FIL dominates	Dominated
Tofacitinib	£110,431	-0.032	-£11,334	357,798 SW	357,798
Infliximab	£105,625	-0.012	-£15,742	1,336,681 SW	Dominated
Vedolizumab SC	£105,921	-0.203	-£19,279	94,782 SW	46,264
Vedolizumab IV	£101,181	-0.174	-£23,425	134,838 SW	Dominated
ERG base-case (ERG changes 1-3)					
Filgotinib	£132,606	0	0	0	
Tofacitinib	£121,054	0.086	-£9,839	FIL dominates	Dominated
Golimumab	£117,579	0.015	-£14,721	FIL dominates	Dominated
Adalimumab	£117,275	0.018	-£14,973	FIL dominates	Dominated
Infliximab	£115,137	0.000	-£17,462	FIL dominates	Dominated
Vedolizumab SC	£116,016	-0.058	-£17,749	306413 SW	306,413
Vedolizumab IV	£107,872	-0.117	-£27,072	231592 SW	158,099

ERG = Evidence Review Group; FIL = filgotinib; ICER = incremental cost effectiveness ratio; IV = intravenous; NMA = network meta-analysis; NMB = net monetary benefit; QALY = quality-adjusted life year; SC = subcutaneous; SW = South-Western; UC = ulcerative colitis

Table 1.17: Biologic-experienced base-case (deterministic)

Technologies	NMB (threshold £20,000 / QALY)	Incremental QALYs FIL vs. X	Incremental costs (£) FIL vs. X	ICER (£/QALY) pairwise FIL vs. X	ICER (£/QALY) fully incremental
Company base-case (biologic-experienced), without conventional care, with company's treatment sequences					
Filgotinib	£113,927	0.000	£0	0	

Technologies	NMB (threshold £20,000 / QALY)	Incremental QALYs FIL vs. X	Incremental costs (£) FIL vs. X	ICER (£/QALY) pairwise FIL vs. X	ICER (£/QALY) fully incremental
Adalimumab	£110,610	0.043	-£2,452	FIL dominates	Dominated
Tofacitinib	£109,527	0.010	-£4,191	FIL dominates	Dominated
Vedolizumab SC	£109,411	0.016	-£4,200	FIL dominates	Dominated
Ustekinumab	£108,259	0.029	-£5,085	FIL dominates	Dominated
Vedolizumab IV	£108,110	0.029	-£5,239	FIL dominates	Dominated
ERG change 1: Do not use NMA results for maintenance (vedolizumab SC based on biologic-naïve)					
Filgotinib	£113,789	0.000	£0	0	
Adalimumab	£108,473	0.100	-£3,326	FIL dominates	Dominated
Tofacitinib	£107,056	0.052	-£5,691	FIL dominates	Dominated
Vedolizumab SC	£106,999	0.015	-£6,488	FIL dominates	Dominated
Ustekinumab	£105,488	0.021	-£7,881	FIL dominates	Dominated
Vedolizumab IV	£105,202	0.021	-£8,157	FIL dominates	Dominated
ERG change 2: Use of 10-week active UC utilities					
Filgotinib	£128,023	0.000	£0	0	
Adalimumab	£124,869	0.035	-£2,452	FIL dominates	Dominated
Tofacitinib	£123,662	0.009	-£4,191	FIL dominates	Dominated
Vedolizumab SC	£123,567	0.013	-£4,200	FIL dominates	Dominated
Ustekinumab	£122,462	0.024	-£5,085	FIL dominates	Dominated
Vedolizumab IV	£122,312	0.024	-£5,239	FIL dominates	Dominated
ERG change 3: Use probability of chronic pouchitis					
Filgotinib	£119,309	0.000	£0	0	
Adalimumab	£116,074	0.042	-£2,400	FIL dominates	Dominated
Tofacitinib	£114,929	0.010	-£4,179	FIL dominates	Dominated
Vedolizumab SC	£114,823	0.015	-£4,181	FIL dominates	Dominated

Technologies	NMB (threshold £20,000 / QALY)	Incremental QALYs FIL vs. X	Incremental costs (£) FIL vs. X	ICER (£/QALY) pairwise FIL vs. X	ICER (£/QALY) fully incremental
Ustekinumab	£113,695	0.028	-£5,051	FIL dominates	Dominated
Vedolizumab IV	£113,545	0.028	-£5,205	FIL dominates	Dominated
ERG base-case (ERG changes 1-3)					
Filgotinib	£132,808	0	0	0	
Adalimumab	£128,027	0.078	-£3,211	FIL dominates	Dominated
Tofacitinib	£126,342	0.042	-£5,634	FIL dominates	Dominated
Ustekinumab	£126,081	0.013	-£6,474	FIL dominates	Dominated
Vedolizumab IV	£124,617	0.017	-£7,857	FIL dominates	Dominated
Vedolizumab SC	£124,332	0.017	-£8,133	FIL dominates	Dominated

ERG = Evidence Review Group; FIL = filgotinib; ICER = incremental cost effectiveness ratio; IV = intravenous; NMA = network meta-analysis; NMB = net monetary benefit; QALY = quality-adjusted life year; SC = subcutaneous; UC = ulcerative colitis

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG Comment
Population	People with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, loss of response or were intolerant to conventional therapy (oral corticosteroids and/or immunomodulators), or a biologic agent (TNF-alpha inhibitor or vedolizumab)	Aligned with NICE scope	NA	The population is in line with the NICE scope. However, there is an issued regarding the precise line of therapy.
Intervention	Filgotinib	Aligned with NICE scope	NA	The intervention is in line with the NICE scope.
Comparator(s)	• Conventional therapies, without biological treatments • TNF-alpha inhibitors (infliximab, adalimumab and golimumab) • Tofacitinib • Ustekinumab • Vedolizumab	Aligned with NICE scope	NA	The comparators are not in line with the NICE scope as 'conventional therapies, without biological treatments' were excluded from the NMAs. However, the ERG questions the relevance of conventional therapy.
Outcomes	The outcome measures to be considered include: • mortality • measures of disease activity • rates of and duration of response, relapse and remission • rates of hospitalisation • rates of surgical intervention	Aligned with final NICE scope (except where noted). • mortality	SELECTION (the pivotal trial in the filgotinib UC programme) does not provide data on filgotinib's effect on mortality due to UC. The remaining outcomes are included.	The outcomes reported are in line with the NICE scope.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG Comment
	• endoscopic healing • mucosal healing (combines endoscopic and histological healing) • corticosteroid-free remission • achieving mucosal healing • adverse effects of treatment • HRQoL			
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 PSS perspective.	Aligned with NICE scope	NA	Partly in line with NICE reference case, however, a fully incremental analysis is not enabled in the model file.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG Comment
	The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.			
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • people who have been previously treated with one or more biologics; • and people who have not received prior biologics therapy.	Aligned with NICE scope	NA	In line with the NICE scope, although there is some doubt as to the precise line of therapy in the biologic experienced subgroup.

Source: CS, Table 1, pages 12-14.[1]

CS = company submission; ERG = Evidence Review Group; HRQoL = health-related quality of life; NA = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; TNF = tumour necrosis factor; UC = ulcerative colitis

2.1 Population

The population defined in the scope is: People with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, loss of response or were intolerant to a previous biologic agent or conventional therapy.[2] In the company submission (CS), the population is the same, with the addition that previous conventional therapies or biologic agents are described as: 'conventional therapy (oral corticosteroids and/or immunomodulators), or a biologic agent (tumour necrosis factor (TNF)-alpha inhibitor or vedolizumab)'.[1]

A variation to the marketing authorisation for filgotinib in the treatment of adults with UC was validated by the European Medicines Agency (EMA) in November 2020 and the Medicines & Health products Regulatory Agency (MHRA) in January 2021. The anticipated date of regulatory approvals was reported in the CS to be between June and September 2021.[1] However, on 16 September, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation to include that, as stated in the CS, filgotinib is indicated for the treatment of adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent.[1]

Filgotinib is contraindicated for patients with: Hypersensitivity to the active substance or to any of the excipients; Active tuberculosis or active serious infections; and Pregnancy.[1]

ERG comment: In the clarification letter the ERG pointed out that Figure 1 in the CS shows that filgotinib can be positioned at more than one place in the biologic experienced population, specifically second-line (2L) or third-line (3L).[1] However, in the network meta-analyses (NMAs) and the cost effectiveness analysis (CEA) the biologic experienced subgroup is treated as a single population i.e. not subdivided by line. The Evidence Review Group (ERG) therefore asked the following questions:[3]

a. Precisely which lines of therapy do the company intend are included in the biologic experienced subgroup? Do they include 3L? Do they include lines later than 3L?

b. Please discuss the implications of this lack of discrimination between treatment lines in the biologic experienced subgroup in terms of potential differences in efficacy

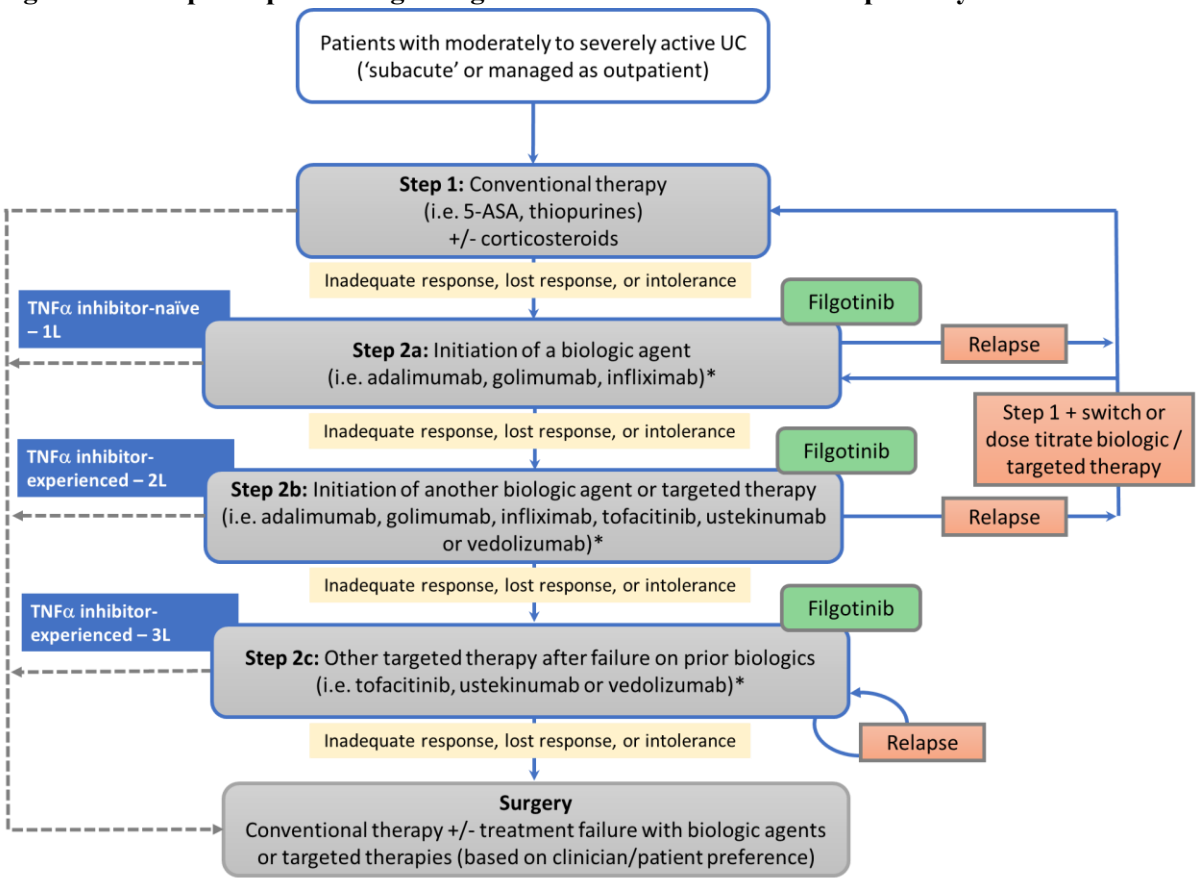
c. Please indicate if the results of the NMA and from the trials included for the biologic experienced subgroup are more applicable to one line than another

d. Given that lines later than 2L would imply the experience of biologics pre-filgotinib, if the company does intend that the biologic subgroup includes, could the cost effectiveness model be amended to remove those biologics already experiences from the sequence subsequent to filgotinib?

e. Does the company consider that the line immediately pre-surgery be included in the biologic subgroup? If so, then could the company amend the model accordingly and include the possibility of dose escalation for filgotinib?

Figure 1 from the response to the request for clarification has been reproduced below.[3]

Figure 2.1: Proposed positioning of filgotinib within NICE treatment pathway



Based on Figure 1 of the response to the request for clarification[3]

The company responded that filgotinib was indicated at any point from failure of first biologic through to immediately prior to surgery.

They also stated "heterogeneity of prior treatment was observed in the included trials of the company NMA; therefore, this was considered an important effect modifier in the current analysis, which led to separate NMAs for trials conducted in biologic experienced patients or biologic naïve patients". They also acknowledged that it is difficult to determine the direction of this impact on efficacy of treatment lines in the biologic-experienced. They also concluded that the most applicable line of therapy was 'second-line of advanced therapy' on the basis in the biologic experienced NMA two (ULTRA 2 and VARSITY) specified that patients be previously 'exposed' to biologics, OCTAVE 1 and 2 (tofacitinib) reported two different subgroup results: 'prior TNF exposure' and 'prior TNF failure' and the remaining studies included patients with biologic failure. The company also updated the CEA to include treatment sequences. However, following filgotinib only vedolizumab IV was permitted even though vedolizumab IV is also a comparator, which, if filgotinib was to be prescribed 3L would, rule vedolizumab IV out. Finally, the company stated that, even though filgotinib could be indicated immediately prior to surgery, dose escalation was not applicable. The place of filgotinib in the care pathway therefore remains a key issue.

2.2 Intervention

The intervention (filgotinib) is in line with the scope.

Filgotinib is orally administered, and the starting recommended dose is 200 mg once daily. Film-coated tablets are available in 100 mg or 200 mg strengths. A dose of 100 mg of filgotinib once daily is recommended for patients with moderate or severe renal impairment (Creatinine clearance (CrCl) 15 to <60 ml/min).[1]

According to the company, no additional tests or investigations are expected to be required; but patients taking filgotinib will be monitored in line with patients on other currently available Janus kinase (JAK) inhibitors and biologic therapies (CS, page 18).[1]

ERG comment: In the clarification letter the ERG asked if, given that the 100 mg dose of filgotinib is not considered in the CEA, would the company agree that the intervention in the decision problem be updated to 200 mg only.[3] Also, the company were asked, if the reason for not including 100 mg is *"this dosing is for a restrictive patient group with renal impairments (Table 2)"* (Section B.3.2.4), then should the population in the decision problem be amended to exclude those with renal impairments. The company responded that the decision problem should retain filgotinib 100 mg and 200 mg doses and that filgotinib 100 mg was not included in the economic analysis due to a paucity of data for both filgotinib and comparators in this subgroup of patients.[3] The lack of data and analyses for the 100 mg dose is therefore a key issue.

2.3 Comparators

The description of the comparators in the NICE scope is as follows: *"TNF-alpha inhibitors (infliximab, adalimumab and golimumab), Tofacitinib, Ustekinumab, Vedolizumab, and Conventional therapies (including aminosalicylates, oral corticosteroids and/or immunomodulators), without biological treatments"*.[2]

In the CS, the evidence for filgotinib is based on the SELECTION clinical programme of induction and maintenance trials; in which the safety and efficacy of filgotinib is compared to placebo in moderately to severely active UC patients.

Two NMAs were performed to inform the economic model for the assessment of the cost effectiveness of filgotinib relative to the other treatments in UC. The NMA for biologic-naïve patients (cohort A) included the following comparator treatments: adalimumab, golimumab, infliximab, tofacitinib, ustekinumab, vedolizumab (17 unique trials). This means that conventional therapies were not included as comparators in the NMA for biologic-naïve patients.

The NMA for biologic-experienced patients (cohort B) included the following comparator treatments: adalimumab, tofacitinib, ustekinumab, vedolizumab (nine unique trials). This means that conventional therapies, golimumab and infliximab were not included as comparators in the NMA for biologic-experienced patients.

ERG Comment: The company did not include any conventional therapies in either of the NMAs. In fact, it looks like these were not included in the searches either, as "studies only comparing conventional therapies including aminosalicylates and corticosteroids" were excluded (CS, Appendix D, Table 8).[4] However, given that the population is patients who have had an inadequate response, loss of response or were intolerant to conventional therapy it makes sense that conventional therapy for these patients would not be indicated. Indeed, as indicated in Figure 2.1 only biologics are indicated at this line of therapy. This is confirmed in the NICE pathways.[5]

2.4 Outcomes

The NICE final scope lists the following outcome measures:

- mortality
- measures of disease activity
- rates of and duration of response, relapse and remission
- rates of hospitalisation (including readmission)
- rates of surgical intervention
- endoscopic healing
- mucosal healing (combines endoscopic and histological healing)
- corticosteroid-free remission
- achieving mucosal healing
- adverse effects of treatment
- health-related quality of life (HRQoL)

These were all assessed in the SELECTION trial. However, the company does mention that *"SELECTION (the pivotal trial in the filgotinib UC programme) does not provide data on filgotinib's effect on mortality due to UC"* (CS, page 13).[1] Nevertheless, the CS does mention under AEs that *"two deaths occurred during the SELECTION maintenance study, both in the filgotinib 200mg treatment group"* (CS, page 111).[1]

For HRQoL, the company reported results for the Inflammatory Bowel Disease Questionnaire (IBDQ), the SF-36 (short form-36 items physical component summary (PCS) and mental component summary), and the EuroQoL-5 Dimensions Health Survey (EQ-5D) visual analogue scale (VAS).

2.5 Other relevant factors

According to the company, filgotinib is innovative because it *"is a second-generation JAK inhibitor that is a preferential and reversible inhibitor of JAK1"*.[1] *"Targeted inhibition of JAK1 could reduce inflammatory cytokine signalling involved in UC, whilst limiting impact on normal physiological function"*.[1] In addition, filgotinib is orally administered, and filgotinib can be administered with commonly used UC drugs without the need for dose adjustments (CS, Section B.2.12).[1]

The list price of filgotinib is £863.10 per bottle of 30,200 mg tablets, which is equivalent to £10,508.24 per year. A Patient Access Scheme (PAS) has been proposed for filgotinib where the proposed with-PAS price is £[redacted] per year for patients with moderately to severely active UC.[1]

This appraisal does not fulfil the end-of-life criteria as specified by NICE because the life expectancy of patients eligible for filgotinib is well beyond 24-months. Therefore, treatment is not indicated for patients with a short life expectancy (normally less than 24-months).

According to the company, *"no equality issues were identified in relation to filgotinib"* (CS, Section B.1.4).

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

3.1.1 Searches

Appendix D of the CS details a systematic literature review (SLR) conducted to identify randomised trials of existing interventions for the treatment and/or surgery of moderate to severe UC. Searches were conducted on 8 May 2019 and subsequently updated on 2 November 2020. As ustekinumab has been recently approved for use in moderate to severe UC, additional searches to identify trials data for ustekinumab were also undertaken on 2 November 2020. Reference lists were also searched for additional relevant studies. No searches were undertaken for AEs or non-randomised or non-controlled studies. Databases were searched from date of inception. A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review

	Resource	Host/Source	Date ranges	Dates searched
Electronic databases	Medline and Medline In-Process	PubMed	Inception - 2.11.20	8.5.19 2.11.20
	Embase	Embase		
	Cochrane Library CDSR CENTRAL CCA	Wiley		
	HTA DARE NHS-EED	CRD		
Conference proceedings	ACG Crohn's and Colitis UK ECCO British Society of Gastroenterology ISPOR	Internet	2016 - 2020	Not stated
Clinical trial registries	ClinicalTrials.gov	http://clinicaltrials.gov/	Not stated	Not stated
	International Clinical Trials Registry Platform	http://www.who.int/ictrp/en/		
	European Union's Clinical Trials Register	http://www.clinicaltralsregister.eu/		
	Klinische Prüfungen PharmNet.Bund	http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/		

ACG = American College of Gastroenterology; CCA = Cochrane Clinical Answers; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CRD = Centre for Reviews and Dissemination; DARE = Database of Abstracts of Reviews of Effects; ECCO = European Crohn's and Colitis

Organisation; EED = Economic Evaluation Database; HTA = Health Technology Assessment; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NHS = National Health Service

ERG comment:

- The CS provided sufficient details for the ERG to appraise the literature searches. A range of databases, conference proceedings and clinical trials registries were searched. Both the original, update and supplementary searches for ustekinumab were overall well-conducted and documented, making them transparent and reproducible. Reference checking was also undertaken.
- A range of thesaurus headings and free text terms were appropriately used for the population facet. However, thesaurus headings were not used for drug interventions in any of the database searches. The use of relevant thesaurus headings would have increased the retrieval of potentially relevant records.
- Study design filters to identify clinical trials were applied, but not referenced. In response to clarification, the company stated that 'The controlled trials study filter used in the review was a modified version of the Scottish Intercollegiate Guidelines Network (SIGN) filter for randomised controlled trials[6]'.[3]
- No searches were conducted to identify AEs or non-controlled or non-randomised evidence. Database searches also excluded observational, longitudinal, retrospective and prospective studies which would have helped identify both AEs and non-controlled and non-randomised evidence. In response to request for clarification, the company stated that *"the systematic literature review inclusion/exclusion criteria was limited to randomised controlled trials; therefore, the search strategy was designed to exclude non-randomised or non-controlled studies from the results. During the screening stages, studies describing a non-randomised trial design or where a randomisation step was not mentioned were considered as non-randomised by the reviewers. Non-controlled studies were identified by reviewers if a study described only one-treatment arm (i.e. there was no comparator for the intervention); comparators can include the same intervention with different doses"*, and that *"the most relevant adverse events were decided by clinical experts from the most common adverse events (> 2%) in the SELECTION trial and from adverse events of interest in treating UC recognised by clinicians"*.[3]. However, guidance by the Centre for Reviews and Dissemination (CRD)[7] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that AEs that are long-term, rare or unanticipated are not missed. The ERG considers that it was possible that some relevant safety data may not have been identified as a consequence of the study design limits applied to the database searches.
- A randomised controlled trial (RCT) filter was applied to searches of Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL) which are already pre-filtered databases, and therefore the use of a filter is considered overly restrictive. In response to request for clarification, the company stated that *"a methodological filter was used in the Cochrane Library search terms as the search terms were translated from the Embase and Medline, we recognise that such a filter may be redundant for this database; however, we believe it did not have a significant impact on the results"*.[3] However, this is against the explicit recommendation of MECIR (Methodological Expectations of Cochrane Intervention Reviews) Manual which states *"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"*.[8]
- An English language limit was applied to Embase searches and to PubMed searches although not to the PubMed search for ustekinumab. In response to clarification, the company stated that:

'It was decided that the systematic literature review was limited to English language for a number of reasons; due to the complexity of the disease area and the associated trial designs, it was considered that extracting data from translated publications may be more likely to introduce errors into the data. Additionally, including non-English language studies add to increase resource use and logistics of the review. Limiting searches to English language, has been shown not to introduce systematic bias.[9] However, we aimed to limit the impact of the English language limit by reviewing the International Clinical Trials Registry to identify any trial data from geographical regions where results are less likely to be published in English language journals. An English language limit was used in the tofacitinib NICE technology appraisal (TA547)[10] which the ERG considered to be appropriate for a submission to NICE.[3] To avoid language bias and to increase precision, the CRD guidance recommends that English language limits should not be applied at the searching stage.[7]

- The reference lists of relevant studies and recent reviews were searched for additional studies. In response to request for clarification, the company stated that *"relevant reviews were identified through free-text searches and included any studies identified via the systematic literature review searches. It was considered to be an appropriate approach as including reviews in the search strategy considerably increased the number of hits, adding additional complexity to the review process"*.[3] The ERG feels that identification of systematic reviews would have been more successful if the CDSR results had not been limited by an RCT filter.

3.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for randomised controlled trials (RCTs) and non-RCTs is presented in Table 3.2.

Table 3.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

	Inclusion Criteria	Exclusion criteria
Population	Adult (≥18 years of age) patients with moderately to severely active ulcerative colitis in adults when conventional therapy cannot be tolerated or the disease has responded inadequately or lost response to conventional§ (biologic-naïve) or biologic (biologic experienced/failed) treatment*.	• Juvenile or paediatric ulcerative colitis • Presence of Crohn's disease, indeterminate colitis, ischemic colitis, fulminant colitis, ulcerative proctitis, or toxic mega-colon • Patients with mild UC; 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 UC • Patients without UC
Interventions	• Biologic drugs, including: ○ Adalimumab (Humira, Trudexa, ABP 501, BI695501, CHS-1420, GP2017, M923, PF-06410293) ○ Apremilast (Otezla) ○ Golimumab (Simponi) ○ Infliximab (Remicade) ○ Ustekinumab (Stelara) ○ Vedolizumab (Entyvio) • Biosimilars, including:	• Studies that do not have an intervention of interest in more than 1 arm • Non-pharmacological studies, e.g., exercise, Chinese medicine, etc. • Studies only comparing conventional therapies including aminosalicylates and corticosteroids

	Inclusion Criteria	Exclusion criteria
	○Adalimumab biosimilars (Amjevita/ABP-501; Cyltezo/BI 695501; SB5) ○Infliximab biosimilars (Remsima; Inflectra; Flixabi; Renflexis/SB2, CT-P13; PF-06438179; PF-06438179; ABP501) • Targeted synthetic drugs including: ○Baricitinib (Oluminant) ○Tofacitinib (Xeljanz) ○Filgotinib (GLPG0634, GS-6034) ○Peficitinib (ASP015K) ○Upadaacitinib (ABT-494) ○PF-06651600 ○PF-06700841 ○TD-1473 • Surgical procedures for managing moderate to severe ulcerative colitis	
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	†To be included in the review, a study must report at least 1 of the following outcomes of interest: †Efficacy measurements: • Mayo Clinic Score (MCS). • Partial Mayo Score • Ulcerative colitis symptom score. • Clinical response • Histologic remission • Clinical Remission • Corticosteroid-free remission • Endoscopic/Mucosal healing Surgery †Safety outcomes reported at study endpoint: • Overall rate of AEs • Overall rate of serious AEs • Discontinuations due to adverse events • Lack of efficacy • AEs Individual AEs, such as the following:	Outcomes of interest not reported

	Inclusion Criteria	Exclusion criteria
	• Arthralgia • Infections, including herpes zoster • Nasopharyngitis • Intestinal perforation • Death • Initial or prolonged inpatient hospitalisation	
Study design	• Randomised, controlled, prospective clinical trials (above phase 1) o RCTs in which patients are re-randomised at the end of induction o RCTs in which patients are stay in their randomised groups at the end of induction (treat-through) • Long-term follow-up studies (e.g., open-label follow-up studies with continuation of treatments in their respective randomised group) • Post hoc analyses of patient sub-groups of interest (biologic-naïve/biologic experienced/biologic failed)	Phase 1 studies Non-randomised clinical trials Single-arm studies Long-term follow-up or extension studies of RCTs of over 1 year (post maintenance phase data) Maintenance studies and step-down treatment studies Preclinical studies Prognostic studies Retrospective observational studies Prospective observational studies Case report Case series
Publication type	Peer-reviewed publications Clinical trial records Conference proceedings	Commentaries and letters (publication type) Pooled analyses Non-systematic reviews Systematic reviews (including meta-analyses)† Consensus reports
Language restrictions	English language only	Studies published in languages other than English
Date restrictions	None	None

Based on CS, Appendix D, Table 8, pages 14-16[1]

†) Systematic reviews and meta-analyses were used for identification of primary studies that may have been missed in the electronic searches; §) Conventional therapy is considered to include topical or oral aminosalicylate, corticosteroids, mercaptopurine, azathioprine or prednisolone; *) Disease severity is defined according to the Truelove and Witts' severity index in line with NICE clinical guidance. Moderate to severely active ulcerative colitis: total Mayo score of 6 to 12.

AE = adverse event; CS = company submission; NICE = National Institute for Health and Care Excellence; RCT = randomised controlled trial; TTP = time to progression; UC = ulcerative colitis; VAS = visual analogue scale

ERG comment: The ERG considers that excluding non-English language studies is not appropriate for obtaining evidence of the comparative effectiveness of filgotinib vs. the comparators in the scope.

3.1.3 Critique of data extraction

The authors state on page 17 of CS, appendix D, that *"in line with good practice recommendations for SLRs, data was extracted by one reviewer and checked by a second reviewer to ensure comprehensiveness and accuracy"*.[4] It is not clear from the information provided whether this process was conducted independently. Furthermore, discrepancies between reviewers were resolved by consensus rather than by a third independent arbitrator. While this may be acceptable, it is noted that during screening, any discrepancies were resolved by a third independent arbitrator where consensus could not be reached (page 17 of CS, Appendix D, Section D.1.7).[4] This was not stated for the process of data extraction. This indicates that the process may not necessarily have been as systematic or consistent as was warranted and that certainly the process of data extraction does not seem to have had the same approach as that of screening and study selection. Table 9 (CS, appendix D, page 18) provides an overview of all variables that were obtained during data extraction and seems to include relevant and appropriate variables.

3.1.4 Quality assessment

The CS states that *"data from eligible studies was extracted and assessed for methodological quality and applicability"* (CS, page 36, Section B.2.1).[1] No further information could be identified and responding to a request for clarification, the company confirmed that *"each study that met criteria for inclusion was critically appraised by a single reviewer and reviewed by a second reviewer using the Cochrane Collaboration's tool for assessing the risk of bias in line with NICE requirements"*.[3]

3.1.5 Evidence synthesis

As there was only one trial available for filgotinib, the SELECTION trial, no meta-analysis was performed for filgotinib trials.

There were no trials identified comparing filgotinib vs. comparators other than placebo. Therefore, the company undertook a systematic literature review (SLR) and NMA which aimed to provide comparison of the efficacy of filgotinib with other comparators listed in the final NICE scope.[2] The company conducted two NMAs, one for the induction phase and one for the maintenance phase. These NMAs are discussed in Sections 3.3 and 3.4 of this report.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Details of the included trial: the SELECTION trial

The clinical effectiveness evidence presented in the CS is based on the SELECTION clinical programme of induction and maintenance trials informing the safety and efficacy of filgotinib in moderately to severely active UC patients. SELECTION is a phase 2b/3, randomised, double-blind, placebo-controlled trial comparing filgotinib 200 mg once daily, filgotinib 100 mg once daily and placebo during a 10-week induction study; followed by a maintenance study (weeks 10 to 58) in which the same interventions are compared to placebo after re-randomisation of those who responded to filgotinib during induction (see also Table 3.3).

Table 3.3: Clinical effectiveness evidence: SELECTION clinical programme

Study	SELECTION (NCT02914522)
Study design	Combined phase 2b/3, randomised, double-blind, placebo-controlled, parallel assignment trial

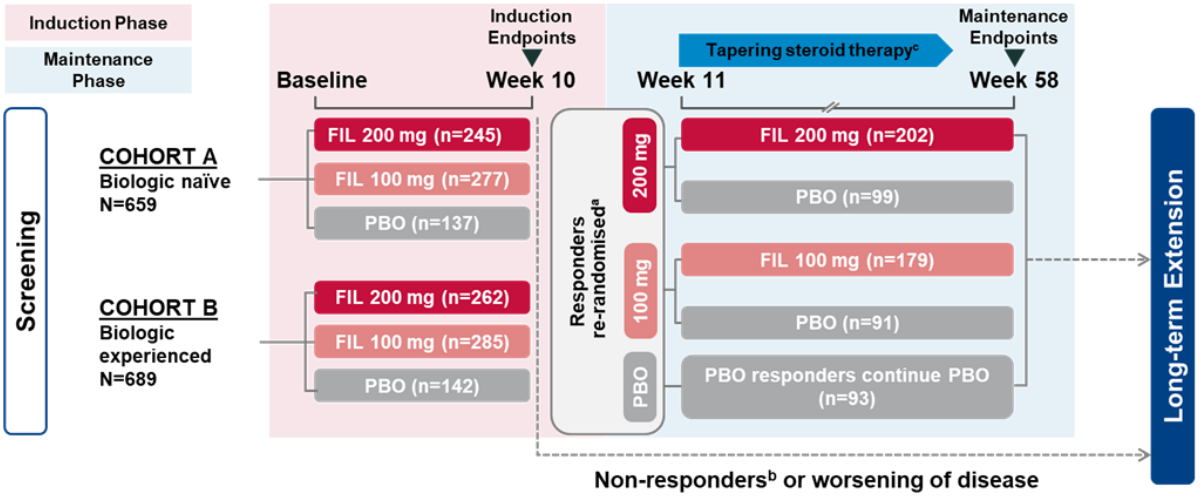
Population	Adults with moderately to severely active UC with previous inadequate response, loss of response, or intolerance to at least one of the following agents: • Corticosteroids • Immunomodulators • TNFα inhibitors • Vedolizumab
Intervention(s)	**Induction study (10 weeks):** • Filgotinib 200 mg once daily • Filgotinib 100 mg once daily People who had taken filgotinib in the induction studies who were eligible for the maintenance study were re-randomised. People receiving filgotinib 200 mg or 100 mg in the induction studies were randomised in a 2:1 manner to either continue on the assigned filgotinib regimen or to placebo for the duration of the maintenance study. **Maintenance study (weeks 10 to 58):** • Filgotinib 200 mg once daily • Filgotinib 100 mg once daily
Comparator(s)	**Induction study (10 weeks)** • Placebo-to-match filgotinib 200 mg once daily • Placebo-to-match filgotinib 100 mg once daily. **Maintenance study (weeks 10 to 58)** • Placebo-to-match filgotinib 200 mg once daily • Placebo-to-match filgotinib 100 mg once daily.
Background treatment	People entering either of the two induction studies may have been on a stable dose of the following: • Oral 5-aminosalicylate (5-ASA) compounds • Azathioprine • 6-mercaptopurine (6-MP) • MTX (dose must have been stable 4 weeks prior to randomisation through 10 weeks after randomisation) • Oral corticosteroid therapy (prednisolone prescribed at a stable dose ≤30 mg/day • Budesonide prescribed at a stable dose of ≤9 mg/day, prescribed dose must have been stable for 2 weeks prior to randomisation through 14 weeks after randomisation).
Reported outcomes specified in the decision problem	• Measures of disease activity (Mayo score) • Rates of duration of response, relapse and remission (Mayo score) • Mucosal healing (endoscopic sub score of 0 or 1) • Endoscopic healing • Corticosteroid-free remission • Adverse effects of treatment • Rates of hospitalisation and of surgical intervention due to ulcerative colitis • Health-related quality of life: IBDQ, SF-36, EQ-5D and WPAI.
Other outcomes	• PK plasma concentrations of filgotinib and its metabolite.

Based on CS, Table 7, pages 36-38.[1]
5-ASA = 5-aminosalicylate; 6-MP = 6-mercaptopurine; CS = company submission; EQ-5D = EuroQoL-5 Dimensions Health Survey; IBDQ = Inflammatory Bowel Disease Questionnaire; MTX = methotrexate; PK =

pharmacokinetics; SF36 = Short Form-36 items; TNF = tumour necrosis factor alpha inhibitors; UC = ulcerative colitis; WPAI = Work Productivity and Activity Impairment Questionnaire.

The SELECTION clinical programme was conducted under a single protocol but designed and analysed as three separate studies: two induction studies and a maintenance study. The population of the induction period was stratified by biologic-naïve (cohort A) and biologic-experienced (cohort B) patients, resulting in the two induction studies. The clinical programme's design is summarised in Figure 3.1 below.

Figure 3.1: Trial design of the SELECTION randomised clinical programme for patients with moderately to severely active UC



Based on CS, Figure 5, page 38.[1]

[a]Participants from Cohorts A and B who achieved either EBS remission or MCS response at Week 10, upon induction phase completion, were re-randomized upon entering the maintenance study at Week 11.

[b]Non-responders were those that did not achieve both EBS remission and MCS response at Week 10.

[c]Participants that enter maintenance phase and on concomitant steroids were required to begin tapering steroid therapy, starting at Week 14 of the study

CS = company submission; EBS = endoscopy/bleeding/stool frequency; FIL = filgotinib; MCS = Mayo clinic score; PBO = placebo; UC = ulcerative colitis

The primary objective of the two induction studies was to evaluate the efficacy of filgotinib as compared with placebo in establishing endoscopy/bleeding/stool frequency (EBS) remission at week 10. EBS is a composite measure of three variables: an endoscopic sub score of 0 or 1, rectal bleeding sub score of 0, and at least one point decrease in stool frequency from baseline to achieve a sub score of 0 or 1. The primary objective of the maintenance study was to evaluate the efficacy of filgotinib when compared to placebo in establishing EBS remission at week 58.

A summary of the methods used in the SELECTION clinical programme is provided in Table 3.4.

Table 3.4: Summary of SELECTION clinical programme methodology

Study	SELECTION (NCT02914522)
Trial design	SELECTION is a combined phase 2b/3, double-blind, randomised, placebo-controlled programme of trials evaluating the efficacy and safety of filgotinib 200 mg or 100 mg in the induction and maintenance of remission in people with moderately to severely active UC. Two induction studies (cohort A and B, N=650) were conducted. Enrolled patients could be males or nonpregnant, nonlactating females between 18 and 75 years of age (inclusive) with moderately to severely active UC.

Study	SELECTION (NCT02914522)
	Following screening (days −30 to −1), eligible people were randomised (day 1) and took part in the blinded induction studies (day 1 to week 11). People who were assigned to active treatment, completed the induction studies and achieved either EBS remission or MCS response at week 10 were re-randomised into the maintenance study at week 11 and took part in the blinded maintenance study (weeks 11 to 58). People were re-randomised into the maintenance study as follows: • People who received filgotinib 200 mg in the induction studies were re-randomised to receive filgotinib 200 mg or placebo • People who received filgotinib 100 mg in the induction studies were re-randomised to receive filgotinib 100 mg or placebo. People who received placebo in the induction studies and achieved either EBS remission or MCS response at week 10 continued to receive placebo in the maintenance study. People who did not achieve EBS remission or MCS response at week 10 had the option to enter a separate, SELECTION LTE study (NCT02914535). People who met disease worsening criteria in the maintenance study were discontinued from blinded treatment and had the option to receive open-label filgotinib in the LTE study. People who completed the week 58 visit had the option to continue study drug in a blinded fashion in the LTE study.
Eligibility criteria for participants	**General eligibility criteria for the induction studies (cohorts A & B):** Eligible people met all the following inclusion criteria for participation in the cohort A or cohort B induction studies: • Males or nonpregnant, nonlactating females, aged 18 to 75 years (inclusive) based on the date of the screening visit • Documented diagnosis of UC of at least 6 months and with a minimum disease extent of 15 cm from the anal verge • Moderately to severely active UC as determined by a centrally read endoscopy score ≥2, a rectal bleeding score ≥1, a stool frequency score ≥1, and Physician's Global Assessment of ≥2 as determined by the Mayo Clinic scoring system with endoscopy occurring during screening; total score between 6 and 12, inclusive • A surveillance colonoscopy was required prior to screening in people with a history of UC for 8 or more years, if one was not performed in the prior 24 months • Must not have had Crohn's disease, indeterminate colitis, ischemic colitis, fulminant colitis, isolated ulcerative proctitis, or toxic mega-colon • Must not have had active TB or history of latent TB that had not been treated. **Additional eligibility criteria for cohort A (biologic-naïve) Induction study:** • Previously demonstrated an inadequate clinical response, loss of response to, or intolerance to at least one of the following agents (depending on current country treatment recommendations/guidelines): o Corticosteroids: active disease despite a history of at least an induction regimen of a dose equivalent to oral prednisolone 30 mg daily for 2 weeks or intravenously (IV) for 1 week, or 2 failed attempts to taper steroids below a dose equivalent to 10 mg daily prednisolone, or a history of steroid intolerance

Study	SELECTION (NCT02914522)
	○ Immunomodulators: active disease despite a history of at least a 12-week regimen of oral azathioprine (≥2 mg/kg/day) or 6-MP (≥1 mg/kg/day), or MTX (25 mg subcutaneously [SC] or intramuscularly [IM] per week for induction and ≥15 mg IM per week for maintenance), or a history of intolerance to at least one immunomodulator. • No prior or current use of any TNFα inhibitor • No prior or current use of vedolizumab at any time. **Additional eligibility criteria for cohort B (biologic-experienced) Induction study:** • Previously demonstrated an inadequate clinical response, loss of response to, or intolerance of at least one of the following agents (depending on current country treatment recommendations/guidelines): ○ TNFα inhibitors: active disease despite a history of at least one induction regimen of a TNFα inhibitor: infliximab (minimum induction regimen of 5 mg/kg at 0, 2, and 6 weeks [in the EU, duration of treatment of 14 weeks]); adalimumab (8-week induction regimen consisting of 160 mg [four 40 mg injections in 1 day or two 40 mg injections per day for two consecutive days] on day 1, followed by a second dose two weeks later of 80 mg and a 40 mg dose two weeks later, followed by a 40 mg dose every other week until week 8); golimumab (minimum induction duration of six weeks [12 weeks in EU] including a 200 mg SC injection at week 0, followed by 100 mg at week 2, and then 100 mg every 4 weeks), or a recurrence of symptoms during maintenance therapy with any of these agents, or a history of intolerance to any TNFα inhibitors ○ Vedolizumab: active disease despite a history of at least a 14-week (ten weeks in EU) induction regimen consisting of 300 mg IV at weeks 0, 2, and 6, or a history of intolerance to vedolizumab. • Must not have used any TNFα inhibitor or vedolizumab ≤8 weeks prior to screening or any other biologic agent ≤8 weeks prior to screening or within five times the half-life of the biologic agent prior to screening, whichever was longer. **Main Eligibility Criteria for maintenance study:** People must have completed the cohort A or cohort B induction study with an MCS response or EBS remission based on week 10 assessments.
Settings and locations where the data were collected	This study was conducted at 341 study centres in 40 countries: Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Czech Republic, France, Germany, Greece, Hong Kong, Hungary, India, Ireland, Israel, Italy, Japan, Malaysia, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Republic of Georgia, Republic of Korea, Romania, Russian Federation, Serbia, Singapore, Slovakia, South Africa, Spain, Sweden, Switzerland, Taiwan, Ukraine, United Kingdom, and the United States.
Trial drugs	**Cohort A induction study:** Interventions: • Filgotinib 200 mg once daily (n=245) • Filgotinib 100 mg once daily (n=277). Comparator:

Study	SELECTION (NCT02914522)
	• Placebo once daily to match filgotinib 200 mg + placebo to match filgotinib 100 mg (n=137). **Cohort B induction study:** Interventions: • Filgotinib 200 mg once daily (n=262) • Filgotinib 100 mg once daily (n=285). Comparator: • Placebo once daily to match filgotinib 200 mg + placebo to match filgotinib 100 mg (n=142). **Maintenance study:** Interventions: Induction filgotinib 200 mg group: • Maintenance filgotinib 200 mg (n=202) Induction filgotinib 100 mg group: • Maintenance filgotinib 100 mg (n=179). Comparator: Induction filgotinib 200 mg group: • Maintenance placebo once daily (n=99) Induction filgotinib 100 mg group: • Maintenance placebo once daily (n=91) Induction placebo group: • Maintenance placebo once daily (n=93).
Permitted and disallowed concomitant medications	Provided that they are maintained at a stable dose for the noted time without dosing alteration or discontinuation, permitted concomitant medications for ulcerative colitis were: • Oral 5-ASA compounds provided the dose prescribed has been stable for at least 4 weeks prior to randomisation; dose must be stable for the first 10 weeks after randomisation • Azathioprine, 6-MP, or MTX provided the dose prescribed has been stable for 4 weeks prior to randomisation; dose must be stable for the first 10 weeks after randomisation • Oral corticosteroid therapy (prednisone prescribed at a stable dose ≤30 mg/day or budesonide prescribed at a stable dose of ≤9 mg/day) provided the dose prescribed has been stable for 2 weeks prior to randomisation; dose must be stable for the first 14 weeks after randomisation. Prohibited medications included anticonvulsants, antimycobacterials, corticosteroids, TNFα inhibitors, Integrin antagonists, Lymphocyte-depleting therapies.
Primary outcomes (including scoring methods and timings of assessments)	Induction study endpoints were assessed at week 10 and maintenance study endpoints were assessed at week 58. **Primary endpoint for induction and maintenance studies:** • Proportion of patients achieving EBS remission.

Study	SELECTION (NCT02914522)
Other outcomes used in the economic model/specified in the scope	Secondary endpoints: **Induction studies:** • Mayo Clinic Score remission • Mayo Clinic Score response • Mucosal healing • Endoscopic sub score of 0 • Histologic remission • Mayo Clinic Score remission (alternative definition). **Maintenance study:** • As above, plus o Sustained EBS remission o 6-month corticosteroid-free remission (components of Mayo Clinic Score).
Pre-planned subgroups	Four types of subgroup analyses were performed for the primary efficacy endpoints for each individual study (cohort A induction study, cohort B induction study, and maintenance study). • Stratification factors: o Concomitant use of systemic corticosteroids at baseline o Concomitant use of immunomodulators at baseline o Prior exposure to biologic agents approved for ulcerative colitis (cohort B only) o Participation in the cohort A induction study or the cohort B induction study (maintenance only) • History of biologic agent use: (cohort B induction study and maintenance study only) o Previous exposure to TNFα inhibitors o Prior failure of TNFα inhibitors o Previous exposure to vedolizumab o Prior failure of vedolizumab o Dual refractory (prior failure of TNFα inhibitors and vedolizumab). • Demographic factors: o Age at baseline o Sex at birth o Race o Geographic region. • Baseline disease characteristics: o hs-CRP at baseline o Faecal calprotectin at baseline o Duration of ulcerative colitis o Mayo clinic score at screening.

Based on CS, Table 8, pages 39-44.[1]
5-ASA = 5-aminosalicylate; 6-MP = 6-mercaptopurine; CRP = C-reactive protein; CS = company submission; EBS = endoscopy/bleeding/stool frequency; EU = European Union; IM = intramuscular; IV = intravenous;

Study	SELECTION (NCT02914522)
LTE = long-term extension; MCS = Mayo clinic score; MTX = methotrexate; TB = tuberculosis; TNF = tumour necrosis factor; UC = ulcerative colitis	

ERG comment: Although re-randomisation of responders to the intervention permits an assessment of outcomes at the end of the maintenance phase conditional on having achieve response, it does not inform the outcomes during the maintenance phase of those who did not achieve response. There is no unbiased estimate (based on randomised trial data) of filgotinib vs. placebo for the non-responders at the end of the maintenance phase because these patients were given the option to enter the long-term extension (LTE) where it is unclear how many patients were lost to follow-up or if they maintained the original treatment allocation.[1] Of course, if it is assumed that in clinical practice that patients will switch treatment on lack of response at induction then this might appear to be less of an issue. Although previous TAs indicate that discontinuation should occur on something resembling lack of response (TA342 recommends that 'benefit' should be observed and TA329 that 'clear evidence of response' be observed), no time limit is expressed either in terms of an induction period.[11, 12] Also, in the CEA, because follow-up of non-responders is limited to the end of induction, the effectiveness of subsequent treatments is assumed to be the same regardless of line of therapy in the biologic experienced. Therefore, re-randomisation precludes an unbiased estimate of the long-term effectiveness of a sequence of biologic therapies. For this reason, the ERG regard it as a key issue.

The ERG requested the number of UK centres and patients in the clarification letter and the company provided tables broken down by phase, cohort and arm.[3] However, it is clear that the numbers are very small: 30/1,348 and 32/1,235 (summed by the ERG) for induction and maintenance phases respectively.[3]

3.2.2 Statistical analyses of the SELECTION trial

The company describes three Analysis sets for the SELECTION trial: The full analysis set (FAS), the per-protocol (PP) Analysis Set, and the Safety Analysis Set (SAS). These are defined below.

3.2.2.1 Full analysis set

The FAS for each induction study included all randomised patients who took at least one dose of study drug in the corresponding induction study.

The FAS for the maintenance study included all patients randomised to either filgotinib 200 mg or filgotinib 100 mg treatment groups in the induction studies who achieved EBS remission or MCS response at week 10, were re-randomised, and took at least one dose of study drug in the maintenance study. The FASs were the primary analysis sets for the efficacy analyses.

3.2.2.2 Per-Protocol Analysis Set

The PP analysis set for each induction study included patients in the respective FAS who met the following criteria:

- Documented diagnosis of UC of at least 6 months with a minimum disease extent of 15 cm from the anal verge and moderately to severely active UC as described in the statistical analysis plan (SAP)
- Moderately to severely active UC as determined by a centrally read endoscopy score ≥2, a rectal bleeding (RB) score ≥1, a stool frequency (SF) score ≥1, and Physician's Global Assessment (PGA) of ≥2 as determined by the Mayo clinic scoring system with endoscopy occurring during screening; total score must have been between 6 and 12, inclusive

- On-treatment adherence of at least 80% for both study drugs (filgotinib and placebo-to-match) during the induction studies
- Had sufficient data to evaluate EBS remission at week 10 or met treatment failure criteria for week 10 EBS remission outcome
- For the Cohort A induction study, were never exposed to any biologics; for the Cohort B induction study, were exposed to at least 1 of the biologics.

The PP Analysis Set for the maintenance study included patients in the FAS who met the following criteria:

- Met the key eligibility criteria from the induction studies, as stated above
- On-treatment adherence of at least 80% for both study drugs (filgotinib and placebo-to-match) during the maintenance study
- Had sufficient data to evaluate EBS remission or met treatment failure criteria for EBS remission outcome at week 58 or discontinued study drug due to protocol-specified disease worsening criterion.

3.2.2.3 Safety Analysis Set

The Safety Analysis Set for each induction study included all patients who took at least one dose of study drug in the corresponding induction study.

The Safety Analysis Set for the maintenance study included all patients who took at least one dose of study drug in the maintenance study.

The Overall Safety Analysis Set for the study included all patients who took at least one dose of study drug in either of the induction studies or the maintenance study.

The Safety Analysis Sets were the primary analysis sets for safety analyses.

The statistical analysis methods and definitions of study groups used in the SELECTION clinical programme are described in below in Table 3.5.

Table 3.5: Summary of statistical analyses in SELECTION

	SELECTION (NCT02914522) induction studies	SELECTION (NCT02914522) maintenance study
Objective	To evaluate the efficacy of filgotinib as compared with placebo in establishing endoscopy/bleeding/stool frequency (EBS) remission at week 10	To evaluate the efficacy of filgotinib as compared with placebo in establishing EBS remission at week 58
Multiple Comparisons/Multiplicity	The graphical approach presented by Bretz 2009 to sequentially reject the null hypotheses in multiple test procedures was used to control a family-wise type I error rate (FWER) at 5% (i.e., α=0.05) for each individual study (cohort A induction study, cohort B induction study, and the maintenance study). This procedure strongly protects the FWER on all the primary and key secondary endpoints.	
Statistical analysis for primary endpoints	The primary analyses consisted of a superiority test of filgotinib 200 mg compared with placebo and filgotinib 100 mg compared with placebo based on the primary endpoint. For each induction study, a stratified Cochran-Mantel-Haenszel (CMH) test was used to compare the treatment effect between the filgotinib 200 mg group and placebo and between the filgotinib 100 mg group and placebo, separately. The CMH tests were stratified by concomitant use of oral, systemic corticosteroids at day 1, and concomitant use of immunomodulators at day 1 for the cohort A induction study, and were stratified by concomitant use of oral, systemic corticosteroids at day 1, concomitant use of immunomodulators at day 1, and exposure to biologic agents (≤1, >1) for the cohort B induction study. The stratified CMH chi-square P-value was provided for each of the above comparisons. Strata with low numbers of patients may have been aggregated for the CMH test. The two-sided 95% CI of EBS remission rate based on normal approximation method with a continuity correction was provided for each treatment group. In addition, non-	A CMH test was used to compare the treatment effect between filgotinib 200 mg and placebo and between filgotinib 100 mg and placebo. The CMH test was stratified by participation in cohort A or cohort B, concomitant use of oral, systemic corticosteroids at re-baseline, and concomitant use of immunomodulators at re-baseline. A CMH test with the same stratification factors was used to compare the treatment effect between filgotinib 100 mg and placebo among the patients from the cohort A and B induction studies combined being treated with filgotinib 100 mg. The stratified CMH chi-square P-value was provided for each of the above comparisons. Strata with low numbers of patients may have been aggregated for the CMH test. The two-sided 95% CI of EBS remission rate based on normal approximation method with a continuity correction was provided for each treatment group. In addition, non-stratified risk difference estimated along with its two-sided 95% CI using the normal approximation (i.e., the Wald method) with a continuity correction for the difference in proportions was

	SELECTION (NCT02914522) induction studies	SELECTION (NCT02914522) maintenance study
	stratified risk difference estimated along with its two-sided 95% CI using the normal approximation (i.e., the Wald method) with a continuity correction for the difference in proportions was provided. Stratification variables based on the electronic Case Report Form data were used for the analysis.	provided. Stratification variables based on the electronic Case Report Form data were used for the analysis.
Statistical analysis secondary endpoints	The same statistical method described for testing the primary efficacy endpoint was used for testing the key secondary efficacy endpoints.	
Sample size, power calculation	Sample size was chosen to ensure that a clinically meaningful difference in EBS remission rate at week 10 could be detected when comparing filgotinib with placebo within each induction study. A sample size of 130 patients in the placebo group and 260 patients in each filgotinib dose (200 mg or 100 mg) group (N=650 per cohort) provided 90% power for each filgotinib dose group comparison with placebo at a two-sided 0.025 significance level to detect a treatment difference in EBS remission rate of 15% (25% on filgotinib and 10% on placebo).	Assuming a response rate of 55% among patients receiving filgotinib 200 mg or 100 mg in the induction studies, approximately 285 patients from each filgotinib dose group from cohorts A and B combined would have been eligible to be re-randomised into the maintenance study. Sample size was chosen to ensure that a clinically meaningful difference in EBS remission rate at week 58 could be detected when comparing each filgotinib dose group with placebo in the maintenance study. A sample size of 95 patients in the placebo group and 190 patients in the filgotinib group at the same dose level as the induction dose provided more than 85% power for each filgotinib dose group comparison with placebo at a two-sided 0.025 significance level to detect a treatment difference in maintenance EBS remission rate of 20% (40% on filgotinib and 20% on placebo).
Data management, patient withdrawals	To evaluate the impact from missing data on the EBS remission rates at week 10 and week 58, the following missing value imputations were used: <u>Observed cases only</u> Observed cases were used for analysis without any imputation. Only patients in the FAS with both baseline and week 10 (or week 58) data were included for analysis.	

	SELECTION (NCT02914522) induction studies	SELECTION (NCT02914522) maintenance study
	Missing=Success Patients in the FAS who did not have sufficient data to decide on EBS remission status were imputed as having achieved EBS remission. Missing=Success for the placebo and Missing=Failure for the filgotinib groups Patients in the FAS who did not have sufficient data to decide on EBS remission status were imputed as having achieved EBS remission for the placebo group and not having achieved EBS remission for the filgotinib groups. Multiple imputation Patients in the FAS who did not have sufficient data to decide on EBS remission status at week 10 for the induction studies or week 58 for the maintenance study were imputed using the multiple imputation procedure. A logistic regression model was used to perform the imputation with baseline values of EBS sub scores, treatment, and stratification factors as independent variables.	
Source: CS, Table 12, pages 56-59.[1] CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CS = company submission; EBS = endoscopy/bleeding/stool frequency; FAS = full analysis set; FWER = family-wise type I error rate		

ERG comment: The ERG requested some clarification regarding methods of imputation and the addition of the results by each method to which the company responded by stating that the 'non-responder's imputation' (NRI) analysis (Missing = Failure for all groups) was specified as the primary method as per the protocol.[3] The company also provided the additional results, a summary of which is presented in Section 3.2.5.

3.2.3 Baseline characteristics of the SELECTION trial

Demographic and disease characteristics of participants for all three studies are presented in Table 3.6 for induction study cohort A, in Table 3.7 for induction study cohort B and in Table 3.8 for the maintenance study.

Table 3.6: Demographics and disease baseline characteristics, induction study cohort A (Safety Analysis Set)

Characteristic	Filgotinib 200 mg (N=245)	Filgotinib 100 mg (N=277)	Placebo (N=137)	Total (N=659)
Age, mean (SD)	42 (13.1)	42 (13.3)	41 (12.9)	42 (13.1)
Sex at birth, Female, n (%)	122 (49.8%)	120 (43.3%)	50 (36.5%)	292 (44.3%)
Weight in kg, mean (SD)	70.1 (17.89)	69.6 (17.69)	69.5 (15.89)	69.7 (17.39)
Body Mass Index in kg/m^2, mean (SD)	24.7 (5.82)	24.2 (4.91)	24.0 (4.31)	24.3 (5.16)
Race				
American Indian or Alaska Native, n (%)	1 (0.4%)	0	0	1 (0.2%)
Asian, n (%)	77 (31.4%)	79 (28.5%)	38 (27.7%)	194 (29.4%)
Black or African American, n (%)	2 (0.8%)	3 (1.1%)	1 (0.7%)	6 (0.9%)
Native Hawaiian or Pacific Islander, n (%)	0	0	0	0
White, n (%)	165 (67.3%)	192 (69.3%)	95 (69.3%)	452 (68.6%)
Other, n (%)	0	2 (0.7%)	2 (1.5%)	4 (0.6%)
Not Permitted, n (%)	0	1 (0.4%)	1 (0.7%)	2 (0.3%)
Geographic Region				
United States, n (%)	14 (5.7%)	33 (11.9%)	19 (13.9%)	66 (10.0%)
Non-US, n (%)	231 (94.3%)	244 (88.1%)	118 (86.1%)	593 (90.0%)
UC History				
Duration of UC in years, mean (SD)	7.2 (6.87)	6.7 (7.41)	6.4 (7.39)	6.8 (7.20)
Mayo Clinic Score, mean (SD)	8.6 (1.31)	8.6 (1.43)	8.7 (1.32)	8.6 (1.36)
Partial Mayo Clinic Score, mean (SD)	6.0 (1.24)	5.9 (1.31)	6.1 (1.29)	6.0 (1.28)
Endoscopy Score of 3, n (%)	133 (54.3%)	159 (57.4%)	76 (55.5%)	368 (55.8%)
Faecal calprotectin in µg/g, mean (SD)	2059 (2639.1)	2001 (3447.8)	2231 (2916.9)	2070 (3055.5)
C-reactive protein in hs-CRP, mg/l; mean (SD)	8.63 (16.274)	7.75 (17.384)	5.82 (7.600)	7.67 (15.426)

Characteristic	Filgotinib 200 mg (N=245)	Filgotinib 100 mg (N=277)	Placebo (N=137)	Total (N=659)
Concomitant use of systemically absorbed corticosteroids and immunomodulators				
Systemic corticosteroids only, n (%)	54 (22.0%)	67 (24.2%)	34 (24.8%)	155 (23.5%)
Immunomodulators only, n (%)	53 (21.6%)	63 (22.7%)	33 (24.1%)	149 (22.6%)
Both systemic corticosteroids and immunomodulators, n (%)	20 (8.2%)	19 (6.9%)	8 (5.8%)	47 (7.1%)
Neither systemic corticosteroids nor immunomodulators, n (%)	118 (48.2%)	128 (46.2%)	62 (45.3%)	308 (46.7%)
Based on CS, Table 9, pages 44-46.[1] CS = company submission; hs-CRP = high-sensitivity C-reactive Protein; SD = standard deviation; UC = ulcerative colitis; US = United States				

Table 3.7: Demographic and disease baseline characteristics, induction study cohort B, Safety Analysis Set

Characteristic	Filgotinib 200 mg (n=262)	Filgotinib 100 mg (n=285)	Placebo (n=142)	Total (N=689)
Age, mean (SD)	43 (14.2)	43 (14.3)	44 (14.9)	43 (14.4)
Sex at birth, Female, n (%)	114 (43.5%)	99 (34.7%)	56 (39.4%)	269 (39.0%)
Weight in kg, mean (SD)	73.1 (18.68)	74.7 (17.01)	73.1 (16.74)	73.8 (17.61)
Body Mass Index in kg/m^2, mean (SD)	25.1 (5.70)	25.0 (4.90)	24.7 (5.28)	25.0 (5.29)
Race				
American Indian or Alaska Native, n (%)	0	0	0	0
Asian, n (%)	50 (19.1%)	51 (17.9%)	27 (19.0%)	128 (18.6%)
Black or African American, n (%)	4 (1.5%)	6 (2.1%)	3 (2.1%)	13 (1.9%)
Native Hawaiian or Pacific Islander, n (%)	0	0	0	0
White, n (%)	190 (72.5%)	212 (74.4%)	98 (69.0%)	500 (72.6%)
Other, n (%)	0	0	1 (0.7%)	1 (0.1%)
Not Permitted, n (%)	18 (6.9%)	16 (5.6%)	13 (9.2%)	47 (6.8%)
Geographic Region				
United States, n (%)	36 (13.7%)	58 (20.4%)	21 (14.8%)	115 (16.7%)
Non-US, n (%)	226 (86.3%)	227 (79.6%)	121 (85.2%)	574 (83.3%)

Characteristic	Filgotinib 200 mg (n=262)	Filgotinib 100 mg (n=285)	Placebo (n=142)	Total (N=689)
UC History				
Duration of UC in years, mean (SD)	9.8 (7.64)	9.7 (7.15)	10.2 (8.22)	9.8 (7.56)
Mayo Clinic Score, mean (SD)	9.2 (1.39)	9.3 (1.27)	9.3 (1.42)	9.3 (1.35)
Partial Mayo Clinic Score, mean (SD)	6.5 (1.38)	6.4 (1.26)	6.4 (1.40)	6.4 (1.33)
Endoscopy Score of 3, n (%)	203 (77.5%)	222 (77.9%)	111 (78.2%)	536 (77.8%)
Faecal calprotectin in µg/g, mean (SD)	2845 (4076.5)	2236 (3094.9)	2479 (3571.4)	2517 (3596.7)
C-reactive protein in hs-CRP, mg/l; mean (SD)	12.21 (14.850)	11.72 (17.986)	13.98 (24.280)	12.37 (18.405)
Number of prior Biologic Agents				
0, n (%)	3 (1.1%)	2 (0.7%)	3 (2.1%)	8 (1.2%)
1, n (%)	80 (30.5%)	98 (34.4%)	46 (32.4%)	224 (32.5%)
2, n (%)	90 (34.4%)	109 (38.2%)	45 (31.7%)	244 (35.4%)
≥ 3, n (%)	89 (34.0%)	76 (26.7%)	48 (33.8%)	213 (30.9%)
Prior use of TNFα inhibitor				
Yes, n (%)	242 (92.4%)	266 (93.3%)	130 (91.5%)	638 (92.6%)
1, n (%)	126 (48.1%)	136 (47.7%)	66 (46.5%)	328 (47.6%)
2, n (%)	90 (34.4%)	117 (41.1%)	54 (38.0%)	261 (37.9%)
≥ 3, n (%)	26 (9.9%)	13 (4.6%)	10 (7.0%)	49 (7.1%)
Prior use of vedolizumab				
Yes, n (%)	164 (62.6%)	145 (50.9%)	85 (59.9%)	394 (57.2%)
Treatment failure worst outcome, n (%)	148 (56.5%)	132 (46.3%)	76 (53.5%)	356 (51.7%)
Intolerance worst outcome, n (%)	11 (4.2%)	9 (3.2%)	2 (1.4%)	22 (3.2%)
Other, n (%)	11 (4.2%)	4 (1.4%)	7 (4.9%)	16 (2.3%)
Prior Use of both TNFα inhibitor and vedolizumab				
Prior Use of both TNFα inhibitor and vedolizumab, Yes, n (%)	147 (56.1%)	128 (44.9%)	76 (53.5%)	351 (50.9%)
Concomitant use of systemically absorbed corticosteroids and immunomodulators				
Systemic corticosteroids only, n (%)	94 (35.9%)	103 (36.1%)	51 (35.9%)	248 (36.0%)
Immunomodulators only, n (%)	34 (13.0%)	34 (11.9%)	21 (14.8%)	89 (12.9%)
Both systemic corticosteroids and	28 (10.7%)	28 (9.8%)	11 (7.7%)	67 (9.7%)

Characteristic	Filgotinib 200 mg (n=262)	Filgotinib 100 mg (n=285)	Placebo (n=142)	Total (N=689)
immunomodulators, n (%)				
Neither systemic corticosteroids nor immunomodulators, n (%)	106 (40.5%)	120 (42.1%)	59 (41.5%)	285 (41.4%)
Based on CS, Table 10, pages 46-48.[1] CS = company submission; hs-CRP = high-sensitivity C-reactive Protein; SD = standard deviation; TNF = tumour necrosis factor; UC = ulcerative colitis; US = United States				

Across treatment groups, 58.9% (391/651) of patients entered the maintenance study from the cohort A induction study (biologic-naïve patients) and 41.1% (273/689) entered the maintenance study from the cohort B induction study (biologic-experienced patients)

Table 3.8: Demographic and disease baseline characteristics, maintenance study, Safety Analysis Set

SELECTION (NCT02914522)	Induction filgotinib 200 mg			Induction filgotinib 100 mg			Induction Placebo	Overall Total (N=664)
	Maintenance filgotinib 200 mg (N=202)	Maintenance placebo (N=99)	Total (N=301)	Maintenance filgotinib 100 mg (N=179)	Maintenance placebo (N=91)	Total (N=270)	Maintenance placebo (N=93)	
Age, mean (SD)	43 (13.8)	42 (13.0)	43 (13.5)	42 (12.6)	43 (15.1)	42 (13.5)	43 (13.0)	43 (13.4)
Sex at birth, Female, n (%)	107 (53.0%)	51 (51.5%)	158 (52.5%)	78 (43.6%)	42 (46.2%)	120 (44.4%)	44 (47.3%)	322 (48.5%)
Weight in kg, mean (SD)	71.2 (18.31)	73.0 (18.12)	71.8 (18.24)	72.3 (19.97)	73.7 (18.06)	72.8 (19.32)	69.2 (16.03)	71.8 (18.41)
Body Mass Index in kg/m^2, mean (SD)	71.8 (18.41)	25.7 (5.54)	25.1 (5.63)	24.9 (5.39)	25.2 (5.51)	25.0 (5.42)	24.0 (4.17)	24.9 (5.37)
Race								
American Indian or Alaska Native, n (%)	0	0	0	0	0	0	0	0
Asian, n (%)	56 (27.7%)	29 (29.3%)	85 (28.2%)	41 (22.9%)	19 (20.9%)	60 (22.2%)	28 (30.1%)	173 (26.1%)
Black or African American, n (%)	4 (2.0%)	0	4 (1.3%)	4 (2.2%)	0	4 (1.5%)	0	8 (1.2%)
Native Hawaiian or Pacific Islander, n (%)	0	0	0	0	0	0	0	0
White, n (%)	138 (68.3%)	68 (68.7%)	206 (68.4%)	130 (72.6%)	71 (78.0%)	201 (74.4%)	63 (67.7%)	470 (70.8%)
Other, n (%)	0	0	0	1 (0.6%)	0	1 (0.4%)	1 (1.1%)	2 (0.3%)
Not Permitted, n (%)	4 (2.0%)	2 (2.0%)	6 (2.0%)	3 (1.7%)	1 (1.1%)	4 (1.5%)	1 (1.1%)	11 (1.7%)
Geographic Region								
United States, n (%)	19 (9.4%)	12 (12.1%)	31 (10.3%)	29 (16.2%)	12 (13.2%)	41 (15.2%)	8 (8.6%)	80 (12.0%)
Non-US, n (%)	183 (90.6%)	87 (87.9%)	270 (89.7%)	150 (83.8%)	79 (86.8%)	229 (84.8%)	85 (91.4%)	584 (88.0%)

SELECTION (NCT02914522)	Induction filgotinib 200 mg			Induction filgotinib 100 mg			Induction Placebo	Overall Total (N=664)
	Maintenance filgotinib 200 mg (N=202)	Maintenance placebo (N=99)	Total (N=301)	Maintenance filgotinib 100 mg (N=179)	Maintenance placebo (N=91)	Total (N=270)	Maintenance placebo (N=93)	
UC History								
Duration of UC in years, mean (SD)	8.4 (7.37)	8.9 (7.61)	8.6 (7.44)	8.9 (8.40)	7.5 (7.45)	8.4 (8.10)	7.0 (6.78)	8.3 (7.64)
Faecal calprotectin in µg/g, mean (SD)	627 (944.9)	934 (2621.7)	728 (1692.4)	662 (1291.2)	760 (1474.7)	695 (1353.9)	1043 (1545.9)	758 (1544.3)
C-reactive protein in hs-CRP, mg/L; mean (SD)	3.74 (10.131)	2.72 (4.443)	3.41 (8.686)	3.04 (5.721)	3.53 (5.392)	3.21 (5.607)	3.30 (5.299)	3.31 (7.127)
Participated cohort A, n (%)	109 (54.0%)	54 (54.5%)	163 (54.2%)	107 (59.8%)	54 (59.3%)	161 (59.6%)	67 (72.0%)	391 (58.9%)
Participated cohort B, n (%)	93 (46.0%)	45 (45.5%)	138 (45.8%)	72 (40.2%)	37 (40.7%)	109 (40.4%)	26 (28.0%)	273 (41.1%)
Number of prior biologic agents used								
0, n (%)	110 (54.5%)	55 (55.6%)	165 (54.8%)	106 (59.2%)	56 (61.5%)	162 (60.0%)	68 (73.1%)	395 (59.5%)
1, n (%)	36 (17.8%)	16 (16.2%)	52 (17.3%)	32 (17.9%)	9 (9.9%)	41 (15.2%)	12 (12.9%)	105 (15.8%)
2, n (%)	31 (15.3%)	10 (10.1%)	41 (13.6%)	22 (12.3%)	15 (16.5%)	37 (13.7%)	4 (4.3%)	82 (12.3%)
≥ 3, n (%)	25 (12.4%)	18 (18.2%)	43 (14.3%)	19 (10.6%)	11 (12.1%)	30 (11.1%)	9 (9.7%)	82 (12.3%)
Prior use of TNFα antagonist								
Yes	84 (41.6%)	43 (43.4%)	127 (42.2%)	68 (38.0%)	32 (35.2%)	100 (37.0%)	21 (22.6%)	248 (37.3%)
1, n (%)	47 (23.3%)	21 (21.2%)	68 (22.6%)	37 (20.7%)	9 (9.9%)	46 (17.0%)	10 (10.8%)	124 (18.7%)
2, n (%)	29 (14.4%)	19 (19.2%)	48 (15.9%)	26 (14.5%)	21 (23.1%)	47 (17.4%)	9 (9.7%)	104 (15.7%)
≥3, n (%)	8 (4.0%)	3 (3.0%)	11 (3.7%)	5 (2.8%)	2 (2.2%)	7 (2.6%)	2 (2.2%)	20 (3.0%)

SELECTION (NCT02914522)	Induction filgotinib 200 mg			Induction filgotinib 100 mg			Induction Placebo	Overall Total (N=664)
	Maintenance filgotinib 200 mg (N=202)	Maintenance placebo (N=99)	Total (N=301)	Maintenance filgotinib 100 mg (N=179)	Maintenance placebo (N=91)	Total (N=270)	Maintenance placebo (N=93)	
Prior use of vedolizumab								
Yes, n (%)	49 (24.3%)	24 (24.2%)	73 (24.3%)	32 (17.9%)	16 (17.6%)	48 (17.8%)	15 (16.1%)	136 (20.5%)
Treatment Failure worst outcome, n (%)	40 (19.8%)	21 (21.2%)	61 (20.3%)	28 (15.6%)	14 (15.4%)	42 (15.6%)	12 (12.9%)	115 (17.3%)
Intolerance worst outcome, n (%)	5 (2.5%)	3 (3.0%)	8 (2.7%)	3 (1.7%)	1 (1.1%)	4 (1.5%)	2 (2.2%)	14 (2.1%)
Other, n (%)	4 (2.0%)	0	4 (1.3%)	1 (0.6%)	1 (1.1%)	2 (0.7%)	1 (1.1%)	7 (1.1%)
Prior Use of both TNFα inhibitors and vedolizumab								
Prior Use of both TNFα inhibitors and vedolizumab, yes, n (%)	41 (20.3%)	23 (23.2%)	64 (21.3%)	27 (15.1%)	13 (14.3%)	40 (14.8%)	11 (11.8%)	115 (17.3%)
Concomitant use of systemically absorbed corticosteroids and immunomodulators								
Systemic corticosteroids only, n (%)	61 (30.2%)	31 (31.3%)	92 (30.6%)	62 (34.6%)	28 (30.8%)	90 (33.3%)	25 (26.9%)	207 (31.2%)
Immunomodulators only, n (%)	35 (17.3%)	18 (18.2%)	53 (17.6%)	27 (15.1%)	15 (16.5%)	42 (15.6%)	23 (24.7%)	118 (17.8%)
Both systemic corticosteroids and immunomodulators, n (%)	19 (9.4%)	9 (9.1%)	28 (9.3%)	17 (9.5%)	9 (9.9%)	26 (9.6%)	7 (7.5%)	61 (9.2%)
Neither systemic corticosteroids nor immunomodulators, n (%)	87 (43.1%)	41 (41.4%)	128 (42.5%)	73 (40.8%)	39 (42.9%)	112 (41.5%)	38 (40.9%)	278 (41.9%)

Based on CS, Table 11, pages 50-53[1]
CS = company submission; hs-CRP = high-sensitivity C-reactive Protein; SD = standard deviation; TNF = tumour necrosis factor; UC = ulcerative colitis; US = United States

ERG comment: The ERG noted that the baseline characteristics are not evenly distributed across treatment arms. For instance, in the induction study - cohort A, the Filgotinib 200 group has relatively more women (49.8%) than the placebo group (36.5%); and the Filgotinib 200 group has relatively more non-US patients (94.3%) than the placebo group (86.1%), the effect of which the company were asked to discuss.[3] In response to request for clarification, the company provided the results of pre-planned subgroup analyses of EBS remission stating that *"Pre-specified sub-group analyses (Table 9 for Cohort A, Table 10 for Cohort B and Table 11 for the maintenance phase) showed consistent treatment effect of both filgotinib 200mg and filgotinib 100mg for EBS remission across most subgroups by demographic factors, indicating that minor baseline imbalances did not significantly impact the overall treatment effects and conclusions for the comparison between filgotinib and placebo"*.[3] On the whole it seems that the results for the subgroups are either not too dissimilar or the numbers are too small to permit inference with any confidence. However, it does seem that effectiveness of filgotinib 200 mg is greater for women than for the whole population: 13.1% [2.5% to 23.6%] vs. 7.2% [1.6% to 12.8%]. Therefore, the ERG considers that the baseline differences might have caused an overestimate of the treatment effect, although it is difficult to be confident of this given the cumulative effect of other baseline differences.

3.2.4 Risk of bias assessment of the SELECTION trial

The risk of bias assessment of the SELECTION clinical programme is presented in Table 3.9.

Table 3.9: Risk of bias assessment results for the SELECTION clinical programme

Study question	SELECTION (NCT02914522)	
	Company	ERG
Was randomisation carried out appropriately?	Yes (CS, Table 8)	Yes
Was the concealment of treatment allocation adequate?	Yes (CS, Table 8)	No
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes (CS, Table 8)	No
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes (CS, Table 8)	Unclear
Were there any unexpected imbalances in drop-outs between groups?	No (CS, Table 12)	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No (CS, Tables 7 and 8)	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 (CS, Table 12)	Partial
CS = company submission; ERG = Evidence Review Group		

ERG comment:

- While the authors emphasise the double blinded nature of the study as a strength, and an essential characteristic of the design, there is inadequate information provided to allow full understanding of exactly how treatment allocation was administered and managed.
- Although, there appeared to be general comparability between arms, baseline characteristics were not evenly distributed across treatment arms for all characteristics. See Section 3.2.3.

- The authors state clearly that *"both patients and investigators remained blinded throughout the studies"* (Section B.2.5, page 60/205, CS) however it is unclear exactly how the process of blinding was fully implemented and managed.[1] The company did not provide full details on the blinding process but in their response to clarification stated *"in the event of a medical emergency where breaking the blind was required to provide medical care to the patient, the investigator obtained treatment assignment directly from the IWRS for that patient"* and *"Blinding of study treatment was critical to the integrity of this clinical trial; therefore, if a patient's treatment assignment was disclosed to the investigator, the patient had his or her study treatment discontinued"* (page 12/126, response to clarification).[3] While this suggests that full blinding was implemented, more detail could have been provided on its implementation.
- Efficacy was analysed using the FAS. For the comparison between filgotinib 200 mg and placebo in cohort A, this was equivalent to an ITT analysis. In cohort B, one patient that had been randomised to placebo was not included in the FAS.

3.2.5 Efficacy results of the SELECTION trial

The primary endpoint for the induction and maintenance studies was the proportion of patients achieving EBS remission. EBS remission is defined as an endoscopic sub score of 0 or 1, RB sub score of 0, and at least one-point decrease in SF from baseline to achieve a sub score of 0 or 1. However, the primary outcome was not used in the economic model. The only outcomes used in the economic model were Mayo Clinic Score (MCS) response (defined as: A MCS reduction of ≥3 points and at least 30% from baseline score with an accompanying decrease in RB sub score of ≥1 point or an absolute RB sub score of 0 or 1) and MCS remission (defined as: A MCS of 2 or less and no single sub score higher than 1).

The company presents results for two filgotinib arms, 100 mg and 200 mg, in their submission. However, filgotinib 100 mg is recommended only for patients who have moderate or severe renal impairment. In addition, the company states that *"Although filgotinib 100 mg was studied in SELECTION (and is included in the NMA), patients within this treatment arm who are classified as having moderate or severe renal impairment are limited. As such, filgotinib 100 mg was not included in the economic analysis due to a paucity of data for both filgotinib and comparators in this subgroup of patients"*.[3] Therefore, only the results for the filgotinib 200 mg arm will be discussed in this report.

Results are reported using NRI analysis (Missing = Failure for all groups). This was specified as the primary method to handle missing efficacy data as per the protocol[3]

Patients who do not have sufficient measurements to determine efficacy endpoints will be considered failures (i.e., failing to reach the primary time point of interest or to measure it could be seen as a failure of the treatment regimen and hence the endpoints are considered not met ("failure")).

The definitions of the efficacy endpoints applied in the trial are presented in Table 3.10.

Table 3.10: Definition of efficacy endpoints

Endpoint	Definition	Used in economic model
EBS remission	An endoscopic sub score of 0 or 1, RB sub score of 0, and at least one-point decrease in SF from baseline to achieve a sub score of 0 or 1	No
Sustained EBS remission	EBS remission at both weeks 10 and 58	No

MCS response	A MCS reduction of ≥3 points and at least 30% from baseline score with an accompanying decrease in RB sub score of ≥1 point or an absolute RB sub score of 0 or 1	Yes
MCS remission	A MCS of 2 or less and no single sub score higher than 1	Yes
MCS remission (alternative definition)	RB, SF, and PGA sub scores of 0 and an endoscopic sub score of 0 or 1; overall MCS of ≤1	No
Mucosal healing	An endoscopic sub score of 0 or 1	No
Endoscopic sub score of 0	And endoscopic sub score of 0	No
Geboes Histologic remission	Based on the Geboes Scale, all of the following must have been met to be considered in Geboes histologic remission at: Grade 0 of ≤0.3, Grade 1 of ≤1.1, Grade 2a of ≤2A.3, Grade 2b of 2B.0, Grade 3 of 3.0, Grade 4 of 4.0, and Grade 5 of 5.0	No
6-months corticosteroid-free remission	EBS remission with no corticosteroid use for the indication of UC for at least 6 months prior to week 58 among subjects who are on corticosteroid at re-baseline (baseline of maintenance study). Subjects who weaned off steroids but required re-initiation within 6 months prior to week 58 assessment were considered to have not met this endpoint.	No

Based on CS, Table 14, page 61.[1]
CS = company submission; EBS = endoscopy/bleeding/stool frequency; MCS = Mayo clinic score; PGA = Physician's Global Assessment; RB = rectal bleeding; SF = stool frequency; UC = ulcerative colitis

3.2.5.1 Cohort A induction study

The cohort A induction study met its primary endpoint. A statistically significantly higher proportion of patients achieved EBS remission at week 10 in the filgotinib 200 mg group compared with the placebo group (see Table 3.11). At week 10, 26.1% [CI=20.4% to 31.8%] of patients in the filgotinib 200 mg and 15.3% [CI=8.9% to 21.7%] of patients in the placebo group achieved EBS remission (P=0.0157). All other outcomes reported in Table 3.12 also showed statistically significant differences in favour of filgotinib 200 mg when compared with placebo.

Table 3.11: Summary of main efficacy and HRQoL outcomes for cohort A induction study, week 10 (Non-responders' imputation; Full Analysis Set)

Endpoint	Filgotinib 200 mg (n=245)	Placebo (n=137)	Difference
Main efficacy outcomes			**Difference***
EBS remission n (%) [95% CI]	64 (26.1%) [20.4% to 31.8%]	21 (15.3%) [8.9% to 21.7%]	10.8% [2.1% to 19.5%]
MCS response n (%) [95% CI]	163 (66.5%) [60.4% to 72.6%]	64 (46.7%) [38.0% to 55.4%]	19.8% [9.0% to 30.6%]
MCS remission n (%) [95% CI]	60 (24.5%) [18.9% to 30.1%]	17 (12.4%) [6.5% to 18.3%]	12.1% [3.8% to 20.4%]
Mucosal healing n (%) [95% CI]	83 (33.9%) [27.7% to 40.0%]	28 (20.4%) [13.3% to 27.6%]	13.4% [3.9%, 23.0%]

Endpoint	Filgotinib 200 mg (n=245)	Placebo (n=137)	Difference
Endoscopic sub score of 0, n (%) [95% CI]	30 (12.2%) [7.9% to 16.6%]	5 (3.6%) [0.1% to 7.2%]	8.6% [2.9% to 14.3%]
Geboes Histologic remission, n (%) [95% CI]	86 (35.1%) [28.9% to 41.3%]	22 (16.1%) [9.5% to 22.6%]	19.0% [9.9% to 28.2%]
MCS remission (alternative definition) n (%) [95% CI]	30 (12.2%) [7.9% to 16.6%]	6 (4.4%) [0.6% to 8.2%]	7.9% [1.9% to 13.8%]
Health-related quality of life outcomes			**Difference****
IBDQ total score, Change from baseline***	51 (2.4) [46% to 56%]	30 (3.1) [24% to 36%]	21 (3.7) [13% to 28%]
SF-36, physical component, Change from baseline***	6.31 (0.437) [5.45% to 7.17%]	2.80 (0.565) [1.69% to 3.91%]	3.52 (0.678) [2.19% to 4.85%]
SF-36, mental component, Change from baseline***	7.87 (0.600) [6.69% to 9.05%]	4.85 (0.778) [3.33% to 6.38%]	3.02 (0.933) [1.18% to 4.85%]
EQ-5D VAS, Change from baseline***	17 (1.2) [15% to 19%]	7 (1.5) [4% to 10%]	9 (1.8) [6% to 13%]

Based on response to request for clarification, Tables 12 and 13[3]
*) Non-stratified risk difference in proportions % (95% CI). The 95% CIs are calculated based on normal approximation with a continuity correction; **) LS mean treatment difference n (SE) [95% CI]; ***) Change from baseline (LOCF imputed) LS mean (SE) [95% CI]
CI = confidence interval; EBS = endoscopy/bleeding/stool frequency; EQ-5D = EuroQoL-5 Dimensions Health Survey; HRQoL = health-related quality of life; IBDQ = inflammatory bowel disease questionnaire; LS = least square; LOCF = last observation carried forward; MCS = Mayo clinic score; SE = standard error; SF-36 = Short form-36 items; VAS = visual analogue scale

3.2.5.2 Cohort B induction study

The cohort B induction study also met its primary endpoint (see Table 3.12). A statistically significantly higher proportion of patients achieved EBS remission at week 10 in the filgotinib 200 mg group compared with the placebo group. At week 10, EBS remission was achieved by 11.5% [CI=7.4% to 15.5] of patients in the filgotinib 200 mg group and 4.2% [CI=0.6% to 7.9%] of patients in the placebo group (P=0.0103). As can be seen in Table 3.11, most other outcomes also showed statistically significant differences in favour of filgotinib 200 mg when compared with placebo. However, MCS remission, Endoscopic sub score of 0, and MCS remission (alternative definition) no longer showed statistically significant differences between groups.

Table 3.12: Summary of efficacy and HRQoL outcomes for cohort B induction study (Non-responders' imputation; Full Analysis Set)

Endpoint	Filgotinib 200 mg (n=262)	Placebo (n=142)	Difference
Main efficacy outcomes			**Difference***
EBS remission n (%) [95% CI]	30 (11.5%) [7.4% to 15.5%]	6 (4.2%) [0.6% to 7.9%]	7.2% [1.6% to 12.8%]
MCS response n (%) [95% CI]	139 (53.1%) [46.8% to 59.3%]	25 (17.6%) [11.0% to 24.2%]	35.4% [26.2% to 44.7%]
MCS remission n (%) [95% CI]	25 (9.5%) [5.8% to 13.3%]	6 (4.2%) [0.6% to 7.9%]	5.3% [-0.1% to 10.7%]

Endpoint	Filgotinib 200 mg (n=262)	Placebo (n=142)	Difference
Mucosal healing n (%) [95% CI]	45 (17.2%) [12.4% to 21.9%]	11 (7.7%) [3.0% to 12.5%]	9.4% [2.5% to 16.3%]
Endoscopic sub score of 0, n (%) [95% CI]	9 (3.4%) [1.0% to 5.8%]	3 (2.1%) [0.0% to 4.8%]	1.3% [-2.5% to 5.1%]
Geboes Histologic remission, n (%) [95% CI]	52 (19.8%) [14.8% to 24.9%]	12 (8.5%) [3.5% to 13.4%]	11.4% [4.2% to 18.6%]
MCS remission (alternative definition) n (%) [95% CI]	10 (3.8%) [1.3% to 6.3%]	3 (2.1%) [0.0% to 4.8%]	1.7% [-2.2% to 5.6%]
Health-related quality of life outcomes			**Difference****
IBDQ total score, Change from baseline***	43 (2.3) [38% to 47%]	14 (3.1) [8% to 20%]	28 (3.6) [21% to 35%]
SF-36, physical component, Change from baseline***	6.31 (0.444) [5.44% to 7.18%]	2.29 (0.585) [1.14% to 3.44%]	4.02 (0.691) [2.66, 5.37]
SF-36, mental component, Change from baseline***	6.99 (0.588) [5.83% to 8.14%]	2.02 (0.772) [0.51% to 3.54%]	4.97 (0.913) [3.17% to 6.76%]
EQ-5D VAS, Change from baseline***	17 (1.3) [15% to 20%]	6 (1.6) [2% to 9%]	12 (1.9) [8% to 15%]

Source: Response to Clarification, Tables 14 and 15.[3]
*) Non-stratified risk difference in proportions % (95% CI). The 95% CIs are calculated based on normal approximation with a continuity correction; **) LS mean treatment difference n (SE) [95% CI]; ***) Change from baseline (LOCF imputed) LS mean (SE) [95% CI]
CI = confidence interval; EBS = endoscopy/bleeding/stool frequency; EQ-5D = EuroQoL-5 Dimensions Health Survey; HRQoL = health-related quality of life; IBDQ = inflammatory bowel disease questionnaire; LS = least square; LOCF = last observation carried forward; MCS = Mayo clinic score; SE = standard error; SF-36 = Short form-36 items; VAS = visual analogue scale

3.2.5.3 Maintenance study

The maintenance study also met its primary endpoint (see Table 3.13). A statistically significantly higher proportion of subjects achieved EBS remission at week 58 in the filgotinib 200 mg group compared with the placebo group. At week 58, 37.2% [CI=30.2% to 44.2%] of patients in the filgotinib 200 mg and 11.2% [CI=4.5% to 18.0%] of patients in the placebo group achieved EBS remission (P<0.0001). As can been in Table 3.13, all other outcomes also showed statistically significant differences in favour of filgotinib 200 mg when compared with placebo

Table 3.13: Summary of efficacy and HRQoL outcomes for maintenance study, week 58 (Non-responders' imputation; Full Analysis Set)

Endpoint	Induction filgotinib 200 mg followed by		Difference
	Maintenance filgotinib 200 mg (n=199)	Maintenance placebo (n=98)	
Main efficacy outcomes			**Difference***
EBS remission n (%) [95% CI]	74 (37.2%) [30.2% to 44.2%]	11 (11.2%) [4.5% to 18.0%]	26.0% [16.0% to 5.9%]
Sustained EBS remission n (%) [95% CI]	36 (18.1%) [12.5% to 3.7%]	5 (5.1%) [0.2% to 0.0%]	13.0% [5.3% to 20.6%]

Endpoint	Induction filgotinib 200 mg followed by		Difference
	Maintenance filgotinib 200 mg (n=199)	Maintenance placebo (n=98)	
MCS response n (%) [95% CI]	133 (66.8%) [60.0% to 73.6%]	32 (32.7%) [22.9% to 42.4%]	34.2% [22.1% to 46.3%]
MCS remission n (%) [95% CI]	69 (34.7%) [27.8% to 41.5%]	9 (9.2%) [3.0% to 15.4%]	25.5%, [16.0% to 35.0%]
Mucosal healing n (%) [95% CI]	81 (40.7%) [33.6% to 47.8%]	15 (15.3%) [7.7% to 22.9%]	25.4% [14.8% to 36.0%]
Endoscopic sub score of 0, n (%) [95% CI]	31 (15.6%) [10.3% to 20.9%]	6 (6.1%) [0.9% to 11.4%]	9.5% [1.8% to 17.1%]
Geboes Histologic remission, n (%) [95% CI]	76 (38.2%) [31.2% to 45.2%]	13 (13.3%) [6.0% to 20.5%]	24.9% [14.6% to 35.2%]
MCS remission (alternative definition) n (%) [95% CI]	44 (22.1%) [16.1% to 28.1%]	6 (6.1%) [0.9% to 11.4%]	16.0% [7.8% to 24.2%]
6-months corticosteroid-free remission**** n (%) [95% CI]	25 (27.2%) [17.5% to 36.8%]	3 (6.4%) [0.0% to 14.4%]	20.8% [7.7% to 33.9%]
Health-related quality of life outcomes			**Difference****
IBDQ total score, Change from baseline***	5 (2.0) [1% to 9%]	-9 (2.7) [-14.0% to -3.0%]	13 (3.2) [7% to 20%]
SF-36, physical component, Change from baseline***	1.65 (0.425) [0.81% to 2.48%]	-0.37 (0.572) [-1.49% to 0.76%]	2.01 (0.665) [0.71% to 3.32%]
SF-36, mental component, Change from baseline***	0.91 (0.600) [-0.27% to 2.09%]	-1.71 (0.809) [-3.30% to -0.11%]	2.62 (0.941) [0.77% to 4.47%]
EQ-5D VAS, Change from baseline***	3 (1.2) [0% to 5%]	-3 (1.6) [-6% to 0%]	5 (1.8) [2% to 9%]

Source: Response to Clarification, Tables 16 and 17.[3]
*) Non-stratified risk difference in proportions % (95% CI). The 95% CIs are calculated based on normal approximation with a continuity correction; **) LS mean treatment difference n (SE) [95% CI]; ***) Change from baseline (LOCF imputed) LS mean (SE) [95% CI]; ****) Denominator of percentage is the number of Full Analysis Set subjects who were on corticosteroid at maintenance baseline
CI = confidence interval; EBS = endoscopy/bleeding/stool frequency; EQ-5D = EuroQoL-5 Dimensions Health Survey; HRQoL = health-related quality of life; IBDQ = inflammatory bowel disease questionnaire; LS = least square; LOCF = last observation carried forward; MCS = Mayo clinic score; SE = standard error; SF-36 = Short form-36 items; VAS = visual analogue scale

ERG comment: Filgotinib 200 mg is statistically significantly more effective than placebo in terms of all outcomes for both cohorts in the induction phase and the maintenance phase with only one exception, MCS remission (alternative definition) for cohort B. The results for filgotinib 100 mg have not been presented because the focus of the CS in on the 200 mg dose (see Section 2.1 for a discussion about the implications of this), but the difference between filgotinib 100 mg and placebo was mostly not statistically significant for the main outcomes of EBS remission, MCS remission and mucosal healing. An exception was MCS response in both cohorts A and B: 12.5% [1.8% to 23.2%] and 18.2% [9.3% to 27.1%].

In its clarification letter, the ERG asked the company to clarify what they meant by 'non-responder's imputation', the imputation approach taken, why they have been reported, and the results for each imputation method listed in Table 12 of the CS.[1,13] The company in its response to clarification explained that the NRI analysis was the primary method to handle missing efficacy data as per the protocol, that the imputation methods (Observed cases only, Missing=Success, Missing=Success for the placebo, Missing=Failure for the filgotinib groups, and Multiple imputation) described in Table 12 of the CS[1] were specifically planned for sensitivity analyses of the primary endpoint, EBS remission rates at week 10, and that missing data imputation was not planned for sensitivity analyses of other endpoints because *"those analyses were not pre-planned and because of the questionable clinical relevance of the effects being estimated"*.[3]

- NRI analysis (Missing = Failure for all groups) was specified as the primary method to handle missing efficacy data as per the protocol: patients who did not have sufficient measurements to determine efficacy endpoints were considered failures i.e., failing to reach the primary time point of interest or to measure it could be seen as a failure of the treatment regimen and hence the endpoints are considered not met ("failure").
- Missing = Success: Favours active if more dropouts in active (e.g., for safety reasons) or favours placebo if more dropouts in placebo (e.g., dropouts on placebo for lack of efficacy).
- Missing = Success for placebo and failure for filgotinib: penalises filgotinib without clinical rationale
- Multiple imputation: Relies on unverifiable assumptions regarding the missing data pattern (that the missing data can be explained (predicted) by other observed variables). In some instances, this assumption makes clinical sense, when patients are gradually getting worse until the dropout occurs.

The company provided tables detailing sensitivity analyses for the proportion of patients who achieved EBS emission in cohorts A and B induction studies and maintenance studies using observed cases only imputation, missing = success imputation, missing = success for the placebo, missing = failure for the filgotinib groups, and multiple imputation methods. These can be found in Tables 20 to 31 in the response to request for clarification.[3] Although there are noticeable differences in the results for proportion of patients who did (or did not) achieve EBS emission between imputation methods across induction study cohorts A and B, and the maintenance study, on the whole these differences are unlikely to alter the clinical effectiveness conclusions. The ERG has included sensitivity analyses results for the 'observed cases only' and, for another plausible scenario, multiple imputation methods (Tables 3.14 to 3.19).

Table 3.14: Observed cases only: Summary of EBS remission for Cohort A induction study, week 10 (Full Analysis Set)

Endpoint	Filgotinib 200 mg (n=236)	Filgotinib 100 mg (n=261)	Placebo (n=128)
EBS remission n (%) [95% CI for the proportion]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
EBS remission not achieved n (%)	[redacted]	[redacted]	[redacted]

Endpoint	Filgotinib 200 mg (n=236)	Filgotinib 100 mg (n=261)	Placebo (n=128)
Observed non-responders n (%)	[redacted]	[redacted]	[redacted]
Non-responders due to treatment failure	[redacted]	[redacted]	[redacted]

Based on Table 20 of the response to request for clarification[3]
The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. Treatment failure refers to commencement or dose escalation of potentially effective non-study treatment for UC. Patients with insufficient data due to reasons other than treatment failure are excluded.
CI = confidence interval; EBS = endoscopy/bleeding/stool frequency; NA = not applicable

Table 3.15: Observed cases only: Summary of EBS remission for Cohort B induction study, week 10 (Full Analysis Set)

Endpoint	Filgotinib 200 mg (n=239)	Filgotinib 100 mg (n=258)	Placebo (n=129)
EBS remission n (%) [95% CI for the proportion]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
EBS remission not achieved n (%)	[redacted]	[redacted]	[redacted]
Observed non-responders n (%)	[redacted]	[redacted]	[redacted]
Non-responders due to treatment failure	[redacted]	[redacted]	[redacted]

Based on Table 21 of the response to request for clarification[3]
The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. Treatment failure refers to commencement or dose escalation of potentially effective non-study treatment for UC. Patients with insufficient data due to reasons other than treatment failure are excluded.
CI = confidence interval; EBS = endoscopy/bleeding/stool frequency; NA = not applicable

Table 3.16: Observed cases only: Summary of EBS remission for Maintenance study, week 10 (Full Analysis Set)

Subgroup	Induction filgotinib 200 mg		Induction filgotinib 100 mg	
	Maintenance filgotinib 200 mg (n=182)	Maintenance placebo (n=89)	Maintenance filgotinib 100 mg (n=153)	Maintenance placebo (n=78)
EBS remission n (%) [95% CI for the	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Induction filgotinib 200 mg		Induction filgotinib 100 mg	
	Maintenance filgotinib 200 mg (n=182)	Maintenance placebo (n=89)	Maintenance filgotinib 100 mg (n=153)	Maintenance placebo (n=78)
proportion]				
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]	[redacted]
EBS remission not achieved n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Observed non-responders n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Non-responders due to treatment failure	[redacted]	[redacted]	[redacted]	[redacted]
Protocol specified disease worsening (PSDW)	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 22 of the response to request for clarification[3]

Subgroup	Induction filgotinib 200 mg		Induction filgotinib 100 mg	
	Maintenance filgotinib 200 mg (n=182)	Maintenance placebo (n=89)	Maintenance filgotinib 100 mg (n=153)	Maintenance placebo (n=78)
The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. Treatment failure refers to commencement or dose escalation of potentially effective non-study treatment for UC. Patients with insufficient data due to reasons other than treatment failure are excluded. CI = confidence interval; EBS = endoscopy/bleeding/stool frequency; NA = not applicable; PSDW = protocol specified disease worsening				

Table 3.17: Multiple imputation: Summary of EBS remission for Cohort A induction study, week 10 (Full Analysis Set)

Endpoint	Filgotinib 200 mg (n=245)	Filgotinib 100 mg (n=277)	Placebo (n=137)
EBS remission n (%) [95% CI for the proportion]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
Based on Table 29 of the response to request for clarification[3] The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. Treatment failure refers to commencement or dose escalation of potentially effective non-study treatment for UC. Patients with insufficient data due to reasons other than treatment failure are excluded. CI = confidence interval; EBS = endoscopy/bleeding/stool frequency; NA = not applicable			

Table 3.18: Multiple imputation: Summary of EBS remission for Cohort B induction study, week 10 (Full Analysis Set)

Endpoint	Filgotinib 200 mg (n=262)	Filgotinib 100 mg (n=285)	Placebo (n=142)
EBS remission n (%) [95% CI for the proportion]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
Based on Table 30 of the response to request for clarification[3] The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. Treatment failure refers to commencement or dose escalation of potentially effective non-study treatment for UC. Patients with insufficient data due to reasons other than treatment failure are excluded. CI = confidence interval; EBS = endoscopy/bleeding/stool frequency; NA = not applicable			

Table 3.19: Multiple imputation: Summary of EBS remission for Maintenance study, week 10 (Full Analysis Set)

Subgroup	Induction filgotinib 200 mg		Induction filgotinib 100 mg	
	Maintenance filgotinib 200 mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 100 mg (n=172)	Maintenance placebo (n=89)
EBS remission n (%) [95% CI for the proportion]				
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)				
P-value				

Based on Table 31 of the response to request for clarification[3]
The 95% CIs are calculated based on normal approximation with a continuity correction. P-value is based on Cochran-Mantel-Haenszel (CMH) test stratified by concomitant use of oral, systemic corticosteroids (Yes or No) and of immunomodulators (Yes or No) at Day 1. Treatment failure refers to commencement or dose escalation of potentially effective non-study treatment for UC. Patients with insufficient data due to reasons other than treatment failure are excluded.
CI = confidence interval; EBS = endoscopy/bleeding/stool frequency; NA = not applicable

5.2.5.4 Subgroup analysis

In additional to analysis by prior biologic exposure, the company presented subgroup data according to previous exposure to TNFα inhibitors (CS, Section B.2.7).[1] In the cohort A induction study, subgroup analyses were based on stratification factors, but not on history of biologic agent use, therefore subgroup analysis according to prior TNFα inhibitor exposure is only presented for the cohort B induction study and maintenance study, according to the following outcomes: EBS remission, MCS response, MCS remission, Mucosal healing, and Six-month corticosteroid-free EBS remission (maintenance study only).

In the cohort B induction study, 92.6% of patients had previously received treatment with a TNFα inhibitor. In general, the company stated that patients without prior exposure to TNFα inhibitors achieved higher rates of EBS remission, MCS response, MCS remission and mucosal healing across all treatment arms.

ERG comment: At the request of the ERG the results of the risk difference were reported in the clarification letter response for EBS remission, MCS response, MCS remission and mucosal healing (Tables 3.20 and 3.21).[3]

Table 3.20: Cohort B induction study by previous exposure to TNFα inhibitors (non-responder imputation) at week 10

Endpoint	Filgotinib 200 mg (n=262)	Filgotinib 100 mg (n=285)	Placebo (n=142)
Previous exposure to TNFα inhibitors (yes)			
EBS remission n (%) [95% CI]			
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)			
P-value			
MCS response n (%) [95% CI]			
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)			
P-value			
Mucosal healing n (%) [95% CI]			
Comparison with placebo			
Non-stratified risk difference in proportio			

Endpoint	Filgotinib 200 mg (n=262)	Filgotinib 100 mg (n=285)	Placebo (n=142)
ns % (95% CI)			
P-value			
MCS remission n (%) [95% CI]			
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)			
P-value			
Previous exposure to TNFα inhibitors (no)			
EBS remission n (%) [95% CI]			
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)			
P-value			
MCS response n (%) [95% CI]			
Comparison with placebo			
Non-stratified risk difference in proportio			

Endpoint	Filgotinib 200 mg (n=262)	Filgotinib 100 mg (n=285)	Placebo (n=142)
ns % (95% CI)			
P-value	[redacted]	[redacted]	[redacted]
Mucosal healing n (%) [95% CI]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
MCS remission n n (%) [95% CI]	[redacted]	[redacted]	[redacted]
Comparison with placebo			
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]

Based on Table 18 of the response to request for clarification[3]
CI = confidence interval; EBS = endoscopy/bleeding/stool frequency; NA = not applicable; MCS = Mayo clinic score; TNF = tumour necrosis factor

Table 3.21: Maintenance study by previous exposure to TNFα inhibitors (non-responder imputation) at week 58

Subgroup	Induction filgotinib 200 mg		Induction filgotinib 100 mg	
	Maintenance filgotinib 200 mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 100 mg (n=172)	Maintenance placebo (n=89)
Previous exposure to TNFα inhibitors (yes)	[redacted]	[redacted]	[redacted]	[redacted]
EBS remission n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]	[redacted]
MCS response n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]	[redacted]
Six-month corticosteroid-free	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Induction filgotinib 200 mg		Induction filgotinib 100 mg	
	Maintenance filgotinib 200 mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 100 mg (n=172)	Maintenance placebo (n=89)
EBS remission (%) [95% CI]				
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)				
P-value				
Mucosal healing n (%) [95% CI]				
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)				
P-value				
MCS remission n n (%) [95% CI]				
Comparison with placebo				
Non-stratified risk difference in proportions %				

Subgroup	Induction filgotinib 200 mg		Induction filgotinib 100 mg	
	Maintenance filgotinib 200 mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 100 mg (n=172)	Maintenance placebo (n=89)
(95% CI)				
P-value	[redacted]	[redacted]	[redacted]	[redacted]
Previous exposure to TNFα inhibitors (no)	[redacted]	[redacted]	[redacted]	[redacted]
EBS remission n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]	[redacted]
MCS response n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]	[redacted]
Six-month corticosteroid-	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Induction filgotinib 200 mg		Induction filgotinib 100 mg	
	Maintenance filgotinib 200 mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 100 mg (n=172)	Maintenance placebo (n=89)
free EBS remission (%) [95% CI]				
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]	[redacted]
Mucosal healing n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]	[redacted]
MCS remission n n (%) [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with placebo				
Non-stratified risk difference in proportions %	[redacted]	[redacted]	[redacted]	[redacted]

Subgroup	Induction filgotinib 200 mg		Induction filgotinib 100 mg	
	Maintenance filgotinib 200 mg (n=199)	Maintenance placebo (n=98)	Maintenance filgotinib 100 mg (n=172)	Maintenance placebo (n=89)
(95% CI)				
P-value	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 19 of the response to request for clarification[3]
CI = confidence interval; EBS = endoscopy/bleeding/stool frequency; NA = not applicable; MCS = Mayo clinic score; TNF = tumour necrosis factor

3.2.6 Adverse events

The SAS for each of the induction or maintenance studies included all patients who took at least one dose of study drug.

3.2.6.1 Exposure data

In the induction study, cohort A, 659 out of 660 randomised patients received at least one dose of filgotinib or placebo on day 1. In the induction study, cohort B, 689 out of 691 randomised patients received at least one dose of filgotinib or placebo on day 1. In the maintenance study, 664 out of 664 re-randomised patients received at least one dose of filgotinib or respective placebo at week 11. The mean (standard deviation, SD) durations of study drug exposure are summarised in Table 3.22 for each treatment arm and study phase.

Table 3.22: Exposure data for inductions studies

	Filgotinib 200 mg	Filgotinib 100 mg	Placebo
SELECTION cohort A induction study			
Duration of exposure, weeks, mean (SD)	[redacted]	[redacted]	[redacted]
Number of patients	245	277	137
SELECTION cohort B induction study			
Duration of exposure, weeks, mean (SD)	[redacted]	[redacted]	[redacted]
Number of patients	262	285	142

	Filgotinib 200 mg	Respective placebo	Filgotinib 100 mg	Respective placebo
SELECTION Maintenance study				
Duration of exposure, weeks, mean (SD)	39.4 (14.33)	28.8 (17.68)	34.5 (16.84)	29.2 (18.57)
Number of patients	202	99	179	91

Based on CS, Tables 28 and 29, page 103[1]
CS = company submission; SD = standard deviation

3.2.6.2 Common adverse events

The most common AEs affecting ≥5% of patients in the overall SELECTION study were nasopharyngitis, worsening ulcerative colitis, headache, anaemia, nausea, abdominal pain and upper respiratory tract infection, (Tables 3.23 and 3.24). Slightly more AEs were observed in SELECTION

induction cohort B compared to cohort A. In the SELECTION maintenance study, the frequencies of these events were generally similar across the filgotinib 200 mg and filgotinib 100 mg maintenance groups.

Full details of all treatment-emergent AEs affecting ≥2% of patients in any group by system organ class and preferred term as well as serious AEs are shown in Appendix F of the CS.[14]

Table 3.23: Summary of treatment-emergent adverse events in SELECTION, induction studies, cohorts A and B (Safety Analysis Set)

	Cohort A induction study			Cohort B induction study		
Safety assessment	**Filgotinib 200 mg (n=245)**	**Filgotinib 100 mg (n=277)**	**Placebo (n=137)**	**Filgotinib 200 mg (n=262)**	**Filgotinib 100 mg (n=285)**	**Placebo (n=142)**
Adverse events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any Grade 3 or higher adverse events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common Grade 3 or higher adverse events (≥2% of subjects), n (%)						
Colitis ulcerative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphatemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious adverse events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most frequent adverse events (≥5% of subjects), n (%)						
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Colitis ulcerative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections, n (%)						
Any infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event of special interest, n (%)						
Herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Opportunistic infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Malignancies (excluding non-melanoma skin cancers)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Cohort A induction study			Cohort B induction study		
Safety assessment	**Filgotinib 200 mg (n=245)**	**Filgotinib 100 mg (n=277)**	**Placebo (n=137)**	**Filgotinib 200 mg (n=262)**	**Filgotinib 100 mg (n=285)**	**Placebo (n=142)**
Non-melanoma skin cancers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal perforation events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thromboembolic events ǂ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event leading to discontinuation of study drug, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abnormal laboratory results (Grade 3 or 4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abnormal laboratory results (Grade 4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on CS, Table 30, pages 106-108[1]

ǂ Thromboembolic events refers venous thrombosis, pulmonary embolism, arterial thrombosis, or cerebrovascular events.

Table 3.24: Summary of adverse events in SELECTION maintenance study (Safety Analysis Set)

Safety assessment	Induction Filgotinib 200 mg		Induction Filgotinib 100 mg		Induction Placebo
	Maintenance Filgotinib 200 mg (n=202)	Maintenance Placebo (n=99)	Maintenance Filgotinib 100 mg (n=179)	Maintenance Placebo (n=91)	Maintenance Placebo (n=93)
Adverse events, n (%)	135 (66.8%)	59 (59.6%)	108 (60.3%)	60 (65.9%)	57 (61.3%)
Any Grade 3 or higher adverse events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common Grade 3 or higher adverse events (≥2% of patients), n (%)					
Colitis ulcerative	2 (1.0%)	1 (1.0%)	3 (1.7%)	3 (3.3%)	3 (3.2%)
Serious adverse events, n (%)	9 (4.5%)	0	8 (4.5%)	7 (7.7%)	4 (4.3%)
Most frequent adverse events (≥5% of patients), n (%)					
Colitis ulcerative	21 (10.4%)	20 (20.2%)	19 (10.6%)	16 (17.6%)	11 (11.8%)
Nasopharyngitis	22 (10.9%)	6 (6.1%)	12 (6.7%)	6 (6.6%)	5 (5.4%)
Arthralgia	8 (4.0%)	7 (7.1%)	6 (3.4%)	3 (3.3%)	4 (4.3%)
Headache	7 (3.5%)	0	11 (6.1%)	5 (5.5%)	5 (5.4%)
Abdominal pain	8 (4.0%)	6 (6.1%)	6 (3.4%)	2 (2.2%)	4 (4.3%)
Upper respiratory tract infection	11 (5.4%)	3 (3.0%)	6 (3.4%)	3 (3.3%)	3 (3.2%)
Infections, n (%)					
Any infection	71 (35.1%)	25 (25.3%)	46 (25.7%)	27 (29.7%)	21 (22.6%)
Serious infection	2 (1.0%)	0	3 (1.7%)	2 (2.2%)	1 (1.1%)
Adverse event of special interest, n (%)					
Herpes zoster	1 (0.5%)	0	0	1 (1.1%)	0
Malignancies (excluding non-melanoma skin cancers)	1 (0.5%)	0	1 (0.6%)	0	0
Non-melanoma skin cancers	0	0	1 (0.6%)	0	0

Safety assessment	Induction Filgotinib 200 mg		Induction Filgotinib 100 mg		Induction Placebo
	Maintenance Filgotinib 200 mg (n=202)	Maintenance Placebo (n=99)	Maintenance Filgotinib 100 mg (n=179)	Maintenance Placebo (n=91)	Maintenance Placebo (n=93)
Gastrointestinal perforation events	0	0	0	0	0
Thromboembolic events ǂ	0	0	2 (1.1%)	0	2 (2.2%)
Death	2 (1.0%)	0	0	0	0
Adverse event leading to discontinuation of study drug, n (%)	7 (3.5%)	2 (2.0%)	10 (5.6%)	4 (4.4%)	3 (3.2%)
Abnormal laboratory results (Grade 3 or 4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abnormal laboratory results (Grade 4), n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on CS, Table 31, pages 108-110[1]

ǂ Thromboembolic events refers venous thrombosis, pulmonary embolism, arterial thrombosis, or cerebrovascular event.

3.2.6.3 Serious adverse events

Serious AEs were defined as an event that, at any dose, resulted in any of the following outcomes:

- Death
- Life-threatening situation (immediate risk of death)
- Inpatient hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Other medically significant events that based upon appropriate medical judgment may have jeopardised the subject or may have required medical or surgical intervention to prevent one of the outcomes listed above.

In SELECTION induction cohort A, SAEs were reported by treatment group as follows: [redacted] of patients in the filgotinib 200 mg group, [redacted] of patients in the filgotinib 100 mg group and [redacted] of patients in the placebo group. In SELECTION induction cohort B, the corresponding SAEs were as follows: [redacted] of patients in the filgotinib 200 mg group, [redacted] of patients in the filgotinib 100 mg, and [redacted] of patients in the placebo group. The most commonly occurring SAE was ulcerative colitis in the induction study.

In The SELECTION maintenance study, SAEs were reported by treatment group as follows: 4.5% of patients in the filgotinib 200 mg group, 0.0% of patients in respective placebo; 4.5% of patients in the filgotinib 100 mg group and 7.7% of patients in respective placebo.

The most frequent SAE in the SELECTION clinical programme overall was ulcerative colitis, and most SAEs were related to ulcerative colitis. Serious AEs reported for each arm are summarised in Table 3.23 for the induction studies and in Table 3.24 for the maintenance study.

3.2.6.4 Events leading to discontinuation

Across treatment groups, worsening of ulcerative colitis was the most commonly occurring AE leading to premature discontinuation of study drug. In the SELECTION maintenance study, rates of events leading to discontinuation were lower in the filgotinib 200 mg treatment group (3.5%) than 100 mg treatment group (5.6%), and lower in the respective placebo groups than the treatment groups.

A summary of AEs in the SELECTION induction and maintenance studies are shown in Tables 3.23 and 3.24 respectively.

3.2.6.5 Adverse events of special interest

Adverse events of special interest in the SELECTION clinical programme were infections, malignancies (excluding non-melanoma skin cancers), non-melanoma skin cancers, gastrointestinal perforation events and thromboembolic events (venous thrombosis, pulmonary embolism, arterial thrombosis, or cerebrovascular events). These AEs are summarised in Tables 3.23 and 3.24.

In the cohort A induction trial, overall infections were reported in [redacted]% of the placebo group, [redacted]% of the filgotinib 100 mg group and [redacted]% of the filgotinib 200 mg group. In the cohort B induction trial, corresponding adverse event rates were [redacted]%, [redacted]% and [redacted]%, respectively. In the maintenance trial, infections were reported in 71 patients (35.1%) in the filgotinib 200 mg group and 25 patients (25.3%) in the respective placebo group, 46 patients (25.7%) in the filgotinib 100 mg group and 27 patients (29.7%) in the respective placebo group. Rates of serious infections for filgotinib 200 mg and filgotinib 100 mg were ≤3% across all arms [redacted] maintenance studies of the SELECTION clinical programme.

With the exception of overall infections, rates of AEs of special interest were consistently low across the SELECTION clinical trial programme; [redacted]% in all groups of the two induction studies, and ≤3% in all groups of the maintenance study. Full details of all AEs of special interest for each of the induction and maintenance studies are presented in Appendix F.

3.2.6.6 Deaths

Two deaths occurred during the SELECTION maintenance study, both in the filgotinib 200 mg treatment group.

- One death occurred on day 81. The subject was hospitalised for a glaucoma surgery and died the next day. The primary cause of death was determined to be left ventricular heart failure. The investigator assessed the left ventricular failure as not related to study drug
- One death was reported on day 302 attributed to asthma exacerbation. The investigator assessed the AE as not related to study drug.

3.2.7 Ongoing studies

The company mentioned the following two ongoing studies in their submission: SELECTION LTE[15] and the MANTA study.[16]

SELECTION LTE[15] is an ongoing long-term extension study, to assess the long-term safety of filgotinib in patients who completed SELECTION or met protocol-specified efficacy discontinuation criteria. SELECTION LTE is a non-randomised, double-blind, placebo-controlled, parallel assignment trial. The double-blind study has three treatment arms, in which patients receive filgotinib 200 mg or filgotinib 100 mg, and/or placebo for up to 336 weeks. The two open-label treatment arms receive filgotinib 200 mg or filgotinib 100 mg for up to 336 weeks. The study is expected to complete in December 2023.

The MANTA study is an ongoing study conducted to evaluate the testicular safety of filgotinib in adult males with moderately to severely active Ulcerative colitis (UC) or Crohn's disease (CD).[16] MANTA is a randomised, double-blind, placebo-controlled phase 2 study. In the double-blind phase of the trial, patients will receive a 200 mg dose of filgotinib or placebo once-daily for 13 weeks. Patients will continue on blinded treatment for up to an additional 13 weeks, or commence open-label filgotinib, based on IBD response status and sperm parameters.[16] In the long term extension phase, eligible patients will receive either open-label filgotinib or blinded study drug (filgotinib or placebo) for up to 195 weeks.[16]

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

There were no trials identified comparing filgotinib vs. comparators other than placebo, so the company undertook a SLR and NMA which aimed to provide comparison of the efficacy of filgotinib with other comparators listed in the final NICE scope.[2]

3.3.1 Population

The NMA included the population specified in the final NICE scope: adults with moderately to severely active ulcerative colitis who have had an inadequate response, loss of response or were intolerant to conventional therapy (oral corticosteroids and/or immunomodulators), or a biologic agent (TNFα inhibitor or vedolizumab). Because of the evidence in the SELECTION trial allowed for these subgroups' analysis, the company separates their analysis into two populations:

- **biologic naïve** (cohort A population: patients without prior use of any biologic (TNFα inhibitor or vedolizumab), which aligns to the SELECTION cohort A); and
- **biologic experienced** (cohort B population: patients who have previously demonstrated an inadequate clinical response, loss of response to, or intolerance to any biologic (TNFα inhibitor or vedolizumab), which aligns to the SELECTION cohort B).

The biologic-naïve and biologic-experienced populations were considered to be clinically distinct groups of patients, they were analysed in separate networks. All 17 records included in the NMA involved biologic-naïve patients, and 9 of them involved biologic-experienced patients.

3.3.2 Intervention and comparators

For the biologic naïve, the SLR identified two articles for adalimumab vs. placebo, one for filgotinib vs. placebo, two for golimumab vs. placebo, five for infliximab vs. placebo, three for tofacitinib vs. placebo, one for ustekinumab vs. placebo, two for vedolizumab vs. placebo, and one for vedolizumab vs. adalimumab (see Table 3.25 below [Table 23 in CS]). For the biologic experienced, the SLR identified one article for adalimumab vs. placebo, one for filgotinib vs. placebo, three for tofacitinib vs. placebo, one for ustekinumab vs. placebo, two for vedolizumab vs. placebo, and one for vedolizumab vs. adalimumab (see Table 3.26 below [Table 24 in CS]).

3.3.3 Outcomes

The company states that the outcomes included in the NMA were: clinical remission, clinical response, mucosal healing.[1] Remission was defined as Mayo Clinic Score (MCS) of ≤ 2 points and no individual sub score > 1 point. Response was defined as a decrease from baseline in the MCS ≥ 30% and ≥ 3 points, accompanied by a rectal bleeding sub score of 0 or 1 or a decrease from baseline in the rectal bleeding sub score ≥ 1. Mucosal healing was defined as endoscopic sub score of 0–1, from the MCS. The following outcomes listed in the NICE scope were not included in the NMA: mortality, rates of hospitalisation (including readmission), rates of surgical intervention, endoscopic healing, corticosteroid-free remission, AEs of treatment, health-related quality of life.

In their response to the clarification letter, the company stated that health related quality of life (HRQoL) measure was not required for the cost effectiveness model. The outcomes are listed in Tables 3.27 and 3.28.

3.3.4 Time of assessment

Two NMAs were carried out for each outcome in each population:

- Induction phase
- Maintenance phase

The induction period in the SELECTION trial was 10 weeks, and the maintenance period was 48 weeks from re-randomisation. In the other trials, induction periods ranged from 6–14 weeks and maintenance periods from 44–54 weeks. The company stated that the timepoints in the approved posology reflect how treatments would be used in clinical practice for assessment of response/stopping treatment. To maximise the information included in each network, no restriction was imposed based on the exact week an outcome was observed. This is consistent with previous TAs (TA633[17] and TA547[10]). It is important to note that for the maintenance phase outcomes at 58 weeks were conditional on response at 10 weeks.[1]

3.3.5 Heterogeneity

The CS noted that there was considerable heterogeneity in the trials within the NMAs. Specifically, there were differences in the length of induction phases, and efficacy results for more than one time point for the same comparator were not provided. The company noted a number of deviations from the definition of remission in several of the trials. In their response to the clarification letter, the company stated that a clinical expert noted that "It would be clinically reasonable to assume that the induction phase outcomes were comparable, despite differences in the length of induction phase".[3] However, an evidential basis for the clinical expert view was not provided.

It was also noted that the studies in the NMA were heterogenous in terms of study design. Six of the included trials used a 're-randomised' design (whereby patients achieving a response are re-randomised for the maintenance phase) and three trials used a 'treat-through' designs (patients continue receiving treatment according to the initial randomisation irrespective of whether a response was achieved). To compare treatments across different trial types, the company re-weighted the results from the treat-through trials to mimic a re-randomised trial before the NMA. Specifically, to estimate remission at 58 weeks conditional on response at 10 weeks in the treat-through type, an adjustment was made whereby the proportion of remitters at 58 weeks was recalculated as the number who experienced response plus remission at 58 weeks divided by the number who responded at 10 weeks. Doing this involves a number of assumptions including that the number of responders at the end of the induction phase is used as a proxy for the total number of patients entering the maintenance phase. The company did a sensitivity analysis where they excluded the two types of studies and found similar results.[1]

3.3.6 Risk of bias

Most studies in the NMA were phase III randomised clinical trials and 71% of studies included were considered to have a low risk of bias. In their response to the clarification letter, the company stated that the risk of bias was assessed by two independent reviewers.

Table 3.25: Summary of studies included for each NMA outcome – biologic-naïve

Trials	Comparator	Induction				Maintenance				
		Time (weeks)	Clinical remission	Clinical response	Mucosal healing	Length (weeks)	Time (weeks)	Clinical remission	Clinical response	Mucosal healing
ULTRA 1[18]	ADA vs placebo	8	✓	✓	✓	NA	NA	✓	✓	✓
ULTRA 2[19-22]		8	✓	✓	✓	44	52	✓	✓	✓
SELECTION	FIL vs placebo	10	✓	✓	✓	48	58	✓	✓	✓
PURSUIT-SC Induction[23]	GOL vs placebo	6	✓	✓	✓	NA	NA	✓	✓	✓
PURSUIT-SC Maintenance[24]		6	✓	✓	✓	54	60	✓	✓	✓
ACT 1[25]	IFX vs placebo	8	✓	✓	✓	54	54	✓	✓	✓
ACT 2[25]		8	✓	✓	✓	NA	NA	✓	✓	✓
Kobayashi 2016 (Japic)[26]		8	✓	✓	✓	NA	NA	✓	✓	✓
Jiang 2015[27]		8	✓	✓	✓	NA	NA	✓	✓	✓
NCT01551290[28]		8	✓	✓	✓	NA	NA	✓	✓	✓
OCTAVE 1[29]	TOF vs placebo	8	✓	✓	✓	NA	NA	✓	✓	✓
OCTAVE 2[29]		8	✓	✓	✓	NA	NA	✓	✓	✓
OCTAVE SUSTAIN[30]		8	✓	✓	✓	52	60	✓	✓	✓
UNIFI[31]	UST vs. placebo	8	✓	✓	✓	44	52	✓	✓	✓
GEMINI 1[32]	VDZ vs placebo	6	✓	✓	✓	46	52	✓	✓	✓
VISIBLE[33]		6	✓	✓	✓	46	52	✓	✓	✓
VARSITY[34]*	VDZ vs ADA	14	✓	✓	✓	52	52	✓	✓	✓
Based on Table 23 of the CS[1]										

Trials	Comparator	Induction				Maintenance				
		Time (weeks)	Clinical remission	Clinical response	Mucosal healing	Length (weeks)	Time (weeks)	Clinical remission	Clinical response	Mucosal healing
Notes: *The VARSITY study identified in the SLR was excluded from the maintenance phase remission/response analysis, as it lacked data for maintenance period responders by population.[35] However, recently published data were identified for this trial which allowed for estimation of the number of maintenance period responders based on published percentages of induction responders.[34] ADA = adalimumab; CS = company submission; FIL = filgotinib; GOL = golimumab; IFX = infliximab; NA = not applicable; NMA = network meta-analysis; TOF = tofacitinib; UST = ustekinumab; VDZ = vedolizumab										

Table 3.26: Summary of studies included for each NMA outcome – biologic- experienced

Trials	Comparator	Induction				Maintenance				
		Time (weeks)	Clinical remission	Clinical response	Mucosal healing	Length (weeks)	Time (weeks)	Clinical remission	Clinical response	Mucosal healing
ULTRA 2[19-22]	ADA vs placebo	8	✓	✓	✓	44	52	✓	✓	✓
SELECTION	FIL vs placebo	10	✓	✓	✓	48	58	✓	✓	✓
OCTAVE 1[29]	TOF vs placebo	8	✓	×	×	NA	NA	×	×	×
OCTAVE 2[29]		8	✓	×	×	NA	NA	×	×	×
OCTAVE SUSTAIN[30]		NA	×	×	×	52	60	✓	✓	×
UNIFI[31]	UST vs placebo	8	✓	✓	✓	44	52	✓	✓	✓
GEMINI 1[32]	VDZ vs placebo	6	✓	✓	✓	46	52	✓	✓	✓
VISIBLE[33]		6	×	×	×	46	52	✓	×	×
VARSITY[34]*	VDZ vs ADA	14	✓	✓	×	52	52	✓	×	✓
Source: Table 24 of the CS[1] *The VARSITY study identified in the SLR was excluded from the maintenance phase remission/response analysis, as it lacked data for maintenance period responders by population.[35] However, recently published data were identified for this trial which allowed for estimation of the number of maintenance period responders based on published percentages of induction responders.[34] ADA = adalimumab; CS = company submission; FIL = filgotinib; GOL = golimumab; IFX = infliximab; NA = not applicable; NMA = network meta-analysis; TOF = tofacitinib; UST = ustekinumab; VDZ = vedolizumab										

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 Method of analysis

For both the induction and maintenance phase NMAs, 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 SELECTION clinical programme. The primary outcomes (and those used in the CEA – see Section 4.2.6) of response and remission are based on the MCS, a continuous score, with no response, response without remission and response with remission essentially ordered categories on a continuous scale. The analysis for these outcomes therefore utilised a multinomial likelihood with a probit link (allowing for analysis of an ordered categorical variable and accounting for the correlation between response and remission outcomes). The company stated that this approach was preferred by the ERG in TA547.[10] The secondary endpoint of mucosal healing is a single binary endpoint, and as such was analysed with a binomial likelihood with a logit link. Analysis was undertaken in WinBUGS version 1.4.3.

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, and models were compared using the deviance information criterion (DIC), in keeping with NICE Decision Support Unit (DSU) guidelines.[36] As the analysis networks included limited data, fixed effect models were preferred for the analysis base-case in the case of similar DIC for the two models.[36] Full results for all three outcomes were presented in Appendix D.[4]

3.4.2 NMA results

3.4.2.1 Induction phase results

The NMA statistics for the posterior distribution of relative effects on the probit scale for the models and the probabilities of achieving MCS response and remission in the induction phase are summarised in Table 3.27. The CS states that for the biologic-naïve population, [redacted] whilst for the biologic-exposed population, [redacted][1] Also, in the biologic-naïve population, Filgotinib 200 mg was [redacted] and this was [redacted].[1] Likewise, in the biologic-exposed population, Filgotinib 200 mg was [redacted].[1]

3.4.2.2 Maintenance phase results

The results for the posterior distribution of relative effects on the probit scale and the probabilities of achieving MCS response and remission in the NMA conducted on the maintenance phase are summarised in Table 3.28. The CS states that for the biologic-naïve population, [redacted] whilst for the biologic-exposed population, [redacted][1] Also, in the biologic-naïve population, Filgotinib 200 mg was [redacted]

[redacted]. Likewise, in the biologic-exposed population, Filgotinib 200 mg was [redacted].[1]

Table 3.27: Induction phase base-case NMA results – relative effects of treatments on the probit scale and probabilities of achieving response and remission

Treatment	Results on the probit scale vs placebo, median (95% CrI)	Results on the probit scale vs filgotinib 200 mg, median (95% CrI)	Results on the probit scale vs filgotinib 100 mg, median (95% CrI)	Modelled probability of response – posterior median (95% CrI)	
				MCS response	MCS remission
Biologic-naïve population					
Placebo					
FIL 200 mg					
FIL 100 mg					
ADA 160/80/40 mg					
GOL 200/100 mg					
IFX 5 mg/kg					
TOF 10 mg					
UST 6 mg/kg					
VDZ 300 mg					
Biologic-experienced population					
Placebo					

Treatment	Results on the probit scale vs placebo, median (95% CrI)	Results on the probit scale vs filgotinib 200 mg, median (95% CrI)	Results on the probit scale vs filgotinib 100 mg, median (95% CrI)	Modelled probability of response – posterior median (95% CrI)	
				MCS response	MCS remission
FIL 200 mg					
FIL 100 mg					
ADA 160/80/40 mg					
TOF 10 mg					
UST 6 mg/kg					
VDZ 300 mg					

Based on Table 25 of the CS[1]
Notes: Positive values favour the first treatment. Negative values favour the second treatment.
ADA = adalimumab; CrI = credible interval; CS = company submission; FIL = filgotinib; GOL = golimumab; IFX = infliximab; MCS = Mayo clinic score; TOF = tofacitinib; UST = ustekinumab; VDZ = vedolizumab

Table 3.28: Maintenance phase base-case NMA results - relative effects of treatments on the probit scale and probabilities of achieving response and remission

Treatment	Results on the probit scale vs placebo, median (95% CrI)	Results on the probit scale vs filgotinib 200 mg, median (95% CrI)	Results on the probit scale vs filgotinib 100 mg, median (95% CrI)	Modelled probability of response – posterior median (95% CrI)	
				MCS response	MCS remission
Biologic-naïve population					
Placebo					
FIL 200 mg					

Treatment	Results on the probit scale vs placebo, median (95% CrI)	Results on the probit scale vs filgotinib 200 mg, median (95% CrI)	Results on the probit scale vs filgotinib 100 mg, median (95% CrI)	Modelled probability of response – posterior median (95% CrI)	
				MCS response	MCS remission
FIL 100 mg					
ADA 160/80/40 mg					
GOL 50 mg Q4W					
GOL 100 mg Q4W					
IFX 5 mg/kg					
TOF 5 mg					
TOF 10 mg					
UST 90 mg Q12W					
UST 90 mg Q8W					
VDZ 108 mg SC Q2W					
VDZ 300 mg Q8W					
VDZ 300 mg Q4W					

Treatment	Results on the probit scale vs placebo, median (95% CrI)	Results on the probit scale vs filgotinib 200 mg, median (95% CrI)	Results on the probit scale vs filgotinib 100 mg, median (95% CrI)	Modelled probability of response – posterior median (95% CrI)	
				MCS response	MCS remission
Biologic-experienced population					
Placebo					
FIL 200 mg					
FIL 100 mg					
ADA 160/80/40 mg					
TOF 5 mg					
TOF 10 mg					
UST 90 mg Q12W					
UST 90 mg Q8W					
VDZ 108 mg SC Q2W					
VDZ 300 mg Q8W					
VDZ 300 mg Q4W					

Source: Table 26 of the CS[1]

Notes: Positive values favour the first treatment. Negative values favour the second treatment.

Treatment	Results on the probit scale vs placebo, median (95% CrI)	Results on the probit scale vs filgotinib 200 mg, median (95% CrI)	Results on the probit scale vs filgotinib 100 mg, median (95% CrI)	Modelled probability of response – posterior median (95% CrI)	
				MCS response	MCS remission
ADA = adalimumab; CrI = credible interval; CS = company submission; FIL = filgotinib; GOL = golimumab; IFX = infliximab; MCS = Mayo clinic score; Q2W = once every 2 weeks; Q4W = once every 4 weeks; Q8W = once every 8 weeks; Q12W = Once every 12 weeks; TOF = tofacitinib; UST = ustekinumab; VDZ = vedolizumab					

ERG comment: The ERG considers that the NMAs were conducted using appropriate methods and that the induction phase NMA is appropriated to inform the question as the effectiveness of filgotinib 200 mg in comparison to the comparators in the decision problem in terms of response and remission.

However, the ERG questions the validity of the maintenance phase NMA on the grounds that it implies that all treatments are comparators in this phase when actually the only valid comparator is no treatment. This is because in clinical practice on entry to the maintenance phase the choice is either to continue with the treatment on which response occurred (the induction treatment) or curtail the induction treatment. Therefore, to inform that choice the only relevant data is the effectiveness of continuing the induction treatment relative to curtailing the induction treatment, which can only be informed by trials of that particular maintenance treatment. In other words, the effectiveness of any maintenance treatment relative to any other, as investigated in any other trial, is irrelevant. To put this another way, the effectiveness of the maintenance treatment relative to another would be relevant if in clinical practice the choice was between continuing with the induction treatment or switching to another, but switching is not considered in the CS.

The maintenance NMA could also be considered to have questionable validity in terms of heterogeneity. This is because the population on entry to the maintenance phase is those patients who have responded on the induction treatment, which, of course, varies between trials of different treatments. For there to be acceptable homogeneity one would have to assume that the effectiveness of a treatment in the maintenance phase does not depend on the nature of the induction treatment. Therefore, even if switching was possible in clinical practice, this NMA of remission at 58 weeks conditional on response having been achieved at 10 weeks would still be questionable.

In the clarification letter, the ERG asked the company to discuss this issue and provide a CEA scenario where the probability of remission at 58 weeks conditional on response at 10 weeks for each treatment was informed by only trials of that maintenance treatment vs. placebo.[3] However, the company seemed to completely misunderstand the issue and instead defended the NMA by stating that *"…the NMA doesn't pool any maintenance phase treatments where patients enter the maintenance phase with different induction phase treatment experiences"*.[3] The company therefore refused to conduct the requested analyses. As just explained, it is precisely because this is true that the studies should not be pooled, e.g., if there were trials of comparators at maintenance where the induction treatment had been filgotinib as opposed to the same comparator then it could make sense to pool them both because the populations at the start of maintenance would be homogenous, i.e., responded to filgotinib, and if the question to be answered was which treatment to switch to given responded to filgotinib. Therefore, this remains a key issue, which the ERG attempted to address in Section 3.5.

3.5 Additional work on clinical effectiveness undertaken by the ERG

Using the company method reported in Section B.3.3.1,[1] the ERG calculated per cycle values for 50-week probabilities of no response, response (no remission) and remission conditional on response at 10 weeks to replace the values from the maintenance phase NMA based on the individual RCT values at the end of the maintenance period as reported in Appendix D, see Tables 3.29 and 3.30).[4]

Table 3.29: Efficacy outcomes: MCS response/remission at maintenance – Biologic naïve patients

Trial	Treatment	n	No response* n (%)	Response without remission* n (%)	Response with remission* n (%)
ACT 1[25]	PBO	121*	28 (23.1%)*	7 (5.8%)*	10 (8.3%)*
	IFX 5 mg/kg Q8W	121*	32 (57.1%)*	10 (17.9%)*	14 (25.0%)*
GEMINI 1[32]	PBO	79	58 (73.4%)	6 (7.6%)	15 (19%)
	VDZ 300 mg Q8W	72	25 (34.7%)	14 (19.4%)	33 (45.8%)
	VDZ 300 mg Q4W	73	32 (43.8%)	6 (8.2%)	35 (47.9%)
OCTAVE SUSTAIN[30]	PBO	109	82 (75.2%)	15 (13.8%)	12 (11%)
	TOF 5 mg	115	50 (43.5%)	17 (14.8%)	48 (41.7%)
	TOF 10 mg	104	37 (35.6%)	21 (20.2%)	46 (44.2%)
PURSUIT-M[24]	PBO	154	106 (68.8%)	14 (9.1%)	34 (22.1%)
	GOL 100 mg Q4W	151	80 (53%)	21 (13.9%)	51 (33.8%)
	GOL 50 mg Q4W	151	76 (50.3%)	24 (15.9%)	50 (33.1%)
SELECTION	PBO	54	32 (59.3%)	15 (27.8%)	7 (13%)
	FIL 200 mg QD	107	27 (25.2%)	31 (29%)	49 (45.8%)
	PBO	54	26 (48.1%)	19 (35.2%)	9 (16.7%)
	FIL 100 mg QD	105	44 (41.9%)	35 (33.3%)	26 (24.8%)
ULTRA 2[19-22]	PBO	89*	32 (57.1%)*	10 (17.9%)*	14 (25.0%)*
	ADA 160/80/40 mg Q2W	56*	45 (50.6%)	16 (17.9%)	28 (31.5%)
UNIFI[31]	PBO	87	43 (49.4%)	17 (19.5%)	27 (31%)
	UST 90 mg Q12W	102	24 (23.5%)	28 (27.5%)	50 (49%)
	UST 90 mg Q8W	85	19 (22.4%)	25 (29.4%)	41 (48.2%)
VARSITY[34]	ADA/160/80/40 mg Q2W	212*	53 (25.0%)*	55 (25.9%)*	104 (49.1)*
	VDZ 300 mg Q8W	151*	53 (35.1%)*	24 (15.9%)*	74 (49.0%)*
VISIBLE[33]	PBO	37	30 (81.1%)	NR	7 (18.9%)
	VDZ 108 mg SC Q2W	67	31 (46.3%)	NR	36 (53.7%)
	VDZ 300 mg Q8W	32	15 (46.9%)	NR	17 (53.1%)

Based on Appendix D of the CS, Table 15[4]
* Values re-weighted as outlined in NMA methodology to account for heterogeneity between "treat-through" and "re-randomised trial design"
ADA = adalimumab; CS = company submission; FIL = filgotinib; GOL = golimumab; IFX = infliximab; NMA = network meta-analysis; QD = once daily; Q4W = once every 4 weeks; Q8W = once every 8 weeks; Q12W = Once every 12 weeks; TOF = tofacitinib; UST = ustekinumab; VDZ = vedolizumab

Table 3.30: Efficacy outcomes: MCS response/remission at maintenance – Biologic experienced patients

Trial	Treatment	n	No response* n (%)	Response without remission* n (%)	Response with remission* n (%)
GEMINI 1[32]	PBO	38	32 (84.2%)	4 (10.5%)	2 (5.3%)
	VDZ 300 mg Q4W	43	26 (60.5%)	6 (14.0%)	16 (37.2%)
	VDZ 300 mg Q8W	40	20 (50%)	1 (2.5%)	14 (35%)
OCTAVE SUSTAIN[30]	PBO	89	76 (85.4%)	3 (3.4%)	10 (11.2%)
	TOFA 5 mg	83	46 (55.4%)	17 (20.5%)	20 (24.1%)
	TOFA 10 mg	93	38 (40.9%)	21 (22.6%)	34 (36.6%)
SELECTION	PBO	44	34 (77.3%)	8 (18.2%)	2 (4.5%)
	FIL 200 mg QD	92	39 (42.4%)	33 (35.9%)	20 (21.7%)
	PBO	35	28 (80%)	4 (11.4%)	3 (8.6%)
	FIL 100 mg QD	67	41 (61.2%)	13 (19.4%)	13 (19.4%)
ULTRA 2[19-22]	PBO	29*	23 (79.3%)*	3 (10.3%)*	3 (10.3%)*
	ADA 160/80/40 mg Q2W	36*	21 (58.3%)*	7 (19.4%)*	8 (22.2%)*
UNIFI[31]	PBO	88	54 (61.3%)	19 (21.6%)	15 (17%)
	UST 90 mg Q12W	70	31 (44.3%)	23 (32.9%)	16 (22.9%)
	UST 90 mg Q8W	91	32 (35.2%)	23 (25.3%)	36 (39.6%)
VISIBLE[33]	PBO	19	NR	NR	1 (5.3%)
	VDZ 108 mg SC Q2W	39	NR	NR	13 (33.3%)
	VDZ 300 mg Q8W	22	NR	NR	6 (27.3%)
VARSITY[34]	VDZ 300 mg Q8W	44*	20 (45%)*	8 (18%)*	16 (36%)*
	ADA 160/80/40 mg Q2W	26*	13 (50%)*	0 (0%)*	13 (50%)*

Based on Appendix D of the CS, Table 20[4]
* Values re-weighted as outlined in NMA methodology to account for heterogeneity between "treat-through" and "re-randomised trial design"
ADA = adalimumab; CS = company submission; FIL = filgotinib; GOL = golimumab; IFX = infliximab; NMA = network meta-analysis; QD = once daily; Q4W = once every 4 weeks; Q8W = once every 8 weeks; Q12W = Once every 12 weeks; TOF = tofacitinib; UST = ustekinumab; VDZ = vedolizumab

The values from the RCTs used were per arm as opposed to the treatment effect e.g., relative risk given the following assumptions:

1) Maintenance probability for each intervention = relative risk (intervention vs. placebo) * probability (standard care) = probability (intervention)/probability (placebo) * baseline probability (standard care)
2) Baseline risk is different for each intervention given that induction achieved with the same intervention (see explanation above). Therefore, given no standard care estimate from observational data in UK clinical practice, the best estimate of the probability (standard care) is that from the placebo arm of the same trial, i.e., probability (standard care) = probability (placebo)
3) Therefore, maintenance probability for intervention = probability (intervention)

One problem with (2) is the possible presence of a placebo effect that might vary between trials. However, this is no more of a problem as existed in the NMA. Also, it might be argued that the placebo effect might be minimal given that patients on randomisation to intervention or placebo have already responded to treatment, which means that there can be no regression to the mean (the spontaneous improvement due to recruitment at a low point in a fluctuating condition). There might also be little Hawthorne effect (improvement simply by in a trial) since the ceiling for this might already have been reached during the induction phase.

The maintenance probabilities for standard care would have been difficult to estimate using these assumptions given that the placebo values were based on induction with the intervention rather than with placebo in the re-randomisation trials, which were in the majority. However, two of the placebo-controlled trials were treat-through and so could have provided values at the end of the maintenance phase (ULTRA 2 and ACT 1 for biologic naïve and ULTRA 2 for biologic experienced).[19-22, 25] Unfortunately, the numbers were not available for remission, but only no response or response (including remission). Therefore, the ERG could have done as the company did and applied the weighted average placebo data for % of responders who were remitters from the combined placebo arms of the other trials (58%) (See Tables 16 and 21 from Appendix D).[4] However, as discussed in Section 2.3, the ERG considered the comparison with standard care to be irrelevant.

3.6 Conclusions of the clinical effectiveness section

The clinical effectiveness evidence presented in the CS is based on the SELECTION clinical programme of induction and maintenance trials informing the safety and efficacy of filgotinib in moderately to severely active UC patients. SELECTION is a phase 2b/3, randomised, double-blind, placebo-controlled trial comparing filgotinib 200 mg once daily, filgotinib 100 mg once daily and placebo during a 10-week induction study; followed by a maintenance study (weeks 10 to 58) in which the same interventions are compared to placebo after re-randomisation of those who responded to filgotinib during induction[1]. The population of the induction period was stratified by biologic-naïve (cohort A) and biologic-experienced (cohort B) patients, resulting in the two induction studies. Although re-randomisation of responders to the intervention permits an assessment of outcomes at the end of the maintenance phase conditional on having achieve response, it does not inform the outcomes during the maintenance phase of those who did not achieve response. There is no unbiased estimate (based on randomised trial data) of filgotinib vs. placebo for the non-responders at the end of the maintenance phase because these patients were given the option to enter the LTE where it is unclear how many patients were lost to follow-up or if they maintained the original treatment allocation. Of course, if it is assumed that in clinical practice that patients will switch treatment on lack of response at induction then this might appear to be less of an issue. Although previous TAs indicate that discontinuation should occur on something resembling lack of response (TA342 recommends that

'benefit' should be observed and TA329 that 'clear evidence of response' be observed), no time limit is expressed either in terms of an induction period.[11, 12] Also, in the CEA, because follow-up of non-responders is limited to the end of induction, the effectiveness of subsequent treatments is assumed to be the same regardless of line of therapy in the biologic experienced. Therefore, re-randomisation also precludes an unbiased estimate of the long-term effectiveness of a sequence of biologic therapies. There were also issues identified in the risk of bias assessment of the SELECTION trial, particularly in terms of the balance of baseline characteristics, the effect of which is difficult to estimate.

In the induction phase, in cohort A, all efficacy outcomes in SELECTION showed statistically significant differences in favour of filgotinib 200 mg when compared with placebo.[3] In cohort B, a statistically significantly higher proportion of patients achieved EBS remission at week 10 in the filgotinib 200 mg group compared with the placebo group, but MCS remission, Endoscopic sub score of 0, and MCS remission (alternative definition) did not show statistically significant differences between groups. In the maintenance phase, all efficacy outcomes in SELECTION showed statistically significant differences in favour of filgotinib 200 mg when compared with placebo.

There were no trials identified comparing filgotinib vs. comparators other than placebo, so the company undertook a SLR and Bayesian NMA which aimed to provide comparison of the efficacy of filgotinib with other comparators listed in the final NICE scope.[1, 2] The company separated their analysis into two populations:

- **biologic naïve** (cohort A population: patients without prior use of any biologic (TNFα inhibitor or vedolizumab), which aligns to the SELECTION cohort A); and
- **biologic experienced** (cohort B population: patients who have previously demonstrated an inadequate clinical response, loss of response to, or intolerance to any biologic (TNFα inhibitor or vedolizumab), which aligns to the SELECTION cohort B).

The outcomes included in the NMA were: clinical remission, clinical response, mucosal healing.[1] These were assessed at two different time points, at the end of the Induction phase, and the end of the Maintenance phase, assumed to be, as in the SELECTION trial, 10 weeks, and 48 weeks from re-randomisation respectively. It is important to note that for the maintenance phase outcomes at 58 weeks were conditional on response at 10 weeks. Results for the primary outcomes, which were those used in the CEA, depended on the phase and the population. In the induction phase in the biologic-naïve population, filgotinib 200 mg was [redacted] and this was [redacted]. However, in the induction phase in the biologic-exposed population, filgotinib 200 mg was [redacted]. In the maintenance phase in the biologic-naïve population, filgotinib 200 mg was [redacted]. Likewise, in maintenance phase in the biologic-exposed population, filgotinib 200 mg was [redacted].

The ERG considers that the NMAs were conducted using appropriate methods and that the induction phase NMA is appropriated to inform the question as the effectiveness of filgotinib 200 mg in comparison to the comparators in the decision problem in terms of response and remission. However, the ERG questions the validity of the maintenance phase NMA on the grounds that it implies that all treatments are comparators in this phase when actually the only valid comparator, according to expected clinical practice, is no treatment or the curtailment of the intervention on which induction was achieved.

The NMA could also be considered to have questionable validity in terms of heterogeneity. This is because the population on entry to the maintenance phase is those patients who have responded on the induction treatment, which, of course, varies between trials of different treatments. In the clarification letter, the ERG asked the company to discuss this issue and provide a CEA scenario where the probability of remission at 58 weeks conditional on response at 10 weeks for each treatment was informed by only trials of that maintenance treatment vs. placebo.[3] However, the company seemed to completely misunderstand the issue and refused to conduct the requested analyses. Therefore, the ERG calculated values for 50-week probabilities of no response, response (no remission) and remission conditional on response at 10 weeks to replace the values from the maintenance phase NMA based on the individual RCT values at the end of the maintenance period as reported in Tables 15 and 20 Appendix D.[4]

4. COST EFFECTIVENESS

4.1 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 CS. 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.

4.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the CS.

4.1.1.1 Searches for cost effectiveness analysis review

Appendices G, H and I provided details of searches conducted to identify studies for cost effectiveness, HRQoL and cost and healthcare resource use for UC.[37-39] Searches were conducted on 8 May 2019 (cost effectiveness), 2 August 2019 (HRQoL), 19 September 2019 (cost and healthcare resource identification) and updated on 3 November 2020 (cost effectiveness, cost and healthcare resource identification) and 5 November 2020 (HRQoL). An English language restriction was applied to the Embase and PubMed searches and a date limit from 1 January 2000 to 3 November 2020 was reported for cost effectiveness searches. Relevant studies and recent systematic reviews were scanned for further studies. A summary of the searches is provided in Table 4.1.

Table 4.1: Data sources for cost effectiveness, HRQoL and healthcare resource use

Resource	Host/Source	Date ranges	Dates searched
Cost effectiveness			
Electronic databases			
Medline and Medline In-Process	PubMed	1.1.2000 - 3.11.20	8.5.19 3.11.20
Embase	Embase		
Cochrane Library CDSR CENTRAL CCA	Wiley		
HTA Database DARE NHS-EED	CRD		
EconLit	EBSCO		
Econpapers	Research Papers in Economics		
CEA Registry	Tufts Medical Center		
Conference proceedings			
ACG	Internet	2016 - 2020	Not stated
Crohn's and Colitis UK			
ECCO			

Resource	Host/Source	Date ranges	Dates searched
British Society of Gastroenterology			
ISPOR			
UEG Weeks			
HTA websites			
NICE SMC AWMSG PBAC in Australia HAS in France AIFA IQWiG in Germany National HTA agency in Spain	Internet	Not stated	Not stated
Health-related quality of life			
Electronic databases			
Medline and Medline In-Process	PubMed	Inception - 5.11.21	2.8.19 5.11.20
Embase	Embase		
Cochrane Library CDSR CENTRAL CCA	Wiley		
DARE HTA Database NHS-EED	CRD		
EconLit	EBSCO		
Econpapers	Research Papers in Economics		
CEA Registry	Tufts Medical Center		
Conference proceedings			
ACG	Internet	2016 - 2020	Not stated
Crohn's and Colitis UK			
ECCO			
British Society of Gastroenterology			
ISPOR			
UEG			
HTA websites			
NICE SMC AWMSG PBAC in Australia HAS in France	Internet	Not stated	Not stated

Resource	Host/Source	Date ranges	Dates searched
AIFA IQWiG in Germany National HTA agency in Spain			
Cost and healthcare resource identification			
Electronic databases			
Medline and Medline In-Process	PubMed	Inception - 3.11.21	19.9.19 3.11.20
Embase	Embase		
Cochrane Library CDSR CENTRAL CCA	Wiley		
HTA DARE NHS-EED	CRD		
EconLit	EBSCO		
Econpapers	Research Papers in Economics		
Conference proceedings			
ACG	Internet	2016 - 2020	Not stated
Crohn's and Colitis UK			
ECCO			
ISPOR			
UEG			
HTA websites			
NICE SMC AWMSG PBAC in Australia HAS in France AIFA IQWiG in Germany National HTA agency in Spain	Internet	Not stated	Not stated

ACG = American College of Gastroenterology; AIFA = Agenzia Italiana del Farmaco; AWMSG = All Wales Medicines Strategy Group; CCA = Cochrane Clinical Answers; CDSR = Cochrane Database of Systematic Reviews; CEA = cost effectiveness analysis; CENTRAL = Cochrane Central Register of Controlled Trials; CRD = Centre for Reviews and Dissemination; DARE = Database of Abstracts of Reviews of Effects; ECCO = European Crohn's and Colitis Organisation; EED = Economic Evaluation Database; HAS = Haute Autorité de Santé; HRQoL = health-related quality of life; HTA = health technology assessment; IQWiG = Institute for Quality and Efficiency in Healthcare; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; UEG = United European Gastroenterology; UK = United Kingdom

ERG comment:

- Searches were undertaken for separate SLRs to identify all cost effectiveness, HRQoL and healthcare resource use for UC. The CS provided sufficient details for the ERG to appraise the literature searches. A range of databases and conference proceedings were searched as well as HTA organisations.
- Searches were clearly structured using a combination of thesaurus headings and free text terms with synonyms and truncation.
- A date limitation was applied to cost effectiveness searches from 1 January 2000 to 8 May 2019. The ERG deemed that this span was adequate to find relevant cost effectiveness studies.

4.1.2 Inclusion/exclusion criteria

A SLR of cost effectiveness studies in UC was conducted to inform the economic model structure. The aim was to identify published economic evaluations of interventions for the treatment of moderately to severely active UC. The protocol was designed according to the PRISMA-P checklist.[40]

Span of review is 1 January 2000 to 3 November 2020. The PRISMA flow diagram, and study quality assessment are provided in Appendix G of the CS.[37]

In- and exclusion criteria for the review on cost effectiveness studies are presented in Table 4.2.

Table 4.2: Eligibility criteria (PICOS framework) for inclusion of studies in SLR

	Inclusion criteria	Exclusion criteria
Population	Adult (≥18 years) with moderately to severely active UC in whom conventional therapy cannot be tolerated, or the disease has responded inadequately or lost response to conventional (biologic-naïve) or biologic (biologic experienced) treatment	Crohn's disease, indeterminate colitis, ischemic colitis, fulminant colitis, ulcerative proctitis, toxic mega-colon. Patients with mild UC; if the study population is mixed (i.e., mild to severe), exclusion of studies in which data are not reported separately for moderate or severely active UC.
Intervention and comparators	Any licensed (country of analysis) interventions for the management of moderately to severely active UC	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 or pharmaco-economic evaluation, cost effectiveness, cost-utility, cost-benefit, 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
Language restrictions	English only	Other than English
Date restriction	None	None

	Inclusion criteria	Exclusion criteria
ICER = incremental cost effectiveness ratio; LYG = life years gained; PICOS = population, intervention, comparator, outcomes and study design; QALY = quality-adjusted life years; SLR = systematic literature review; UC = ulcerative colitis		

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. The rationales for excluding cost effectiveness studies after full paper reviewing are considered appropriate given the defined in- and exclusion criteria. There were some inconsistencies regarding the inclusion/exclusion criteria stated in Appendix G of the CS.[37] However, the company clarified this in its response to the request for clarification and it is unlikely that any relevant studies were excluded.[3]

4.1.3 Conclusions of the cost effectiveness review

The SLR identified 34 unique cost effectiveness models in UC. Of these, 12 studies, addressing 9 models, were specific to the UK. All models specific to the UK applied a Markov cohort model, in some cases combined with a decision tree (for the induction phase), a 'hybrid' model approach. Of the 12 UK studies, 11 studies adopted a long-term perspective, i.e., between a 10-year and a lifetime time horizon. A summary of the UK based cost effectiveness studies identified in the SLR is presented in Table 32 of the CS.[1] In Appendix G (Table 8) some model inputs of the included studies, such as utilities and costs, including sources are given as well.[37] Table 9 in Appendix G shows the rates of surgery and post-surgical complications.[37] A quality assessment of the included studies is given in an embedded Excel spread sheet.

ERG comment: Eligibility criteria were suitable for the SLR performed. The CS provides an adequate overview of the included studies, a structure of the commonly used Markov model, types of utilities and costs used as model inputs per study, inclusive sources/references. All studies were assessed for methodological quality.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 4.3: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	In line with NICE reference case
Perspective on costs	NHS and PSS	In line with NICE reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Partly in line with NICE reference case, however, a fully incremental analysis is not enabled in the model file
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	In line with NICE reference case

Element of health technology assessment	Reference case	ERG comment on company's submission
Synthesis of evidence on health effects	Based on systematic review	In line with NICE reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	In line with NICE reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	In line with NICE reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	In line with NICE reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	In line with NICE reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	In line with NICE reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	In line with NICE reference case

EQ-5D = EuroQoL-5 Dimensions Health Survey; ERG = Evidence Review Group; NHS = National Health Service; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom

4.2.2 Model structure

The model is constructed as a Markov model with nine health states and two transient states (Figure 4.1) and a 10-weekly cycle length. Distribution among health states in the first 10 weeks is based on the induction phase of the medication. After these first 10 weeks, the distribution among health states is based on the maintenance phase of the medication.

Patients start in the model with advanced therapy and have three options with regards to health states: Active UC, Response without remission and Remission. The definitions of these health states are as follows:

- Remission: A Mayo score of ≤ 2 points and no individual sub score > 1 point
- Response without remission: Not meeting remission definition, and a decrease from baseline in Mayo score of ≥ 30% and ≥ 3 points, accompanied by a decrease from baseline in the rectal bleeding sub score ≥ 1, or an absolute rectal bleeding sub score of 0 or 1
- Active UC: Remission and response without remission not achieved. Patients are also assumed to enter the model with moderately to severely active UC, as determined by a total Mayo score between 6 and 12 and the following sub scores: endoscopy score and Physician's Global Assessment score ≥2, rectal bleeding score and stool frequency score ≥1

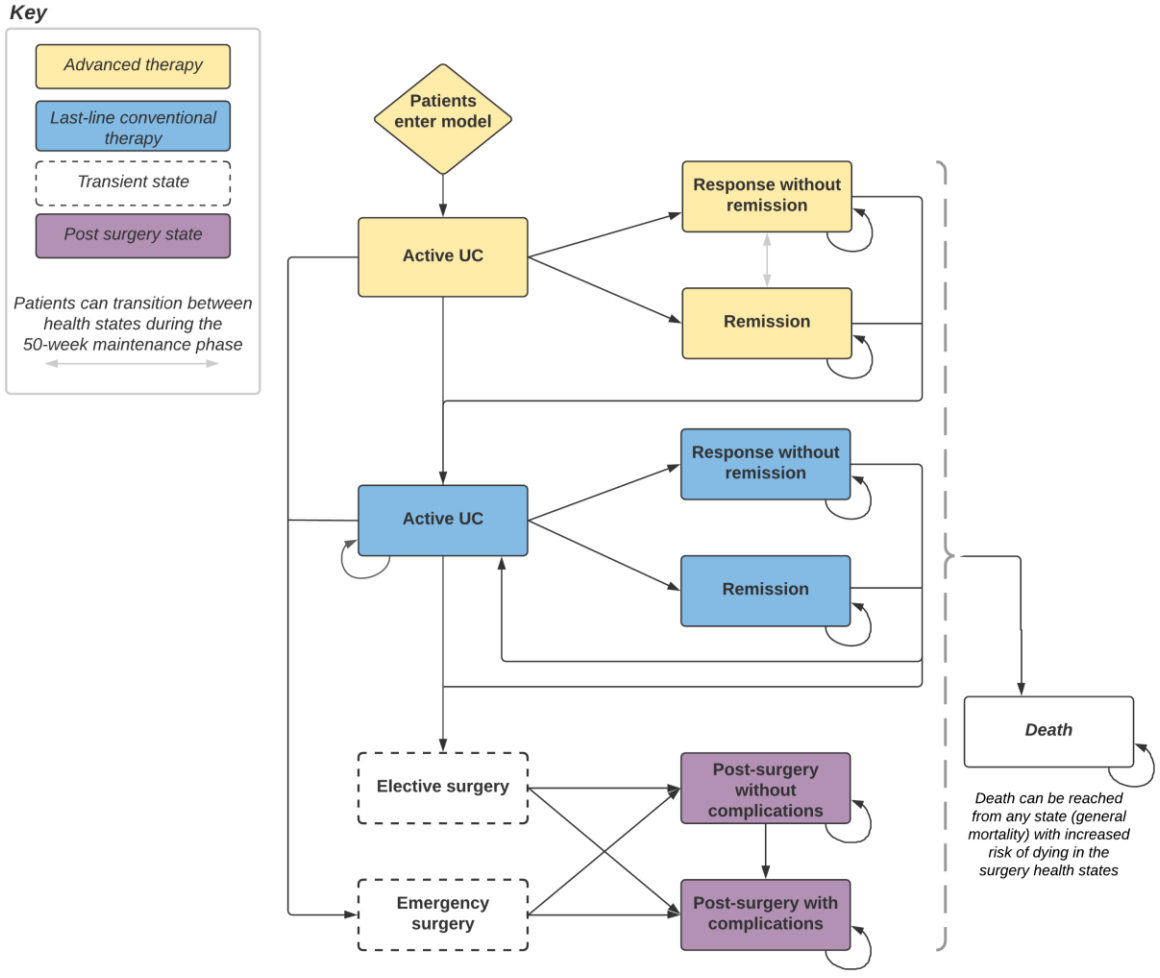
In case of treatment failure (going to active UC), patients receive last-line conventional treatment and also have three options with regards to health states: Active UC, response without remission and Remission. When patients are in Active UC during last-line (conventional) treatment there is the option that patients get surgery. Two types of surgery are included in the model: emergency surgery and elective surgery. These operations are modelled as transient states via which patients move to post-surgery states with or without complications. In these post-surgery states all drugs are stopped.

In the base-case analyses no treatment sequences are modelled, i.e., there is no possibility to have different advanced therapies before going to last-line conventional treatment. However, the model does give the opportunity to include up to four lines of advanced treatments, which was used for the scenario analyses.

The model was constructed with Excel.

Figure 4.1 shows the model structure with the health states in coloured blocks (including the death state in white) and transient states in blocks with dashed lines.

Figure 4.1: Model structure



Based on Figure 15 of the CS[1]
CS = company submission; UC = ulcerative colitis

ERG comment: The ERG asked three clarification questions regarding the model structure focussing on a) The absence of a specific relapse state in the model b) The use of a Markov model instead of a hybrid model (combination of Markov model with a decision tree to model the induction period and initial response) and c) the cycle length of 10 weeks.

a) In clarification question B6 the company was asked to explain why relapses were not specifically included in the model. The company explained that, in line with previous TAs (TA342, TA547, TA329 and TA633), relapse is modelled as the loss of response.[3] The ERG's clinical expert stated that relapse is not always due to loss of response but can also be triggered by (clostridium) infection or non-compliance. Remission could be obtained by other means than the switch of treatment in these cases, e.g., by using steroids or dose escalation. Although the company's assumption is a simplification of reality and may induce some bias, the ERG acknowledges that it would have been challenging to include relapses in the modelling. The ERG therefore considers the company's approach as likely appropriate. [41 41 41]
b) The company justified the use of a Markov model with the fact that it is widely used in ulcerative colitis and with the fact that is was used previously in TA329 and TA547.[10, 12] Also the company stated that it expected only minimal differences between a hybrid model and a Markov model since it was assumed that all patients in the first cycle had active UC. The ERG agrees that it is likely that the difference will be minimal due to that assumption and considers a Markov model appropriate.
c) In clarification question B8 the company was asked to explain why a cycle length of 10 weeks was chosen while some induction therapies only have a 6-week duration. The ERG asked whether a shorter cycle length (e.g., two weeks) might be more appropriate and whether different outcomes could be expected when using a shorter cycle length. The company explained that a cycle length of two weeks was not deemed appropriate since it is unlikely that a loss of response would already be detected within two weeks, which was confirmed by the ERG in appraisal TA633.[3] Also, during NICE Early Scientific Advice, experts also confirmed that a 10-week cycle length was appropriate with minimal bias. Overall, the ERG considers the company's choice of cycle length appropriate.

4.2.3 Population

The analysis considers patients with moderately to severely active UC who have had an inadequate response, loss of response or were intolerant to a previous biologic agent or conventional therapy. Two subgroups of patients are considered, according to prior exposure to biologic treatment (biologic-naïve and biologic-experienced). This is in accordance with the appraisal scope.

The baseline population characteristics (demographics) applied in the model are based on the SELECTION trial induction study population. Age, sex, and weight as present in the two SELECTION trial cohorts, biologic-naïve (n=659) and biologic-experienced (n=689) patients at the beginning of the trial are presented as inputs for the model. These are expressed as mean and SD (age and weight) and as proportion (sex) and are summarized in Table 33 of the CS.[1]

ERG comment: The ERG concerns relate to a) no subgroup analysis being conducted by age to reflect the bimodal distribution of age in UC, and b) the third subgroup of biologic-experienced patients with third-line of treatment missing from the analysis.

a) In the CS it was not explained how the demographics from the SELECTION trial were used for modelling. According to the response of the company in the clarification letter, mean age was used for modelling and this was used only for background mortality and age-specific utility. Age and sex dependent response to treatment (response to medication and surgery, side effects, etc.) are not incorporated in the model. The average age was 42 and 43 years in the SELECTION trial. Modelling based on mean age and SD does not reflect the bimodal incidence of UC as in the general population with the peak incidence between 15 and 25 years and a small secondary peak between 55 and 65 years. Also, men have a significantly higher incidence after age of 45. According to the

results of the SELECTION trial women tend to have higher remission rates than men. The impact of changing baseline age was tested in the DSA (±20%) and this showed that this parameter is not a key model driver. Further, two scenario analyses were conducted for two specific starting ages, 20 and 60 years old. Also, subgroup analyses on age group (<65 and ≥65 years) and sex (female and male) have been performed using the SELECTION trial data. These are however not very informative as the ERG assumes that no other model parameters were age-specific in these analyses.

b) Two populations of patients were considered in the company's base-case: Biologic-naïve patients and biologic-experienced patients. NICE guideline [NG130] as shown in Figure 4 of the CS (Document B page 28) suggests there may be three relevant subgroups: first-line advanced (first biologic), second-line advanced (after failed first biologic) and third-line advanced (after failed second biologic or targeted therapy).[1] In the CS it is not stated why two subgroups were defined instead of three.

The company responded that the two subgroups applied in the economic analysis (biologic-naïve and biologic-experienced) were defined as specified in the final decision problem scope issued by NICE.[3] This is also in line with previous submissions in UC (TA633,[17] TA547,[10] TA342[11]). Also, efficacy results for comparators identified in the SLR were not further split by line of therapy. The ERG acknowledges the lack of available estimates by treatment line, but considers that cost effectiveness estimates may differ even when the same efficacy estimates are used because of the positioning in the treatment pathway. Differential analyses for the biologic-experienced population should therefore be provided for the different treatment lines (that is second and third-line).

4.2.4 Interventions and comparators

The intervention considered in the model is filgotinib 200 mg, administered orally once daily. Filgotinib 100 mg is not considered in the model (this dosing is for a restrictive patient group with renal impairments). Comparators considered in the cost effectiveness analysis are first line biologics (TNFα inhibitors: infliximab, adalimumab, and golimumab), advanced biologics (ustekinumab, vedolizumab) and a JAK inhibitor (tofacitinib), see Table 4.4. This is in line with NICE recommendations, and the final NICE scope for filgotinib.[2]

All comparators have been included in the NMA of MCS response/remission for the biologic-naïve patients in both phases, induction and maintenance (see Figures 8 and 9 in the CS).[1] All included comparators except infliximab and golimumab have been included in the NMA of MCS response/remission for the biologic-experienced patients in both phases, induction and maintenance (see Figures 10 and 11 in the CS).[1] Conventional therapy is considered as a comparator and also modelled as a last line therapy.

Table 4.4: Intervention and comparators

Treatment	Route of administration	Dosing instruction	Standard dose (maintenance)	Escalated dose (maintenance)
Filgotinib	Orally	200 mg daily	200 mg qd	NA
Adalimumab	SC	Initially 160 mg, then 80 mg at week 2, and 40 mg every other week thereafter	40 mg q2w	40 mg qw
Golimumab	SC	Initially 200 mg, then 100 mg at week 2, and 50 mg every 4 weeks thereafter	50 mg q4w	100 mg q4w

Treatment	Route of administration	Dosing instruction	Standard dose (maintenance)	Escalated dose (maintenance)
Infliximab	IV	Initially 5 mg/kg, repeated at week 2 and 6, then every 8 weeks thereafter	5 mg/kg q8w	5 mg/kg q4w
Tofacitinib	Orally	10 mg twice daily for 8 weeks, then 5 mg twice daily	5 mg bid	10 mg bid
Ustekinumab	IV initially, then SC	Initial IV dose based on body weight: ≤ 55 kg: 260 mg >55 kg to ≤ 85 kg: 390 mg > 85 kg: 520 mg Followed by a 90 mg dose at week 8, then 90 mg every 12 weeks thereafter	90 mg q12w	90 mg q8w
Vedolizumab IV	IV	300 mg initially, repeated at week 2 and 6, then every 8 weeks thereafter	300 mg q8w	300 mg q4w
Vedolizumab SC	IV initially, then SC	300 mg IV dose initially, repeated at week 2 and 6, then 108 mg every 2 weeks thereafter	108 mg q2w	NA

Source: Table 36, CS[1]
IV = intravenous; NA = not applicable; q2w = once every 2 weeks; q4w = once every 4 weeks; q8w = once every 8 weeks; qd = once daily; qw = once weekly; SC = subcutaneous

A single dosing regimen is applied during the induction phase. For the maintenance phase, two dosing regimens are considered in the analysis: standard dose and escalated dose. Dose escalation was only assumed to impact the cost of treatments, and not treatment response.

Conventional therapy is modelled as a last-line therapy (in line with TA329) and consists of a variety of therapies (Table 4.5). In the model base-case, patients initiate advanced treatment, but following treatment failure, patients are assumed to initiate and remain on conventional treatment (indefinitely irrespective of whether they achieve response), unless they undergo surgery.

Table 4.5: Conventional therapy

Treatment	Route of administration	Dosing instruction	Patient usage
Amino salicylates			
Balsalazide	Orally	1.5 mg twice daily adjusted according to response (maximum 6 g per day)	12.6%
Mesalazine	Orally	1.2 to 2.4 g once daily	12.6%

Treatment	Route of administration	Dosing instruction	Patient usage
Olsalazine	Orally	500 mg twice daily	12.6%
Sulfasalazine	Suppository	0.5 to 1 g twice daily	12.6%
Corticosteroids			
Budesonide	Topically	1 metered application once daily on alternate days	3.8%
Prednisolone	Orally	Initially 20–40 mg daily until remission occurs, followed by reducing dose	44.1%
Immunomodulators			
Azathioprine	Orally	2.0 to 2.5 mg/kg daily	46.4%
Source: Table 37[1]			

For the biologic-naïve population, the model compared all strategies consisting of an advanced treatment in first-line, using all comparators available from the NMA, excluding ustekinumab which is not recommended for this population (as according to the NICE scope ustekinumab should be used only if a TNFα inhibitor has failed or cannot be tolerated).[2] This is followed by last-line conventional therapy (Table 38 in CS).[1] A treatment strategy considering conventional therapy alone, based on the placebo efficacy results from the NMA, was also included. Last-line conventional therapy efficacy is based on assumed very low levels of efficacy (99% non-responders).

For the biologic-experienced population, the model is assumed to start later in the treatment pathway (patients had previous exposure to a biologic treatment). All comparator therapies available from the NMA were considered (Table 39 in CS).[1]

Alternative treatment sequences, which consider multiple lines of advanced treatment, are explored in a scenario analysis. The treatment sequences are based on the NICE guidelines (CS Section B.1.3.4), clinician validation (CS Section B.3.10), and data from the IBD registry (CS ref 144).[1] These sources suggest that the majority of biologic-naïve patients are treated with vedolizumab or another TNFα inhibitor following failure of a TNFα inhibitor in first-line, with tofacitinib or ustekinumab commonly used as a third-line treatment. For comparisons, the same treatment sequences were applied for all comparators (CS Section B.3.8).[1]

ERG comment: The main concerns of the ERG relate to a) the composition of conventional therapy, b) the appropriateness of conventional therapy as a comparator, and c) the exclusion of treatment sequences.

a) In conventional therapy only azathioprine is included as an immunosuppressant. Mercaptopurine (6MP) and cyclosporine are not considered although these drugs are also being used for the treatment of UC. No justification is given why these drugs are not included. It is unclear whether costs of these are comparable with azathioprine. The company states in their response that cyclosporine may be used for severe acute UC refractory to corticosteroid treatment. They expect that the impact of the inclusion of cyclosporine to conventional therapy in the model would be minimal. They also state that mercaptopurine is used less often than azathioprine in the UK because it is only considered as an option to use in UC when patients are unable to tolerate azathioprine. Also, according to the literature the efficacy between 6-mercaptopurine and azathioprine should be

similar. The company finds that including azathioprine only represents this treatment option well. These statements seem appropriate.

b) Conventional care should not be included as a comparator, see Section 2.3. In the NICE treatment pathway, it is proposed that Filgotinib should be used for patients who had an inadequate response, lost response, or are intolerant to conventional therapy. This is also the modelled population. The comparators to Filgotinib (drugs suitable for such patients) at this point and further down the treatment pathway are either biologics or a JAK inhibitor. Conventional therapy is not competing with Filgotinib and should not be used in a cost effectiveness comparison.

c) No treatment sequences were modelled in the company's original base-case. Given the treatment pathway, the ERG considers that the original company base-case does not represent clinical practice. The company updated the base-case to include treatment sequences, to account for the potential impact of treatment sequences on cost effectiveness outcomes, after the ERG requested it (Table 4.6). The ERG considers there to be uncertainty about and variability in clinical practice but broadly agrees with the selection of subsequent treatments. The ERG's clinical expert also confirmed that the company's treatment sequences looked mostly appropriate. However, the expert considered that an alternative sequence in the biologic-naïve population could be adalimumab followed by vedolizumab IV and tofacitinib, and in the biologic-experienced population vedolizumab IV followed by tofacitinib. The ERG explored these sequences in scenarios.

Table 4.6: Treatment sequences in base-case

First line	Second-line	Third-line
Biologic-naïve population		
Filgotinib	Adalimumab	Vedolizumab IV
Conventional therapy	-	-
Golimumab	Vedolizumab IV	Ustekinumab
Adalimumab	Vedolizumab IV	Ustekinumab
Infliximab	Vedolizumab IV	Ustekinumab
Tofacitinib	Adalimumab	Vedolizumab IV
Vedolizumab SC	Tofacitinib	Ustekinumab
Vedolizumab IV	Tofacitinib	Ustekinumab
Biologic-experienced population		
Filgotinib	Vedolizumab IV	-
Conventional therapy	-	-
Adalimumab	Vedolizumab IV	-
Tofacitinib	Vedolizumab IV	-
Ustekinumab	Vedolizumab IV	-
Vedolizumab SC	Ustekinumab	-
Vedolizumab IV	Ustekinumab	-
Source: Response to clarification[3] IV = intravenous; SC = subcutaneous		

4.2.5 Perspective, time horizon and discounting

Costs are considered from the NHS and Personal Social Services perspective in England and Wales (in line with current NICE guidance). Therefore, patients' out of pocket expenses, carers' costs, and lost productivity are excluded.

A lifetime horizon was used for the base-case analysis. It was assumed that patients did not live past the age of 100. The model applies a fixed 10-week cycle length throughout the time horizon to allow for a continuous sequence of treatments, and a half-cycle correction was implemented.

Discount rates of 3.5% are applied to both, costs and benefits. This is in line with the NICE reference case. Discount rate was varied in deterministic sensitivity analyses (DSAs; 0% and 6%).

ERG comment: The company's approach is appropriate.

4.2.6 Treatment effectiveness and extrapolation

The main sources of evidence on treatment effectiveness used for intervention and comparators is the NMA reported in Section B.2.9 of the CS.[1]

In the economic model, the induction and maintenance phase are modelled separately with their own set of transitions and assumptions. The phases will be discussed separately here as well.

4.2.6.1 Induction phase

The distribution of patients at the end of the induction phase was informed by the NMA for the induction period alone as reported in Table 25 of the CS.[1] The NMA results included probability of overall response and remission. The proportion of patients achieving response (i.e., without remission) was estimated as the difference of patients receiving overall response (including remission), and patients achieving remission. The remainder of the population (1 minus overall response) would be in active UC at the end of the induction phase. See Table 4.7 for induction efficacy as implemented in the model.

Table 4.7: Estimated treatment efficacy based on NMA of trials at induction

Treatment	Active UC	Response without remission[#]	Remission[#]
Biologic-naive			
Filgotinib	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]	[redacted]
Conventional therapy	[redacted]	[redacted]	[redacted]
Conventional therapy (last-line)[*]	[redacted][*]	[redacted]	[redacted]
Biologic-exposed			
Filgotinib	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]
Vedolizumab	[redacted]	[redacted]	[redacted]
Conventional therapy	[redacted]	[redacted]	[redacted]
Conventional therapy (last-line)*	[redacted]	[redacted]	[redacted]
Based on Table 40 of the CS[1]			

Treatment	Active UC	Response without remission[#]	Remission[#]
[#] Please note that in Table 40 in the CS, the probabilities for response without remission and remission were switched – the ERG has corrected this here; * assumption CS = company submission; ERG = Evidence Review Group; NMA = network meta-analysis; UC = ulcerative colitis			

4.2.6.2 Maintenance phase

According to the CS, maintenance phase transition probabilities were converted from estimates of non-response, response (including remission), and remission in the maintenance NMA to 10-weekly probabilities which were applied in the model over the 50-week maintenance phase period in the following way:[1]

The output of the maintenance NMA was assumed to reflect results over 60 weeks of treatment; 10 weeks in induction, and 50 weeks in maintenance. Then, assuming a constant risk, the probability of no response was adjusted to a 10-weekly rate using

$$\text{10-weekly loss of response} = 1 - \exp(-\lambda)$$

where

$$\lambda = -\frac{\text{Cycle length}}{\text{Maintenance length}} \log(1 - \Pr(\text{no response at maintenance}))$$

Effectively, the probability of no response was first calculated as one overall response (including remission). Then, this probability of no response was then recalculated into a 10-week probability (please note that the company used ln where the formula in the CS states log without specifying the base). This 10-weekly loss of response was then applied to the total group of responders (including remission) to calculate transitions to the active UC health state. The relative proportions of patients in response without remission and remission were assumed to remain constant, so there would be no modelled transitions from remission to response without remission or vice versa.

For instance, in the biologic naïve population, for conventional therapy (taken from the NMA placebo arm), the probability of response (without remission) was equal to the probability of remission, that is, probability of response including remission was [redacted] and probability of remission was [redacted], making the probability of response without remission [redacted] – [redacted] = [redacted] as well; a 50/50 proportion (see Table 26 of the CS).[1] The probability of no response would therefore be 1 – [redacted] = [redacted] which translates into a 10-weekly probability of [redacted] for loss of response. The remaining [redacted] would then be divided 50/50 over response (without remission) and remission at [redacted] each. See Table 4.8 for probabilities calculated in this way for all treatments.

The risk of loss of response was extrapolated beyond the trial periods and assumed to be constant. Also, the distribution over the response (without remission) and remission states according to the situation in the maintenance phase was assumed to remain constant in subsequent cycles.

After the 50-week maintenance period, patients are assumed to remain at the same level of response, and on the same treatment indefinitely, until they lose response and move to the active UC health state.

However, since in clinical practice patients in stable remission may discontinue treatment, a stopping rule is explored in a scenario for a proportion of patients.

Table 4.8: Estimated treatment efficacy based on NMA of trials at maintenance

Treatment	Loss of response (10-weekly rate)	Response without remission (proportion of patients)	Remission (proportion of patients)
Biologic-naive			
Filgotinib	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]
Tofacitinib^	[redacted]	[redacted]	[redacted]
Vedolizumab IV	[redacted]	[redacted]	[redacted]
Vedolizumab SC	[redacted]	[redacted]	[redacted]
Conventional therapy	[redacted]	[redacted]	[redacted]
Conventional therapy (last-line)*	[redacted]	[redacted]	[redacted]
Biologic-exposed			
Filgotinib	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]
Tofacitinib	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]
Vedolizumab IV	[redacted]	[redacted]	[redacted]
Vedolizumab SC	[redacted]	[redacted]	[redacted]
Conventional therapy	[redacted]	[redacted]	[redacted]
Conventional therapy (last-line)*	[redacted]	[redacted]	[redacted]

Based on Table 41 of the CS[1]
^ In Table 41 of the CS, the probabilities for tofacitinib were mistakenly represented by the probabilities for ustekinumab. The ERG corrected this in the current table; * assumption
CS = company submission; ERG = Evidence Review Group; IV = intravenous; NMA = network meta-analysis; SC = subcutaneous

4.2.6.3 Surgery and surgery complications

In the model, a 10-weekly probability of 0.066% for elective surgery was used, and 0.0025% for emergency surgery. In the absence of recent literature on colectomy rates, these probabilities were derived from a retrospective 15-year study of the UK Hospital Episode Statistics database.[42]

Rates of perioperative (short-term) complications were taken from the UK 2014 national audit of inpatient care for adults with UC, where perioperative complications were reported in 32% and 35% of patients who underwent elective and non-elective surgery, respectively.[43]

Post-surgery long-term complications were entered in the model as a 10-weekly probability of 1.81% which was based on Ferrante et al. reporting the rate of pouchitis in UC patients over a 6.5 years follow-

up. The probability of long-term complications was assumed constant over the entire time horizon of the model, irrespective of when the surgery took place.[44]

Age- and sex-related all-cause mortality obtained from UK life tables was applied in the model. UC disease severity or treatment in the pre- and post-surgery states were assumed not to affect mortality. A peri-operative mortality of 2.84% was applied to all patients undergoing surgery, as derived from Archer et al.[45]

ERG comment: The main concerns of the ERG relate to a) the assumption of 'non-response' being the same concept as 'loss of response'; b) questionable validity of maintenance NMA; c) equal loss of response assumed for remission and response; d) constant loss of response assumed based on observed non-response at end of maintenance phase; e) validity of treat-through trial results to obtain estimates of loss of response; f) there is uncertainty on whether and how dose escalations were included in the efficacy estimates of the comparator treatments; g) the probability of developing post-surgery complications; and h) the probability of post-surgery complications being assumed constant over lifetime.

a) The reasoning of the company is that all patients who are not in remission or response at the end of the maintenance phase have lost their response. However, 'loss of response' as such was not an endpoint in the NMA. It is, however, used as the main parameter to base maintenance phase (and therefore long-term) efficacy on. The ERG is concerned that centering treatment efficacy around an outcome that was not officially reported in the NMA introduces bias which cannot be captured or quantified and the ERG would therefore classify this assumption as a potential source of structural uncertainty.
b) As discussed in Section 3.4.2 the ERG questions the validity of the maintenance NMA on the grounds that all treatments are comparators in this phase when the only valid comparator would be no treatment. Based on this key issue (key issue 4) the ERG in their base-case replaced the probabilities for loss of response, response, and remission in the maintenance phase, by those derived from individual trial results.
c) Loss of response is assumed to be equal for those in remission and those in only response (without remission), in the sense that the proportion of those in response (without remission) to those in remission as observed at the end of the maintenance phase is maintained for the entire time horizon. This would imply that if at the end of the maintenance phase, there are fewer patients in remission than in response, this cannot turn around anymore. The ERG questions the clinical plausibility of this assumption. Remission may be more difficult to attain than response, but once in remission, patients may be more stable, and stay in remission longer before they lose response than patients in response without remission. The ERG's clinical expert confirmed this. Unfortunately, the model does not allow for this to happen. In response to clarification question B16d asking about this assumption of equal proportions (among other things) the company replied that *"in the base-case, the long-term loss of response over the model time horizon was estimated from the NMA results and the rates did not differ by health state (e.g. the response but not remission state vs. remission state)"*.[3] The ERG does not consider this to be a fair justification of having equal loss of response between response states as the NMA did not deliver any results or information that could show equal or differential loss of response rates. Adjusting the model to allow for differential loss of response would require structural changes beyond what the ERG can do given limited time, but the ERG considers this assumption to potentially have a substantial impact on model results.
d) Related to the above point, the loss of response is not only assumed equal for response and remission, it is also assumed to be constant over lifetime based on the proportion of non-responders at the end of the maintenance phase. In their response to clarification question B16a on how likely

this is, the company stated that loss of response will probably decrease over time, but there is no evidence to say exactly how. As a consequence, the company stated, the current constant loss of response rates would likely underestimate the average duration of treatment. The ERG would like to emphasize that constant loss of response rates would also likely favour treatments with lower observed non-response where it concerns effectiveness (with filgotinib having the lowest non-response at end of maintenance in the biologic-naïve population). The company provided a scenario where the loss of response rate was lowered by 25% after the first year of maintenance. The ERG observed that implementing this scenario had mixed effects on the net monetary benefits, probably because of interplay between costs (related to treatment duration) and the proportions of patients in active UC, response and remission states, which are all affected by the rate of loss of response. Because of uncertainty on the true reduction, and also on whether the reduction should be equal for all comparators, the ERG applied the 25% reduction in a scenario.

e) The probability of loss of response is calculated from the percentage of responders in the maintenance phase. In the re-randomized trials, indeed all patients that started the maintenance phase were responders at the end of the induction phase. However, in the treat-through trials, at start of maintenance not all patients would be responders. On page 89 of the CS there is explanation on accounting and correcting for this in the NMA. These corrections mostly pertain to re-estimating response and remission, as this is what the NMA estimated. The ERG is unsure whether this correction solves the issue that for treat-through trials the proportion of people not responding after one year is estimated based on a mix of both responders and non-responders at the start of the maintenance period. Furthermore, as stated above, the ERG considered the NMA inappropriate in the maintenance phase and used individual trial data to inform effectiveness estimates. The ERG excluded those comparators whose effectiveness estimates were based on treat-through trials from the analysis in a scenario.

f) Dose escalations were implemented for all comparators but not for filgotinib. The escalated doses were included in the cost calculations. However, no efficacy estimates were provided contingent on dose escalation. Therefore, dose escalations will only weigh on the costs of the comparators and will not have a benefit, potentially inducing a bias in favour of filgotinib.

g) The probability of post-surgery complications was taken from a Belgian study that reported complications after proctocolectomy over a period of 6.5 years.[44] The study reported that out of 173 patients, 46% developed at least 1 episode of pouchitis, while chronic pouchitis was seen in 33 patients (19%). The company then use the 46% to calculate the 10-weekly constant probability of developing post-surgery complications, which lets patients move to the post-surgery complications health state, and assigns them the associated substantially lowered utility score for the remainder of their lifetime. However, most of these patients do not have chronic pouchitis but the acute form which can be treated. The ERG considers the 46% to be an overestimation of the true probability of developing chronic complications. Although the same probability was used in TA547, it was not appropriate there either as in the TA547 CS, the company stated that post surgery complications were assumed to be represented by chronic pouchitis.[10] Overestimating long-term incidence of post-surgery complications would favour treatments where surgery takes place less often, which would ultimately be treatments with low loss of response since surgery only takes place in patients in active UC. The ERG therefore uses the probability of chronic pouchitis in its base-case.

h) Observed post-surgery complication rates taken from the above study with a 6.5 year follow-up were recalculated into a 10-weekly probability which was implemented as a constant probability over the entire time horizon of the model.[44] In question B18 of the clarification letter the ERG asked the company to comment on the likelihood of patients developing post-surgery complications multiple decades after they had the surgery, also in light of the limited follow-up this was based on. The company responded that *"clinical experts have stated that post-surgical complications can be*

short- and long-term in nature. For those considered to be long term, these can be experienced multiple decades after surgery e.g. pouch failure".[3] The ERG feels that in this response, the company is rather referring to experiencing the consequences of existing long-term complications than to the incidence of new complications, and so the issue remains.

The ERG also identified the following:

a) An error in the induction phase transitions for response and remission as reported in CS Table 40.[1] The probabilities for response without remission and remission seem to have been switched in CS Table 40 (and for both populations) – in the model the probabilities were implemented correctly though. The ERG corrected the probabilities in Table 4.7 above.
b) An error in the maintenance phase percentages for tofacitinib in Table 41 of the CS. The numbers for tofacitinib in the treatment naïve population in Table 41 of the CS actually reflected the ustekinumab percentages – in the model the probabilities were implemented correctly though. The ERG included the correct percentages for tofacitinib in the treatment naïve population in Table 4.8 above.
c) Some inconsistencies in the loss of response formula: log should be replaced by ln to reproduce probabilities used and it uses 50 weeks of maintenance phase although the CS stated that the maintenance NMA was assumed to reflect 60 weeks of treatment results. The ERG considers it justified to use a 50-week period for calculating the loss of response from maintenance phase to a 10-weekly probability, but is in doubt as to what the company intends to say when they state that the maintenance NMA was assumed to reflect 60 weeks of treatment results.

4.2.7 Adverse events

The main source of evidence on treatment AEs used for intervention and comparators is the safety NMA described in Section B.2.9.13 of the CS.[1] Only serious infections were included in the health economic analysis due to the substantial impact on costs and HRQoL.

The probabilities of serious infection from the safety NMA were converted into 10-weekly probabilities, see Table 4.9. In a scenario analysis, the rates of serious infections applied in TA547[10] were used, based on a safety NMA as reported by Lohan et al. 2019.[46] This alternative NMA did however not include filgotinib and ustekinumab. In the scenario, filgotinib was assigned the highest infection rate observed in the NMA (which was for tofacitinib), and ustekinumab the lowest (vedolizumab).

Table 4.9: Serious infection rate applied in base-case and scenario

Treatment	Probability from Safety NMA	10-week probability base-case	10-week probability scenario
Filgotinib	[redacted]	[redacted]	3.8%
Adalimumab	[redacted]	[redacted]	0.9%
Golimumab	[redacted]	[redacted]	0.1%
Infliximab	[redacted]	[redacted]	0.4%
Tofacitinib	[redacted]	[redacted]	3.8%
Ustekinumab	[redacted]	[redacted]	0.2%
Vedolizumab	[redacted]	[redacted]	0.2%
Conventional therapy	[redacted]	[redacted]	0.9%

Based on Tables 42 and 43 of the CS[1]
CS = company submission; NMA = network meta-analysis

ERG comment: The ERG considers the approach taken by the company with regard to incorporating AEs to be reasonable. A minor issue may be that only serious infection is taken into account while other infections were quite prevalent for filgotinib (see Table 30 of the CS).[1] However, including only serious infection was in line with the approach taken in TA547 and TA633.[10, 17] Also, the scenario performed by the company had a minimal effect on final model results, and so uncertainty in the AE rate probably only impacts overall uncertainty in cost effectiveness results to a small extent.

4.2.8 Health-related quality of life

EQ-5D-5L data were collected alongside the SELECTION trial at baseline, week 10 (induction study), and week 58 (maintenance study). EuroQoL-5 Dimensions-5 Levels Health Survey (EQ-5D-5L) measurements were mapped to EuroQoL-5 Dimensions-3 Levels Health Survey (EQ-5D-3L) values using the crosswalk described by van Hout.[47] The data were analysed to predict the mean utility for the pre-surgical health states of the model: remission, response without remission, and active UC.

For the surgery with complications and post-surgery states the SELECTION trial did not provide data. The systematic review identified a modelling study by Arsenau et al. that provided the utilities for surgical and post-surgical health states.[48] The utility values were based on TTO exercises with 48 patients. The ratios between each state and remission were calculated using the values from Arsenau et al[484848]. 2006.[48] These ratios were then applied to the remission utility value in SELECTION.

The company reports there is the possibility that the utility values for the more severe health states may be skewed upwards due to adaptation of patients to UC. There is also the risk of selection bias when using the trial data since patients who do not feel well may not fill in the questionnaire, resulting in higher utility scores.

Notably, there is a lack of consistency between the estimated health utility values from SELECTION and from published literature identified in the systematic review, which is particularly true for the active UC health state. The CS explains that the active UC health state in the model includes patients where no further biologic treatment would be given, and patients remain in this health state until they receive surgery or die.[1] This is not true for patients entering the SELECTION trial. Therefore, it is likely that the utility value for the active UC state is overestimated in the base-case.

No treatment dependent utilities were applied.

4.2.8.1 Disutility values

The only disutility value applied in the model is for the adverse event of a serious infection due to pharmaceutical treatment (Section B.3.3.3). A disutility for pneumonia (-0.52) was obtained from a cost effectiveness study by Wilson et al.[49] This disutility was applied to all serious infections and was adjusted for the expected duration of the event (7 days, in line with TA547, resulting in a disutility of 0.052 applied over the 10-weekly cycle.[10]

Note that an adjustment of health state utility values by age and sex was applied to all patients in the model to account for the natural decline of quality of life due to age and comorbidities. For active UC the EQ-5D-5L data from the SELECTION trial programme as measured at baseline was used, and for the health states remission, and response without remission, the EQ-5D-5L data at 10 weeks was used. These estimates were used because a higher number of patients completed the EQ-5D-5L survey at 10 weeks than at 58 weeks. A scenario analysis using the estimates at 58 weeks (for the health states remission and response without remission) is provided in Section B.3.8.4 of the CS. One disutility value (-0.052) for all serious infections was used.

4.2.8.2 Health state utility values

A summary of all utility values used in the cost effectiveness analysis is provided in Table 4.10.

Table 4.10: Summary of utility values used for the cost effectiveness analysis base-case

State	Utility value: mean (standard error)	Reference in submission (Section and page number)	Justification
Baseline	Dependent on age and sex	Section B.3.4.5	To reflect the natural decline of patients' quality of life associated with age
Remission	[redacted]	Section B.3.4.5	Estimated from the SELECTION clinical trial
Response without remission	[redacted]	Section B.3.4.5	
Active UC	[redacted]	Section B.3.4.5	
Surgery	[redacted]	Section B.3.4.5	Surgery and post-surgery states imputed using the rates in Arsenau et al. [48], as surgical health state utilities were not available from SELECTION
Surgery with complications	[redacted]	Section B.3.4.5	
Post-surgery without complications	[redacted]	Section B.3.4.5	
Post-surgery with complications	[redacted]	Section B.3.4.5	
Disutility due to serious infection	-0.052 (0.019)	Section B.3.4.4	Consistent with TA547

Source: Table 45, CS[1]
TA = technology appraisal; UC = ulcerative colitis

4.2.8.3 Scenario analysis

As there are a number of published studies reporting utility values in UC that have been noted as appropriate sources in previous technology appraisals, scenario analyses are provided using a range of utility inputs. Most studies did not report values for the surgery and post-surgery states, and therefore these values were imputed using the values from Arsenau et al., similar to the base-case. A summary of the values used in scenario analyses is provided in **Error! Reference source not found.** of the CS.[48]

ERG comment: The main concerns of the ERG relate to a) considerable uncertainty about plausible utility estimates; b) progression of disease not taken into account in utility values; c) utility decrement of serious infection not verifiable; and d) lack of clarity on one utility input.

a) There is considerable uncertainty regarding the most plausible utility estimates. There is a range of sources and a lack of consistency between the values that were estimated or used. The ERG also observed that a mix of sources is used for the base-case analysis.
    i. Notably, baseline values of the SELECTION trial for active UC were used, and 10 weeks values for response without remission, and remission. The company did not provide justification for this discrepancy. The baseline values do not capture potential improvements in HRQoL experienced by patients over the trial (induction) period. Furthermore, baseline estimates include those of potential responders (with or without remission) as well as non-responders. The baseline utility estimates are therefore likely

biased and not reflective of the longer-term non-responders they are applied to. The ERG used in its base-case analysis the 10 weeks data of the SELECTION trial for the active UC state.

ii. In the clarification response the company provided utility values stratified for biologic-naïve and biologic-experienced patients. The ERG believes it is more in line with the effectiveness and cost parameters of the model to use utility values specific for biologic-naïve and biologic-experienced patients in the respective models.

iii. It was noted in the clarification response that the EQ-5D-5L data were also collected at 26 weeks into the trial (week 15 of the maintenance phase). The ERG wonders why this data has not been used.[3] It should be explored whether using this data (stratified for biologic-naive and -experienced patients) instead of the 10 and 58 weeks data for the response without remission and remission health states leads to different results. In the clarification response the utility values are provided per treatment arm, but not by MCS status and hence the potential impact is difficult to judge. Using the 26 weeks data may be the most appropriate for the base-case analysis, even if the sample is smaller, since it better represents health in the maintenance phase than the 10 weeks data collected at the end of the induction phase. However, these data may also be prone to selection bias as some patients (non-responders) may have dropped out of the study or not completed surveys. But in general, a mix of all study participants (of the maintenance study) should be included, i.e., participants with response/remission/active UC. If the company could perform scenario analysis using 26 weeks data this may help judge the potential impact.

iv. Finally, a scenario analysis could be added by the company in which differential utilities are employed for the induction and maintenance phases (stratified for biologic-naïve and experienced patients if the sample sizes allow).

b) Utilities are adjusted for sex and age, and thus associated co-morbidities, but these utilities do not incorporate a decline in utility due to disease progression. The ERG recognizes there is no evidence available to model this decline and that also in previous appraisals disease progression within a health state was not taken into account. The ERG therefore considers the company's approach as appropriate.

c) The ERG was unable to verify the utility decrement of -0.052 for serious infection that the company stated was in line with TA 547.[10] Yet, the impact on the ICER is likely to be minor.

d) The ERG notes that in Table 4.10 the mean utility estimate for response without remission is [redacted] while in the model a value of [redacted] is used. The latter is also reported in Table 44 of the CS (document B).[1] The company has confirmed that the value in Table 44 of the CS is correct, and that the value of reported in Table 45 is a typographical error..

4.2.9 Resources and costs

Costs included in the model included drug acquisition and administration costs, costs associated with management of AEs, background disease management costs, and miscellaneous costs. Unit prices were based on 2018/19 NHS reference prices (published in 2020),[50] and the Monthly Index of Medical Specialties (MIMS) 2021[51].

4.2.9.1 Resource use and costs data identified in the review

An SLR was conducted to identify costs and resource use in the first-line treatment and ongoing management of patients with moderately to severely active ulcerative colitis, see Appendix I of the CS.[39] The literature search identified 32 UK-specific studies reporting the cost and resource use associated with UC. The study by Tsai et al. 2008 was used as a source for health care resource use by model health state.[52]

4.2.9.2 Treatment costs

Drug acquisition costs are based on UK costs and dosing regimens from MIMS 2021.[51] Treatment costs per 10-weekly cycle are based on the recommended dosage for each treatment. Dose escalation and weight-based dosing was applied for some of the treatments. Table 47 in the CS presents the costs per cycle for the intervention and advanced treatments, including their pack cost, sizes and dosing regimens (including a proportion of patients having dose escalation). The table can also be found below (Table 4.11).

Approximately 30% of patients were assumed to be treated with the escalated dose based on a literature review in Crohn's disease which found that approximately 30% of patients treated with adalimumab or infliximab had a dose escalation.[53] The same proportion is applied for vedolizumab, ustekinumab, golimumab and tofacitinib. Details on dose escalation per treatment can be found in Sections B.3.8.3 and B.3.2.1. of the CS.[1]

Table 4.11: Summary of pack cost, sizes and dosing regimens for each treatment

Treatment		Pack cost	Pack size	Dosing regimen (maintenance)	Cost per cycle	
					Induction	Maintenance
FIL	Jyseleca® (brand)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	Amgevita ™ (biosimilar)	£633.60	40 mg x 2	40 mg q2w, or dose escalated to qw	£2,851.20	£2,057.62
GOL	Simponi® (brand)	£762.97	162 mg x 4	50 mg q4w, or dose escalated to 100 mg q4w	£2,659.71[c]	£1,907.43
IFX	Inflectra™ (biosimilar)	£377.00	100 mg x 1	5 mg/kg q8w	£3,941.54[a]/ £4,173.39[b]	£2,133.36[a]/ £2,258.85[b]
TOF	Xeljanz® (brand)	£690.03	5 mg x 56	5 mg bid, or dose escalated to 10 mg bid	£3,208.29	£2,240.87
VDZ SC	Entyvio® (brand)	£1,025.00	108 mg x 2	108 mg q2w	£6,150.00	£2,562.50
VDZ IV	Entyvio® (brand)	£2,050.00	300 mg x 1	300 mg q8w, or dose escalated to 300 mg q4w	£6,150.00	£3,328.69
UST	Stelara® (brand)	£2,147.00	13 mg x 1 IV 90 mg x 1 SC	90 mg q12w, or dose escalated to 90 mg q8w	£6,697.63[b]	£2,056.65

Source: Table 47, CS[1]

[a] Based on the baseline weight for the biologic-naïve subgroup; [b] Based on the baseline weight for the biologic-exposed subgroup; [c] Induction dose is 2 doses (initially and at week 2) therefore not all patients may receive a third dose at week 6. Average price reflects the % of patients who are responders as estimated in the NMA (all assumed to receive the third dose), and assumes 0 % of non-responders would receive a third dose.

ADA = adalimumab; bid = twice daily; FIL = filgotinib; GOL= golimumab; IFX = infliximab; IV = intravenous; NMA = network meta-analysis; q2w = once every 2 weeks; q4w = once every 4 weeks; q8w =

Treatment	Pack cost	Pack size	Dosing regimen (maintenance)	Cost per cycle	
				Induction	Maintenance
once every 8 weeks; q12w = once every 12 weeks; SC = subcutaneous; TOF = tofacitinib; UST = ustekinumab; VDZ = vedolizumab					

Simponi® (golimumab) has a non-confidential PAS scheme, where a higher dose is provided at a fixed price. Therefore, the cost of treatment with dose escalation is the same as for the standard dose. Confidential PAS prices were excluded for Xeljanz® (tofacitinib), Entyvio® (vedolizumab), and Stelara® (ustekinumab). Biosimilars are costed in the same way. Biosimilars for adalimumab and infliximab are included in the model. The model only considers the lowest priced biosimilars as comparators.

4.2.9.2.1 Conventional therapy costs

Drug acquisition costs provided in the model are based on UK costs obtained from MIMS 2021.[51] The usage of each treatment was sourced from TA547, both for conventional therapy alone, and as a concomitant therapy with advanced treatments.[10] Results are presented in Table 4.12. The resulting per cycle cost of conventional therapy alone was £83.08, and £65.96 as a concomitant therapy with biologics. The cost of concomitant treatment with JAK inhibitors (tofacitinib and filgotinib) differs from that of the biologics, as immunomodulators are not recommended for concomitant use with JAK inhibitors, and the estimated cost of concomitant therapy was £63.16. Unit drug costs and total costs per year for each concomitant treatment are summarised in Table 48 of the CS.[1]

Table 4.12. Calculation of concomitant conventional therapy costs

Treatment	Total cost per cycle	Conventional therapy		Advanced therapy	
		Usage as conventional therapy alone[a]	Average cost per patient	Usage concomitant to advanced therapy[b]	Average cost per patient
Balsalazide (Colazide®)	£65.52	12.6%	£8.26	11.6%	£7.60
Mesalazine (Asacol®)	£27.13	12.6%	£3.42	11.6%	£3.15
Olsalazine	£375.67	12.6%	£47.33	11.6%	£43.58
Sulfasalazine	£46.20	12.6%	£5.82	11.6%	£5.36
Prednisolone (Pevanti®)	£8.87	44.1%	£3.91	19.9%	£1.76
Budesonide (Budenofalk®)	£285.55	3.8%	£10.85	0.6%	£1.71
Azathioprine	£7.53	46.4%	£3.49	37.2%/0%[c]	£2.80/£0.00[c]
Total cost of conventional therapy per cycle		£83.08		£65.96/£63.16[c]	
Source: Table 48, CS[1]					

Treatment	Total cost per cycle	Conventional therapy		Advanced therapy	
		Usage as conventional therapy alone[a]	Average cost per patient	Usage concomitant to advanced therapy[b]	Average cost per patient
[a] Proportion of use of in conventional treatment as part of the conventional therapy mix, sourced from TA547[10]; [b] Proportion of use of conventional treatments as concomitant therapy to advanced therapy, sourced from TA547[10]; [c] Immunomodulators are not recommended in concomitant use with filgotinib and tofacitini TA = technology appraisal					

4.2.9.3 Treatment administration costs

Costs of administration were dependent on mode of administration, i.e., IV, SC, or oral. Orally administered drugs (filgotinib and tofacitinib) were assumed to have no administration cost. It was assumed that for subcutaneous injections, patients either self-inject their medication, or acquire no administration costs otherwise due to homecare and support schemes offered by the manufacturers. Consistent with TA547 and TA633, the administration costs for IV drugs were assumed to be equal to the cost of an outpatient visit, which was estimated to be £133.19.[10, 17]

4.2.9.4 Health-state unit costs and resource use

The model includes disease management costs comprising regular outpatient visits, blood tests, endoscopy, and hospitalization episodes. In line with previous submissions, no additional treatment-related monitoring costs were assumed.[10-12, 17] Resource use inputs were based on a UK cost effectiveness model, Tsai et al. 2008.[52] [525252] The health state definitions for active UC, remission, and response without remission applied in Tsai et al. align with the definitions in the cost effectiveness model.[52]

The number of hospitalisation episodes in the model deviate from Tsai et al. 2008 and were increased based on expert opinion.[52] The estimated annual hospitalisation episodes were increased from 0.30 reported in Tsai et al. to 1.20 for the response without remission health state, and to 1.50 for the active UC health state. This adjustment is applied based on the notion that hospitalisation rates increase as patient health worsens, based on clinical expert advice referenced in TA547.[10] All other resource use inputs were obtained directly from Tsai et al. 2008[525252], and are summarised in Table 51 of the CS.[1]

The costs for the surgery health states with and without complications were £7,887.46 and £6,622.91, respectively. The costs associated with surgery (i.e. colectomy) were obtained from the NHS reference costs 2018/19 using a weighted average of elective inpatient costs for proximal and distal colon procedures, see Table 55 of the CS.[1, 50]

The costs associated with the post-surgery health states with and without complications were £11,079.16 and £493.01 respectively. The costs were obtained from the resource use inputs (and unit prices) for these health states from Tsai et al. 2008.[52] The main cost driver for the post-surgery with complications health state was the number of hospitalisation episodes, which was estimated to be 3.25 times per annum.

The annual costs associated with each health state are summarised in Table 4.13.

Table 4.13: Total annual cost of resource use by health state

Health state	Annual cost
Active UC	£6,275.61
Response without remission	£4,669.25
Remission	£1,305.29
Surgery (without complications)	£6,622.91
Surgery (with complications)	£7,887.46
Post-surgery (without complications)	£493.01
Post-surgery (with complications)	£11,079.16
Source: Table 52, CS[1] UC = ulcerative colitis	

4.2.9.5 Scenario analysis

The study by Tsai et al. was published in 2008, and it has been highlighted in previous appraisals that these estimates may be higher than expected in current clinical practice in England and Wales.[10, 52] The SLR conducted did not identify more recently published studies reporting updated resource use estimates (CS Appendix I).[39] Therefore, the company interviewed five gastroenterologists who provided estimates of health care resource use applied in a scenario analysis. See Table 53 of the CS for the resource use estimations.[1]

4.2.9.6 Adverse reaction unit costs and resource use

Cost of serious infection was calculated based on the average of six types of serious infections: sepsis, tuberculosis, pneumonia, skin and soft tissue infection, bone and joint infection and urinary tract infection. The costs were estimated from the NHS reference costs 2018/19 by applying weight based on the number of finished consultant episodes reported for each event type, see Table 50 of the CS. The cost of serious infections was estimated at £2,841.18.[1, 50]

ERG comment: The main concerns of the ERG relate to a) the application of dose escalation to all comparators but filgotinib and b) uncertainty surrounding resource use estimates for health states.

a) Dose escalation was applied to some comparators, but not to filgotinib and the ERG was unsure why this was the case. In the FAC, the company then clarified that this was in line with the SmPCs of filgotinib and comparators and the ERG therefore considered the incorporation of dose escalation in the model as appropriate for the ERG base case.[54-59] However, given that dose escalation does not appear to be recommended in the NICE guideline for ulcerative colitis NG130 at any line including immediately prior to surgery, it remains a key issue.[5]
b) There is uncertainty surrounding the resource use estimates for the health states, especially the active UC and response without remission health states. Based on early scientific advice, expert input from five UK clinicians was sought by the company, as described in Section B.3.10 of the CS.[1] However, this input was not used in the base-case analysis. The clinical experts advised lower hospitalisation rates and outpatient visits in the more severe health states (i.e., active UC and response without remission). Applying higher health state costs for active UC and response without remission in the base-case is favourable for those treatments that result in lower proportions of patients in those health states.

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

Base-case deterministic results are shown for the biologic-naïve population (Table 5.1) and the biologic experienced population (Table 5.2 below). Incremental outcomes are presented against filgotinib. ICERs are presented against filgotinib and as incremental analyses.

Table 5.1: Base-case deterministic results for the biologic-naïve population

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. FIL (£/QALY)	ICER incremental (£/QALY)
Filgotinib	[redacted]	21.210	[redacted]	-	-	-	-	-
Conventional therapy	[redacted]	21.208	[redacted]	82.29	-0.002	-0.153	Dominated	Dominated
Golimumab	[redacted]	21.209	[redacted]	6,142.37	0.001	0.076	Dominated	81,199.75
Adalimumab	[redacted]	21.209	[redacted]	420.13	0.000	-0.003	Dominated	Dominated
Infliximab	[redacted]	21.210	[redacted]	4,625.55	0.001	0.074	Dominated	62,789.42
Tofacitinib	[redacted]	21.210	[redacted]	123.04	0.000	0.040	340,399.67 SW	3,069.36
Vedolizumab SC	[redacted]	21.210	[redacted]	4,144.06	0.000	0.011	351,564.50 SW	386,409.23
Vedolizumab IV	[redacted]	21.210	[redacted]	4,064.54	0.000	-0.032	1,666,942.24 SW	Dominated

FIL = filgotinib; IV = intravenous; LYG = life years gained; QALY = quality-adjusted life year; SC = subcutaneous; SW = South-Western

Table 5.2: Base-case deterministic results for the biologic-experienced population

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)
Conventional therapy	[redacted]	20.907	[redacted]	-	-	-	4,637.07	-
Filgotinib	[redacted]	20.908	[redacted]	278.99	0.001	0.060	-	4,637.07
Adalimumab	[redacted]	20.907	[redacted]	2,375.20	-0.001	-0.044	Dominated	Dominated
Tofacitinib	[redacted]	20.907	[redacted]	1,796.87	0.000	0.033	Dominated	53,927.89
Ustekinumab	[redacted]	20.907	[redacted]	853.65	0.000	-0.019	Dominated	Dominated
Vedolizumab SC	[redacted]	20.908	[redacted]	1,880.76	0.000	0.032	2,477,170.72 SW	58,087.87
Vedolizumab IV	[redacted]	20.907	[redacted]	1,018.23	0.000	-0.013	Dominated	Dominated

FIL = filgotinib; IV = intravenous; LYG = life years gained; QALY = quality-adjusted life year; SC = subcutaneous; SW = South-Western

Overall, the technology is modelled to affect QALYs by:

- Difference in percentage of patients with response (with and without remission) impacting quality of life
- Difference in percentage of patients with response (with and without remission) resulting in a different proportion of patients who end up with surgery impacting both mortality and quality of life
- Difference in AEs (serious infections) of treatment impacting quality of life

Overall, the technology is modelled to affect costs by:

- Difference in costs of medication
- Difference in percentage of patients with response (with and without remission)
- Difference in percentage of patients with response (with and without remission resulting) in a different proportion of patients with last-line conventional therapy
- Difference in percentage of patients with response (with and without remission resulting) in a different proportion of patients who end up with surgery

Disaggregated results were not provided by the company to show the individual impact of these four aspects on costs.

ERG comment: The ERG concerns relate to a) the lack of treatment sequence modelling in the base-case and b) fully incremental results were not implemented in the model.

a) The main concern of the ERG was that treatment sequences were not modelled in the base-case analyses although treatment sequences are used in clinical practice (clarification question B12).[13] Based on this comment the company included treatment sequences in the base-case analyses (see Section 4.2.4).[3] The changed base-case results, including the treatment sequences, and also a change in the age adjustment of utility values requested by the ERG, are presented below for the biologic-naïve (Table 5.3) and the biologic-experienced population (Table 5.4).

Table 5.3: New base-case results for the biologic-naïve population including treatment sequences

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)	Net Health Benefit
Filgotinib	[redacted]	21.213	[redacted]	-	-	-	-	62,350.24	-
Conventional therapy	[redacted]	21.210	[redacted]	15,997.73	0.003	0.257	62,350.24	-	-0.98
Golimumab	[redacted]	21.212	[redacted]	-10,931.16	0.001	0.056	Dominated	Dominated	0.90
Tofacitinib	[redacted]	21.213	[redacted]	-11,297.56	0.000	-0.033	345,631 SW	4,119.95	0.84
Adalimumab	[redacted]	21.212	[redacted]	-11,360.53	0.001	0.059	Dominated	Dominated	0.94
Infliximab	[redacted]	21.213	[redacted]	-15,721.69	0.000	-0.012	1,273,598 SW	60,897.92	1.20
Vedolizumab SC	[redacted]	21.215	[redacted]	-19,040.43	-0.002	-0.210	90,695 SW	16,795.73	1.26
Vedolizumab IV	[redacted]	21.215	[redacted]	-23,219.62	-0.002	-0.179	129,463 SW	Dominated	1.62

FIL = filgotinib; IV = intravenous; LYG = life years gained; QALY = quality-adjusted life year; SC = subcutaneous; SW = South-Western

Table 5.4: New base-case results for the biologic-experienced population including treatment sequences

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)	Net Health Benefit
Filgotinib	[redacted]	20.910	[redacted]	-	-	-	-	96,056.10	-
Conventional therapy	[redacted]	20.909	[redacted]	11,489.68	0.001	0.120	96,056.10	-	-0.77
Adalimumab	[redacted]	20.909	[redacted]	-2,452.30	0.001	0.043	Dominated	Dominated	0.23
Tofacitinib	[redacted]	20.910	[redacted]	-4,191.25	0.0001	0.010	Dominated	53,006.51	0.33
Vedolizumab SC	[redacted]	20.910	[redacted]	-4,199.83	0.0002	0.016	Dominated	Dominated	0.34
Ustekinumab	[redacted]	20.910	[redacted]	-5,084.88	0.0003	0.029	Dominated	Dominated	0.42

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs FIL (£/QALY)	ICER incremental (£/QALY)	Net Health Benefit
Vedolizumab IV	[redacted]	20.910	[redacted]	-5,238.67	0.0003	0.029	Dominated	751,844.73	0.43

FIL = filgotinib; IV = intravenous; LYG = life years gained; QALY = quality-adjusted life year; SC = subcutaneous; SW = South-Western

b) The company did not provide the model functionality to generate fully incremental results. This should be incorporated in the next model versions at technical engagement.

5.2 Company's sensitivity analyses

5.2.1 Sensitivity analyses of the original base-case (no treatment sequences)

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses for their original base-case analyses (without treatment sequences). Results from the PSA were comparable to the deterministic results in both groups in the original base-case results.

The original probabilistic CS analyses indicated cost effectiveness probabilities of 100% of filgotinib for both the biologic-naïve population and the biologic-experienced population at a willingness to pay threshold of £20,000 per QALY gained. Cost of medication was not varied in the PSA.

Deterministic sensitivity analyses were performed to show which assumptions have the greatest effect on the net monetary benefit of filgotinib vs. conventional therapy only. Cost of medication was not varied in these sensitivity analyses. The company did not provide information about the assumptions that have the greatest effect on the ICERs or NMBs against other advanced therapies.

The modelling assumptions that have the greatest effect on the NMB of filgotinib vs. conventional therapy (not including medication costs) for the biologic-naïve population are:

- Remission health state cost
- Filgotinib maintenance transition probabilities
- Active UC health state cost
- Response health state cost

The modelling assumptions that have the greatest effect on the NMB of filgotinib vs. conventional therapy (not including medication costs) for the biologic-experienced population are:

- Remission health state cost
- Active UC health state cost
- Response health state cost
- Post-surgery complication cost

The company conducted several scenario analyses. For both the biologic-naïve and the biologic-experienced population the results were consistent with the base-case analysis, i.e., Filgotinib was cost effective in all scenarios. The most influential scenarios were the scenarios in which different treatment efficacy results were used based on sensitivity analyses in the NMA, and where alternative utility values were used.

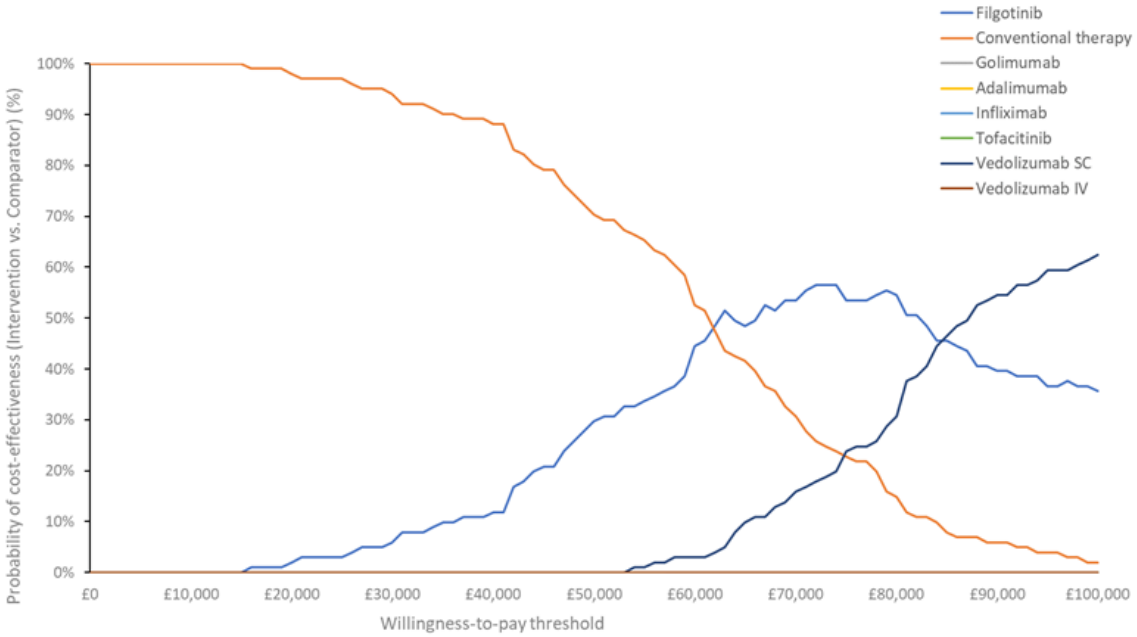
5.2.2 Sensitivity analyses of the new base-case analyses (with treatment sequences)

The company performed new sensitivity analyses on the new base-case (including treatment sequences). Also, for this new base-case the results of the probabilistic sensitivity analysis (PSA) were similar to the deterministic analyses. New PSA scatterplots and PSA cost effectiveness acceptability curves were provided for both populations.

For the biologic-naïve population the results of the PSA showed that at a willingness-to-pay (WTP) threshold of £20,000 per QALY, Filgotinib had a 1.98% probability of being the optimal treatment. At

this threshold conventional therapy has a very high probability to be cost-effective. The acceptability curve for the new base-case PSA for the biologic-naïve population is shown in Figure 5.1 below.

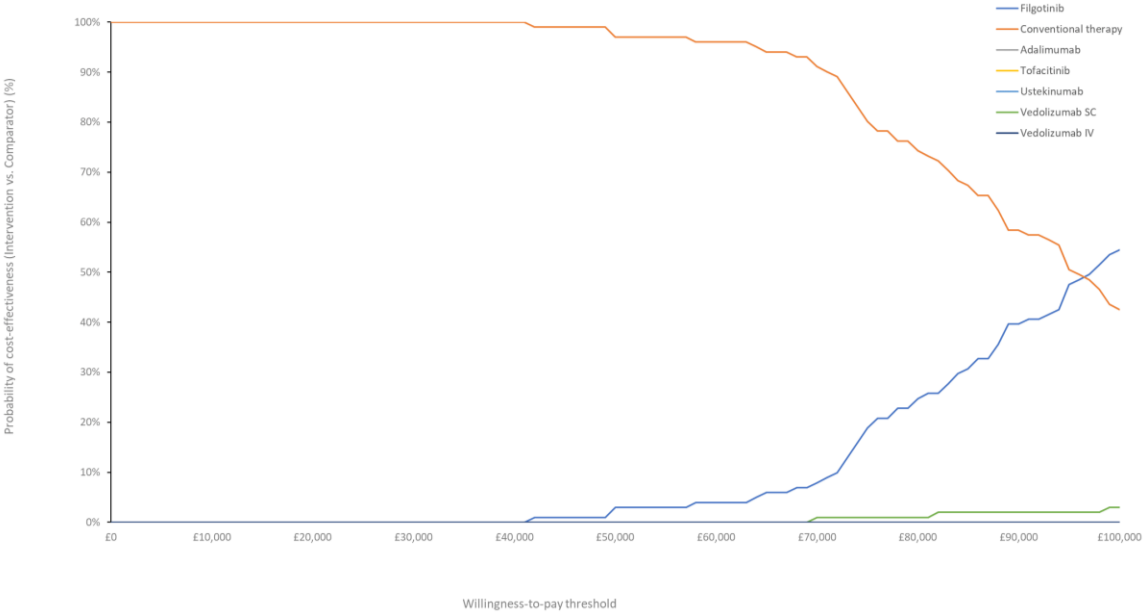
Figure 5.1: CEAC for biologic-naive population (including treatment sequences)



CEAC = cost effectiveness acceptability curve; IV = intravenous; SC = subcutaneous

For the biologic-experienced population the PSA showed that at a WTP threshold of £20,000 per QALY filgotinib had a 0% probability of being the optimal treatment. At this threshold there was a 100% probability that conventional therapy was the optimal treatment. The acceptability curve for the new base-case PSA for the biologic-experienced population is shown in Figure 5.2 below.

Figure 5.2: CEAC for biologic-experienced population (including treatment sequences)



CEAC = cost effectiveness acceptability curve; IV = intravenous; SC = subcutaneous

ERG comment: The main concerns of the ERG relate to a) PSA results were only based on 1,000 model runs; b) lack of some informative scenario analyses and c) important parameters were not included in the PSA.

a) The ERG raised the concern that the PSA results were only based on 1,000 model runs. The company therefore provided convergence plots showing that results were stable at 1,000 model runs.
b) No scenario analyses were provided with the new base-case analyses (including treatment sequences). Also, in the original scenario analyses there was no scenario analyses regarding the continuation of treatment effect (i.e., loss of response) beyond the maintenance phase although this is a major source of uncertainty in the model. In response to clarification letter, the company did provide an alternative scenario assuming that after one year of treatment, loss of response would be reduced by 25% (see Section 4.2.6).[3]
c) In the clarification letter the ERG raised the concern that the Convergence Diagnostic and Output Analysis (CODA) samples obtained from the NMA were not included in the PSA, and uncertainty about relative effectiveness was therefore not appropriately accounted for.[13] Based on this concern, the company included results from the NMA in the PSA.

5.3 Model validation and face validity check

5.3.1 Face validity assessment

The company sought early scientific advice with the building of the model. This included a clinical expert, patient expert, HTA expert, and a health economics expert. A wide range of topics was covered, including the NMA methodology, the model structure, treatment pathway, surgery, resource use and utility inputs as well as on assumptions related to dose escalation, AEs, and a stopping rule (the latter only applied in scenario analysis).

5.3.2 Technical verification

The company stated that internal quality assurance measures were undertaken throughout the model development. This involved extreme values and formula auditing to ensure the consistency of model estimates, and systematic variation of the model input parameters.

5.3.3 Comparisons with other technology appraisals / cost effectiveness analyses

The model was validated against the published cost effectiveness analysis for tofacitinib by Lohan et al. 2019.[46] Using the reported parameter values, it was possible to achieve similar estimates of modelled costs and QALYs for all comparators which were all within 3% of the published results.

ERG comment: The main concerns of the ERG relate to: a) lack of external validation, and b) internal validation.

a) Whilst the company did provide a comparison with another cost effectiveness analysis (cross validation), the company did not provide comparisons with external data (whether used to develop the economic model or not), also not in response to a clarification question requesting this (B30).[13] This may be because of a lack of long-term data for UC, but this remains unclear to the ERG.
b) Internal validation: the company performed thorough model checks and completed the TECH-VER checklist.[60] The ERG considers this as sufficient. However, the ERG has remaining concerns about the appropriateness of using the evidence from the NMA (which is based on remission) to model loss of response in the long term. The company stated that this was considered appropriate by their experts but the ERG considers that there is considerable uncertainty associated with the modelling

of long-term loss of response. A similar approach to the one chosen by the company was also used in the cost effectiveness analysis by Lohan et al. 2019.[46] Here the authors acknowledge the limitations of this approach and consider that *"this approach introduced a strong correlation between maintenance phase response and discontinuation but had the advantage of directly translating the trial evidence to the economic model structure and avoided further assumptions and data manipulation from model calibration techniques. […] Nevertheless, it is noted that further research is required to identify the reasons for treatment discontinuation and in parallel to accurately derive estimates of long-term drug persistence rates"*.[46]

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. 2020:[61]

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide confidence intervals, small sample sizes, or immaturity of data)
- Bias & indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/ or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the ERG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this ERG report, 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):[62]

- 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)

6.1.1 ERG base-case

Adjustments made by the ERG, to derive the ERG base-case (using the CS base-case as starting point) are listed below. Tables 6.2 and 6.3 show how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the ERG base-case. The ERG's analyses exclude conventional therapy as a comparator (see Sections 2.3 and 4.2.4) and use treatment sequences as per the company's analyses submitted in response to the clarification letter (Section 4.2.4).[3]

6.1.1.1 Fixing violations

1. The NMA for the maintenance phase is inappropriate (Section 3)
   Trial results used instead.
2. Active UC utilities should not be based on baseline (Section 4.2.8)
   10-week utility value ([redacted]) (Table 44 of the clarification response) used instead for active UC state.[3]
3. The probability of pouchitis is not in line with the utility value (should be only for chronic) (Section 4.2.6)
   The probability for chronic pouchitis (0.62% instead of 1.8%) is used.

6.1.2 ERG exploratory scenario analyses

The ERG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the ERG base-case.

6.1.2.1 Exploratory scenario analyses

1. Loss of response was held constant but should be decreasing over time (Section 4.2.6).
   Loss of response decreasing by 25% after first year.
2. Alternative treatment sequences (Section 4.2.4)
   With vedolizumab, then tofacitinib following adalimumab in the naïve population, and tofacitinib following vedolizumab in the experienced population.
3. Exclusion of treat-through trials (Section 4.2.6)
   Exclusion of adalimumab and infliximab for the naïve population and of infliximab for the experienced population.

6.1.3 ERG subgroup analyses

No subgroup analyses were performed by the ERG.

Table 6.1: Overview of key issues related to the cost effectiveness

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact[a]	Resolved in ERG base-case[b]	Required additional evidence or analyses
5. Conventional care not appropriate comparator	2.3 / 4.2.4	Methods	Exclude conventional care	Not applicable	Yes	No
6. Inclusion of and uncertainty about appropriate treatment sequences	4.2.4	Methods	Include treatment sequences, explore in scenarios	+/-	Partly by company, explored further by ERG	Yes, if available further scenarios based on expert opinion
7. Third-line population not included in model analyses	4.2.3	Methods	Provide scenario	+/-	No	Yes
8. Loss of response likely differential for response without remission and remission health states	4.2.6	Methods, Indirectness	Estimate loss of response per health state	+/-	No	Yes
9. Assumption of constant loss of response not likely to hold	4.2.6	Methods, Indirectness	Decreasing loss of response over time	+	Scenario	Yes, if available / expert opinion
10. Probability of pouchitis (all) not aligned with utility (chronic)	4.2.6	Methods	Use chronic pouchitis utility	-	Yes	No
11. Uncertainty about health-related quality of life impact	4.2.8	Indirectness	Population-specific utilities	+/-	No	Yes

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact[a]	Resolved in ERG base-case[b]	Required additional evidence or analyses
12. Use of baseline utility values likely inappropriate	4.2.8	Methods	10-week utility values	-	Yes	No
13. Application of dose escalation in model questionable	4.2.9	Transparency, Methods	Disable dose escalation	+	No, remains unclear	Yes
14. Fully incremental results not provided in the model	5.1	Methods		Not applicable	No	Yes

[a] Likely conservative assumptions (of the intervention vs. 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 vs. at least one comparator; [b] Explored
ERG = Evidence Review Group; FE = Fixing errors; FV = fixing violations; MJ = matters of judgement; ICER = incremental cost effectiveness ratio

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

In Section 6.1 the ERG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 and 6.3 show how individual changes impact the results plus the combined effect of all changes simultaneously. No probabilistic sensitivity analysis was performed because effectiveness estimates would not have been included as the ERG changed from using the NMA for maintenance trial efficacy to using trial estimates, which could not easily be incorporated in the PSA. This should be addressed at technical engagement. The exploratory scenario analyses are presented in Tables 6.4 and 6.5. These are all conditional on the ERG base-case. The analyses numbers in Tables 6.2-5 correspond to the numbers reported in Section 6.1. The submitted model file contains technical details on the analyses performed by the ERG (e.g., the "ERG" sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic ERG base-case biologic-naïve population

Technologies	Total LYs	Total QALYs	Total costs (£)	NMB	Incremental LYs FIL vs X	Incremental QALYs FIL vs X	Incremental costs (£) FIL vs X	ICER (£/QALY) pairwise FIL vs X	ICER (£/QALY) fully incremental
Company base-case (biologic-naïve), without conventional care, with company's treatment sequences									
Filgotinib	21.213	[redacted]	[redacted]	£115,860	0.000	0.000	£0	0	
Golimumab	21.212	[redacted]	[redacted]	£103,804	0.001	0.056	-£10,931	FIL dominates	Dominated
Tofacitinib	21.213	[redacted]	[redacted]	£105,216	0.000	-0.033	-£11,298	345631 SW	345,631
Adalimumab	21.212	[redacted]	[redacted]	£103,314	0.001	0.059	-£11,361	FIL dominates	Dominated
Infliximab	21.213	[redacted]	[redacted]	£100,385	0.000	-0.012	-£15,722	1273598 SW	Dominated
Vedolizumab SC	21.215	[redacted]	[redacted]	£101,019	-0.002	-0.210	-£19,040	90695 SW	43,683
Vedolizumab IV	21.215	[redacted]	[redacted]	£96,228	-0.002	-0.179	-£23,220	129463 SW	Dominated
ERG change 1: Do not use NMA results for maintenance									
Filgotinib	21.214	[redacted]	[redacted]	£114,280	0.000	0.000	£0	0	
Tofacitinib	21.213	[redacted]	[redacted]	£102,135	0.001	0.109	-£9,964	FIL dominates	Dominated
Golimumab	21.214	[redacted]	[redacted]	£99,118	0.000	0.021	-£14,750	FIL dominates	Dominated
Adalimumab	21.214	[redacted]	[redacted]	£98,782	0.000	0.024	-£15,008	FIL dominates	Dominated
Infliximab	21.214	[redacted]	[redacted]	£96,761	0.000	0.002	-£17,472	FIL dominates	Dominated

Technologies	Total LYs	Total QALYs	Total costs (£)	NMB	Incremental LYs FIL vs X	Incremental QALYs FIL vs X	Incremental costs (£) FIL vs X	ICER (£/QALY) pairwise FIL vs X	ICER (£/QALY) fully incremental
Vedolizumab SC	21.215	[redacted]	[redacted]	£98,154	-0.001	-0.076	-£17,648	231,845 SW	231,845
Vedolizumab IV	21.216	[redacted]	[redacted]	£90,376	-0.002	-0.149	-£26,894	179,898 SW	126,007
ERG change 2: Use of 10-week active UC utilities									
Filgotinib	21.213	[redacted]	[redacted]	£129,555	0.000	0.000	£0	0	
Golimumab	21.212	[redacted]	[redacted]	£117,684	0.001	0.047	-£10,931	FIL dominates	Dominated
Tofacitinib	21.213	[redacted]	[redacted]	£118,796	0.000	-0.027	-£11,298	419,503 SW	419,503
Adalimumab	21.212	[redacted]	[redacted]	£117,207	0.001	0.049	-£11,361	FIL dominates	Dominated
Infliximab	21.213	[redacted]	[redacted]	£114,022	0.000	-0.009	-£15,722	1,667,830 SW	Dominated
Vedolizumab SC	21.215	[redacted]	[redacted]	£113,967	-0.002	-0.173	-£19,040	110,306 SW	53,148
Vedolizumab IV	21.215	[redacted]	[redacted]	£109,282	-0.002	-0.147	-£23,220	157601 SW	Dominated
ERG change 3: Use probability of chronic pouchitis									
Filgotinib	21.213	[redacted]	[redacted]	£121,132	0.000	0.000	£0	0	
Golimumab	21.212	[redacted]	[redacted]	£109,166	0.001	0.055	-£10,873	FIL dominates	Dominated
Adalimumab	21.212	[redacted]	[redacted]	£108,683	0.001	0.058	-£11,298	FIL dominates	Dominated

Technologies	Total LYs	Total QALYs	Total costs (£)	NMB	Incremental LYs FIL vs X	Incremental QALYs FIL vs X	Incremental costs (£) FIL vs X	ICER (£/QALY) pairwise FIL vs X	ICER (£/QALY) fully incremental
Tofacitinib	21.213	[redacted]	[redacted]	£110,431	0.000	-0.032	-£11,334	357,798 SW	357,798
Infliximab	21.213	[redacted]	[redacted]	£105,625	0.000	-0.012	-£15,742	1,336,681 SW	Dominated
Vedolizumab SC	21.215	[redacted]	[redacted]	£105,921	-0.002	-0.203	-£19,279	94,782 SW	46,264
Vedolizumab IV	21.215	[redacted]	[redacted]	£101,181	-0.002	-0.174	-£23,425	134,838 SW	Dominated
ERG base-case (ERG changes 1-3)									
Filgotinib	21.214	14.550	£158,397	£132,606	0	0	0	0	
Tofacitinib	21.213	14.465	£168,236	£121,054	0.001	0.086	-£9,839	FIL dominates	Dominated
Golimumab	21.214	[redacted]	[redacted]	£117,579	0.000	0.015	-£14,721	FIL dominates	Dominated
Adalimumab	21.214	[redacted]	[redacted]	£117,275	0.000	0.018	-£14,973	FIL dominates	Dominated
Infliximab	21.214	[redacted]	[redacted]	£115,137	0.000	0.000	-£17,462	FIL dominates	Dominated
Vedolizumab SC	21.215	[redacted]	[redacted]	£116,016	-0.001	-0.058	-£17,749	306413 SW	306,413
Vedolizumab IV	21.216	[redacted]	[redacted]	£107,872	-0.002	-0.117	-£27,072	231592 SW	158,099

ERG = Evidence Review Group; FIL = filgotinib; ICER = incremental cost effectiveness ratio; IV = intravenous; NMA = network meta-analysis; NMB = net monetary benefit; QALY = quality-adjusted life year; SC = subcutaneous; SW = South-Western; UC = ulcerative colitis

Table 6.3: Deterministic ERG base-case biologic-experienced population

Technologies	Total LYs	Total QALYs	Total costs (£)	NMB	Incremental LYs FIL vs X	Incremental QALYs FIL vs X	Incremental costs (£) FIL vs X	ICER (£/QALY) pairwise FIL vs X	ICER (£/QALY) fully incremental
Company base-case (biologic-experienced), without conventional care, with company's treatment sequences									
Filgotinib	20.910	[redacted]	[redacted]	£113,927	0.000	0.000	£0	0	
Adalimumab	20.909	[redacted]	[redacted]	£110,610	0.001	0.043	-£2,452	FIL dominates	Dominated
Tofacitinib	20.910	[redacted]	[redacted]	£109,527	0.000	0.010	-£4,191	FIL dominates	Dominated
Vedolizumab SC	20.910	[redacted]	[redacted]	£109,411	0.000	0.016	-£4,200	FIL dominates	Dominated
Ustekinumab	20.910	[redacted]	[redacted]	£108,259	0.000	0.029	-£5,085	FIL dominates	Dominated
Vedolizumab IV	20.910	[redacted]	[redacted]	£108,110	0.000	0.029	-£5,239	FIL dominates	Dominated
ERG change 1: Do not use NMA results for maintenance (vedolizumab SC based on biologic-naïve)									
Filgotinib	20.911	[redacted]	[redacted]	£113,789	0.000	0.000	£0	0	
Adalimumab	20.910	[redacted]	[redacted]	£108,473	0.001	0.100	-£3,326	FIL dominates	Dominated
Tofacitinib	20.910	[redacted]	[redacted]	£107,056	0.001	0.052	-£5,691	FIL dominates	Dominated
Vedolizumab SC	20.911	[redacted]	[redacted]	£106,999	0.000	0.015	-£6,488	FIL dominates	Dominated
Ustekinumab	20.911	[redacted]	[redacted]	£105,488	0.000	0.021	-£7,881	FIL dominates	Dominated
Vedolizumab IV	20.911	[redacted]	[redacted]	£105,202	0.000	0.021	-£8,157	FIL dominates	Dominated
ERG change 2: Use of 10-week active UC utilities									
Filgotinib	20.910	[redacted]	[redacted]	£128,023	0.000	0.000	£0	0	
Adalimumab	20.909	[redacted]	[redacted]	£124,869	0.001	0.035	-£2,452	FIL dominates	Dominated
Tofacitinib	20.910	[redacted]	[redacted]	£123,662	0.000	0.009	-£4,191	FIL dominates	Dominated
Vedolizumab SC	20.910	[redacted]	[redacted]	£123,567	0.000	0.013	-£4,200	FIL dominates	Dominated
Ustekinumab	20.910	[redacted]	[redacted]	£122,462	0.000	0.024	-£5,085	FIL dominates	Dominated
Vedolizumab IV	20.910	[redacted]	[redacted]	£122,312	0.000	0.024	-£5,239	FIL dominates	Dominated

Technologies	Total LYs	Total QALYs	Total costs (£)	NMB	Incremental LYs FIL vs X	Incremental QALYs FIL vs X	Incremental costs (£) FIL vs X	ICER (£/QALY) pairwise FIL vs X	ICER (£/QALY) fully incremental
ERG change 3: Use probability of chronic pouchitis									
Filgotinib	20.910	[redacted]	[redacted]	£119,309	0.000	0.000	£0	0	
Adalimumab	20.909	[redacted]	[redacted]	£116,074	0.001	0.042	-£2,400	FIL dominates	Dominated
Tofacitinib	20.910	[redacted]	[redacted]	£114,929	0.000	0.010	-£4,179	FIL dominates	Dominated
Vedolizumab SC	20.910	[redacted]	[redacted]	£114,823	0.000	0.015	-£4,181	FIL dominates	Dominated
Ustekinumab	20.910	[redacted]	[redacted]	£113,695	0.000	0.028	-£5,051	FIL dominates	Dominated
Vedolizumab IV	20.910	[redacted]	[redacted]	£113,545	0.000	0.028	-£5,205	FIL dominates	Dominated
ERG base-case (ERG changes 1-3)									
Filgotinib	20.911	[redacted]	[redacted]	£132,808	0	0	0	0	
Adalimumab	20.910	[redacted]	[redacted]	£128,027	0.001	0.078	-£3,211	FIL dominates	Dominated
Tofacitinib	20.910	[redacted]	[redacted]	£126,342	0.001	0.042	-£5,634	FIL dominates	Dominated
Vedolizumab SC	20.911	[redacted]	[redacted]	£126,081	0.000	0.013	-£6,474	FIL dominates	Dominated
Ustekinumab	20.911	[redacted]	[redacted]	£124,617	0.000	0.017	-£7,857	FIL dominates	Dominated
Vedolizumab IV	20.911	[redacted]	[redacted]	£124,332	0.000	0.017	-£8,133	FIL dominates	Dominated

ERG = Evidence Review Group; FIL = filgotinib; ICER = incremental cost effectiveness ratio; IV = intravenous; NMA = network meta-analysis; NMB = net monetary benefit; QALY = quality-adjusted life year; SC = subcutaneous; UC = ulcerative colitis

Table 6.4: Deterministic scenario analyses biologic-naïve population (conditional on ERG base-case)

Technologies	Total LYs	Total QALYs	Total costs (£)	NMB	Incremental LYs FIL vs X	Incremental QALYs FIL vs X	Incremental costs (£) FIL vs X	ICER (£/QALY) pairwise FIL vs X
ERG base-case (biologic-naïve)								
Filgotinib	21.214	[redacted]	[redacted]	£132,606	0.000	0.000	£0	0
Tofacitinib	21.213	[redacted]	[redacted]	£121,054	0.001	0.086	-£9,839	FIL dominates
Golimumab	21.214	[redacted]	[redacted]	£117,579	0.000	0.015	-£14,721	FIL dominates

Adalimumab	21.214	[redacted]	[redacted]	£117,275	0.000	0.018	-£14,973	FIL dominates
Infliximab	21.214	[redacted]	[redacted]	£115,137	0.000	0.000	-£17,462	FIL dominates
Vedolizumab SC	21.215	[redacted]	[redacted]	£116,016	-0.001	-0.058	-£17,749	306413 SW
Vedolizumab IV	21.216	[redacted]	[redacted]	£107,872	-0.002	-0.117	-£27,072	231592 SW
Scenario 1: decreasing loss of response								
Filgotinib	21.215	[redacted]	[redacted]	£132,324	0.000	0.000	£0	0
Tofacitinib	21.213	[redacted]	[redacted]	£118,832	0.002	0.107	-£11,358	FIL dominates
Golimumab	21.215	[redacted]	[redacted]	£115,298	0.000	0.024	-£16,553	FIL dominates
Adalimumab	21.214	[redacted]	[redacted]	£114,949	0.000	0.026	-£16,855	FIL dominates
Infliximab	21.215	[redacted]	[redacted]	£112,685	0.000	0.008	-£19,482	FIL dominates
Vedolizumab SC	21.216	[redacted]	[redacted]	£113,288	-0.001	-0.061	-£20,254	332607 SW
Vedolizumab IV	21.217	[redacted]	[redacted]	£103,440	-0.002	-0.133	-£31,548	236918 SW
Scenario 2: alternative treatment sequence for adalimumab (vedolizumab, tofacitinib)								
Filgotinib	21.214	[redacted]	[redacted]	£132,606	0.000	0.000	£0	0
Adalimumab	21.213	[redacted]	[redacted]	£121,284	0.001	0.076	-£9,798	FIL dominates
Tofacitinib	21.213	[redacted]	[redacted]	£121,054	0.001	0.086	-£9,839	FIL dominates
Golimumab	21.214	[redacted]	[redacted]	£117,579	0.000	0.015	-£14,721	FIL dominates
Infliximab	21.214	[redacted]	[redacted]	£115,137	0.000	0.000	-£17,462	FIL dominates
Vedolizumab SC	21.215	[redacted]	[redacted]	£116,016	-0.001	-0.058	-£17,749	306413 SW
Vedolizumab IV	21.216	[redacted]	[redacted]	£107,872	-0.002	-0.117	-£27,072	231592 SW
Scenario 3: exclude treat-through trials								
Filgotinib	21.214	[redacted]	[redacted]	£132,606	0.000	0.000	£0	0
Tofacitinib	21.213	[redacted]	[redacted]	£121,054	0.001	0.086	-£9,839	FIL dominates
Golimumab	21.214	[redacted]	[redacted]	£117,579	0.000	0.015	-£14,721	FIL dominates
Vedolizumab SC	21.215	[redacted]	[redacted]	£116,016	-0.001	-0.058	-£17,749	306413 SW
Vedolizumab IV	21.216	[redacted]	[redacted]	£107,872	-0.002	-0.117	-£27,072	231592 SW

Table 6.5: Deterministic scenario analyses biologic-experienced population (conditional on ERG base-case)

Technologies	Total LYs	Total QALYs	Total costs (£)	NMB	Incremental LYs FIL vs X	Incremental QALYs FIL vs X	Incremental costs (£) FIL vs X	ICER (£/QALY) pairwise FIL vs X
ERG base-case (biologic-experienced)								
Filgotinib	20.911	[redacted]	[redacted]	£132,808	0.000	0.000	£0	0
Adalimumab	20.910	[redacted]	[redacted]	£128,027	0.001	0.078	-£3,211	FIL dominates
Tofacitinib	20.910	[redacted]	[redacted]	£126,342	0.001	0.042	-£5,634	FIL dominates
Vedolizumab SC	20.911	[redacted]	[redacted]	£126,081	0.000	0.013	-£6,474	FIL dominates
Ustekinumab	20.911	[redacted]	[redacted]	£124,617	0.000	0.017	-£7,857	FIL dominates
Vedolizumab IV	20.911	[redacted]	[redacted]	£124,332	0.000	0.017	-£8,133	FIL dominates
Scenario 1: decreasing loss of response								
Filgotinib	20.911	[redacted]	[redacted]	£132,427	0.000	0.000	£0	0
Adalimumab	20.910	[redacted]	[redacted]	£127,027	0.001	0.093	-£3,547	FIL dominates
Tofacitinib	20.911	[redacted]	[redacted]	£125,152	0.001	0.051	-£6,262	FIL dominates
Vedolizumab SC	20.911	[redacted]	[redacted]	£125,023	0.000	0.015	-£7,109	FIL dominates
Ustekinumab	20.911	[redacted]	[redacted]	£123,383	0.000	0.020	-£8,646	FIL dominates
Vedolizumab IV	20.911	[redacted]	[redacted]	£123,057	0.000	0.020	-£8,961	FIL dominates
Scenario 2: alternative treatment sequence for vedolizumab (use tofacitinib)								
Filgotinib	20.911	[redacted]	[redacted]	£132,808	0.000	0.000	£0	0
Vedolizumab SC	20.911	[redacted]	[redacted]	£129,627	0.000	0.037	-£2,438	FIL dominates
Adalimumab	20.910	[redacted]	[redacted]	£128,027	0.001	0.078	-£3,211	FIL dominates
Vedolizumab IV	20.910	[redacted]	[redacted]	£127,883	0.001	0.042	-£4,090	FIL dominates
Tofacitinib	20.910	[redacted]	[redacted]	£126,342	0.001	0.042	-£5,634	FIL dominates
Ustekinumab	20.911	[redacted]	[redacted]	£124,617	0.000	0.017	-£7,857	FIL dominates

Technologies	Total LYs	Total QALYs	Total costs (£)	NMB	Incremental LYs FIL vs X	Incremental QALYs FIL vs X	Incremental costs (£) FIL vs X	ICER (£/QALY) pairwise FIL vs X
Scenario 3: exclude treat-through trials								
Filgotinib	20.911	[redacted]	[redacted]	£132,808	0.000	0.000	£0	0
Tofacitinib	20.910	[redacted]	[redacted]	£126,342	0.001	0.042	-£5,634	FIL dominates
Vedolizumab SC	20.911	[redacted]	[redacted]	£126,081	0.000	0.013	-£6,474	FIL dominates
Ustekinumab	20.911	[redacted]	[redacted]	£124,617	0.000	0.017	-£7,857	FIL dominates
Vedolizumab IV	20.911	[redacted]	[redacted]	£124,332	0.000	0.017	-£8,133	FIL dominates

6.3 ERG's preferred assumptions

The ERG base-case and scenarios indicate that at its current price, and disregarding confidential PAS for comparators, filgotinib dominates some comparators (adalimumab and golimumab in the company's base-case, all but vedolizumab IV and SC in the ERG's base-case) in the biologic-naïve population and dominates all comparators in the biologic-experienced population. However, there are limitations in the modelling (namely the assumption that patients in response lose response at an equal rate to patients in remission) that could not be addressed by the ERG and will likely be influential. Hence, these results may be subject to change.

6.4 Conclusions of the cost effectiveness section

Searches were undertaken for separate SLRs to identify all cost effectiveness, HRQoL and healthcare resource use for UC. The CS provided sufficient details for the ERG to appraise the literature searches. A range of databases and conference proceedings were searched as well as HTA organisations.

The CS was in line with the NICE reference case, with the exception that fully incremental analyses were not enabled in the model file. The modelling approach and structure with the inclusion of subsequent treatment sequences were appropriate and the model was technically verified by the company. There are remaining issues. The ERG has significant doubts over whether conventional care can indeed be a comparator in the population of interest and, in fact, removed it based on it not being indicated in the NICE care pathway. There were concerns about how effectiveness estimates were incorporated into the model: the most important model driver was expected to be the distribution over the three health states (active UC, response, remission) over time – but it is not possible to truly estimate this distribution over time with this model. This is because: a) loss of response was not a trial endpoint but was instead based on the proportion of patients in the active UC health state at the end of the trial maintenance period (and this would be biased in treat-through trials as these contain non-responders from the initiation phase); b) loss of response was thereafter assumed to be constant; c) there are no transitions between the health states response and remission; d) equal loss of response is assumed for patients in response and remission. These limitations mean that there is some doubt over whether the model accurately captures the effectiveness of filgotinib vs. its comparators over time. Some of these issues can be addressed or explored, but not all will be easily resolved. Another concern with the effectiveness estimates is that the maintenance NMA was likely inappropriate as treatments were not comparators in this phase. The ERG proposed an alternative approach (calculating membership in health states conditional on response in the induction phase). Furthermore, the company assumed dose escalation to be performed for all comparators but not for filgotinib at the line prior to surgery. Although the company stated that this was based on the SmPCs, it remains unclear whether this is in line with NHS clinical practice. There is also uncertainty about the impact on HRQoL, with inconsistency between trial estimates and those from the literature. The ERG considers that this uncertainty can be addressed by further exploring alternative utility inputs (all based on the trial). The ERG also considers that the use of baseline utilities for the active UC state, which is based on a mix of future responders and non-responders, is likely inappropriate.

The ERG made the following adjustments to the model for its base-case:

- Use trial results instead of maintenance NMA
- Use week 10 utility values for the active UC state
- Change the probability of pouchitis to reflect only chronic pouchitis (in line with utility value used)

The ERG base-case and scenarios indicate that at its current price, and disregarding confidential PAS for comparators, filgotinib dominates all comparators except vedolizumab SC and IV in the biologic-

naïve population and dominates all comparators in the biologic-experienced population (in both biologic-naïve and -experienced population). However, there are limitations in the modelling (namely the assumption that patients in response lose response at an equal rate to patients in remission) that could not be addressed by the ERG and will likely be influential. Hence, these results may be subject to change.

In conclusion, most issues can likely be addressed with alterations to the estimates in the model and exploratory analyses. However, uncertainty will likely remain about the long-term effectiveness of filgotinib vs. its comparators.

7. END OF LIFE

Not applicable.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Filgotinib for treating moderately to severely active ulcerative colitis [ID3736]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 18 November 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Lack of analyses for filgotinib 100mg dose

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report incorrectly states that no NMA was conducted for the 100mg dose of filgotinib. Page 14, Table 1.3 *"The company did not present any NMA or CEA for the 100 mg dose of filgotinib or patients with moderate or severe renal impairment where 100 mg is recommended."*	Updating the text: *"**The company presented NMAs for the 100 mg dose of filgotinib, but no CEA for the 100mg dose** or patients with moderate or severe renal impairment where 100 mg is recommended."*	The 100mg dose of filgotinib was included in all NMA analyses (see e.g., Table 25 and Table 26 of the CS).	Corrected.

Issue 2 Modelling of loss of response rates

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Minor inaccuracies in critique of the modelling of loss of response. Page 108: *"The ERG would like to emphasize that constant loss of response rates would also likely favour treatments with lower observed non-response where it concerns effectiveness (with filgotinib having the lowest non-response at end of*	Page 108, addition of the underlined text: *"The ERG would like to emphasize that constant loss of response rates would also likely favour treatments with lower observed non-response where it concerns effectiveness (with filgotinib having the lowest non-response at end of maintenance **in the***	On page 108, the non-response was only lowest for filgotinib among the comparators in the biologic-naïve population, not the biologic-experienced population (see Table 41 in the CS).	Page 108: Amended. Page 139: Not a factual inaccuracy.

maintenance).” Page 139: *“There were concerns about how effectiveness estimates were incorporated into the model: the most important model driver was expected to be the distribution over the three health states (active UC, response, remission) over time – but it is not possible to truly estimate this distribution over time with this model. This is because: a) loss of response was not a trial endpoint but was instead based on the proportion of patients in the active UC health state at the end of the trial maintenance period (and this would be biased in treat-through trials as these contain non-responders from the initiation phase); b) loss of response was thereafter assumed to be constant; c) there are no transitions between the health states response and remission; d) equal loss of response is assumed for patients in response and remission*	***biologic-naïve population**).”* Page 139, addition of the underlined text: *“There were concerns about how effectiveness estimates were incorporated into the model: the most important model driver was expected to be the distribution over the three health states (active UC, response, remission) over time – but it is not possible to truly estimate this distribution over time due to lack of long-term data to incorporate to the model. The modelled is subject to the following limitations: a) loss of response was not a trial endpoint but was instead based on the proportion of patients in the active UC health state at the end of the trial maintenance period (and this would be biased in treat-through trials as these contain non-responders from the initiation phase); b) loss of response was thereafter assumed to be constant; c) there are no transitions between the health states response and remission; d) equal loss of response is assumed for patients in response and remission; **e) there are lack of rigorous and long-term data to inform the model with regards to points b), c) and d)**.”*	At page 139, Galapagos believe that the list of limitations is not exhaustive, and thus does not accurately reflect the model limitations, as the assumptions made for the model listed in points b)-d) reflected the lack of long-term data to inform the model. As noted in response to clarification question B26, there is no publicly available data to inform the estimates of response and remission rates in the second and subsequent years for patients receiving the modelled treatments in the first year. This was noted by the ERG in TA633 and TA547, who additionally also accepted the use of a constant rate due to lack of available data.	

Issue 3 Minor wording corrections

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 124: *"In the clarification letter the ERG raised the concern that the results from the NMA were not included in the PSA"*	Page 124, updating the underlined text to the following: *"the Convergence Diagnostic and Output Analysis (CODA) samples obtained from the NMA"*	Minor wording changes to ensure the information presented is accurate. On page 124, the company note that the results from the NMA were originally included in the NMA, but not the CODA outputs from the NMA.	Amended.
Page 77: *"In their response to the clarification letter, the company stated that health related quality of life (HRQoL) measure was not required for the cost effectiveness model."*	Page 77, addition of the underlined text: *"In their response to the clarification letter, the company stated that **comparative** health related quality of life (HRQoL) measure was not required for the cost effectiveness model **since HRQoL is health state-specific**."*	On page 77, the company note that HRQoL was required for the model, but not comparative HRQoL.	Not a factual inaccuracy. This is in the indirect treatment comparison section, and thus the "comparative" is implied.
Page 37: *"The company conducted two NMAs, one for the acute phase and one for the maintenance phase."*	Page 37, updating the underlined text: *"The company conducted two NMAs, one for the **induction** phase and one for the maintenance phase."*	On page 37, the company note that the first phase of treatment should be referred to as an induction phase.	Amended.
Page 112: *"The ERG notes that in Table 4.10 the mean utility estimate for response without remission is [redacted] while in the model a value of [redacted] is used. The latter is also reported in Table 44 of the CS (document B).1 The ERG believes [redacted] is the*	Page 112, updating the underlined text: *"The ERG notes that in Table 4.10 the mean utility estimate for response without remission is [redacted] while in the model a value of [redacted] is used. The latter is also reported in Table 44 of the CS (document B).1 The **company has confirmed that the value in Table 44 of the CS is correct, and that the value of***	On page 112, the company would like to clarify as requested by the ERG that the correct utility value is as stated by the ERG.	Amended.

correct utility value but would welcome clarification."	***reported in Table 45 is a typographical error."***		
Page 115: *"The main cost driver for the post-surgery with complications health state was the number of hospitalisation episodes, which was estimated to be 3.5 times per annum."*	Page 115, updating the underlined text: *"The main cost driver for the post-surgery with complications health state was the number of hospitalisation episodes, which was estimated to be **3.25** times per annum."*	On page 115, there is a typographical error (see Table 51 in the CS for the number of hospitalisation episodes).	Amended.

Issue 4 Maintenance NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Criticism of the maintenance phase of the NMA by the ERG is not accurately presented to reflect that this is the views of the ERG only and not a statement of fact. Page 15: *"The maintenance phase NMA implies that all treatments are comparators in this phase when actually the only valid comparator, according to expected clinical practice, is no treatment or the curtailment of the intervention on which induction was achieved."*	Page 15, updating of the underlined text: *"The maintenance phase NMA implies that all treatments are comparators in this phase **when the ERG considers the only valid comparator, according to expected clinical practice, to be no treatment or the curtailment of the intervention on which induction was achieved."***	The company request for the ERG to clearly specify that all statements referring to the maintenance NMA as 'irrelevant' or 'invalid' reflect only the opinion of the ERG and are not factually correct. This is because the methodology applied to obtain relative efficacy in the maintenance phase was verified in NICE Early Scientific Advice sought by the company, and is well established, having been applied in previous NICE TAs, and published in peer-reviewed journals[1]. A similar methodology was applied in NICE TA547 and TA633, and a	Not a factual inaccuracy. This reflects the judgement of the ERG.

Page 86: *"However, the ERG questions the validity of the maintenance phase NMA on the grounds that it implies that all treatments are comparators in this phase when actually the only valid comparator is no treatment."*	Page 86, updating of the underlined text: *"However, the ERG questions the validity of the maintenance phase NMA on the grounds that it implies that all treatments are comparators in this phase,* ***when the ERG considers no treatment to be the only valid comparator****."*	maintenance NMA comparing treatments with different induction phases was also carried out by the assessment group in the well-established multiple technology appraisal TA329. The ERG does not acknowledge these previous assessments in the report, and the company therefore notes that referring to the maintenance NMA as 'inappropriate' does not reflect the fact that the methodology has been considered appropriate for decision making on multiple occasions. This inaccuracy can be corrected if the ERG clarify that this reflects their views only. The company would additionally like to clarify for the CEA requested by the ERG described on page 86, that after consultation with the ERG where it was discussed to conduct an analysis using a naïve comparison of efficacy results (as per the ERG base case), the company considered this to be inappropriate. The analyses were therefore not completed since the company does not believe that a naïve comparison is appropriate	
Page 86: *"Therefore, to inform that choice the only relevant data is the effectiveness of continuing the induction treatment relative to curtailing the induction treatment, which can only be informed by trials of that particular maintenance treatment. In other words, the effectiveness of any maintenance treatment relative to any other, as investigated in any other trial, is irrelevant. To put this another way, the effectiveness of the maintenance treatment relative to another would be relevant if in clinical practice the choice was between continuing with the induction treatment or switching to another, but switching is not considered in the CS."*	Page 86, updating of the underlined text: *"Therefore, to inform that choice* ***the ERG considers the only relevant data to be*** *the effectiveness of continuing the induction treatment relative to curtailing the induction treatment, which can only be informed by trials of that particular maintenance treatment. In other words, the effectiveness of any maintenance treatment relative to any other, as investigated in any other trial,* ***is considered irrelevant by the ERG****. To put this another way,* ***the ERG considers*** *that the effectiveness of the maintenance treatment relative to another would be relevant if in clinical practice the choice was between continuing with the induction treatment or switching to another, but switching is not considered in the CS."*		Not a factual inaccuracy. This reflects the judgement of the ERG.

Page 86: *"In the clarification letter, the ERG asked the company to discuss this issue and provide a CEA scenario where the probability of remission at 58 weeks conditional on response at 10 weeks for each treatment was informed by only trials of that maintenance treatment vs. placebo. <u>However, the company seemed to completely misunderstand the issue and instead defended the NMA by stating that</u> "…the NMA doesn't pool any maintenance phase treatments where patients enter the maintenance phase with different induction phase treatment experiences". The company therefore refused to conduct the requested analyses."*	Page 86, updating of the underlined text: *"In the clarification letter, the ERG asked the company to discuss this issue and provide a CEA scenario where the probability of remission at 58 weeks conditional on response at 10 weeks for each treatment was informed by only trials of that maintenance treatment vs. placebo. **<u>The company clarified that</u>** "…the NMA doesn't pool any maintenance phase treatments where patients enter the maintenance phase with different induction phase treatment experiences". **<u>The company additionally considered a cost-effectiveness analysis that naïvely compares treatment efficacy for the model comparators to be inappropriate, and therefore did not conduct the requested analysis</u>**."*	when an NMA using well-established methods can be applied.	
Page 90: *"However, the ERG questions the validity of the maintenance phase NMA on the grounds that it implies that all treatments are comparators in this phase when <u>actually the only valid comparator, according to expected clinical practice, is</u> no treatment or the curtailment of the intervention on which induction was achieved."*	Page 90, updating of the underlined text: *"However, the ERG questions the validity of the maintenance phase NMA on the grounds that it implies that all treatments are comparators in this phase when **<u>the ERG considers the only valid comparator, according to expected clinical practice, to be</u>** no treatment or the curtailment of the intervention on which induction was achieved."*		Not a factual inaccuracy. This reflects the judgement of the ERG.

Page 91: *"In the clarification letter, the ERG asked the company to discuss this issue and provide a CEA scenario where the probability of remission at 58 weeks conditional on response at 10 weeks for each treatment was informed by only trials of that maintenance treatment vs. placebo. <u>However, the company seemed to completely misunderstand the issue and refused to conduct the requested analyses."</u>*	Page 91: *"In the clarification letter, the ERG asked the company to discuss this issue and provide a CEA scenario where the probability of remission at 58 weeks conditional on response at 10 weeks for each treatment was informed by only trials of that maintenance treatment vs. placebo. **<u>The company considered a cost-effectiveness analysis that naïvely compares treatment efficacy for the model comparators to be inappropriate, and therefore did not conduct the requested analysis"</u>***</u>		
Page 107: *"As discussed in Section 3.4.2 the ERG questions the validity of the maintenance NMA on the grounds that all treatments are comparators in this phase <u>when the only valid comparator would be no treatment</u>."*	Page 107, updating of the underlined text: *"As discussed in Section 3.4.2 the ERG questions the validity of the maintenance NMA on the grounds that all treatments are comparators in this phase **<u>when the ERG considers the only valid comparator to be no treatment</u>**."*		Not a factual inaccuracy. This reflects the judgement of the ERG.
Page 126: *"<u>The NMA for the maintenance phase is inappropriate</u> (Section 3)"*	Page 126, updating the underlined text: *"**<u>The NMA for the maintenance phase is considered inappropriate by the ERG</u>** (Section 3)"*		Not a factual inaccuracy. This reflects the judgement of the ERG.

Page 139: *"Another concern with the effectiveness estimates is that <u>the maintenance NMA was likely inappropriate as treatments were not comparators in this phase</u>."*	Page 139, updating of the underlined text: *"Another concern with the effectiveness estimates is that **<u>the ERG believes that treatments were not comparators in this phase and considered the maintenance NMA to be inappropriate</u>"***		

Issue 5 Disaggregated results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report inaccurately states that disaggregated results are not included in the CS. Page 13 and page 119: *"Overall, the technology is modelled to affect QALYs by:* • *Difference in percentage of patients with response (with and without remission) impacting quality of life* • *Difference in percentage of patients with response (with and without remission) resulting in a different proportion of patients who end up with surgery impacting both mortality and quality of life*	Removal of the underlined text.	Disaggregated results by treatment strategy, treatment line and health states for both costs and QALYs are presented in Appendix J.	Amended.

• *Difference in AEs (serious infections) of treatment impacting quality of life* • *Disaggregated results were not provided by the company to show the individual impact of these three aspects on QALYs.* *Overall, the technology is modelled to affect costs by:* • *Difference in costs of medication* • *Difference in percentage of patients with response (with and without remission)* • *Difference in percentage of patients with response (with and without remission resulting) in a different proportion of patients with last-line conventional therapy* • *Difference in percentage of patients with response (with and without remission resulting) in a different proportion of patients who end up with surgery* *Disaggregated results were not provided by the company to show the individual impact of these four aspects on costs."*			

Issue 6 Dose escalation for filgotinib

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report mentions dose escalation for filgotinib throughout. However, dose escalation for filgotinib is not appropriate and should not be considered in the economic analysis. Table 1.2, page 13: *"Also, dose escalation was ruled out even though the company stated that placement could be immediately prior to surgery"* Table 1.2, page 14: *"Also, if 3L is included then dose escalation should be applied to filgotinib if applied to other comparators."* Table 1.14, page 19: *"Dose escalation was applied to all comparators but not to filgotinib without justification for why this was*	Removal of the underlined text.	Dose escalation for filgotinib is not appropriate because the approved doses only include the 200mg and 100mg dose (as per the summary of product characteristics (SmPC)). For other comparators, dose escalation is used in clinical practice (as indicated in the SmPC) as discussed in section B.3.2.4 in the CS and confirmed in early scientific advice and with UK clinicians. On page 116, the ERG notes that the source of the target dose is not included, but the company would like to clarify that this is as per label, and the SmPC were considered for each comparator, as done in previous technical appraisals TA547 and TA633.	The ERG acknowledges that the comparators' SmPCs include statements on dose escalation, whilst this is not included for filgotinib. The ERG therefore amended its critique of this and also updated the ERG base-case accordingly.

the case." *"Evidence on use of dose escalation in trials; justification of why dose escalation would not be used for filgotinib."* Page 116: *"No dose escalation was applied to filgotinib without a proper justification for this decision, resulting in relatively lower costs of filgotinib compared to its comparators."* And *"Furthermore, it was unclear what the source for the target dose (of dose escalation) was for each comparator"*			

Corrections to confidential marking

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
In document **ID3736 [ID3736] Filgotinib - ERG report FINAL REPORT - LI 251021 [ACIC],** Section 3.2.6.3 Serious adverse events, on page 75	The serious adverse events for SELECTION induction cohort A and B were not marked AIC. As indicated in ID3736 Filgotinib Document B.	In SELECTION induction cohort A, SAEs were reported by treatment group as follows: [redacted] of patients in the filgotinib 200mg group, [redacted] of patients in the filgotinib 100mg group and [redacted] of patients in the placebo group. In SELECTION induction cohort B, the corresponding SAEs were as follows: [redacted] of patients in the filgotinib 200mg group, [redacted] of patients in the filgotinib 100mg, and [redacted] of patients in the placebo group.	Corrected.
ID3736 [ID3736] Filgotinib - ERG report FINAL REPORT - LI 251021 [ACIC], Section 4.2.8.3 Scenario analysis, page 112	The utility value for patients in response without remission is not marked AIC in the text.	The ERG notes that in Table 4.10 the mean utility estimate for response without remission is [redacted] while in the model a value of [redacted] is used. The latter is also reported in Table 44 of the CS (document B).1 The ERG believes [redacted] is the correct utility value but would welcome clarification.	Corrected.

References

1. Lohan C, Diamantopoulos A, LeReun C, Wright E, Bohm N, Sawyer LM. Tofacitinib for the treatment of moderately to severely active ulcerative colitis: a systematic review, network meta-analysis and economic evaluation. BMJ Open Gastroenterol. 2019;6(1):e000302.

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Technical engagement response form

Filgotinib for moderately to severely active ulcerative colitis [ID3736]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG 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.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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.

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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.

Deadline for comments by **5pm on 24th January 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

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About you

Table 1 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)	**Galapagos Biotech Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Potential lack of clarity in the precise line of therapy where filgotinib would be indicated	*Yes*	The proposed positioning of filgotinib within the NICE treatment pathway is as follows (Figure 1 in the CS): • First-line treatment for biologic-naïve patients (no previous exposure to biologic therapy TNFα inhibitor or vedolizumab) • Treatment for biologic-experienced patients (previous exposure to biologic therapy TNFα inhibitor or vedolizumab), regardless of line of therapy Filgotinib is still intended to be used as third-line advanced therapy. The two subgroups applied in the economic analysis (biologic-naïve and biologic-experienced), instead of the three subgroups (first-line advanced (first biologic), second-line advanced (after failed first biologic) and third-line advanced (after failed second biologic or targeted therapy)), were defined as specified in the final decision problem scope issued by NICE. This is also in line with previous submissions in UC (TA633[1], TA547[2], TA342[3]). Moreover, efficacy results for comparators identified in the SLR were not further split by line of therapy.

		A scenario analysis of filgotinib as the third-line advanced treatment has been provided in the Filgotinib clarification letter (Table 3 for A9). Company would like to note that because of lacking of data for comparators, it was assumed the efficacy in the second-line and third-line remain the same regardless of treatment line for all interventions in this scenario. Dose escalation for filgotinib is not appropriate because the approved doses only include the 200mg and 100mg dose (as per the summary of product characteristics (SmPC)), where Filgotinib 100mg is only recommended only for patients who have moderate or severe renal impairment. For other comparators, dose escalation is used in clinical practice (as indicated in the SmPC) as discussed in section B.3.2.4 in the CS and confirmed in early scientific advice and with clinicians in England. See more responses in Issue 13.
Issue 2: Lack of data and analyses for 100 mg dose	*Yes*	The SELECTION study was a Phase IIB/III dose ranging study and patients were randomised to 100mg or 200mg of filgotinib or placebo. As presented in the CS Section B.2.6.2, at week 10 and week 58, higher proportion of patients receiving filgotinib 200mg achieved Mayo Clinic Score (MCS) response, compared with the filgotinib100mg group. Endoscopy/bleeding/stool (EBS) remission was not statistically significant differ between filgotinib 100mg arm and placebo arm at week 10, however was statistically significant differ by week 58. Therefore, the recommended dose for filgotinib to patients with ulcerative colitis is 200mg. The approved posology for filgotinib is that a dose of 100mg of once daily is recommended for patients with moderate or severe renal impairment (Creatinine clearance [CrCL] 15 to < 60 mL/min). This recommendation is based on a separate clinical pharmacology study which demonstrated that increase in exposures of filgotinib were observed in patients with moderate or severe renal impairment patients (see more details in the full SmPC in Appendix C). Furthermore, based on the inclusion/exclusion criteria of the SELECTION trial, only patients whose estimated CrCL>40 mL/min were included in the trial. Although the filgotinib 100mg was studied in SELECTION trial, the patient population (CrCL>40 mL/min) does not overlap with the patients within the approved indication (CrCL15 - < 60 mL/min). Therefore, it is not possible to accurately model the efficacy of filgotinib 100mg for patients with moderate or severe renal impairment based on the trial

		data. As such, filgotinib 100mg was not included in the economic analysis due to a paucity of data for both filgotinib and comparators in this subgroup of patients.
Issue 3: Lack of evidence of effectiveness of a sequence of biologics	*No*	Filgotinib is still intended to be used as third-line advanced therapy. However, efficacy results for comparators identified in the SLR were not further split by line of therapy. Thus, it was unable to conduct any comparison between filgotinib and other comparators. See more responses in Issue 1.
Issue 4: Questionable validity of the maintenance phase NMA	*No*	The methodology applied to obtain relative efficacy in the maintenance phase was verified in NICE Early Scientific Advice sought by the company, and is well established, having been applied in previous NICE TAs, and published in peer-reviewed journals[4]. A similar methodology was applied in NICE TA547[2] and TA633[1], and a maintenance NMA comparing treatments with different induction phases was also carried out by the assessment group in the well-established multiple technology appraisal TA329[5]. After consultation with the ERG where it was discussed to conduct an analysis using a naïve comparison of efficacy results (as per the ERG base case), the company considered this to be inappropriate. The analyses were therefore not completed since the company does not believe that a naïve comparison is appropriate when an NMA using well-established methods can be applied. Furthermore, the ERG scenario analyses result also indicate that using maintenance NMA results instead of trial results tend to be a conservative assumption of the filgotinib versus all comparators (ERG report, Table 6.1).
Issue 5: Conventional care not appropriate as comparator	*No*	Conventional therapy was identified as a comparator for filgotinib within the NICE scope and was included as a comparator in the previous TAs (TA342[3], TA547[2],TA329[5] and TA633[1]). Thus, conventional therapy was considered as a relevant comparator for filgotinib, and its results were presented in the CS for completeness. Furthermore, ERG commented that "*The company did not include any conventional therapies in either of the NMAs. In fact, it looks like these were not included in the searches either…*" Company would like

		to clarify that the conventional therapies were included in both SLR and NMAs. Only the studies that only included the conventional therapies (without any biologic or targeted therapy as the intervention arm) were excluded because these studies could not be used in the NMA.
Issue 6: Inclusion of and uncertainty about appropriate treatment sequences	*No*	ERG suggested to explore further scenarios informed by expert opinion if available. The treatment sequences included in current base case are informed by the England clinical experts' opinion (Filgotinib clarification letter, Table 42), which could be considered as representing the England practice. Furthermore, additional treatment sequences were explored in the scenario analysis (Filgotinib clarification letter, Table 80 and Table 81). Thus, company believe that the currently submitted analyses could illustrate the treatment sequences in the clinical practice in England. Company is very willing to conduct further scenario analyses around the treatment sequence if other sequence could be suggested by ERG.
Issue 7: Third-line population not modelled	*No*	Filgotinib is still intended to be used as third-line advanced therapy. A scenario analysis results of filgotinib as the third-line advanced treatment has been provided in the Filgotinib clarification letter (Table 3 for A9). See more responses in Issue 1.
Issue 8: Loss of response likely differential for response without remission and remission health state	*Yes*	In the base case, the long-term loss of response over the model time horizon was estimated from the NMA results and the rates did not differ by health state (e.g., the response but not remission state vs. remission state). As noted in Filgotinib clarification letter B16, clinical experts in England agree that if a patient is considered to be in response or remission, their response to treatment would not wane over time. Thus, the loss of response is assumed to be same in response without remission and remission health state could be considered as appropriate in the base case. Table 1 presents the proportion of subjects with pMCS remission over time during the maintenance period. It shows a difference of [redacted] in the pMCS remission rates between maintenance baseline ([redacted]) and week 58 ([redacted]) for filgotinib 200mg induction patients who remained on 200mg in the maintenance phase, which indicates the pMCS remission rates are relatively constant over time. Although the loss of response per health states (i.e., response with and without remission) was unclear, assuming 25%

reduction in the loss of response rate after the first year of maintenance treatment is a conservative estimation for filgotinib.

Table 1. Proportion of Subjects with pMCS Remission (Non-Responder Imputation) by visit in maintenance study

Endpoint	Induction filgotinib 200mg	
	Maintenance filgotinib 200mg (n=199)	Maintenance placebo (n=98)
pMCS Remission at week 11 (Maintenance Baseline), n (%) [95%CI]	[redacted]	[redacted]
p-value	[redacted]	[redacted]
pMCS Remission at week 14, n (%) [95%CI]	[redacted]	[redacted]
p-value	[redacted]	[redacted]
pMCS Remission at week 20, n (%) [95%CI]	[redacted]	[redacted]
p-value	[redacted]	[redacted]
pMCS Remission at week 26, n (%) [95%CI]	[redacted]	[redacted]
p-value	[redacted]	[redacted]
pMCS Remission at week 34, n (%) [95%CI]	[redacted]	[redacted]
p-value	[redacted]	[redacted]
pMCS Remission at week 42, n (%) [95%CI]	[redacted]	[redacted]
p-value	[redacted]	[redacted]
pMCS Remission at week 50, n (%) [95%CI]	[redacted]	[redacted]
p-value	[redacted]	[redacted]
pMCS Remission at week 58, n (%) [95%CI]	[redacted]	[redacted]
p-value	[redacted]	[redacted]

Abbreviations: CI, confidence interval; pMCS, partial Mayo Clinic Score; NA, not applicable.

		Notes: *p-values from Stratified Cochran-Mantel-Haenszel Test. pMCS remission is defined as pMCS <=2 and no individual sub score >1
Issue 9: Assumption of constant loss of response not likely to hold	*No*	The assumption that probability of loss of response is constant over time is likely an overestimation. Extrapolation of these rates from the maintenance trials is therefore likely to underestimate the average duration of treatment. This assumption was made in the absence of evidence, specifically, there is no publicly available data to inform the estimates of response and remission rates in the second and subsequent years for patients receiving the modelled treatments in the first year. This was noted by the ERG in TA633[1] and TA547[2], who additionally also accepted the use of a constant rate due to lack of available data. It was noted by the ERG in TA547[2] that clinical experience indicates the risk of relapse is greatest in the first 6-12 months; and falls thereafter. Additionally, the ERG in TA633[1] noted that Ferrante et al.[6] reported longer follow-up in 81 people with refractory UC treated with infliximab. The results suggested an increasing risk in the first year, but the ERG noted that rate appears relatively constant after that. In TA633[1], the company provided a scenario assuming 25% reduction in the loss of response rate after the first year of maintenance treatment. As mentioned in the issue 8, a difference of [redacted] in the pMCS remission rates between week 11 and week 58 for filgotinib 200mg was observed in the SELECTION trial, which indicates the using 25% reduction rate is a more conservative for filgotinib. Due to lack of robust long-term data for the treatments considered in the model, a similar assumption was made, assuming that the loss of response rate is reduced after the first year by applying the 25% reduction. The results are provided in the Filgotinib clarification letter (Table 44 and Table 45 for B16). Additionally, the model has been updated such that a custom reduction on risk of relapse can be applied after the first year.
Issue 10: Probability of pouchitis not aligned with utility	*No*	The rates of long-term complications post-surgery were obtained from Ferrante et al.[6] which is consistent with TA547[2].

<table>
<tr><td></td><td></td><td>Company agreed with the ERG approach that the probability of chronic pouchitis tends to be the most appropriate source to use in the post-surgery with complications health states, as this state is designed to capture the impact of post-surgery chronic complications.

Ferrante et al.[6] reported that 46.2% patients developed at least one episode of acute pouchitis, while only 19.1% patients developed chronic pouchitis over 6.5 years of follow-up. Because the probability of acute pouchitis is higher than the probability chronic pouchitis, the CS tends to overestimate the incidence of post-surgery complication. As commented by ERG “Overestimating long-term incidence of post-surgery complications would favour treatments where surgery takes place less often, which would ultimately be treatments with low loss of response since surgery only takes place in patients in active UC.” Thus, a conservative assumption of the intervention versus all comparators is applying in the CS.</td></tr>
<tr><td>Issue 11: Uncertainty about health-related quality of life impact</td><td>Yes</td><td><u>Week-10 utility data</u>

As requested by the ERG, the scenario using week-10 utilities data for all pre-surgery health states (i.e., ‘active UC’, ‘remission’, and ‘response without remission’ states) were conducted. Table 2 details the utility values used for this scenario and the results are presented in Table 3 and Table 4 for biologic-naïve and biologic-experienced population, respectively.

Table 2. Estimated week-10 utility values from SELECTION by health state
<table>
<tr><th>Outcome</th><th>Non responder/active UC Baseline (total cohort)</th><th>Response without remission (Week 10)</th><th>Remission (Week 10)</th></tr>
<tr><td>N</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Mean utility (SE)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Abbreviations: SE, standard error; UC, ulcerative colitis</td></tr>
</table>

Table 3. Scenario analysis supporting Issue 11 - biologic-naïve, week-10 utilities data for all pre-surgery health states

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER vs FIL (£/QALY)	ICER Incr. (£/QALY)	Net Health Benefit
Filgotinib	[redacted]	21.213	[redacted]	-	-	-	-	76,178.01	-
Conventional therapy	[redacted]	21.210	[redacted]	15,997.73	0.003	0.210	76,178.01	-	-1.03
Golimumab	[redacted]	21.212	[redacted]	-10,931.16	0.001	0.047	Dominated	Dominated	0.89
Tofacitinib	[redacted]	21.213	[redacted]	-11,297.56	0.000	-0.027	419,502.53 SW	4,954.86	0.85
Adalimumab	[redacted]	21.212	[redacted]	-11,360.53	0.001	0.049	Dominated	Dominated	0.93
Infliximab	[redacted]	21.213	[redacted]	-15,721.69	0.000	-0.009	1,667,829.56 SW	74,132.77	1.21
Vedolizumab SC	[redacted]	21.215	[redacted]	-19,040.43	-0.002	-0.173	110,305.99 SW	20,336.87	1.30
Vedolizumab IV	[redacted]	21.215	[redacted]	-23,219.62	-0.002	-0.147	157,601.44 SW	Dominated	1.65

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; Incr., Incremental; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 4. Scenario analysis supporting Issue 11 - biologic-experienced, week-10 utilities data for all pre-surgery health states

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER vs FIL (£/QALY)	ICER Incr. (£/QALY)	Net Health Benefit
Filgotinib	[redacted]	20.910	[redacted]	-	-	-	-	118,324.22	-
Conventional therapy	[redacted]	20.909	[redacted]	11,489.68	0.001	0.097	118,324.22	-	-0.79
Adalimumab	[redacted]	20.909	[redacted]	-2,452.30	0.001	0.035	Dominated	Dominated	0.22
Tofacitinib	[redacted]	20.910	[redacted]	-4,199.83	0.000	0.013	Dominated	78,495.30	0.34
Vedolizumab SC	[redacted]	20.910	[redacted]	-4,191.25	0.000	0.009	Dominated	Dominated	0.33

Ustekinumab	[redacted]	20.910	[redacted]	-5,084.88	0.000	0.024	Dominated	Dominated	0.42
Vedolizumab IV	[redacted]	20.910	[redacted]	-5,238.67	0.000	0.024	Dominated	897,696.38	0.43

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; Incr., Incremental; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Week-26 utility data

As requested by the ERG, the week-26 data for the pre-surgery health states 'response without remission' and 'remission' is presented in Table 5 below.

Table 5. Estimated week-26 utility values from SELECTION by health state

Outcome	Non responder/active UC*	Response without remission*	Remission*
N	[redacted]	[redacted]	[redacted]
Mean utility (SE)	[redacted]	[redacted]	[redacted]

Notes: *Partial MCS (pMCS) Responder and pMCS Remissioner used for Week 26. Baseline, Week 10 and Week 58 use MCS Responder and MCS Remissioner. Partial Remissioner are by definition also regarded to be Partial Responders.

It should be noted that the partial MCS remission utilities (i.e., MCS excludes the endoscopy sub scores), instead of the full MCS remission utilities, were collected at week 26. Thus, the week-26 utilities data presented in the Table 5 were not necessarily comparable with the baseline, week-10 and week-58 utilities presented in the CS, table 44. Therefore, the scenario analysis using week 26 utilities data was not provided.

Scenario analysis using the data collected at week-58 data was conducted in the CS and showing the results for filgotinib were robust. As the week 26 utilities are an interim results, the week-58 scenario could demonstrate that the results for filgotinib were robust when using HRQoL data collecting at the different timepoint.

Using differential utilities for the induction and maintenance phase

As suggested by ERG, a scenario analysis using differential utilities for the induction and maintenance phase were conducted. The results are presented in the Table 6 and Table 7 for biologic-naïve and biologic-experienced population, respectively. Scenario analysis results indicates that it tends to be a conservative assumption of the filgotinib versus all comparators when applying same utilities value for the induction and maintenance phase.

In this scenario, week-10 utility (mean utility = [redacted]) from SELECTION trial was used for the induction phase active UC and the active UC utility (mean utility = 0.55) from the Swinburn et al. 2012[7] was applied for the maintenance phase. Company noted that there is a potential for adaptation and selection bias of the utility values collected at week 58 in the SELECTION trial. Since UC is a chronic disease, patients may overestimate their EQ-5D scores, e.g., report that they have no problems with their usual activities because they have adapted to living with their disease. There is also a general limitation with EQ-5D data collected in trials due to selection bias (i.e., patients who do not feel well do not fill in the questionnaire). In both cases, the utility for the non-responder/active UC at week 58 may be skewed upwards. Moreover, the sample size of the non-responder/active UC group at week-58 is relatively small (n=35). Thus, the week 58 data from the SELECTION trial was not tested in this scenario. Alternatively, the active UC utility value from the Swinburn et al. 2012[7] was applied in the active UC health state in maintenance because it reported a relatively similar utilities value for 'remission' and 'response without remission' state as SELECTION trial observed (see more detailed data in CS section B3.4.5, Table 46).

Table 6. Scenario analysis supporting Issue 11 - biologic-naïve, using differential utilities for the induction and maintenance phase

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER vs FIL (£/QALY)	ICER Incr. (£/QALY)	Net Health Benefit
Filgotinib	[redacted]	21.213	[redacted]	-	-	-	-	41,654.68	-
Conventional therapy	[redacted]	21.210	[redacted]	15,997.73	0.003	0.384	41,654.68	-	-0.85
Golimumab	[redacted]	21.212	[redacted]	-10,931.16	0.001	0.081	Dominated	Dominated	0.93

		Tofacitinib [redacted] 21.213 [redacted] -11,297.56 0.000 -0.048 233,583.39 2,824.22 0.82 Adalimumab [redacted] 21.212 [redacted] -11,360.53 0.001 0.086 Dominated Dominated 0.96 Infliximab [redacted] 21.213 [redacted] -15,721.69 0.000 -0.020 773,462.97 SW 40,959.81 1.20 Vedolizumab SC [redacted] 21.215 [redacted] -19,040.43 -0.002 -0.312 60,947.50 SW 11,362.40 1.16 Vedolizumab IV [redacted] 21.215 [redacted] -23,219.62 -0.002 -0.267 86,835.96 SW Dominated 1.53 **Abbreviations:** FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; Incr., Incremental; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west **Table 7. Scenario analysis supporting Issue 11 - biologic-experienced, using differential utilities for the induction and maintenance phase** **First-line treatment** / **Total costs (£)** / **Total LYG** / **Total QALYs** / **Incr. costs (£)** / **Incr. LYG** / **Incr. QALYs** / **ICER vs FIL (£/QALY)** / **ICER Incr. (£/QALY)** / **Net Health Benefit** Filgotinib [redacted] 20.910 [redacted] - - - - 63,085.71 - Conventional therapy [redacted] 20.909 [redacted] 11,489.68 0.001 0.182 63,085.71 - -0.71 Adalimumab [redacted] 20.909 [redacted] -2,452.30 0.001 0.066 Dominated Dominated 0.26 Tofacitinib [redacted] 20.910 [redacted] -4,199.83 0.000 0.024 Dominated 41,903.08 0.35 Vedolizumab SC [redacted] 20.910 [redacted] -4,191.25 0.000 0.016 Dominated Dominated 0.34 Ustekinumab [redacted] 20.910 [redacted] -5,084.88 0.000 0.044 Dominated Dominated 0.44 Vedolizumab IV [redacted] 20.910 [redacted] -5,238.67 0.000 0.044 Dominated 897,696.38 0.45 **Abbreviations:** FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; Incr., Incremental; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west
Issue 12: Use of baseline utility values likely inappropriate	*No*	Company noticed that there is a lack of consistency between the estimated health utility values from SELECTION and from published literature, which is particularly true for the active UC health state. It should be noted that the active UC health state in the model includes patients where no further biologic treatment would be given, and patients remain in this health state until they receive surgery or die. This

		is not true for patients entering the SELECTION trial. Therefore, it is likely that using the utility value from the SELECTION trial overestimate the utility in the active UC state. Thus, using the baseline value (mean utility = [redacted]) instead of week-10 value (mean utility = [redacted]) is considered as a more conservative approach to apply. Based on feedback from early scientific advice, various sources of utility inputs were tested in the scenario analysis. Scenario analyses demonstrated that the results for filgotinib were robust when utility estimates were varied. The ERG scenario analyses result also indicate that use of baseline utility values tend to be a conservative assumption of the filgotinib versus all comparators (ERG report, Table 6.1)
Issue 13: Application of dose escalation in model questionable	*Yes*	Dose escalation for filgotinib is not appropriate because the approved doses only include the 200mg and 100mg dose (as per SmPC). For other comparators, dose escalation is used in clinical practice (as indicated in the SmPC) as discussed in section B.3.2.4 in the CS and confirmed in early scientific advice and with clinicians in England. The SELECTION study was a Phase IIB/III study (i.e., dose finding study) whose results have demonstrated that the effective does for filgotinib is 200mg. The comparator treatments in the model are the biological agents. Patients on biologics can experience secondary loss of response following an immunological response to the treatment leading to anti-drug antibody production. These antibodies may reduce the therapeutic effect of the treatment. An accepted clinical strategy, that is reflected in the marketing authorisations of the comparators, is to undertake therapeutic drug monitoring and in appropriate patients to escalate the dose to improve the clinical response. In contrast, filgotinib is a small molecule drug and so will not be affected by immunogenicity. Therefore, therapeutic drug monitoring and subsequent dose escalation is not an appropriate clinical approach for filgotinib.
Issue 14: Fully incremental results not provided in the model	*Yes*	The model was updated to provide the fully incremental results as suggested by ERG.

Additional issues

Nil.

Summary of changes to the company's cost-effectiveness estimate(s)

Nil.

Reference

1. NICE. TA633: Ustekinumab for treating moderately to severely active ulcerative colitis Available at: https://www.nice.org.uk/guidance/ta633. Last Accessed: November 2020. 2020;
2. NICE. TA547: Tofacitinib for moderately to severely active ulcerative colitis. Available at: https://www.nice.org.uk/guidance/ta547. Last Accessed: November 2020. 2018;
3. NICE. TA342: Vedolizumab for treating moderately to severely active ulcerative colitis. Available at: https://www.nice.org.uk/guidance/ta342. Last Accessed: November 2020. 2015;
4. Lohan C, Diamantopoulos A, LeReun C, Wright E, Bohm N, Sawyer LM. Tofacitinib for the treatment of moderately to severely active ulcerative colitis: a systematic review, network meta-analysis and economic evaluation. *BMJ Open Gastroenterol*. 2019;6(1):e000302. doi:10.1136/bmjgast-2019-000302
5. NICE. TA329: Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy. Available at: https://www.nice.org.uk/guidance/ta329. Last Accessed: November 2020. 2015;
6. Ferrante M, Declerck S, De Hertogh G, et al. Outcome after proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis. *Inflamm Bowel Dis*. Jan 2008;14(1):20-8. doi:10.1002/ibd.20278
7. Swinburn P, Elwick H, Bean K, et al. PTU-127 The impact of surgery on health related quality of life in ulcerative colitis. *Gut*. 2012;61(Suppl 2):A237. doi:10.1136/gutjnl-2012-302514c.127

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Filgotinib for moderately to severely active ulcerative colitis [ID3736]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing 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. The ERG 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.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (sections 1.3 to 1.5). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.
Clinical 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. 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.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. 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.

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.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm on 27th January 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

Clinical expert statement

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.

Part 1: Treating moderately to severely active ulcerative colitis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Gordon W. Moran
2. Name of organisation	University of Nottingham
3. Job title or position	Clinical Associate Professor of Gastroenterology
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 ulcerative colitis? ☒ A specialist in the clinical evidence base for ulcerative colitis or filgotinib? ☐ 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 did not submit one, I do not 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
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
8. What is the main aim of treatment for moderately to severely active ulcerative colitis?	To induce clinical and endoscopic remission leading to normalisation of quality of life

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in disease activity by a certain amount)	A cessation of bleeding, normalisation of stool frequency and absence of ulceration/bleeding on endoscopy
10. In your view, is there an unmet need for patients and healthcare professionals in moderately to severely active ulcerative colitis?	Yes there. Approximately a 1/3 of patients will relapse during a 12 month calendar. Infliximab therapy is affected by loss of response while the performance of other anti-TNFs is suboptimal. The majority of patients do not fully respond (response ~60%, remission 30-40%) to other biologics (as seen in phase III data and NMA) and colectomy rates are still stable ~10%.
11. How is moderately to severely active ulcerative colitis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would filgotinib have on the current pathway of care?	Care Pathways are clearly defined and the British Society of Gastroenterology has recently issued guidelines (2019). These are being presently updated with myself as lead author. New guidelines are due to be issued in 2024. Filgotinib would: 1. Add another 1st/2nd line biologic option 2. Stable response/remission rates 3. Able to be given as monotherapy 4. Oral medication with a better safety profile than Tofacitinib.
12. Will the filgotinib be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the filgotinib and current care? • In what clinical setting should filgotinib be used? (for example, primary or secondary care, specialist clinic)	No investments are needed to introduce filgotinib. I do not expect any different health care resource use between filgotinib and current clinical care. I would expect filgotinib to be prescribed in secondary care/speciality clinics.

• What investment is needed to introduce filgotinib? (for example, for facilities, equipment, or training)	
13. Do you expect filgotinib to provide clinically meaningful benefits compared with current care? • Do you expect filgotinib to increase length of life more than current care? • Do you expect filgotinib to increase health-related quality of life more than current care?	The mortality rate in UC is 30% higher than age-matches so overall Filgotinib will not have a great effect on mortality. Its efficacy is similar to other agents as presented by the company's NMA.
14. Are there any groups of people for whom filgotinib would be more or less effective (or appropriate) than the general population?	More effective in a biologic naïve population and vice-versa in a more refractory biologic exposed cohort
15. Will filgotinib 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)	Definitely a bonus. It's a targeted JAK 1 inhibitor delivered as an oral formulation. Will definitely be more acceptable to the end user. This will affect its cost as will not be liable to VAT and other infusion costs incurred by competitors. This will make it welcome to funding agencies as well.
16. Will any rules (informal or formal) be used to start or stop treatment with filgotinib? Do these include any additional testing?	Present rules will apply which are basically an objective assessment by colonoscopy prior to starting 2nd line therapy. This is followed by periodical clinical/biomarker assessments with an appraisal at 12 months to justify continued prescribing if response/remission has been achieved.
17. Do you consider that the use of filgotinib will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of filgotinib or have some been	The instruments used will be suitable.

missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider filgotinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is filgotinib a 'step-change' in the management of the condition? • Does the use of filgotinib address any particular unmet need of the patient population?	Filgotinib will be in the same class as Tofacitinib though NMA data suggest that differences are not significant within class. This drug will not provide a step change.
19. How do any side effects or adverse effects of filgotinib affect the management of the condition and the patient's quality of life?	The common (>5%) side effect reported were either disease-related or expected with this class of drug. The frequency of SAEs reported were comparable to those observed in the placebo arm of the SELECTION trial
20. Do the clinical trials on filgotinib reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The design of this clinical trial and endpoints used are reflective of what is mandated by regulatory agencies world-wide. Moreover endpoints used are similar to other therapies that have been NICE approved. Accepting the limitations of a licencing phase 3 trial SELECTION, the design and outcome is reflective of standard care within the UK. The clinical and endoscopic assessments are what would be used within the NHS and so is the patient population selection. The re-randomisation design rather than a 'run through' result makes the maintenance data less meaningful in the real world.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No not aware of any such evidence

22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA329, TA342, TA547 and TA633]?	No not aware of any such evidence
23. How do data on real-world experience compare with the trial data?	Published 'real-world' experience is limited and not immediately available
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people.	I do not think there are any equality issues in this appraisal. The patients recruited in SELECTION are representative of the UK population.

Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

PART 2 – Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: Potential lack of clarity in the precise line of therapy where filgotinib would be indicated - company submission shows that filgotinib can be positioned at more than one place in the biologic experienced population	Agree but this issue blights all NMAs and trials stratified by biologic exposure. The groups are dichotomous and a more granular assessment has never been attempted. It is likely though that such assessments are impossible at this stage as underpowered. I do not feel that the present data can provide more guidance bar using Filgotinib as a 1st or 2nd agents after failing conventional therapy.

Clinical expert statement

(second-line or third-line). However, in the network meta-analyses and the cost-effectiveness analysis, the biologic experienced subgroup is treated as a single population i.e., not subdivided by line.	
Key issue 2: Lack of data and analyses for the 100 mg dose -The company did not present cost-effectiveness analyses for 100 mg dose of filgotinib or patients with moderate or severe renal impairment where 100 mg is recommended.	The efficacy data for the 100mg dosage is relatively suboptimal so is likely that this dose may be relatively poor in cost-effectiveness. Agree that decision problem may be restricted to the 200mg dosage. Renal impairment is relatively rare in this patient population so this issue may not be clinically relevant.

Key issue 3: Lack of evidence of the effectiveness of a sequence of biologics- Re-randomisation of responders to the intervention permits an assessment of outcomes at the end of the maintenance phase conditional on having achieved response, it does not inform the outcomes during the maintenance phase of those who did not achieve a response.	Agree with this issue and it makes the findings at the end of 58 weeks less representative of the real world. Non-responders receive OLE and go into an LTE cohort with the results not stratified by prior response. No real world observational data presently available to answer this at present.
Key issue 4: Questionable validity of the maintenance phase network meta-analyses (NMA)- the ERG highlighted that the	No treatment is not a valid comparator as this is not a real life scenario. The heterogeneity of the maintenance population is a problem across all studies with different design.

maintenance phase of the company's NMA implies that all treatments are comparators in the maintenance phase when the only valid comparator is no treatment or curtailment of the intervention on which induction was achieved. Further, heterogeneity may exist in the NMA as the population who respond to induction treatment may differ between trials.	
Key issue 5: Conventional care not appropriate as a comparator- in the NICE treatment pathway, it is proposed that filgotinib should	Agree. Filgotininb will always be used after conventional care has failed and hence should not be a comparator.

be used for patients who had an inadequate response, lost response, or are intolerant to conventional therapy. This is also the modelled population. The comparators to filgotinib (drugs suitable for such patients) at this point and further down the treatment pathway are either biologics or a JAK inhibitors.	
Key issue 6: Inclusion of and uncertainty about appropriate treatment sequences - There is uncertainty about the most appropriate treatment sequences.	Multiple scenarios here are possible obviously depending where Filgotinib will be positioned in the treatment pathway though the ones described in the NMA presented by the company are comprehensive and include all agents used as second line or downstream.

Key issue **7: Third-line population not modelled-** two populations of patients were considered in the company's base-case: Biologic-naïve patients and biologic-experienced patients (i.e. second-line only).	This will be difficult to model in my opinion. Presently the model is based on biologic exposure i.e. Infliximab. This is based in clinician experience as this is the commonest drug to be used first line. After TNF failure there is no real guidance on which should be the next biologic so modelling (unless v complex and allows for all options) may be very difficult.
Key issue 8: Loss of response likely differential for response without remission and remission health states – the company assumed loss of response to be equal for those in remission and those in only response (without remission) in the sense that the proportion of those in	Yes indeed and this is an imperfect model. The best chance of long term remission is histological remission, so if a patient achieves histological remission, the hospitalisation rate is 7% at ~ 3 years. While patients who do not achieve this endpoint, the hospitalisation rate is 36% (PMID: 33822915). Same applies to patients who achieve endoscopic remission or not. (STRIDE guideline , Gastroenterology 2021; 160:1570-1583).

response (without remission) to those in remission as observed at the end of the maintenance phase is maintained for the entire modelled time horizon. So, at the end of the maintenance phase, there are fewer patients in remission than in response and this cannot change.	
Key issue 9: Assumption of constant loss of response not likely to hold – loss of response rates are assumed to be constant over a lifetime based on the proportion of	This is not possible to answer at this point. Is there any data from the SELECTION LTE to try and shed some light on this? Loss of response will be individual to each class with TNFs especially Inflximab montherapy affected by a very high loss of response ~ 60% (see PANST data set). Combination therapy especially in TNFs decreases loss of response. This observation does not hold true to integrins, IL12/23 and JAKi.

non-responders at the end of the maintenance phase.	
Key issue 10: Probability of pouchitis not aligned with utility – the probability of pouchitis used in the model was related to the incidence of all pouchitis events, but the utility used was related to chronic pouchitis.	Chronic pouchitis happens in ~5% of cases and is defined as a person needing 4 or more courses of antibiotics in a calendar year. Pouchitis is much more common and happens in 40-70% of cases.
Key issue 11: Uncertainty about health-related quality of life impact- The ERG identified a range of sources and a lack of consistency between the values that were estimated or used. It also identified that a mix of	Unable to comment on this issue

sources is used for the base-case analysis.	
Key issue 12: Use of baseline utility values likely inappropriate The ERG consider baseline utility values for the active UC states to be biased as they include non-responders and responders and do not include any improvement from treatment.	Unable to comment
Key Issue 13: Application of dose escalation in model questionable – the ERG noted that dose escalation does not appear to be recommended in the NICE	Dose escalation is key and is very commonly practiced in the NHS. This should be modelled in for Filgotinib and all comparators Real world data may be useful in this setting. Adalimumab: https://doi.org/10.1093/ecco-jcc/jjx093 Vedolizumab: PMID: **32657179,** PMID: 30768123

guideline for ulcerative colitis NG130 at any line including immediately prior to surgery.	Ustekinumab: PMID: **33860795**
Key issue 14: **Fully incremental results not provided in the model**- The company's model does not enable the generation of fully incremental results.	Cannot comment on this issue

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Filgotinib is effective in biologic naïve and experienced cohorts with a good safety profile
Based on present data its use may be justified both in niave and biologic exposed cohorts
Loss of response should not be assumed to be stable over time and loss of response is different depending is the patient is in remission or not
Dose intensification should be used in modelling
Clinical expert statement

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Technical engagement response form

Filgotinib for moderately to severely active ulcerative colitis [ID3736]

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About you

Table 1 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 of Gastroenterology
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NIL**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Potential lack of clarity in the precise line of therapy where filgotinib would be indicated	~~Yes/~~No	Given the expected effect on the cost effectiveness estimates is currently unknown this is likely to affect the precise line of therapy. The company also initially appeared uncertain which group is best suited to this drug?
Lack of data and analyses for 100 mg dose	~~Yes/~~No	There is uncertainty here and it is important to acknowledge that those patients with renal impairment will require monitoring.
Lack of evidence of effectiveness of a sequence of biologics	~~Yes~~/No	There is insufficient evidence to ascertain the sequence.
Questionable validity of the maintenance phase NMA	~~Yes/~~No	There is a level questionable validity in terms of the heterogeneity. There is need for further clarity on the rate of response.
Conventional care not appropriate as comparator	~~Yes/~~No	It is important for this to be ascertain if this drug will be used in practice.
Inclusion of and uncertainty about appropriate treatment sequences	~~Yes/~~No	Treatment sequences are important. More evidence is required.

Third-line population not modelled	~~Yes/~~No	Would this evidence be necessary?
Loss of response likely differential for response without remission and remission health state	Yes/~~No~~	This information is required and needs to be defined.
Assumption of constant loss of response not likely to hold	~~Yes/~~No	It is difficult to ascertain at this point. However, there needs to be further clarification.
Probability of pouchitis not aligned with utility	~~Yes/~~No	Indication is for active UC unsure whether this is much supporting evidence for pouchitis.
Uncertainty about health-related quality of life impact	~~Yes/~~No	There needs to be clarity HRQoL as this will be an expectation of patients which might be difficult for HCP to manage.
Use of baseline utility values likely inappropriate	~~Yes/~~No	Insufficient data which relates to sequencing.
Application of dose escalation in model questionable	Yes~~/No~~	This needs to be clarified as dose escalation will affect cost and again will need to be managed by CCG and HCP
Fully incremental results not provided in the model	Yes/No	Agreed and therefore more information is required.

Additional issues

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Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
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Summary of changes to the company's cost-effectiveness estimate(s)

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Table 4 Changes to the company's cost-effectiveness estimate

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Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
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Technical engagement response form

Filgotinib for moderately to severely active ulcerative colitis [ID3736]

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Potential lack of clarity in the precise line of therapy where filgotinib would be indicated	Yes	Filgotinib appears to be effective in biologic naïve and biologic experienced patients from data in the SELECTION trial. They state that positioning beyond biologic exposure is challenging to study due to heterogeneity of prior treatments in included the companies NMA as several of the trials do not differentiate between biologic exposure, biologic failure and anti-TNF failure. Therefore, different treatment sequences are proposed (first, second and third line) which would be informed by clinical opinion. I would agree with this analysis with regards to its positioning as stated by the company - *filgotinib is intended for inclusion as an option at all lines of advanced therapy i.e. as a first advanced therapy following the failure of conventional therapy, as well as second- and third-line advanced therapy, immediately prior to surgery*
Lack of data and analyses for 100 mg dose	Yes	100mg dosing not explored as part of NMA however this was studied in SELECTION trial. In view of the drug pharmacokinetics and clearance, the company recommends 100mg only for patients with moderate to severe renal impairment. Within SELECTION those in this group were limited therefore they state that the dose was not included in the economic analysis

Lack of evidence of effectiveness of a sequence of biologics	Yes	As per first comment, the clinical trials do not differentiate in the network meta-analysis do not all differentiate between anti-TNF failure, biologic exposure and biologic failure.
Questionable validity of the maintenance phase NMA	Yes	The company states that maintenance phase treatments should only be pooled if the induction phase treatment was the same for all sources of data for the pooled treatments. They provide appropriate rationale for this approach based on the registration trials for other advanced therapies.
Conventional care not appropriate as comparator	Yes/No	I am not sure if this has been addressed in the responses. B12 response is unclear (states - *Up to four lines of active therapy followed by conventional therapy may be included in the model. All sequences must end with conventional therapy as the final line*) to me however may be based on modelling. Conventional therapy should be followed by first / second / third line treatments, not the other way round.
Inclusion of and uncertainty about appropriate treatment sequences	Yes/No	As per first response.
Third-line population not modelled	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Loss of response likely differential for response without remission and remission health state	Yes/No	Agree with ERG's statement. Loss of response is less likely to occur in patients who have achieved remission in comparison to responders. The company however states '*the long-term loss of response over the model time horizon was estimated from the NMA results and the rates did not differ by health state (e.g. the response but not remission state vs. remission state)'* – they have therefore assumed that loss of response would be constant over time for both scenarios.
Assumption of constant loss of response not likely to hold	Yes	Loss of response over time is unlikely to be constant – greatest loss of response is seen in the first year of therapy (two meta-analyses have previously demonstrated that loss of response for adalimumab was 20% and for infliximab 13% per patient year), however the long-term data is lacking. The company provided a scenario assuming 25% reduction in the loss of response rate after the first year of maintenance treatment which is reasonable.

Probability of pouchitis not aligned with utility	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Uncertainty about health-related quality of life impact	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Use of baseline utility values likely inappropriate	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Application of dose escalation in model questionable	Yes/No	Dose escalation (dose and / or frequency of administration) for biological therapies and small molecules is routinely done in NHS clinical practice if there is evidence of subtherapeutic drug levels and / or loss of response to that therapy. This is recommended as part of national and international guidelines and forms part of standard of care.
Fully incremental results not provided in the model	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

Additional issues

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Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**Galapagos Biotech Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG critique
Issue 1: Potential lack of clarity in the precise line of therapy where filgotinib	*Yes*	The proposed positioning of filgotinib within the NICE treatment pathway is as follows (Figure 1 in the CS): • First-line treatment for biologic-naïve patients (no previous exposure to biologic therapy TNFα inhibitor or vedolizumab)	The company have not demonstrated that efficacy remains the same between lines of therapy in the biologic experienced population. In fact the ERG have found evidence in the form a a conference abstract by Peyrin-Biroulet et al. 2021 based on an analysis of the company's own trial, SELECTION, that efficacy reduces.[1] This shows the proportion who achieve remission at 10 weeks for filgotinib 200mg decreases from 16.3% to 7.4% in moving from one biologic failure to at least two. There

would be indicated		• Treatment for biologic-experienced patients (previous exposure to biologic therapy TNFα inhibitor or vedolizumab), regardless of line of therapy Filgotinib is still intended to be used as third-line advanced therapy. The two subgroups applied in the economic analysis (biologic-naïve and biologic-experienced), instead of the three subgroups (first-line advanced (first biologic), second-line advanced (after failed first biologic) and third-line advanced (after failed second biologic or targeted therapy)), were defined as specified in the final decision problem scope issued by NICE. This is also in line with previous submissions in UC (TA633[1], TA547[2], TA342[3]). Moreover, efficacy results for comparators identified in the SLR were not further split by line of therapy. A scenario analysis of filgotinib as the third-line advanced treatment has been provided in the Filgotinib clarification letter (Table 3 for A9). Company would like to note that because of lacking of data for comparators, it was assumed the efficacy in the second-line and third-line remain the same regardless of treatment line for all interventions in this scenario.	is also a decrease for placebo from 2.0% to 1.6%, but because this is much smaller, the treatment effect in the form of a relative risk, as calculated by the ERG, also decreases from 8.2 to 2.0. Of course, it is unclear how this would compare to other biologics, although it might be reasonable to assume a similar reduction in effectiveness. Therefore, the ERG recommends that any analysis at third line should be informed by empirical estimates where available, informed by a systematic review to identify any for the comparators, supplemented by plausible assumptions where empirical estimates are not available. In terms of dose escalation, the company have not demonstrated adequately how this might occur in clinical practice: the SmPC does not show this. However, there is a systematic review by Gemayel, 2019, that was cited by Peyrin-Biroulet et al. 2021, of treatment dose escalation in ulcerative colitis.[1, 2] This shows that the percentage who undergo dose escalation of anti-TNFs is quite uncertain, varying from 5.0% to 70.8% depending on the treatment. Also, the time to escalation varied with one study showing an increase with time from 16% at 6 months to 44% at 36 months. What appears to be clear is that it is not the case that it only occurs immediately prior to surgery, as modelled by the company. Indeed, the company assume 30% of patients undergo escalation based on as study in Crohn's by Einarson et al. 2017, but that study states: "In general, dose escalation was used when patients had a partial response, absence of response, or loss of response".[3] Also, it is unclear why there is only an

		Dose escalation for filgotinib is not appropriate because the approved doses only include the 200mg and 100mg dose (as per the summary of product characteristics (SmPC)), where Filgotinib 100mg is only recommended only for patients who have moderate or severe renal impairment. For other comparators, dose escalation is used in clinical practice (as indicated in the SmPC) as discussed in section B.3.2.4 in the CS and confirmed in early scientific advice and with clinicians in England. See more responses in Issue 13.	increase in cost with dose escalation given that one would expect that dose escalation occurs in order to either re-induce or prolong a response. Indeed, the study by Gemayel indicates that dose escalation also occurs in those who have responded to initial treatment.[2] It also provides some evidence that dose escalation can be very effective: for example, although only from one small (n=41) study, percentage response and remission with infliximab from 5mg/kg to 10mg/kg at week 8 was 87% and 67% respectively. Therefore, the ERG would recommend that if dose escalation is to be included then it is applied in a more clinically plausible way with an increase in effectiveness, probably as an additional line of therapy with the possibility of response and remission. Estimates to inform the probably of response and remission could come from a systematic review, such as the one by Gemayel, 2019 et al.
Issue 2: Lack of data and analyses for 100 mg dose	*Yes*	The SELECTION study was a Phase IIB/III dose ranging study and patients were randomised to 100mg or 200mg of filgotinib or placebo. As presented in the CS Section B.2.6.2, at week 10 and week 58, higher proportion of patients receiving filgotinib 200mg achieved Mayo Clinic Score (MCS) response, compared with the filgotinib100mg group. Endoscopy/bleeding/stool (EBS) remission was not statistically significant differ between filgotinib 100mg arm and placebo arm at week 10, however was statistically	The company have not demonstrated the efficacy or cost-effectiveness of the 100mg dose.

		significant differ by week 58. Therefore, the recommended dose for filgotinib to patients with ulcerative colitis is 200mg. The approved posology for filgotinib is that a dose of 100mg of once daily is recommended for patients with moderate or severe renal impairment (Creatinine clearance [CrCL] 15 to < 60 mL/min). This recommendation is based on a separate clinical pharmacology study which demonstrated that increase in exposures of filgotinib were observed in patients with moderate or severe renal impairment patients (see more details in the full SmPC in Appendix C). Furthermore, based on the inclusion/exclusion criteria of the SELECTION trial, only patients whose estimated CrCL>40 mL/min were included in the trial. Although the filgotinib 100mg was studied in SELECTION trial, the patient population (CrCL>40 mL/min) does not overlap with the patients within the approved indication (CrCL15 - < 60 mL/min). Therefore, it is not possible to accurately model the efficacy of filgotinib 100mg for patients with moderate or severe renal impairment based on the trial data. As such, filgotinib 100mg was not included in the economic analysis due to a	

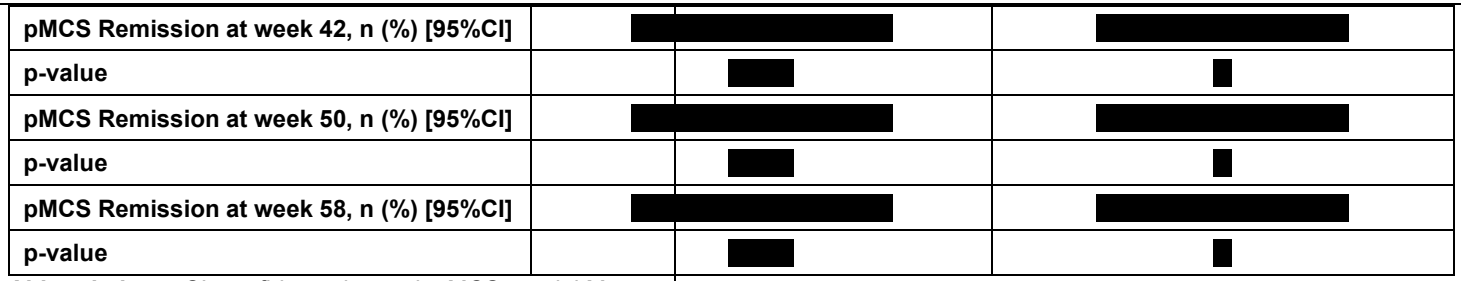
		paucity of data for both filgotinib and comparators in this subgroup of patients.	
Issue 3: Lack of evidence of effectiveness of a sequence of biologics	*No*	Filgotinib is still intended to be used as third-line advanced therapy. However, efficacy results for comparators identified in the SLR were not further split by line of therapy. Thus, it was unable to conduct any comparison between filgotinib and other comparators. See more responses in Issue 1.	See critique of response to Issue 1.
Issue 4: Questionable validity of the maintenance phase NMA	*No*	The methodology applied to obtain relative efficacy in the maintenance phase was verified in NICE Early Scientific Advice sought by the company, and is well established, having been applied in previous NICE TAs, and published in peer-reviewed journals[4]. A similar methodology was applied in NICE TA547[2] and TA633[1], and a maintenance NMA comparing treatments with different induction phases was also carried out by the assessment group in the well-established multiple technology appraisal TA329[5]. After consultation with the ERG where it was discussed to conduct an analysis using a naïve comparison of efficacy results (as per the ERG base case), the company considered this to be inappropriate. The analyses were therefore not completed since the company does not believe that a naïve	The company are factually incorrect in describing the analysis employed in the ERG base case as a "naïve comparison". It was, as is the case with the NMA, based on RCT evidence. The difference between the NMA and the ERG approach was that the ERG did not pool any RCTs of different interventions, but instead informed the effectiveness of each intervention at the maintenance phase using only RCT data for that intervention. The ERG has already provided an explanation in the ERG report why this approach is clinically applicable and methodologically correct and the use of an NMA neither clinically applicable nor methodologically correct. However, it is worth restating these grounds. Firstly, on clinical grounds, the choice at the maintenance phase was, for patients who have responded on induction treatment, whether to continue with the induction treatment or to curtail it. For ease of exposition, let us refer to this treatment as treatment A. Given that response has occurred, the choice does not involve

		comparison is appropriate when an NMA using well-established methods can be applied. Furthermore, the ERG scenario analyses result also indicate that using maintenance NMA results instead of trial results tend to be a conservative assumption of the filgotinib versus all comparators (ERG report, Table 6.1).	switching to another active treatment, e.g. treatment B. Therefore, methodologically, the most appropriate evidence to inform this choice is from an RCT of the induction intervention versus no placebo where randomisation occurs of patients who have responded at the start of the maintenance phase. It makes no sense to compare treatment A with treatment B because, as stated, switching is not a choice for those who have responded. Furthermore, if treatment B were to be a comparator, then, for comparability, its effectiveness should be based on randomisation of patients who had also responded to treatment A. Of course, it is not surprising that none of the RCTs were designed in this way: all of the ones with re-randomisation only compared the same treatment on which response occurred with placebo. There were none that compared treatment A with treatment B on re-randomisation at the maintenance phase and that makes sense because they were designed to inform the clinical choice of continuing treatment A or curtailing it or continuing treatment B or curtailing it. They were not designed to inform the choice of switching from A to B on response to A.
Issue 5: Conventional care not appropriate as comparator	*No*	Conventional therapy was identified as a comparator for filgotinib within the NICE scope and was included as a comparator in the previous TAs (TA342[3], TA547[2],TA329[5] and TA633[1]). Thus, conventional therapy was considered as a relevant comparator for	The ERG continue to argue that conventional therapy is not an appropriate comparator given that the care pathway clearly indicates that lack of or loss of response would lead to a biologic except if a biologic were contraindicated, which would imply a different population. The ERG are correct in stating that no conventional therapy was included as a comparator in the NMAs or in

		filgotinib, and its results were presented in the CS for completeness. Furthermore, ERG commented that "*The company did not include any conventional therapies in either of the NMAs. In fact, it looks like these were not included in the searches either…*" Company would like to clarify that the conventional therapies were included in both SLR and NMAs. Only the studies that only included the conventional therapies (without any biologic or targeted therapy as the intervention arm) were excluded because these studies could not be used in the NMA.	the searches. It is of course true that patients in the control arm of each trial received conventional therapies, but none of these was identified as a comparator.
Issue 6: Inclusion of and uncertainty about appropriate treatment sequences	*No*	ERG suggested to explore further scenarios informed by expert opinion if available. The treatment sequences included in current base case are informed by the England clinical experts' opinion (Filgotinib clarification letter, Table 42), which could be considered as representing the England practice. Furthermore, additional treatment sequences were explored in the scenario analysis (Filgotinib clarification letter, Table 80 and Table 81). Thus, company believe that the currently submitted analyses could illustrate the treatment sequences in the clinical practice in England. Company is very willing	The ERG have noted the company's presentation of England clinical experts' opinion on the most likely treatment sequences. However, the ERG continues to wonder whether there really is no variation in clinical practice. Experts should be consulted again for some likely alternative sequences. The ERG have suggested some alternative treatment sequences that the ERG clinical expert thought might be relevant (adalimumab, vedolizumab, then tofacitinib in the naïve population; vedolizumab, then tofacitinib in the experienced population).

		to conduct further scenario analyses around the treatment sequence if other sequence could be suggested by ERG.	
Issue 7: Third-line population not modelled	*No*	Filgotinib is still intended to be used as third-line advanced therapy. A scenario analysis results of filgotinib as the third-line advanced treatment has been provided in the Filgotinib clarification letter (Table 3 for A9). See more responses in Issue 1.	See critique of Issue 1.
Issue 8: Loss of response likely differential for response without remission and remission health state	*Yes*	In the base case, the long-term loss of response over the model time horizon was estimated from the NMA results and the rates did not differ by health state (e.g., the response but not remission state vs. remission state). As noted in Filgotinib clarification letter B16, clinical experts in England agree that if a patient is considered to be in response or remission, their response to treatment would not wane over time. Thus, the loss of response is assumed to be same in response without remission and remission health state could be considered as appropriate in the base case. Table 1 presents the proportion of subjects with pMCS remission over time during the maintenance period. It shows a difference of [redacted] in the pMCS remission rates between maintenance baseline [redacted] and week 58	It simply does not make sense that the “response to treatment would not wane over time”, particularly since the company and the ERG both agree that it does wane, but disagree as to whether the rate differs depending on the starting point i.e. response without remission or remission. The company have not presented any evidence to inform their assumption of no difference, despite ERG request. The ERG recommends that an analysis of the SELECTION trial be performed to estimate the rates of loss of response for each of the two groups of patients. Mohammed Nabil Quraishi, representing the British Society of Gastroenterology IBD section, stated in response to Technical Engagement “ Loss of response is less likely to occur in patients who have achieved remission in comparison to responders.”, thus supporting the ERG’s view. The ERG notes that assuming the same loss of response rates in response and remission states likely favours filgotinib. The company should enable this

		[redacted] for filgotinib 200mg induction patients who remained on 200mg in the maintenance phase, which indicates the pMCS remission rates are relatively constant over time. Although the loss of response per health states (i.e., response with and without remission) was unclear, assuming 25% reduction in the loss of response rate after the first year of maintenance treatment is a conservative estimation for filgotinib. **Table 1. Proportion of Subjects with pMCS Remission (Non-Responder Imputation) by visit in maintenance study** **Endpoint** / **Maintenanc** **pMCS Remission at week 11 (Maintenance Baseline), n (%) [95%CI]** / [redacted] **p-value** **pMCS Remission at week 14, n (%) [95%CI]** / [redacted] **p-value** **pMCS Remission at week 20, n (%) [95%CI]** / [redacted] **p-value** **pMCS Remission at week 26, n (%) [95%CI]** / [redacted] **p-value** **pMCS Remission at week 34, n (%) [95%CI]** / [redacted] **p-value**	model functionality and explore scenarios with differential loss of response.

		 **Abbreviations:** CI, confidence interval; pMCS, partial Mayo Clinic Score; NA, not applicable. **Notes:** *p-values from Stratified Cochran-Mantel-Haenszel Test. pMCS remission is defined as pMCS <=2 and no individual sub score >1	
Issue 9: Assumption of constant loss of response not likely to hold	*No*	The assumption that probability of loss of response is constant over time is likely an overestimation. Extrapolation of these rates from the maintenance trials is therefore likely to underestimate the average duration of treatment. This assumption was made in the absence of evidence, specifically, there is no publicly available data to inform the estimates of response and remission rates in the second and subsequent years for patients receiving the modelled treatments in the first year. This was noted by the ERG in TA633[1] and TA547[2], who additionally also accepted the use of a constant rate due to lack of available data.	Evidence on treatment-specific long-term loss of response, or expert opinion on loss of response over time, as was requested by the ERG, was not provided by the company. The company did provide numbers of patients in remission for filgotinib 200mg induction patients who remained on 200mg in the maintenance phase between week 11 and 58. Obviously, this neither addresses the longer term, nor differences between treatments, but this also provides limited information about loss of response as it is unclear whether patients could move from remission to response (without remission) and no response states or only to the no response state. Furthermore, the same data were not provided for patients in the response (but no remission) state. It is unclear how the company concluded from there that *"using 25% reduction rate is a more conservative for filgotinib"*, especially since these 25% refer to the

		It was noted by the ERG in TA547[2] that clinical experience indicates the risk of relapse is greatest in the first 6-12 months; and falls thereafter. Additionally, the ERG in TA633[1] noted that Ferrante et al.[6] reported longer follow-up in 81 people with refractory UC treated with infliximab. The results suggested an increasing risk in the first year, but the ERG noted that rate appears relatively constant after that. In TA633[1], the company provided a scenario assuming 25% reduction in the loss of response rate after the first year of maintenance treatment. As mentioned in the issue 8, a difference of [redacted] in the pMCS remission rates between week 11 and week 58 for filgotinib 200mg was observed in the SELECTION trial, which indicates the using 25% reduction rate is a more conservative for filgotinib. Due to lack of robust long-term data for the treatments considered in the model, a similar assumption was made, assuming that the loss of response rate is reduced after the first year by applying the 25% reduction. The results are provided in the Filgotinib clarification letter (Table 44 and Table 45 for B16). Additionally, the model has been updated such that a custom reduction on risk of relapse can be applied after the first year.	reduction in loss of response rate, rather than to the loss of response rate itself. The ERG concludes that the uncertainty about the rate of loss of response therefore remains.

Issue 10: Probability of pouchitis not aligned with utility	*No*	The rates of long-term complications post-surgery were obtained from Ferrante et al.[6] which is consistent with TA547[2]. Company agreed with the ERG approach that the probability of chronic pouchitis tends to be the most appropriate source to use in the post-surgery with complications health states, as this state is designed to capture the impact of post-surgery chronic complications. Ferrante et al.[6] reported that 46.2% patients developed at least one episode of acute pouchitis, while only 19.1% patients developed chronic pouchitis over 6.5 years of follow-up. Because the probability of acute pouchitis is higher than the probability chronic pouchitis, the CS tends to overestimate the incidence of post-surgery complication. As commented by ERG "*Overestimating long-term incidence of post-surgery complications would favour treatments where surgery takes place less often, which would ultimately be treatments with low loss of response since surgery only takes place in patients in active UC."* Thus, a conservative assumption of the intervention versus all comparators is applying in the CS.	As stated before, this inconsistency in the model (between using the rate of all pouchitis events but the disutitily of chronic pouchitis) should be corrected, as was done by the ERG. Second, it should be noted that the quote by the ERG ("*Overestimating long-term incidence of post-surgery complications would favour treatments where surgery takes place less often, which would ultimately be treatments with low loss of response since surgery only takes place in patients in active UC.")* does not imply what the company interprets it to be (*"Thus, a conservative assumption of the intervention versus all comparators is applying in the CS."*). Instead, the ERG considers that the company's implementation is not conservative when filgotinib is compared with treatments with higher loss of response / higher proportion of patients in the active UC health state.

<table>
<tr>
<td>Issue 11: Uncertainty about health-related quality of life impact</td>
<td>Yes</td>
<td>
<u>Week-10 utility data</u>

As requested by the ERG, the scenario using week-10 utilities data for all pre-surgery health states (i.e., ‘active UC’, ‘remission’, and ‘response without remission’ states) were conducted. Table 2 details the utility values used for this scenario and the results are presented in Table 3 and Table 4 for biologic-naïve and biologic-experienced population, respectively.

Table 2. Estimated week-10 utility values from SELECTION by health state
<table>
<tr><th>Outcome</th><th>Non responder/ active UC Baseline (total cohort)</th><th>Response without remission (Week 10)</th><th>Remission (Week 10)</th></tr>
<tr><td>N</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Mean utility (SE)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Abbreviations: SE, standard error; UC, ulcerative colitis

Table 3. Scenario analysis supporting Issue 11 - biologic-naïve, week-10 utilities data for all pre-surgery health states
</td>
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The ERG requested the following three scenarios (see ERG report):

• An analysis using biologic-naïve and biologic-experienced specific utility values applied to the new base-case analysis where 10-weeks data are used for all pre-surgery health states. – Utility values stratified by population (i.e. biologic-naïve and -experienced) were not provided despite multiple requests by the ERG. The company stated that, as requested by the ERG, they added a scenario using week-10 utility data, however, this is not what the ERG requested (this is actually in the company’s original base-case with the exception of the active UC utility value, which was measured at baseline, and is exactly the same as the ERG base-case). The ERG therefore considers that differential utility values per population continue not to be considered in the company’s analyses.

• An analysis using the 26-weeks data for the pre-surgery health states ‘response without remission’ and ‘remission’ (and 10-weeks value for active UC/non-responder). – The company did not provide this scenario arguing that the data collected at 26-weeks were partial MCS remission utilities (i.e., MCS excludes the endoscopy sub scores), instead of the full MCS remission utilities. The company did provide the utilities and the ERG notes that the 26-week utility value for the response without remission health state is [redacted] compared with the 10-week utility
</td>
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</table>

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALY	ICER vs. FIL (QALY)	ICER (QALY)	Incr. Net Health Benefit
Filgotinib	[redacted]	21.213	[redacted]	-	-	-	-	76,178.01	-
Conventional therapy	[redacted]	21.210	[redacted]	15,997.73	0.003	0.210	76,178.01	-	1.03
Golimumab	[redacted]	21.212	[redacted]	-10,931.16	0.001	0.047	Dominated	Dominated	0.89
Tofacitinib	[redacted]	21.213	[redacted]	-11,297.75	0.000	-0.027	419,150.15 SW	1,954.39	1.05
Adalimumab	[redacted]	21.212	[redacted]	-11,360.33	0.001	0.048	Dominated	Dominated	0.93
Infliximab	[redacted]	21.213	[redacted]	-15,721.69	0.000	-0.009	1,667,829.56 SW	74,132.77	1.21
Vedolizumab SC	[redacted]	21.215	[redacted]	-19,040.43	-0.002	-0.173	110,305.99 SW	20,336.87	1.30
Vedolizumab IV	[redacted]	21.215	[redacted]	-23,219.62	0.002	-0.147	157,601.44 SW	Dominated	1.45

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; Incr., Incremental; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 4. Scenario analysis supporting Issue 11 - biologic-experienced, week-10 utilities data for all pre-surgery health states

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs
Filgotinib	[redacted]	20.910	[redacted]	-
Conventional therapy	[redacted]	20.909	[redacted]	11,48
Adalimumab	[redacted]	20.909	[redacted]	-2,45
Tofacitinib	[redacted]	20.910	[redacted]	-4,19
Vedolizumab SC	[redacted]	20.910	[redacted]	-4,19

value, while the 26-week utility value for the remission health state is [redacted] compared with 10 weeks. The 26 week utility values significantly differ from those at 10 weeks and 58 weeks and it is unclear whether this can solely be attributed to the fact that classification of patients was based on partial MCS remission (MSC excluding endoscopy subscores) or whether utility values in the response and remission states are actually decreasing over time (and the relatively high 58-weeks data are subject to selection bias based on people who lost response dropping out, as is also indicated by the company). In conclusion, different scenarios with utilities at 10 and 26 weeks should probably be considered (the ERG explores the 26-week utilities in a scenario).

- An analysis using differential utilities for the induction and maintenance phase. **– The company performed a scenario using differential utility values for the active UC state only, rather than also differentiating the response and remission utilities by induction and maintenance phase (this could have been achieved using 10-week utilities to represent the induction phase utilities and 26-week utilities to represent the maintenance treatment phase, both sourced from SELECTION instead of the literature). Instead of what was requested by the ERG, the company used active UC maintenance utility value sources from the literature (Swinburn et al) due to small sample sizes at 58 weeks in the SELECTION**

Ustekinumab	[redacted]	20.910	[redacted]	-5,084.88	0.000	0.024	Dominated	Dominated	Dominated	0.42
Vedolizumab IV	[redacted]	20.910	[redacted]	-5,238.87	0.000	0.024	Dominated	897,896.38		0.43

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; Incr., Incremental; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Week-26 utility data

As requested by the ERG, the week-26 data for the pre-surgery health states 'response without remission' and 'remission' is presented in Table 5 below.

Table 5. Estimated week-26 utility values from SELECTION by health state

Outcome	Non responder/active UC*	Response without remission*	Remission*
N	[redacted]	[redacted]	[redacted]
Mean utility (SE)	[redacted]	[redacted]	[redacted]

Notes: *Partial MCS (pMCS) Responder and pMCS Remissioner used for Week 26. Baseline, Week 10 and Week 58 use MCS Responder and MCS Remissioner. Partial Remissioner are by definition also regarded to be Partial Responders.

It should be noted that the partial MCS remission utilities (i.e., MCS excludes the endoscopy sub scores), instead of the full MCS remission utilities, were collected at

trial (n=35). The company additionally argue that the SELECTION trial active UC utility value would be over-estimated due to adaptation to the disease and patients that are feeling less well not filling in the questionnaire. Unfortunately the company did not provide the SELECTION utility value, so it is difficult to assess this for the ERG – presumably this was above the baseline and week 10 utility values. The ERG considers that the company's scenario did not help in assessing the full impact of differential utility values per treatment phase on cost-effectiveness.

In conclusion, uncertainty remains about utility values that appropriately reflect UC at the different treatment phases, per health state, per measurement point, and per population. The ERG explores the impact of utility values measured at a different time point in a scenario, but differential utilities per population (biologic-naïve and -experienced) should be provided by the company.

		week 26. Thus, the week-26 utilities data presented in the Table 5 were not necessarily comparable with the baseline, week-10 and week-58 utilities presented in the CS, table 44. Therefore, the scenario analysis using week 26 utilities data was not provided. Scenario analysis using the data collected at week-58 data was conducted in the CS and showing the results for filgotinib were robust. As the week 26 utilities are an interim results, the week-58 scenario could demonstrate that the results for filgotinib were robust when using HRQoL data collecting at the different timepoint. **Using differential utilities for the induction and maintenance phase** As suggested by ERG, a scenario analysis using differential utilities for the induction and maintenance phase were conducted. The results are presented in the Table 6 and Table 7 for biologic-naïve and biologic-experienced population, respectively. Scenario analysis results indicates that it tends to be a conservative assumption of the filgotinib versus all comparators when applying same utilities value for the induction and maintenance phase.	

		In this scenario, week-10 utility (mean utility = [redacted]) from SELECTION trial was used for the induction phase active UC and the active UC utility (mean utility = 0.55) from the Swinburn et al. 2012[7] was applied for the maintenance phase. Company noted that there is a potential for adaptation and selection bias of the utility values collected at week 58 in the SELECTION trial. Since UC is a chronic disease, patients may overestimate their EQ-5D scores, e.g., report that they have no problems with their usual activities because they have adapted to living with their disease. There is also a general limitation with EQ-5D data collected in trials due to selection bias (i.e., patients who do not feel well do not fill in the questionnaire). In both cases, the utility for the non-responder/active UC at week 58 may be skewed upwards. Moreover, the sample size of the non-responder/active UC group at week-58 is relatively small (n=35). Thus, the week 58 data from the SELECTION trial was not tested in this scenario. Alternatively, the active UC utility value from the Swinburn et al. 2012[7] was applied in the active UC health state in maintenance because it reported a relatively similar utilities value for 'remission' and 'response without remission' state as	

SELECTION trial observed (see more detailed data in CS section B3.4.5, Table 46).

Table 6. Scenario analysis supporting Issue 11 - biologic-naïve, using differential utilities for the induction and maintenance phase

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs
Filgotinib	[redacted]	21.213	[redacted]	-
Conventional therapy	[redacted]	21.210	[redacted]	15,99
Golimumab	[redacted]	21.212	[redacted]	-10,93
Tofacitinib	[redacted]	21.213	[redacted]	-11,29
Adalimumab	[redacted]	21.212	[redacted]	-11,36
Infliximab	[redacted]	21.213	[redacted]	-15,72
Vedolizumab SC	[redacted]	21.215	[redacted]	-19,04
Vedolizumab IV	[redacted]	21.215	[redacted]	-23,21

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; Incr., Incremental; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Table 7. Scenario analysis supporting Issue 11 - biologic-experienced, using differential utilities for the induction and maintenance phase

First-line treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs
Filgotinib	[redacted]	20.910	[redacted]	-

Conventional therapy	[redacted]	20.909	[redacted]	11,489.68	0.001	0.182	63,085.71	-	-0.71
Adalimumab	[redacted]	20.909	[redacted]	-2,452.30	0.001	0.066	Dominated	Dominated	0.26
Tofacitinib	[redacted]	20.910	[redacted]	-4,199.83	0.000	0.024	Dominated	41,903.08	0.35
Vedolizumab SC	[redacted]	20.910	[redacted]	-4,191.25	0.000	0.016	Dominated	Dominated	0.34
Ustekinumab	[redacted]	20.910	[redacted]	-5,084.88	0.000	0.044	Dominated	Dominated	0.44
Vedolizumab IV	[redacted]	20.910	[redacted]	-5,238.67	0.000	0.044	Dominated	897,696.38	0.45

Abbreviations: FIL, Filgotinib, ICER, incremental cost-effectiveness ratio; Incr., Incremental; IV, intravenous; LYG: life-years gained; QALY: quality-adjusted life years; SC, subcutaneous; SW, south-west

Issue 12: Use of baseline utility values likely inappropriate	*No*	Company noticed that there is a lack of consistency between the estimated health utility values from SELECTION and from published literature, which is particularly true for the active UC health state. It should be noted that the active UC health state in the model includes patients where no further biologic treatment would be given, and patients remain in this health state until they receive surgery or die. This is not true for patients entering the SELECTION trial. Therefore, it is likely that using the utility value from the SELECTION trial overestimate the utility in the active UC state. Thus, using the baseline value (mean utility = [redacted]) instead of week-10 value (mean utility = [redacted]) is	No further evidence was provided. It is true that this is an area of uncertainty and difficult to know which utility value is more appropriate, if any of the two. The ERG analysis includes the 10-week estimate to capture potential regression to the mean.

		considered as a more conservative approach to apply. Based on feedback from early scientific advice, various sources of utility inputs were tested in the scenario analysis. Scenario analyses demonstrated that the results for filgotinib were robust when utility estimates were varied. The ERG scenario analyses result also indicate that use of baseline utility values tend to be a conservative assumption of the filgotinib versus all comparators (ERG report, Table 6.1)	
Issue 13: Application of dose escalation in model questionable	*Yes*	Dose escalation for filgotinib is not appropriate because the approved doses only include the 200mg and 100mg dose (as per SmPC). For other comparators, dose escalation is used in clinical practice (as indicated in the SmPC) as discussed in section B.3.2.4 in the CS and confirmed in early scientific advice and with clinicians in England. The SELECTION study was a Phase IIB/III study (i.e., dose finding study) whose results have demonstrated that the effective does for filgotinib is 200mg. The comparator treatments in the model are the biological agents. Patients on biologics can experience secondary loss of response following an immunological	See critique of Issue 1.

		response to the treatment leading to anti-drug antibody production. These antibodies may reduce the therapeutic effect of the treatment. An accepted clinical strategy, that is reflected in the marketing authorisations of the comparators, is to undertake therapeutic drug monitoring and in appropriate patients to escalate the dose to improve the clinical response. In contrast, filgotinib is a small molecule drug and so will not be affected by immunogenicity. Therefore, therapeutic drug monitoring and subsequent dose escalation is not an appropriate clinical approach for filgotinib.	
Issue 14: Fully incremental results not provided in the model	*Yes*	The model was updated to provide the fully incremental results as suggested by ERG.	The fully incremental analysis is not correctly implemented. The company calculates ICERs also against those strategies that are dominated. Guidance on fully incremental analysis by Briggs (2006) and Cantor (1994) should be followed.

Additional issues

Nil.

Summary of changes to the company's cost-effectiveness estimate(s)

Nil.

Technical engagement response form

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Technical engagement response form

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Filgotinib for moderately to severely active ulcerative colitis [ID3736] – Addendum post Technical Engagement

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

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

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Contributions of authors

Nigel Armstrong acted as project lead and health economist on this assessment, critiqued the clinical effectiveness methods and evidence, the company's economic model 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. Thea van Asselt, Merel Kimman, Andrea Peeters, Tim Govers, and Charlotte Ahmadu acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Jeremy Howick, Kevin McDermott and Rob Riemsma acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Shelley de Kock and Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore critiqued the company's economic evaluation, contributed to the writing of the report, and provided general health economic 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.

Table 1: ERG base-case biologic-naive population

Technologies	Total LYs	Total QALYs	Total costs (£)	NMB (20k)	NMB (30k)	Incremental LYs FIL vs X	Incremental QALYs FIL vs X	Incremental costs (£) FIL vs X	ICER (£/QALY) pairwise FIL vs X
Company base-case (biologic-naïve), without conventional care, with company's treatment sequences									
Filgotinib	21.213	[redacted]	[redacted]	£115,860	£252,927	0.000	0.000	£0	0
Golimumab	21.212	[redacted]	[redacted]	£103,804	£240,308	0.001	0.056	-£10,931	FIL dominates
Tofacitinib	21.213	[redacted]	[redacted]	£105,216	£242,610	0.000	-0.033	-£11,298	345631 SW
Adalimumab	21.212	[redacted]	[redacted]	£103,314	£239,788	0.001	0.059	-£11,361	FIL dominates
Infliximab	21.213	[redacted]	[redacted]	£100,385	£237,575	0.000	-0.012	-£15,722	1273598 SW
Vedolizumab SC	21.215	[redacted]	[redacted]	£101,019	£240,185	-0.002	-0.210	-£19,040	90695 SW
Vedolizumab IV	21.215	[redacted]	[redacted]	£96,228	£235,088	-0.002	-0.179	-£23,220	129463 SW
ERG change 1: Disable dose escalation for all									
Filgotinib	21.213	[redacted]	[redacted]	£117,852	£254,919	0.000	0.000	£0	0
Tofacitinib	21.213	[redacted]	[redacted]	£110,358	£247,752	0.000	-0.033	-£8,148	249268 SW
Adalimumab	21.212	[redacted]	[redacted]	£106,837	£243,311	0.001	0.059	-£9,830	FIL dominates
Golimumab	21.212	[redacted]	[redacted]	£105,812	£242,316	0.001	0.056	-£10,915	FIL dominates
Infliximab	21.213	[redacted]	[redacted]	£105,106	£242,296	0.000	-0.012	-£12,993	1052557 SW
Vedolizumab IV	21.215	[redacted]	[redacted]	£104,137	£242,997	-0.002	-0.179	-£17,303	96473 SW
Vedolizumab SC	21.215	[redacted]	[redacted]	£104,410	£243,576	-0.002	-0.210	-£17,641	84030 SW
ERG change 2: Do not use NMA results for maintenance									
Filgotinib	21.214	[redacted]	[redacted]	£114,280	£252,280	0.000	0.000	£0	0
Tofacitinib	21.213	[redacted]	[redacted]	£102,135	£239,044	0.001	0.109	-£9,964	FIL dominates
Golimumab	21.214	[redacted]	[redacted]	£99,118	£236,911	0.000	0.021	-£14,750	FIL dominates
Adalimumab	21.214	[redacted]	[redacted]	£98,782	£236,536	0.000	0.024	-£15,008	FIL dominates
Infliximab	21.214	[redacted]	[redacted]	£96,761	£234,737	0.000	0.002	-£17,472	FIL dominates

Vedolizumab SC	21.215	[redacted]	[redacted]	£98,154	£236,915	-0.001	-0.076	-£17,648	231845 SW
Vedolizumab IV	21.216	[redacted]	[redacted]	£90,376	£229,870	-0.002	-0.149	-£26,894	179898 SW
ERG change 3: Use of 10-week active UC utilities									
Filgotinib	21.213	[redacted]	[redacted]	£129,555	£273,470	0.000	0.000	£0	0
Golimumab	21.212	[redacted]	[redacted]	£117,684	£261,128	0.001	0.047	-£10,931	FIL dominates
Tofacitinib	21.213	[redacted]	[redacted]	£118,796	£262,980	0.000	-0.027	-£11,298	419503 SW
Adalimumab	21.212	[redacted]	[redacted]	£117,207	£260,627	0.001	0.049	-£11,361	FIL dominates
Infliximab	21.213	[redacted]	[redacted]	£114,022	£258,031	0.000	-0.009	-£15,722	1667830 SW
Vedolizumab SC	21.215	[redacted]	[redacted]	£113,967	£259,608	-0.002	-0.173	-£19,040	110306 SW
Vedolizumab IV	21.215	[redacted]	[redacted]	£109,282	£254,670	-0.002	-0.147	-£23,220	157601 SW
ERG change 4: Use probability of chronic pouchitis									
Filgotinib	21.213	[redacted]	[redacted]	£121,132	£259,105	0.000	0.000	£0	0
Golimumab	21.212	[redacted]	[redacted]	£109,166	£246,593	0.001	0.055	-£10,873	FIL dominates
Adalimumab	21.212	[redacted]	[redacted]	£108,683	£246,080	0.001	0.058	-£11,298	FIL dominates
Tofacitinib	21.213	[redacted]	[redacted]	£110,431	£248,721	0.000	-0.032	-£11,334	357798 SW
Infliximab	21.213	[redacted]	[redacted]	£105,625	£243,717	0.000	-0.012	-£15,742	1336681 SW
Vedolizumab SC	21.215	[redacted]	[redacted]	£105,921	£245,928	-0.002	-0.203	-£19,279	94782 SW
Vedolizumab IV	21.215	[redacted]	[redacted]	£101,181	£240,892	-0.002	-0.174	-£23,425	134838 SW
ERG base-case (ERG changes 1-4)									
Filgotinib	21.214	[redacted]	[redacted]	£135,221	£280,722	0	0	0	0
Tofacitinib	21.213	[redacted]	[redacted]	£126,113	£270,758	0.001	0.086	-£7,396	FIL dominates
Adalimumab	21.214	[redacted]	[redacted]	£122,214	£267,536	0.000	0.018	-£12,649	FIL dominates
Golimumab	21.214	[redacted]	[redacted]	£121,000	£266,349	0.000	0.015	-£13,915	FIL dominates
Infliximab	21.214	[redacted]	[redacted]	£120,590	£266,088	0.000	0.000	-£14,624	FIL dominates
Vedolizumab SC	21.215	[redacted]	[redacted]	£119,476	£265,556	-0.001	-0.058	-£16,904	291828 SW
Vedolizumab IV	21.216	[redacted]	[redacted]	£116,700	£263,371	-0.002	-0.117	-£20,858	178438 SW

Table 2: ERG scenarios biologic-naive population

Technologies	Total LYs	Total QALYs	Total costs (£)	NMB (20k)	NMB (30k)	Incremental LYs FIL vs X	Incremental QALYs FIL vs X	Incremental costs (£) FIL vs X	ICER (£/QALY) pairwise FIL vs X
ERG base-case (biologic-naïve)									
Filgotinib	21.214	[redacted]	[redacted]	£135,221	£280,722	0.000	0.000	£0	0
Tofacitinib	21.213	[redacted]	[redacted]	£126,113	£270,758	0.001	0.086	-£7,396	FIL dominates
Adalimumab	21.214	[redacted]	[redacted]	£122,214	£267,536	0.000	0.018	-£12,649	FIL dominates
Golimumab	21.214	[redacted]	[redacted]	£121,000	£266,349	0.000	0.015	-£13,915	FIL dominates
Infliximab	21.214	[redacted]	[redacted]	£120,590	£266,088	0.000	0.000	-£14,624	FIL dominates
Vedolizumab SC	21.215	[redacted]	[redacted]	£119,476	£265,556	-0.001	-0.058	-£16,904	291828 SW
Vedolizumab IV	21.216	[redacted]	[redacted]	£116,700	£263,371	-0.002	-0.117	-£20,858	178438 SW
Scenario 1: decreasing loss of response									
Filgotinib	21.215	[redacted]	[redacted]	£135,344	£281,414	0.000	0.000	£0	0
Tofacitinib	21.213	[redacted]	[redacted]	£124,713	£269,716	0.002	0.107	-£8,496	FIL dominates
Adalimumab	21.214	[redacted]	[redacted]	£120,718	£266,528	0.000	0.026	-£14,106	FIL dominates
Golimumab	21.215	[redacted]	[redacted]	£119,325	£265,158	0.000	0.024	-£15,546	FIL dominates
Infliximab	21.215	[redacted]	[redacted]	£119,006	£264,997	0.000	0.008	-£16,180	FIL dominates
Vedolizumab SC	21.216	[redacted]	[redacted]	£117,310	£263,989	-0.001	-0.061	-£19,251	316138 SW
Vedolizumab IV	21.217	[redacted]	[redacted]	£113,827	£261,228	-0.002	-0.133	-£24,180	181591 SW
Scenario 2: alternative treatment sequence for adalimumab (vedolizumab, tofacitinib)									
Filgotinib	21.214	[redacted]	[redacted]	£135,221	£280,722	0.000	0.000	£0	0
Adalimumab	21.213	[redacted]	[redacted]	£126,414	£271,154	0.001	0.076	-£7,282	FIL dominates
Tofacitinib	21.213	[redacted]	[redacted]	£126,113	£270,758	0.001	0.086	-£7,396	FIL dominates
Golimumab	21.214	[redacted]	[redacted]	£121,000	£266,349	0.000	0.015	-£13,915	FIL dominates
Infliximab	21.214	[redacted]	[redacted]	£120,590	£266,088	0.000	0.000	-£14,624	FIL dominates
Vedolizumab SC	21.215	[redacted]	[redacted]	£119,476	£265,556	-0.001	-0.058	-£16,904	291828 SW
Vedolizumab IV	21.216	[redacted]	[redacted]	£116,700	£263,371	-0.002	-0.117	-£20,858	178438 SW
Scenario 3: exclude treat-through trials									
Filgotinib	21.214	[redacted]	[redacted]	£135,221	£280,722	0.000	0.000	£0	0
Tofacitinib	21.213	[redacted]	[redacted]	£126,113	£270,758	0.001	0.086	-£7,396	FIL dominates

Golimumab	21.214	[redacted]	[redacted]	£121,000	£266,349	0.000	0.015	-£13,915	FIL dominates
Vedolizumab SC	21.215	[redacted]	[redacted]	£119,476	£265,556	-0.001	-0.058	-£16,904	291828 SW
Vedolizumab IV	21.216	[redacted]	[redacted]	£116,700	£263,371	-0.002	-0.117	-£20,858	178438 SW
Scenario 4: use 26-week utilities									
Filgotinib	21.214	[redacted]	[redacted]	£132,024	£275,926	0.000	0.000	£0	0
Tofacitinib	21.213	[redacted]	[redacted]	£123,241	£266,450	0.001	0.069	-£7,396	FIL dominates
Adalimumab	21.214	[redacted]	[redacted]	£119,318	£263,193	0.000	0.003	-£12,649	FIL dominates
Golimumab	21.214	[redacted]	[redacted]	£118,022	£261,882	0.000	0.004	-£13,915	FIL dominates
Infliximab	21.214	[redacted]	[redacted]	£117,663	£261,698	0.000	-0.013	-£14,624	1109338 SW
Vedolizumab SC	21.215	[redacted]	[redacted]	£115,739	£259,951	-0.001	-0.031	-£16,904	545937 SW
Vedolizumab IV	21.216	[redacted]	[redacted]	£112,983	£257,795	-0.002	-0.091	-£20,858	229475 SW

Table 3: ERG base-case biologic-experienced population

Technologies	Total LYs	Total QALYs	Total costs (£)	NMB (20k)	NMB (30k)	Incremental LYs FIL vs X	Incremental QALYs FIL vs X	Incremental costs (£) FIL vs X	ICER (£/QALY) pairwise FIL vs X
Company base-case (biologic-experienced), without conventional care, with company's treatment sequences									
Filgotinib	20.910	[redacted]	[redacted]	£113,927	£247,120	0.000	0.000	£0	0
Adalimumab	20.909	[redacted]	[redacted]	£110,610	£243,370	0.001	0.043	-£2,452	FIL dominates
Tofacitinib	20.910	[redacted]	[redacted]	£109,527	£242,615	0.000	0.010	-£4,191	FIL dominates
Vedolizumab SC	20.910	[redacted]	[redacted]	£109,411	£242,446	0.000	0.016	-£4,200	FIL dominates
Ustekinumab	20.910	[redacted]	[redacted]	£108,259	£241,160	0.000	0.029	-£5,085	FIL dominates
Vedolizumab IV	20.910	[redacted]	[redacted]	£108,110	£241,013	0.000	0.029	-£5,239	FIL dominates
ERG change 1: Disable dose escalation for all									
Filgotinib	20.910	[redacted]	[redacted]	£115,233	£248,426	0.000	0.000	£0	0
Adalimumab	20.909	[redacted]	[redacted]	£112,279	£245,039	0.001	0.043	-£2,089	FIL dominates
Tofacitinib	20.910	[redacted]	[redacted]	£111,732	£244,820	0.000	0.010	-£3,293	FIL dominates

Ustekinumab	20.910	[redacted]	[redacted]	£109,880	£242,781	0.000	0.029	-£4,770	FIL dominates
Vedolizumab IV	20.910	[redacted]	[redacted]	£109,744	£242,647	0.000	0.029	-£4,910	FIL dominates
Vedolizumab SC	20.910	[redacted]	[redacted]	£109,713	£242,747	0.000	0.016	-£5,204	FIL dominates
ERG change 2: Do not use NMA results for maintenance (vedolizumab SC based on biologic-naïve)									
Filgotinib	20.911	[redacted]	[redacted]	£113,789	£247,778	0.000	0.000	£0	0
Adalimumab	20.910	[redacted]	[redacted]	£108,473	£241,466	0.001	0.100	-£3,326	FIL dominates
Tofacitinib	20.910	[redacted]	[redacted]	£107,056	£240,524	0.001	0.052	-£5,691	FIL dominates
Vedolizumab SC	20.911	[redacted]	[redacted]	£106,999	£240,836	0.000	0.015	-£6,488	FIL dominates
Ustekinumab	20.911	[redacted]	[redacted]	£105,488	£239,267	0.000	0.021	-£7,881	FIL dominates
Vedolizumab IV	20.911	[redacted]	[redacted]	£105,202	£238,976	0.000	0.021	-£8,157	FIL dominates
ERG change 3: Use of 10-week active UC utilities									
Filgotinib	20.910	[redacted]	[redacted]	£128,023	£268,264	0.000	0.000	£0	0
Adalimumab	20.909	[redacted]	[redacted]	£124,869	£264,759	0.001	0.035	-£2,452	FIL dominates
Tofacitinib	20.910	[redacted]	[redacted]	£123,662	£263,818	0.000	0.009	-£4,191	FIL dominates
Vedolizumab SC	20.910	[redacted]	[redacted]	£123,567	£263,679	0.000	0.013	-£4,200	FIL dominates
Ustekinumab	20.910	[redacted]	[redacted]	£122,462	£262,464	0.000	0.024	-£5,085	FIL dominates
Vedolizumab IV	20.910	[redacted]	[redacted]	£122,312	£262,316	0.000	0.024	-£5,239	FIL dominates
ERG change 4: Use probability of chronic pouchitis									
Filgotinib	20.910	[redacted]	[redacted]	£119,309	£253,428	0.000	0.000	£0	0
Adalimumab	20.909	[redacted]	[redacted]	£116,074	£249,775	0.001	0.042	-£2,400	FIL dominates
Tofacitinib	20.910	[redacted]	[redacted]	£114,929	£248,946	0.000	0.010	-£4,179	FIL dominates
Vedolizumab SC	20.910	[redacted]	[redacted]	£114,823	£248,789	0.000	0.015	-£4,181	FIL dominates
Ustekinumab	20.910	[redacted]	[redacted]	£113,695	£247,531	0.000	0.028	-£5,051	FIL dominates
Vedolizumab IV	20.910	[redacted]	[redacted]	£113,545	£247,383	0.000	0.028	-£5,205	FIL dominates
ERG base-case (ERG changes 1-4)									
Filgotinib	20.911	[redacted]	[redacted]	£134,613	£276,395	0	0	0	0
Adalimumab	20.910	[redacted]	[redacted]	£130,298	£271,295	0.001	0.078	-£2,746	FIL dominates

Tofacitinib	20.910	[redacted]	[redacted]	£129,353	£270,720	0.001	0.042	-£4,428	FIL dominates
Ustekinumab	20.911	[redacted]	[redacted]	£127,224	£268,840	0.000	0.017	-£7,055	FIL dominates
Vedolizumab IV	20.911	[redacted]	[redacted]	£126,973	£268,584	0.000	0.017	-£7,297	FIL dominates
Vedolizumab SC	20.911	[redacted]	[redacted]	£126,857	£268,513	0.000	0.013	-£7,504	FIL dominates

Table 4: ERG scenarios biologic-experienced population

Technologies	Total LYs	Total QALYs	Total costs (£)	NMB (20k)	NMB (30k)	Incremental LYs FIL vs X	Incremental QALYs FIL vs X	Incremental costs (£) FIL vs X	ICER (£/QALY) pairwise FIL vs X
ERG base-case (biologic-experienced)									
Filgotinib	20.911	[redacted]	[redacted]	£134,613	£276,395	0.000	0.000	£0	0
Adalimumab	20.910	[redacted]	[redacted]	£130,298	£271,295	0.001	0.078	-£2,746	FIL dominates
Tofacitinib	20.910	[redacted]	[redacted]	£129,353	£270,720	0.001	0.042	-£4,428	FIL dominates
Ustekinumab	20.911	[redacted]	[redacted]	£127,224	£268,840	0.000	0.017	-£7,055	FIL dominates
Vedolizumab IV	20.911	[redacted]	[redacted]	£126,973	£268,584	0.000	0.017	-£7,297	FIL dominates
Vedolizumab SC	20.911	[redacted]	[redacted]	£126,857	£268,513	0.000	0.013	-£7,504	FIL dominates
Scenario 1: decreasing loss of response									
Filgotinib	20.911	[redacted]	[redacted]	£134,494	£276,537	0.000	0.000	£0	0
Adalimumab	20.910	[redacted]	[redacted]	£129,626	£270,743	0.001	0.093	-£3,015	FIL dominates
Tofacitinib	20.911	[redacted]	[redacted]	£128,585	£270,121	0.001	0.051	-£4,895	FIL dominates
Ustekinumab	20.911	[redacted]	[redacted]	£126,386	£268,230	0.000	0.020	-£7,710	FIL dominates
Vedolizumab IV	20.911	[redacted]	[redacted]	£126,103	£267,942	0.000	0.020	-£7,981	FIL dominates
Vedolizumab SC	20.911	[redacted]	[redacted]	£125,924	£267,820	0.000	0.015	-£8,275	FIL dominates
Scenario 2: alternative treatment sequence for vedolizumab (use tofacitinib)									
Filgotinib	20.911	[redacted]	[redacted]	£134,613	£276,395	0.000	0.000	£0	0
Adalimumab	20.910	[redacted]	[redacted]	£130,298	£271,295	0.001	0.078	-£2,746	FIL dominates
Vedolizumab IV	20.910	[redacted]	[redacted]	£130,961	£272,326	0.001	0.042	-£2,818	FIL dominates
Vedolizumab SC	20.911	[redacted]	[redacted]	£130,838	£272,249	0.000	0.037	-£3,032	FIL dominates

Tofacitinib	20.910	[redacted]	[redacted]	£129,353	£270,720	0.001	0.042	-£4,428	FIL dominates
Ustekinumab	20.911	[redacted]	[redacted]	£127,224	£268,840	0.000	0.017	-£7,055	FIL dominates
Scenario 3: exclude treat-through trials									
Filgotinib	20.911	[redacted]	[redacted]	£134,613	£276,395	0.000	0.000	£0	0
Tofacitinib	20.910	[redacted]	[redacted]	£129,353	£270,720	0.001	0.042	-£4,428	FIL dominates
Ustekinumab	20.911	[redacted]	[redacted]	£127,224	£268,840	0.000	0.017	-£7,055	FIL dominates
Vedolizumab IV	20.911	[redacted]	[redacted]	£126,973	£268,584	0.000	0.017	-£7,297	FIL dominates
Vedolizumab SC	20.911	[redacted]	[redacted]	£126,857	£268,513	0.000	0.013	-£7,504	FIL dominates
Scenario 4: use 26-week utilities									
Filgotinib	20.911	[redacted]	[redacted]	£132,558	£273,313	0.000	0.000	£0	0
Adalimumab	20.910	[redacted]	[redacted]	£128,478	£268,567	0.001	0.067	-£2,746	FIL dominates
Tofacitinib	20.910	[redacted]	[redacted]	£127,336	£267,694	0.001	0.040	-£4,428	FIL dominates
Ustekinumab	20.911	[redacted]	[redacted]	£125,197	£265,799	0.000	0.015	-£7,055	FIL dominates
Vedolizumab IV	20.911	[redacted]	[redacted]	£124,937	£265,530	0.000	0.016	-£7,297	FIL dominates
Vedolizumab SC	20.911	[redacted]	[redacted]	£124,719	£265,307	0.000	0.017	-£7,504	FIL dominates