NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Upadacitinib for treating moderately to severely active ulcerative colitis [ID3953]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Upadacitinib for treating moderately to severely active ulcerative colitis [ID3953]

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 **Abbvie**

2. **Company response to NICE's request for clarification**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Crohn's & Colitis UK
   b. British Society of Gastroenterology
   c. UK Clinical Pharmacy Association

4. **Evidence Review Group report** prepared by the **Liverpool Reviews and Implementation Group**

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

6. **Technical engagement response** from **Abbvie**

7. **Technical engagement response & expert statement from experts:**
   a. John Caisley – patient expert, nominated by Crohn's & Colitis UK

8. **Technical engagement response from consultees and commentators:**
   a. Neonatal & Paediatric Pharmacist Group
   b. UK Clinical Pharmacy Association
   c. Janssen

9. **Evidence Review Group critique of company response to technical engagement** prepared by the **Liverpool Reviews and Implementation Group**

10. **Pre-Meeting Briefing slides sent to Committee members ahead of the Committee meeting**

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

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Document B

Company evidence submission

April 2022

File name	Version	Contains confidential information	Date
2c. ID3953_Upadacitinib UC_Doc B_22April2022_Fully redacted	**1.0**	**Yes**	**22 April 2022**

Contents

Tables and figures

Abbreviations

5-ASA	Aminosalicylates
ADA	Adalimumab
ADA-B	Adalimumab-biosimilar
AE	Adverse event
AESI	Adverse event of special interest
AG	Assessment group
AIC	Academic in confidence
ALC	Absolute lymphocyte count
AM	Adapted Mayo
AMS	Adapted Mayo score
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
AO	As observed
ASUC	Acute severe ulcerative colitis
Bio-IR	Biologic therapy-intolerant or inadequate responder
BMI	Body mass index
BNF	British National Formulary
BSG	British Society of Gastroenterology
CD	Crohn's disease
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIC	Commercial in confidence
CMH	Cochran-Mantel-Haenszel
CODA	Convergence Diagnostic and Output Analysis
COVID-19	Coronavirus pandemic 2019
CPK	Creatinine phosphokinase
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CSR	Clinical study report
CT	Conventional therapy/treatment
CTCAE	Common terminology criteria for adverse events
CUA	Cost-utility analysis
CYP3A	Cytochrome P450 3A isoform subfamily
DB	Double-blind
DPD	Depersonalised data
DSA	Deterministic sensitivity analysis
ECCO	European Crohn´s and Colitis Organisation
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EMS	Endoscopic Mayo subscore
EQ-5D	EuroQol 5-dimension questionnaire
EQ-5D-3L	EuroQol 5-dimension-3-level questionnaire
EQ-5D-5L	EuroQol 5-dimension-5-level questionnaire
ERG	Evidence review group
ESR	Erythrocyte sedimentation rate
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FE	Fixed effects
FEA	Fixed effects with baseline-risk adjustment
FM	Full Mayo
FMS	Full Mayo score
GB	Great Britain
GI	Gastrointestinal
GLM	Generalised Linear Model
GOL	Golimumab
Hb	Haemoglobin
HCRU	Healthcare resource use
HRG	Healthcare Resource Group
HMI	Hybrid multiple imputation method
HRQoL	Health-related quality of life
hs-CRP	High-sensitivity C-reactive protein
ICER	Incremental cost-effectiveness ratio
IBD	Inflammatory bowel disease
IBDQ	Inflammatory bowel disease questionnaire
IFU	Instructions for use

IFX	Infliximab
IFX-B	Infliximab-biosimilar
IL	Interleukin
IPAA	Ileal pouch-anal anastomosis
IR	Inadequate response
IRT	Interactive response technology
ISPOR	The Professional Society for Health Economics and Outcomes Research
ITT	Intention-to-treat
IV	Intravenous
JAK	Janus kinase
JAK1	Janus kinase 1
JAKs	Janus kinases/Janus kinase family
LS	Least squares
LY	Life year
MA	Marketing authorisation
MACE	Major adverse cardiac event
MCMC	Markov Chain Monte Carlo
MI	Multiple imputation
MIMS	Monthly Index of Medical Specialities
MMRM	Mixed effect model repeated measurement
NG	NICE guideline
NHB	Net health benefit
NHS	National Health Service
NHSCII	National Health Service Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMSC	Non-melanoma skin cancer
Non-Bio-IR	Inadequate response, loss of response, or intolerance to conventional therapy but not failed biologic therapy
NR	Not reported
NRI	Non-responder imputation
NRI-C	Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19
NRI-NC	Non-responder imputation with no special data handling for missing due to COVID-19

NSAID	Non-steroidal anti-inflammatory drug
OL	Open-label
ONS	Office for National Statistics
PAS	Patient Access Scheme
PBA	Probabilistic sensitivity analysis
PBO	Placebo
PC_IND	Placebo-controlled induction
PGA	Physician Global Assessment
PGIS	Patient Global Impression of Severity
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSRF	Potential Scale Reduction Factor
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q4W	Every 4 weeks
Q8W	Every 8 weeks
Q12W	Every 12 weeks
QALY	Quality-adjusted life year
QD	Once-daily dosing
QoL	Quality of life
RBS	Rectal bleeding subscore
RCP	Royal College of Physicians
RCT	Randomised controlled trial
RD	Risk difference
RE	Random effects
REA	Random effects with baseline-risk adjustment
RR	Re-randomised
RTB-MI	Multiple imputation incorporating return to baseline
SA	Safety analysis
SA-UPA	Safety analysis-upadacitinib
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-36	Short Form 36 questionnaire
SFS	Stool frequency subscore
SLR	Systematic literature review

SMDM	Society for Medical Decision Making
SmPC	Summary of Product Characteristics
SoC	Standard of care
SSA	Study size adjusted
STAT	Signal transducer and activator of transcription
SUCRA	Surface under the cumulative ranking curve
TA	Technology appraisal
TA MD	Therapeutic area medical director
TDM	Therapeutic drug monitoring
TEAE	Treatment-emergent adverse event
TEAESI	Treatment -emergent adverse events of special interest
TNF	Tumour necrosis factor
TNF-α	Tumour necrosis factor-alpha
TNFi	Tumour necrosis factor inhibitor
TOF	Tofacitinib
TT	Treat-through
TTO	Time trade-off
TYK	Tyrosine kinase
UC	Ulcerative colitis
UC-SQ	Ulcerative colitis Symptoms Questionnaire
UK	United Kingdom
UPA	Upadacitinib
US	United States
UST	Ustekinumab
VAS	Visual Analogue Scale
VBA	Visual Basic for Applications
VED	Vedolizumab
VTE	Venous thromboembolism
WPAI	Work Productivity and Activity Impairment
WTP	Willingness to pay

Glossary

Bio-IR	Patients with documented intolerance or inadequate response to one or more of the approved biologics for UC. Bio-IR is considered equivalent to bio-failure
Biologic failure (Bio-failure)	Patients that have had primary or secondary loss of response to a biologic therapy
Biologic exposed (Bio-exposed)	Patients who had an inadequate response or intolerance to conventional therapy, and those who have received biologic therapy in the past but stopped therapy based on reasons other than inadequate response or intolerance
Biologic-naïve (Bio-naïve)	Patients that have had no previous exposure to biologic therapies
CT failure	Conventional therapy failure population is defined as patients who failed treatment with standard of care, including 5-ASA, corticosteroids and immunomodulators but have not had a dose of any biologic/biosimilar treatment
High dose	Upadacitinib 30 mg QD maintenance dose (following upadacitinib 45 mg QD induction), which may be appropriate for some patients, such as those with high burden of disease
Induction dose	Upadacitinib 45 mg QD induction dose received by all patients to induce clinical remission of disease
Non-Bio-IR	Patients who had an inadequate response or intolerance to conventional therapy. This population includes subjects who have previously received biologic therapy but stopped therapy based on reasons other than inadequate response or intolerance. Non-Bio-IR is considered equivalent to bio-naive
Primary non-response	Inadequate or no response to initial treatment with a biologic
Standard dose	Upadacitinib 15 mg QD maintenance dose (following upadacitinib 45 mg QD induction), which may be appropriate for some patients, such as those with low burden of disease and those aged ≥65 years

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

B.1.1 Decision problem

Upadacitinib currently has marketing authorisation in the United Kingdom (UK) for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and atopic dermatitis (1). An application for marketing authorisation in ulcerative colitis (UC) was submitted to the European Medicines Agency (EMA) in [redacted].

The full marketing authorisation for upadacitinib for the indication of relevance to this technology appraisal is anticipated to be for the treatment of [redacted].

The submission covers the technology's full marketing authorisation for this indication. The final scope for upadacitinib for moderately to severely active UC was issued by the National Institute for Health and Care Excellence (NICE) in February 2022. The decision problem for this technology appraisal is an evaluation of the clinical and cost-effectiveness of upadacitinib for the treatment of patients with UC (Table 1).

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Intervention	Upadacitinib (Rinvoq®).	As per final scope	
Population	People with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.	As per final scope	
Comparator(s)	• TNF-α inhibitors (adalimumab, golimumab, and infliximab) • Filgotinib (subject to ongoing NICE appraisal) • Ozanimod (subject to ongoing NICE appraisal) • Tofacitinib • Ustekinumab • Vedolizumab • Conventional therapies (including 5-ASAs, oral corticosteroids and/or immunomodulators), without biological treatments.	• TNF-α inhibitors (adalimumab, golimumab, and infliximab) • Tofacitinib • Ustekinumab • Vedolizumab	• Filgotinib will not be considered as a comparator in this submission as no recommendation for filgotinib in NICE appraisal (ID3736) is currently available. Filgotinib is therefore not currently approved for use in, or considered standard of care for, patients with moderately to severely active UC. • Ozanimod will not be considered as a comparator in this submission as no recommendation for ozanimod in NICE appraisal (ID3841) is currently available. Ozanimod is therefore not currently approved for use in, or considered standard of care for, patients with moderately to severely active UC. • Conventional therapies will not be considered as comparators as patients have had inadequate response to, or intolerance for, multiple treatment before eligibility for advanced therapies.
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 (including readmission)	As per final scope Please also note that 'Endoscopic healing combined with histological improvement corticosteroid free remission' is addressed as two separate outcomes in the submission: • Endoscopic healing combined with	• We believe 'Endoscopic healing combined with histological improvement corticosteroid free remission' is a formatting typo in the final scope and was intended to be two separate outcomes.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Rates of surgical intervention • Endoscopic healing • Endoscopic healing combined with histological improvement corticosteroid-free remission • Achieving mucosal healing • Adverse effects of treatment • Health-related quality of life	histological improvement • Corticosteroid-free remission	
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • People who have been previously treated with 1 or more biologics. • People who have not received a prior biologic.	As per final scope	
Special considerations including issues related to equity or equality	• The availability and cost of biosimilar products should be taken into account. • Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	As per final scope	

Abbreviations: 5-ASAs, aminosalicylates; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; TNF, tumour necrosis factor; UC, ulcerative colitis.

B.1.2 Description of the technology being appraised

Upadacitinib is an orally administered small molecule selective and reversible inhibitor of Janus kinase 1 (JAK1), developed for the treatment of moderately to severely active UC. Details of the technology being appraised in the submission, including the method of administration, dosing, and related costs, are provided in Table 2. A draft Summary of Product Characteristics (SmPC) for information for use regarding upadacitinib is presented in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	UK approved name: Upadacitinib Brand name: Rinvoq®
Mechanism of action	The JAK family of enzymes (intracellular tyrosine kinases) contains four members, JAK1, JAK2, JAK3 and TYK2, which function as dimers to phosphorylate and activate STATs (2, 3) and potentiate inflammatory cytokine signals (4). UPA is a selective and reversible oral JAK inhibitor which has been engineered to have greater affinity for JAK1 and in human cellular assays preferentially inhibits signalling by JAK1 or JAK1/3 (5). UPA selectivity has the potential to reduce side effects related to JAK2 and JAK3 inhibition (6), through which it modulates the signalling of key cytokines. Pro-inflammatory cytokines (primarily IL-6, IL-7, IL-15, and IFN-γ) transduce signals via the JAK1 pathway and are involved in UC pathogenesis. JAK1 inhibition with UPA modulates the signalling of the JAK-dependent cytokines underlying the inflammatory burden and signs and symptoms of UC.
Marketing authorisation/CE mark status	A regulatory submission (centralised procedure type II variation) was made to the EMA in [redacted]. GB marketing authorisation will be requested via the European Commission Decision Reliance Procedure. CHMP positive opinion is anticipated in [redacted] with marketing authorisation expected to be granted by the European Commission in [redacted]. GB marketing authorisation is expected in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication for UPA of relevance to this technology appraisal is as follows: • UPA is indicated for the treatment of [redacted]
Method of administration and dosage	Oral administration. UPA is available as 15 mg and 30 mg prolonged-release tablets (7), and is anticipated to be available as a 45 mg prolonged-release tablet. Each prolonged-release tablet contains UPA hemihydrate equivalent to either 15 mg, 30 mg, or 45 mg of UPA. The recommended dose is anticipated to be: • **Induction:** 45 mg QD for 8 weeks. For patients who do not achieve adequate therapeutic benefit by Week 8, UPA 45 mg QD may be continued for an additional 8 weeks (16 weeks

	total) • **Maintenance:** 15 mg QD or 30 mg QD based on patient presentation. A dose of 15 mg QD may be appropriate for some patients, such as those with lower burden of disease. For patients ≥65 years of age, the recommended maintenance dose is 15 mg QD In patients who have responded to treatment with UPA, corticosteroids may be reduced and/or discontinued in accordance with standard of care.
Additional tests or investigations	Treatment should not be initiated in patients with an ALC <0.5 x 10^9 cells/L, an ANC <1 x 10^9 cells/L or who have Hb levels <8 g/dL. As such, routine blood workup would be performed on patients with active disease who are eligible to receive UPA. However, patients would receive these tests as part of routine clinical practice and so these would not be considered as additional tests or investigations for patients who would receive UPA.
List price and average cost of a course of treatment	UPA is commercially available as a pack of 28 x 15 mg tablets at a list price of £805.56 per pack, and as pack of 28 x 30 mg tablets at a list price of £1,611.12. UPA is also anticipated to be commercially available as a pack of [redacted] tablets at a list price of [redacted] per pack. Treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity.
Patient access scheme (if applicable)	There is a simple PAS agreed with NHS England on the differential list prices, and the PAS price is incorporated in the submission. The PAS equates to an approximate [redacted] discount for each 15 mg, 30 mg, and 45 mg packet. This [redacted] the per packet cost to [redacted] for a 28 x 15 mg packet, to [redacted] for a 28 x 30 mg packet, and to [redacted] for a 28 x 45 mg packet.

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; GB, Great Britain; Hb, haemoglobin; IFU, instructions for use; IL, interleukin; JAK, Janus kinase; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; QD, once-daily dosing; SmPC; summary of product characteristics; STAT, signal transducer and activator of transcription; TYK, tyrosine kinase; UC, ulcerative colitis; UK, United Kingdom; UPA, upadacitinib.

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

B.1.3.1 Disease overview

UC is chronic relapsing systemic inflammatory bowel disease (IBD) that can cause inflammation in the inner lining of the large intestine (8, 9). Inflammation is characteristically restricted to the mucosal surface, starting in the rectum and generally extending proximally in a continuous manner through the entire colon (10). As a result of inflammation, patients can develop abdominal cramps and pain, rectal bleeding, bloody stools, persistent diarrhoea, and fatigue that significantly impacts their quality of life (QoL) (8-11). Surgery is indicated in patients with severe UC admitted to hospital who do not respond to intensive medical treatment (10, 12), and despite mortality related to severe UC attacks substantially decreasing to less than 1% in past decades, a delay in surgery can increase the risk of mortality (10).

Approximately 42% of patients with moderately to severely active UC do not respond to, or cannot tolerate CT (i.e. corticosteroids, immunomodulators, aminosalicylates [5-ASAs]) (13). Subsequent use of advanced therapies (i.e., tumour necrosis factor-alpha [TNF-α] inhibitors, interleukin inhibitors, integrin α4β7 inhibitors, JAK inhibitors) is beneficial but they are associated with primary non-response and loss of response over time (13, 14), limiting the treatment options for clinicians and patients. Surgical removal of the colon and rectum can cure the intestinal manifestations of UC; however, surgery is not without risks and can lead to significant changes in a patient's lifestyle (15). For example, long-term complications include small bowel obstruction, pouch fistulas, and pouchitis (15). Although there is not an impact on life expectancy associated with UC (16), there is a potential increase in the risk of mortality associated with post-operative complications particularly in patients aged >50 years (17).

B.1.3.1.1 Diagnosis and disease severity

Diagnosis of UC is based on clinical symptoms confirmed by objective findings from endoscopic and histological examinations (8, 10, 12), with infectious (e.g., bacterial, parasitic, viral, and fungal) and non-infectious (e.g., microscopic colitis, malabsorption of bile acid, bacterial overgrowth, malignant causes, and diarrhoea induced by drugs) causes of diarrhoea ruled out prior to diagnosis (10, 12). Confirmation of a UC diagnosis, as well as the extent and severity of disease is performed by full ileocolonoscopy, typically within

the first year of symptoms (12).This allows a definitive confirmation of UC versus Crohn's disease to help predict future disease course and influence treatment choices (12).

Disease severity and activity is evaluated using clinical assessments, typically based on endoscopy and/or patient symptoms (18). Several classifications and grades of disease have been proposed which predominantly rely on scoring systems (18). One of the more commonly used scoring systems is the Mayo score, which consists of stool frequency subscore (SFS), rectal bleeding subscore (RBS), Physician's Global Assessment (PGA), and endoscopic appearance (endoscopic subscore), all assessed on a scale of 0–3 with the individual categories summed to give a total score on a scale of 0–12, and where a higher score indicates increasing severity of disease (details provided in Table 8 and Table 9 in Section B.2.3.2).

B.1.3.1.2 Epidemiology

There are approximately 107,881 people in England have UC, of whom 52% have moderate to severe disease (19-21). While UC presents most commonly in adolescence and early adulthood, it may occur at any age (22). Most patients are diagnosed between 17–40 years of age, with the incidence of UC in England ranging between 15.2–18.1 per 100,000 person years (23).

B.1.3.1.3 Burden of disease

B.1.3.1.3.1 Burden to patients

The symptoms of UC, which result from inflammation, are diverse, and commonly include the development of abdominal cramps and pain, rectal bleeding, bloody stools, persistent diarrhoea, and fatigue (8-11). Furthermore, rectal urgency, fatigue, abdominal pain, diarrhoea, need to use the toilet soon after eating, tenesmus, and rectal bleeding have all been identified in patient-reported and physician-reported surveys as common symptoms and symptoms with the greatest impact on QoL (24). As a result, these symptoms can have a substantial impact on patients' functioning, wellbeing, and health-related quality of life (HRQoL) (25, 26), and on daily activities including their ability to work, attend school/places of education, and carry out parenting tasks (27). Additionally, gastrointestinal symptoms and faecal incontinence associated with UC have a dramatic impact on patients' QoL, spanning psychological, physical, sexual, and social domains, with patients experiencing social stigmatisation which leads to further negative consequences and the desire to separate from group interactions (28).

B.1.3.1.3.2 Economic burden on healthcare systems

The medical requirements of patients with UC place a significant burden on healthcare resources (29). The average annual cost of care for treating with UC in the UK was £1,693 for a patient with UC in remission, £2,903 for a patient in relapse with mild to moderate UC, and £10,760 for a patient in relapse with severe UC in 2015 (29). For relapse with severe disease, this cost comprises £8,017 for treatment costs including medical, surgical, outpatient, and inpatient treatment options, £1,982 for adverse events (AEs) including costs of blood tests, costs of treating AEs, and complications of surgery, and £761 for complications of diseases such as cancer, uveitis and iritis, pyoderma gangrenosum, and primary sclerosing cholangitis (29).

Additionally, higher rates of per person primary care visits (6.18 versus 4.49 per year) and secondary care emergency attendances (0.396 versus 0.259 per year) are associated with patients with UC compared with matched controls (30). Finally, many patients with UC require surgery, which contributes to their healthcare resource use (HCRU); the risk of surgery 5 and 10 years after diagnosis of UC has been reported to be 11.6% and 15.6%, respectively (31).

B.1.3.2 Clinical pathway of care

B.1.3.2.1 Overview

The management of UC is through use of several interventions, including diet changes, pharmacotherapy with anti-inflammatories/immunomodulators, and surgery. Disease severity can determine the choice of therapy, with approximately 20–30% of patients with UC eventually requiring surgery primarily due to failure of medical therapy (10, 32).

Management of UC aims to achieve and maintain disease remission (control of disease manifestations to reduce symptoms) and maintain or improve QoL while minimising short- and long-term adverse effects.

B.1.3.2.2 Clinical guidelines

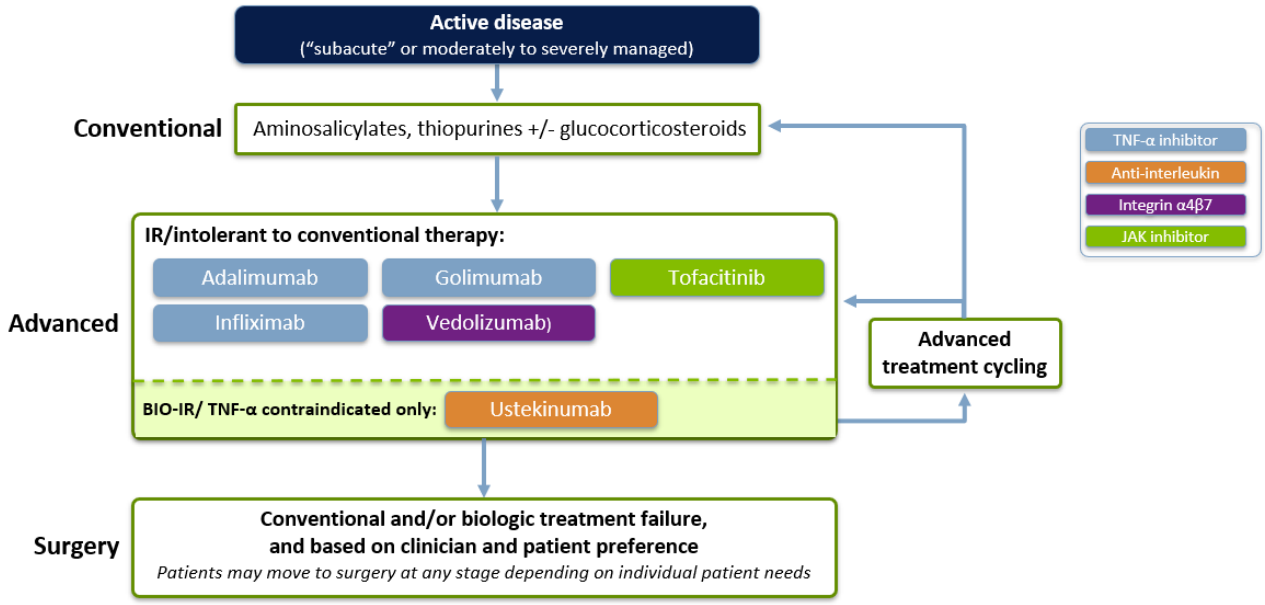
UK clinical guidelines for the management of UC include those by NICE and the British Society of Gastroenterology (BSG) (12, 33) with the target for UC clinical and/or patient-reported remission (12). Clinical management depends on several elements, including disease activity, response to previous treatments, contraindications, and treatment tolerability, and aims to induce and maintain disease remission (12, 33).

Current guidance recommends initial pharmacotherapy with conventional anti-inflammatory and immunomodulator therapy (Figure 1) (12, 33). Advanced therapies, including biological treatments, are subsequently introduced if conventional therapy/treatment (CT) has a poor response, is not tolerated, or is contraindicated (34-37). Several biologic treatment options exist; however, TNF-α inhibitors (adalimumab, infliximab [both have biosimilars that are available]) are typically used as first biologics (Figure 1) (12, 33). The choice of biological treatment should be made on an individual basis, considering patient preference, cost, likely adherence, safety data and speed of response to the drug (12, 33-37). Furthermore, it is recommended that patients receiving high-dose 5-ASA (mesalazine) maintenance therapy be moved on to advanced therapies, including TNF-α inhibitors, vedolizumab, or tofacitinib if they have (12):

- Required ≥2 courses of corticosteroids in the past year, or
- Become corticosteroid-dependent, or
- Become corticosteroid-refractory

Dosing of currently available advanced therapies requires induction therapy, where the drug is administered at an initial higher dose to reduce inflammation and improve UC symptoms. Following induction, a lower dose is administered at regular intervals to maintain control of the disease. However, it is recommended that patients with UC who experience loss of response to a particular TNF-α inhibitor receive an escalated dose (12), and that typically, patients should be reassessed at 12 months after the start of treatment to determine whether treatment should continue, unless treatment has already failed (34-37).

Figure 1: Treatment pathway for UC management



Abbreviations: Bio-IR, patients with inadequate response to biological therapy; IR, inadequate response; JAK, Janus kinase; TNF-α, tumour necrosis factor-α; UC, ulcerative colitis.
Source: AbbVie data on file (38).

B.1.3.3 Unmet need

Despite the availability of several therapies for UC, including biologic therapies such as TNF-α inhibitors, many patients still do not respond adequately to treatment, or gradually lose response over time. Approximately 52% of patients with moderately to severely active disease do not respond to, or cannot tolerate CT (13). Similarly, primary failure of induction therapy with TNF-α inhibitors has been reported in 19–58% of patients in clinical trials, with a further 17–22% of patients having to discontinue due to secondary loss of response within the first 12 months, and dose escalation being required to maintain efficacy in 19–40% of patients (14). Although moving from one TNF-α inhibitor to another may overcome loss of response, a meta-analysis demonstrated that the proportion of patients who discontinued their second-line TNF-α inhibitor due to loss of response over time was 31–41%, with 68–77% discontinuing treatment by the end of Year 1 and 82–90% by the end of Year 2, indicating that treatment failure is substantial among patients undergoing TNF-α inhibitor treatment cycling (14). Lack of clinical response and loss of response over time are also reported for patients treated with vedolizumab, tofacitinib, or ustekinumab, highlighting that there remains a significant unmet need for effective treatments which can provide sustained disease control (39-43).

Finally, long-term mucosal healing (absence of macroscopic mucosal inflammation or ulceration), a target assessed through endoscopic endpoints which is associated with

improved long-term outcomes (e.g., reduced risk of relapse, decreased hospitalisations rates, steroid-free remission, and fewer bowel resections), has been identified as an important treatment target in patients with UC (44-46). It is now considered a major treatment objective in both clinical trials and clinical practice (47, 48). In addition, current guidance by the BSG recognises the importance of different treatment goals, with a recent focus on endoscopic outcomes in addition to controlling clinical symptoms (12). There remains a need, therefore, for treatments that improve mucosal healing which have been shown to reduce risk of relapse, reduce costs associated with UC due to a reduction in hospitalisations and surgery, and lead to an improved HRQoL in patients with UC (47, 49).

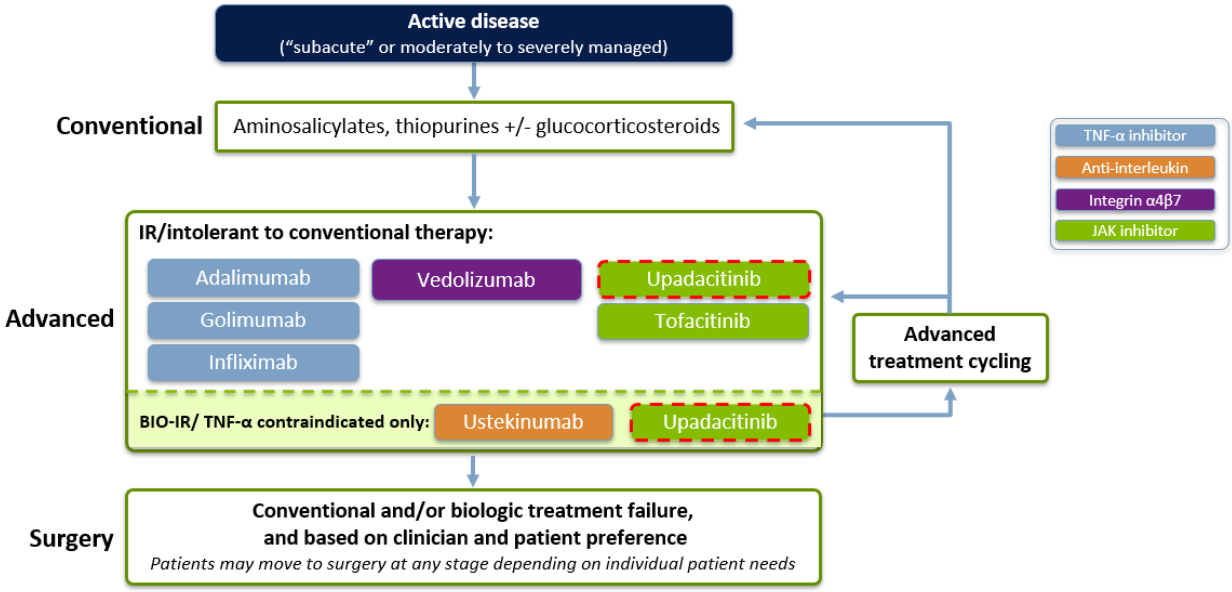
B.1.3.4 Upadacitinib for the treatment of UC

There remains a clear medical need for additional therapeutic options in UC for patients who have had an inadequate response, loss of response, or who were intolerant to either CT or advanced therapies which are available in a convenient oral dosage form that can rapidly improve symptoms that significantly impact patients' daily lives.

Upadacitinib is a selective and reversible oral JAK inhibitor with greater affinity for JAK1 which provides an additional therapeutic option for [redacted] (Figure 2). The data supports the use of upadacitinib in [redacted] (Section B.2).

Upadacitinib would provide a treatment option for [redacted] Upadacitinib would therefore be suitably placed in the existing NICE pathway, ‘Ulcerative colitis: management (NG130) under Section 1.2 ‘Inducing remission in people with ulcerative colitis’, specifically under Section 1.2.14 ‘Biologics and Janus kinase inhibitors for moderately to severely active ulcerative colitis: all extents of disease’.

Figure 2: Proposed positioning of UPA in the treatment pathway for UC management in the UK



Abbreviations: Bio-IR, patients with inadequate response to biological therapy; IR, inadequate response; JAK, Janus kinase; TNF-α, tumour necrosis factor-α; UC, ulcerative colitis; UPA, upadacitinib.

B.1.4 Equality considerations

Upadacitinib is not likely to raise any equality or equity issues in patients with moderately to severely active UC who are eligible to receive treatment.

B.2 Clinical effectiveness

Upadacitinib clinical trial programme

The Phase 3 pivotal induction studies (U-ACHIEVE induction and U-ACCOMPLISH induction) and maintenance study (U-ACHIEVE maintenance) provide the evidence for upadacitinib for the treatment of moderately to severely active UC:

- U-ACHIEVE and U-ACCOMPISH induction studies were Phase 3, two-part, multicentre, randomised, double-blind, placebo controlled, 8-week induction studies which evaluated the efficacy and safety of upadacitinib 45 mg once-daily (QD) versus placebo in subjects with moderately to severely active UC:
  - Part 1: Induction therapy with upadacitinib 45 mg QD (blinded) for 8 weeks
  - Part 2: Extended induction therapy with upadacitinib 45 mg QD for a further 8 weeks for subjects who did not achieve clinical response per Adapted Mayo score with induction therapy in Part 1 (open label).
- U-ACHIEVE maintenance study was a Phase 3, multicentre, randomised, double-blind, placebo controlled, 52-week maintenance study that evaluated the efficacy and safety of upadacitinib 15 mg QD (standard dose) and upadacitinib 30 mg QD (high dose) versus placebo in subjects with moderately to severely active UC who achieved clinical response (per Adapted Mayo score) following induction therapy from U-ACHIEVE induction or U-ACCOMPLISH induction studies.

Definitions of subpopulations of interest

The naming conventions used to describe the populations of interest in the pivotal upadacitinib clinical trials in UC (Bio-IR and non-Bio-IR) are different from corresponding naming conventions used in previous technology appraisals (TAs) for this indication (biologic failure [bio-failure] and biologic naïve [bio-naïve], respectively).

Definitions of the specific populations are as follows:

- **Bio-IR:** Patients with documented intolerance or inadequate response to one or more of the approved biologics for UC. This population is equivalent to bio-failure
- **Non-Bio-IR:** Patients who had an inadequate response or intolerance to CT. This population includes subjects who have previously received biologic therapy but stopped therapy based on reasons other than inadequate response or intolerance. The non-Bio-IR population is considered equivalent to bio-naïve population; only

2% of the non-Bio-IR population had previously been exposed to a biologic treatment.

Efficacy

- All primary and ranked secondary endpoints were met for both the induction (U-ACHIEVE induction and U-ACCOMPLISH induction studies) and maintenance (U-ACHIEVE maintenance study) phases of the clinical trial programme.

Induction phase

- A significantly greater proportion of patients achieved clinical remission per Adapted Mayo score at Week 8 compared with placebo in U-ACHIEVE induction [redacted] and U-ACCOMPLISH induction studies [redacted].
- Upadacitinib 45 mg QD further demonstrated beneficial treatment effects in Bio-IR and non-Bio-IR patients, irrespective of prior biologic use.
  - Improvements in disease activity were observed as early as Week 2 with statistically significant improvements in clinical response in patients receiving upadacitinib 45 mg QD compared with placebo in U-ACHIEVE induction [redacted] and U-ACCOMPLISH induction studies [redacted].
- Upadacitinib 45 mg QD was superior compared with placebo for all ranked secondary endpoints evaluated, providing statistically significant improvements in endoscopic and histologic assessment, disease activity and symptoms, and important QoL indices such as fatigue with 8-week induction treatment.

Maintenance phase

- Patients who received either upadacitinib 15 mg QD or upadacitinib 30 mg QD after 8-week induction on upadacitinib 45 mg QD demonstrated a sustained response for clinical remission per Adapted Mayo score compared with placebo over 52 weeks.
  - A significantly greater proportion of patients achieved clinical remission per Adapted Mayo score at Week 52 compared with placebo in those receiving upadacitinib 15 mg QD [redacted] and upadacitinib 30 mg QD [redacted].
  - Upadacitinib 15 mg QD and upadacitinib 30 mg QD delivered sustained improvements in endoscopic improvement, endoscopic remission, histologic

endoscopic improvement, and mucosal healing through 52 weeks of treatment

- A statistically significantly greater proportion of subjects in the upadacitinib 15 mg QD and upadacitinib 30 mg QD arms achieved clinical remission and were corticosteroid free for ≥90 days compared with placebo.
- Upadacitinib 15 mg QD and upadacitinib 30 mg QD maintenance treatment further demonstrated beneficial treatment effects for Bio-IR or non-Bio-IR subjects for clinical remission and endoscopic response.
- Upadacitinib 15 mg QD and 30 mg QD was superior compared with placebo for all ranked secondary endpoints evaluated, providing statistically significant improvements in endoscopic and histologic assessment, disease activity and symptoms, and important QoL indices such as fatigue with 52-week induction treatment.

Safety

- Across the upadacitinib induction (U-ACHIEVE induction and U-ACCOMPLISH induction) and maintenance (U-ACHIEVE maintenance) studies, no new safety risks were observed, and the overall safety profile was consistent with the known safety profile of upadacitinib.

Conclusion

- Upadacitinib is a highly effective treatment option in subjects with moderately to severely active UC which met all primary and secondary endpoints for both induction and maintenance phases of the clinical trial programme. Upadacitinib demonstrated statistically significant improvements in both clinically relevant measures of disease activity and symptoms, as well as objective improvements in mucosa from as early as Week 2 versus placebo, with similar improvements observed over the 52-week maintenance phase. Upadacitinib is also well tolerated, with a favourable safety profile and no new safety concerns identified versus placebo.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant clinical data assessing the clinical effectiveness and safety of treatments, including upadacitinib and relevant comparators for moderately to severely active UC.

Full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised and relevant comparators, including search strategy, preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram, list of included studies, and list of excluded studies at full paper review, is provided in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The efficacy and safety of upadacitinib for the treatment of moderately to severely active UC was evaluated in three placebo-controlled Phase 3 clinical trials comprising two 8-week induction trials (U-ACHIEVE [M14-234] substudy 2; U-ACCOMPLISH [M14-675]) which provide comparative evidence for upadacitinib 45 mg QD induction therapy, and one 52-week maintenance trial (U-ACHIEVE [M14-234] substudy 3) which provides comparative evidence for upadacitinib 15 mg QD and upadacitinib 30 mg QD maintenance therapy.

It should be noted that the trial design of both induction trials (U-ACHIEVE substudy 2 and U-ACCOMPLISH) was identical. However, although both trials had an inclusion criterion of patients aged ≥16 years, only U-ACCOMPLISH recruited a small number of subjects aged 16–18 years. These patients have been assumed equal to adults and included in all analyses.

Please note: The following study naming convention is used in the submission from this point forward:

- U-ACHIEVE [M14 234] substudy 2 will be referred to as U-ACHIEVE induction study
- U-ACCOMPLISH [M14-675]) will be referred to as U-ACCOMPLISH induction study
- U-ACHIEVE [M14 234] substudy 3 will be referred to as U-ACHIEVE maintenance study

All three pivotal studies are described in detail in Sections B.2.3 onwards, with a summary of these trials provided in Table 3 to Table 5.

Table 3: Clinical effectiveness evidence – U-ACHIEVE induction study (pivotal induction study 1)

Study	U-ACHIEVE (M14-234) induction study† Data sources: CSR (50)
Study design	A two-part, multicentre, randomised, double-blind, placebo-controlled, Phase 3 induction study: • Part 1: Induction therapy with UPA 45 mg QD (blinded) • Part 2: Extended induction therapy with UPA 45 mg QD for subjects who did not achieve clinical response per Adapted Mayo score with induction therapy in Part 1 (open-label)
Population	Subjects with moderately to severely active UC who have had inadequate response, loss of response or intolerance to aminosalicylates, immunomodulator, corticosteroids, or biologic therapies
Intervention(s)	Part 1: UPA 45 mg QD (blinded) Part 2: UPA 45 mg QD (open-label)
Comparator(s)	Part 1: Placebo QD Part 2: None
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	U-ACHIEVE induction study is used in the cost-effectiveness model
Reported outcomes specified in the decision problem‡	• **Mortality** • Measures of disease activity (no bowel urgency and no abdominal pain) • **Rates of and duration of response,** relapse**, and remission** • **Rates of hospitalisation (including readmission)** • **Rates of surgical intervention** • Endoscopic healing (endoscopic remission) • Endoscopic healing combined with histological improvement • Corticosteroid-free remission • Mucosal healing • **Adverse effects of treatment (serious infections)** • **Health-related quality of life (IBDQ and FACIT-F)**
All other reported outcomes‡	• Endoscopic improvement • Histologic improvement

†Please note that while UPA was also evaluated in one Phase 2b study, U-ACHIEVE (M14 234) substudy 1, to identify the induction dose of UPA for further evaluation, this does not form part of the evidence base for UPA in the submission.
‡Outcomes marked in bold are used in the model.
Abbreviations: CSR, clinical study report; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; IBDQ, inflammatory bowel disease questionnaire; QD, once-daily dosing; UC, ulcerative colitis; UPA, upadacitinib.

Table 4: Clinical effectiveness evidence – U-ACCOMPLISH induction study (pivotal induction study 2)

Study	U-ACCOMPLISH (M14-675) induction study Data sources: CSR (51)
Study design	A two-part, multicentre, randomised, double-blind, placebo-controlled, Phase 3 induction study: • Part 1: Induction therapy with UPA 45 mg QD (blinded) • Part 2: Extended induction therapy with UPA 45 mg QD for subjects who did not achieve clinical response per Adapted Mayo score with induction therapy in Part 1 (open-label)
Population	Subjects with moderately to severely active UC who have had inadequate response, loss of response or intolerance to aminosalicylates, immunomodulators, corticosteroids, or biologic therapies
Intervention(s)	Part 1: UPA 45 mg QD (blinded) Part 2: UPA 45 mg QD (open-label)
Comparator(s)	Part 1: Placebo QD Part 2: None
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	U-ACCOMPLISH induction study is used in the cost-effectiveness model
Reported outcomes specified in the decision problem†	• **Mortality** • Measures of disease activity (no bowel urgency and no abdominal pain) • **Rates of and duration of response,** relapse**, and remission** • **Rates of hospitalisation (including readmission)** • **Rates of surgical intervention** • Endoscopic healing (endoscopic remission) • Endoscopic healing combined with histological improvement • Corticosteroid-free remission • Mucosal healing • **Adverse effects of treatment (serious infections)** • **Health-related quality of life (IBDQ and FACIT-F)**
All other reported outcomes†	• Endoscopic improvement • Histologic improvement

†Outcomes marked in bold are used in the model.
Abbreviations: CSR, clinical study report; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; IBDQ, inflammatory bowel disease questionnaire; QD, once-daily dosing; UC, ulcerative colitis; UPA, upadacitinib.

Table 5: Clinical effectiveness evidence – U-ACHIEVE maintenance study (pivotal maintenance study)

Study	U-ACHIEVE (M14-234) maintenance study Data sources: CSR (52)
Study design	A multicentre, randomised, double-blind, placebo-controlled, Phase 3

	maintenance study
Population	Subjects with moderately to severely active UC who achieved clinical response (per Adapted Mayo score) following induction therapy from U-ACHIEVE induction or U-ACCOMPLISH induction studies
Intervention(s)	UPA 15 mg QD UPA 30 mg QD
Comparator(s)	Placebo QD
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	U-ACHIEVE maintenance study is used in the cost-effectiveness model
Reported outcomes specified in the decision problem	• **Mortality** • Measures of disease activity (no bowel urgency and no abdominal pain) • **Rates of and duration of response,** relapse**, and remission** • **Rates of hospitalisation (including readmission)** • **Rates of surgical intervention** • Endoscopic healing (endoscopic remission) • Endoscopic healing combined with histological improvement • Corticosteroid-free remission • Mucosal healing • **Adverse effects of treatment (serious infections)** • **Health-related quality of life (IBDQ and FACIT-F)**
All other reported outcomes	• Endoscopic improvement • Histologic improvement

†Outcomes marked in bold are used in the model.
Abbreviations: CSR, clinical study report; FACIT F, Functional Assessment of Chronic Illness Therapy – Fatigue; IBDQ, inflammatory bowel disease questionnaire; QD, once-daily dosing; UC, ulcerative colitis; UPA, upadacitinib.

B.2.2.1 Additional evidence

B.2.2.1.1 U-ACHIEVE substudy 1

Upadacitinib was evaluated in one Phase 2b study, U-ACHIEVE (M14-234) substudy 1, to identify the induction dose of UPA for further evaluation in Phase 3 studies including U-ACHIEVE maintenance study.

B.2.2.1.2 U-ACTIVATE

Upadacitinib is under investigation in one ongoing long-term extension study of the U-ACHIEVE maintenance study in patients with UC (U-ACTIVATE [M14-533]). Interim results for U-ACTIVATE are expected in October 2022.

Please note: Both U-ACHIEVE substudy 1 and U-ACTIVATE do not form part of the pivotal evidence base for upadacitinib in patients with UC; these trials have not been used to inform the economic model and are therefore not described in Sections B.2.3 onwards.

The evidence for U-ACHIEVE substudy 1 and U-ACHIEVE induction study are contained within the same clinical study report (CSR); please be advised that only methods for U-ACHIEVE induction study have been taken from the CSR and are applicable for this submission.

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

B.2.3.1 Comparative summary of trial methodology

B.2.3.1.1 Induction studies (U-ACHIEVE induction, U-ACCOMPLISH induction)

U-ACHIEVE induction and U-ACCOMPLISH induction studies were Phase 3 multicentre, randomised, double-blind, placebo-controlled, induction studies which evaluated the efficacy and safety of upadacitinib 45 mg QD versus placebo in subjects with moderately to severely active UC.

U-ACHIEVE induction and U-ACCOMPLISH induction studies enrolled subjects according to their prior biologic failure status, categorised as either Bio-IR or non-Bio-IR as defined below. Where data is available from the trials for these two subgroups and considered relevant to the decision problem, this data is provided:

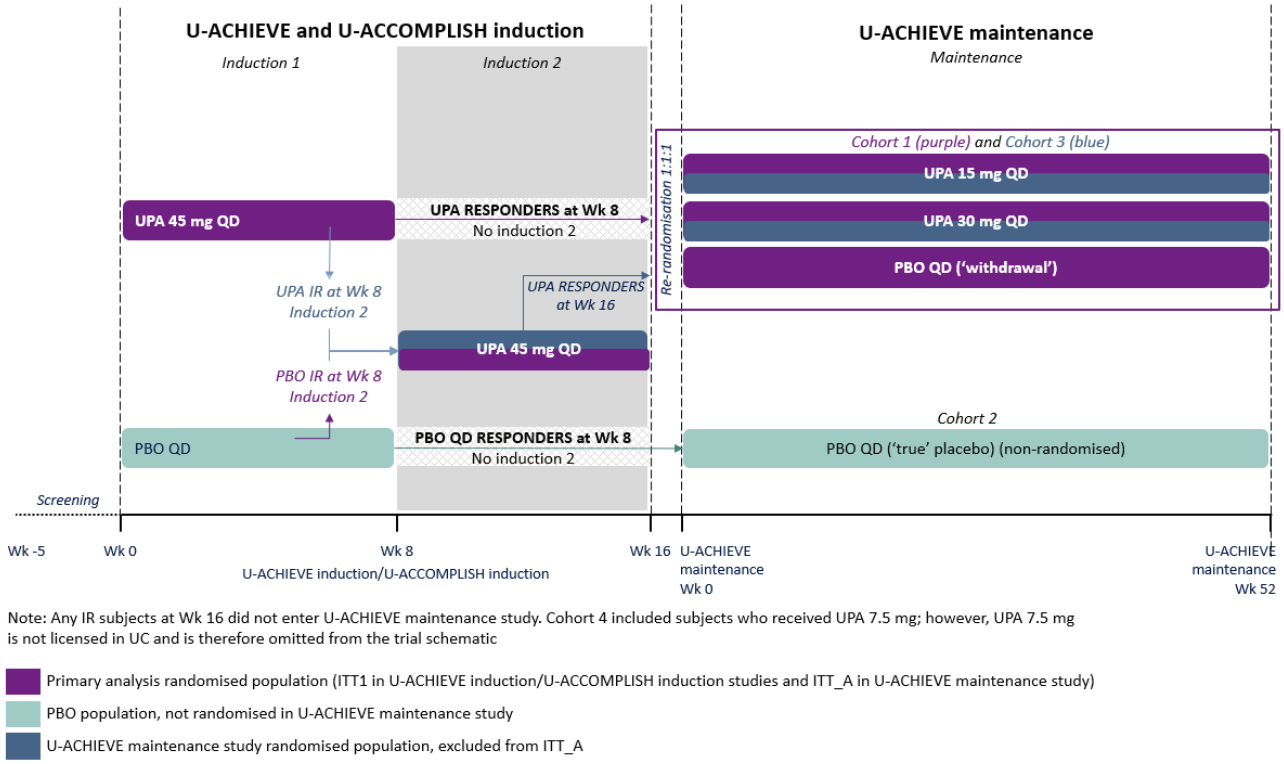
- ***Bio-IR population:*** Subjects with documented inadequate response, loss of response, or intolerance to one or more approved biologics for UC. Both trials allowed up to 30% of enrolled bio-IR subjects who had failed ≥3 biologics
- ***Non-Bio-IR population:*** Subjects who had an inadequate response, loss of response, or intolerance to CT but had not failed biologic therapy. The majority of patients included in the non-Bio-IR population were bio-naïve (95.6% in U-ACHIEVE induction study and 98% in U-ACCOMPLISH induction study). Both trials allowed for up to 20% of non-Bio-IR patients who had prior biologic use and discontinued biologics for reasons other than inadequate response, loss of response, or intolerance.

The design of U-ACHIEVE induction and U-ACCOMPLISH induction studies was identical (Figure 3); subjects received 8 weeks of induction treatment with upadacitinib 45 mg QD (Part 1). Subjects who did not achieve a clinical response (see Table 8 in Section B.2.3.2 for definition) as per Adapted Mayo Score (see Table 9 in Section B.2.3.2 for definition) during Part 1 received a further 8 weeks of upadacitinib 45 mg QD induction treatment (Part 2):

- ***Part 1:*** After a screening period of up to 5 weeks, subjects were randomised in a 2:1 ratio into upadacitinib 45 mg or placebo treatment arms, with subjects in both arms receiving once-daily treatment for 8 weeks (Figure 3)
- ***Part 2:*** Subjects in the upadacitinib or placebo treatment arms who did not achieve a clinical response as per Adapted Mayo Score at Week 8 received UPA 45 mg QD for a further 8 weeks (Figure 3)

Subjects who achieved a clinical response in Part 1 (Week 8) or in Part 2 (Week 16) in U-ACHIEVE induction or U-ACCOMPLISH induction studies could be enrolled in the U-ACHIEVE maintenance study (see Section B.2.3.1.2).

Figure 3: Clinical trial programme design for UPA in UC



Abbreviations: IR, inadequate response; ITT, intention-to-treat; mg, milligram; PBO, placebo; QD, once daily dosing; UC, ulcerative colitis; UPA, upadacitinib; Wk, week.
Source: Adapted from U-ACHIEVE induction study 2 CSR (50), U-ACCOMPLISH induction study CSR (51), and U-ACHIEVE maintenance study 3 CSR (52).

Trial methodologies for U-ACHIEVE induction and U-ACCOMPLISH induction studies are summarised in Table 6.

B.2.3.1.2 Maintenance study (U-ACHIEVE maintenance)

U-ACHIEVE maintenance study was a Phase 3 multicentre, randomised, double-blind, placebo-controlled, maintenance study which evaluated the efficacy and safety of upadacitinib 15 mg QD and upadacitinib 30 mg QD maintenance doses versus placebo in subjects with moderately to severely active UC.

U-ACHIEVE maintenance study enrolled subjects who achieved a clinical response in Part 1 (Week 8) or in Part 2 (Week 16) in U-ACHIEVE induction or U-ACCOMPLISH induction studies (see Section B.2.3.1.1).

In U-ACHIEVE maintenance study, there were four patient cohorts (Figure 3); however, please note that the Cohort of relevance to, and presented in this submission for upadacitinib, is Cohort 1 (Figure 3; purple). Cohort 1 was the only Cohort that was placebo-controlled and included both upadacitinib 15 mg QD and upadacitinib 30 mg QD. However, please note that as extended induction treatment is addressed in a scenario analysis in Section B.3, data for Cohort 3 is presented in Appendix N.

In Cohort 1, after achieving clinical response at Week 8 (or Week 16 in subjects who received placebo in Part 1 and upadacitinib 45 mg QD in Part 2) subjects were re-randomised in a 1:1:1 ratio to upadacitinib 15 mg, upadacitinib 30 mg, or placebo, where all subjects received once-daily treatment for 52 weeks (Figure 3):

- Cohort 1 (Figure 3; purple): Subjects who achieved clinical response with upadacitinib 45 mg QD induction treatment in U-ACHIEVE induction or U-ACCOMPLISH induction studies at Week 8, or subjects who received placebo in Part 1 of either U-ACHIEVE induction or U-ACCOMPLISH induction studies and then achieved clinical response with UPA 45 mg QD in Part 2
- Cohort 2 (Figure 3; green): Subjects who received double-blind placebo QD treatment for 8 weeks in U-ACHIEVE induction or U-ACCOMPLISH induction studies and achieved clinical response at Week 8 continued to receive blinded placebo QD
- Cohort 3 (Figure 3; blue): Subjects who did not achieve clinical response with upadacitinib 45 mg QD induction treatment at Week 8 and who subsequently received open-label upadacitinib 45 mg QD extended induction treatment in U-ACHIEVE induction or U-ACCOMPLISH induction studies and achieved clinical

response at Week 16 were re-randomised 1:1 to receive blinded upadacitinib 15 mg QD or upadacitinib 30 mg QD

- Cohort 4: Subjects who received double-blinded treatment of upadacitinib 7.5 mg for 8 weeks during U-ACHIEVE substudy 1 and achieved clinical response at Week 8 continued to receive blinded treatment of upadacitinib 7.5 mg QD. Please note that upadacitinib 7.5 mg QD is not licensed in UC and is therefore not discussed in this submission

Where data is available from the trial for subjects according to their prior biologic failure status (categorised as either Bio-IR or non-Bio-IR as previously defined [see Section B.2.3.1.1]), and considered relevant to the decision problem, this data is provided. The primary analysis population reported in the submission was the ITT_A population, a subset of the intention-to-treat (ITT) population which was planned to be the first 450 subjects randomised who achieved clinical response after 8 weeks of induction treatment and who were enrolled under the protocol for 52-week maintenance treatment period in Cohort 1 (see Section B.2.4).

The trial methodology for U-ACHIEVE maintenance study is summarised in Table 6.

Table 6: Comparative summary of trial methodology

Trial no. (acronym)	M14-234 (U-ACHIEVE induction study) (N=474)	M14-675 (U-ACCOMPLISH induction study) (N=522)	M14-234 (U-ACHIEVE maintenance study) (N=1,046)
Study objective	To evaluate the efficacy and safety of UPA 45 mg QD versus placebo in inducing clinical remission (see Table 8 for definition) per Adapted Mayo score (see Table 9 for definition) in Bio-IR or non-Bio-IR subjects with moderately to severely active UC		To evaluate the efficacy and safety of UPA 15 mg QD and 30 mg QD versus placebo in maintaining clinical remission (see Table 8 for definition) per Adapted Mayo score (see Table 9 for definition) in bio-IR or non-bio-IR subjects with moderately to severely active UC U-ACHIEVE maintenance study enrolled patients into four Cohorts; however, the primary analysis was performed on patients in Cohort 1 only
Trial design	A two-part, Phase 3, multicentre, randomised, double-blind, placebo-controlled, induction study		A Phase 3, multicentre, randomised, double-blind, placebo-controlled, maintenance study
Duration of study	Up to 16 weeks		Up to 52 weeks
Method of randomisation	Eligible subjects were randomised in a 2:1 ratio to UPA 45 mg QD or placebo. Randomisation was stratified by bio-IR status (Bio-IR vs non-Bio-IR), corticosteroid use (yes or no), and Adapted Mayo score (≤7 or >7) at Baseline. Within the Bio-IR population, the randomisation was further stratified by number of prior biologic treatments (≤1 or >1). Within the non-Bio-IR population, the randomisation was further stratified by previous biologic use (yes or no) Subjects who did not achieve clinical response per Adapted Mayo score at Week 8 in Part 1 could continue in Part 2, in which all subjects received open-label UPA 45 mg QD		In Cohort 1, eligible subjects were randomised in a 1:1:1 ratio to UPA 15 mg QD, UPA 30 mg QD, or placebo. Randomisation was stratified by bio-IR status (Bio-IR vs non-Bio-IR) at Baseline, clinical remission status (yes or no) at Week 0, and corticosteroid use (yes or no), at Week 0.
Method of blinding (care provider, patient, and outcome assessor)-	All AbbVie personnel with direct oversight of the conduct and management of the study (except for the Drug Supply Management Team), as well as the investigator, blinded study site personnel, and the subject remained blinded to each subject's treatment throughout the study. The IRT provided access to blinded subject treatment information in the case of medical emergency. To maintain the blind, the UPA tablets and placebo tablets provided for the study were identical in appearance		

Trial no. (acronym)	M14-234 (U-ACHIEVE induction study) (N=474)	M14-675 (U-ACCOMPLISH induction study) (N=522)	M14-234 (U-ACHIEVE maintenance study) (N=1,046)
Eligibility criteria for participants	***Inclusion criteria (full list in Appendix M)*** • Males or females aged ≥16 to ≤75 years at Baseline • Confirmed diagnosis of UC for ≥90 days prior to Baseline • Moderately to severely active UC, defined as: – Adapted Mayo score of 5 to 9 points – Endoscopy subscore of 2 to 3 • Inadequate response to, loss of response to, or intolerance to ≥1 of the following treatments: corticosteroids, immunomodulators, and/or biologic therapies.		***Inclusion criteria (full list in Appendix M)*** • Clinical response per Adapted Mayo Score after completion of 8-week induction treatment or Extended Treatment Period in U-ACHIEVE induction or U-ACCOMPLISH induction studies
	Exclusion criteria (full list in Appendix M) • Current diagnosis of CD, fulminant colitis and/or toxic megacolon • UC limited to the rectum • History of colectomy (total or subtotal), ileoanal pouch, Kock pouch, or ileostomy, or were planning bowel surgery • Received prohibited medications as specified in the protocol, e.g., JAK inhibitors, corticosteroids, immunomodulators		***Exclusion criteria (full list in Appendix M)*** • Subjects with missing Week 8 or/and Week 16 endoscopy during the period of coronavirus disease 2019 (COVID-19) pandemic
Settings and locations where the data were collected	199 sites across Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Brazil, Canada, China, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Korea (Republic of), Latvia, Lithuania, Malaysia, Mexico, Netherlands, Norway, Poland, Portugal, Russian Federation, Serbia, Slovakia, South Africa, Spain, Switzerland, Taiwan, Turkey,	204 sites across Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Brazil, Canada, Chile, China, Colombia, Croatia, Czech Republic, Estonia, France, Germany, Greece, Hungary, Israel, Italy, Japan, Korea (Republic of), Latvia, Lithuania, Malaysia, Mexico, Norway, Poland, Portugal, Russian Federation, Serbia, Singapore, Slovakia, South Africa, Spain, Switzerland, Taiwan, Turkey, Ukraine,	302 sites in 43 countries: Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Brazil, Canada, Chile, China, Colombia, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Korea (Republic of), Latvia, Lithuania, Malaysia, Mexico, Netherlands, Norway, Poland, Portugal, Russian Federation, Serbia, Singapore, Slovakia, South Africa, Spain, Switzerland, Taiwan, Turkey, Ukraine, **United Kingdom**, and United States, including Puerto Rico

Trial no. (acronym)	M14-234 (U-ACHIEVE induction study) (N=474)	M14-675 (U-ACCOMPLISH induction study) (N=522)	M14-234 (U-ACHIEVE maintenance study) (N=1,046)
	United Kingdom, and the United States, including Puerto Rico	**United Kingdom**, and the United States, including Puerto Rico	
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x])	***Subjects randomised into Part 1 (N=474)*** Intervention: • UPA 45 mg oral QD (n=319) Comparator: • Placebo to match oral QD (n=155)	***Subjects randomised into Part 1 (N=522)*** Intervention: • UPA 45 mg oral QD (n=345) Comparator: • Placebo to match oral QD (n=177)	***Subjects re-randomised into Cohort 1 (n=847)*** Interventions: • UPA 15 mg oral QD (n=289) • UPA 30 mg oral QD (n=276) Comparator: • Matched placebo oral QD (n=282)
Permitted and disallowed concomitant medications	***Permitted therapy*** Concomitant UC-related Medications: • Oral corticosteroids • Antibiotics • 5-ASA • Methotrexate ***Disallowed therapy*** • All biologic therapy with a potential therapeutic impact on the disease being studied including but not limited to the following: – Etanercept, abatacept, anakinra, rituximab, natalizumab, tocilizumab, efalizumab, ustekinumab, belimumab, golimumab, vedolizumab, infliximab, adalimumab, certolizumab pegol, secukinumab • Other JAK inhibitors (e.g., tofacitinib [Xeljanz®], ruxolitinib [Jakafi®], baricitinib [Olumiant®], peficitinib, [Smyraf®], abrocitinib [PF-04965842], and filgotinib • Live vaccines were not allowed during the study and for 30 days after the last dose of study drug • Other medication: – IV corticosteroid use is prohibited within 14 days prior to Screening or during the Screening Period and during the study (Initiating rectal or systemic corticosteroids use is prohibited during the induction treatment period. Patients who initiate rectal or systemic corticosteroid for any reason during the study must be discussed with the TA MD). – Rectal aminosalicylates or corticosteroid enemas/suppositories are prohibited within 14 days prior to Screening endoscopy, during the remainder of the Screening Period, and during the study – Cyclosporine, tacrolimus, mycophenolate mofetil or thalidomide use is prohibited within 30 days prior to Baseline and		

Trial no. (acronym)	M14-234 (U-ACHIEVE induction study) (N=474)	M14-675 (U-ACCOMPLISH induction study) (N=522)	M14-234 (U-ACHIEVE maintenance study) (N=1,046)
	during the study – Azathioprine or mercaptopurine use is prohibited within 10 days prior to Baseline and during the study – NSAID (except topical NSAIDs and the use of low dose aspirin for cardiovascular protection) within 7 days prior to Baseline and during the study – Total parenteral nutrition is prohibited during the study – Cytapheresis treatment is prohibited within 60 days prior to Screening and during the study – Concomitant cannabis use, either recreational or for medical reasons, is prohibited at least 14 days prior to Baseline and during the study – Traditional Chinese medicines are prohibited within 30 days prior to Baseline and during the study • Investigational drugs of a chemical or biologic nature are prohibited within 30 days, or 5 half-lives (whichever is longer) of the drug prior to the Baseline and during the study Systemic use of strong CYP3A inhibitors or strong CYP3A inducers is prohibited from the Screening Visit through the end of the study		
Primary outcomes (including scoring methods and timings of assessments)	See Table 7		
Other outcomes used in the economic model/specified in the scope	See Table 7		
Pre-planned subgroups	See Section B.2.7 for the full list of pre-planned subgroups. The subgroups of relevance to the decision problem are Bio-IR and non-Bio-IR		

Abbreviations: 5-ASA, aminosalicylate; Bio-IR, inadequate response, loss or response, or intolerance to biologic therapy; CD, Crohn's disease; IRT, interactive response technology; JAK, Janus kinase; non-Bio-IR, inadequate response, loss of response, or intolerance to conventional therapy but had not failed biologic therapy; NSAID, non-steroidal anti-inflammatory drug; QALY, quality-adjusted life year; QD, once-daily dosing; RBS, rectal bleeding score; SFS, stool frequency subscore; TA MD, therapeutic area medical director; UC, ulcerative colitis; UPA, upadacitinib.

B.2.3.2 Trial endpoints

The primary and key secondary endpoints for the U-ACHIEVE induction, U-ACCOMPLISH induction, and U-ACHIEVE maintenance studies are presented in Table 7. These endpoints are defined in Table 8, with a description of each endpoint measurement/disease activity index presented in Table 9.

Table 7. Primary and secondary efficacy endpoints in the U-ACHIEVE induction, U-ACCOMPLISH induction, and U-ACHIEVE maintenance studies

	U-ACHIEVE induction study	U-ACCOMPLISH induction study	U-ACHIEVE maintenance study
Primary efficacy endpoint†	• Proportion of subjects who achieved clinical remission per Adapted Mayo score at Week 8 ***Note:*** *Evidence of friability‡ during endoscopy in subjects with otherwise 'mild' endoscopic activity conferred an endoscopic subscore of 2 (see Table 9 for definition)*		• Proportion of subjects who achieved clinical remission per Adapted Mayo score at Week 52

	U-ACHIEVE induction study	U-ACCOMPLISH induction study	U-ACHIEVE maintenance study
Key secondary efficacy endpoints†	Ranked secondary endpoints 1) Proportion of subjects with endoscopic improvement at Week 8 2) Proportion of subjects with endoscopic remission at Week 8 3) Proportion of subjects achieving clinical response per Adapted Mayo score at Week 8 4) Proportion of subjects achieving clinical response per Partial Adapted Mayo score at Week 2 5) Proportion of subjects achieving histologic-endoscopic mucosal improvement at Week 8 6) Proportion of subjects who reported no bowel urgency at Week 8 7) Proportion of subjects who reported no abdominal pain at Week 8 8) Proportion of subjects who achieved histologic improvement at Week 8 9) Change from Baseline in IBDQ at Week 8 10) Proportion of subjects with mucosal healing at Week 8 11) Change from Baseline in FACIT-F score at Week 8		Ranked secondary endpoints 1) Proportion of subjects with endoscopic improvement at Week 52 2) Proportion of subjects who maintained clinical remission per Adapted Mayo score at Week 52 among subjects who achieved clinical remission per Adapted Mayo score in U-ACHIEVE induction or U-ACCOMPLISH induction studies 3) Proportion of subjects who achieved clinical remission at Week 52 per Adapted Mayo score and were corticosteroid free for ≥90 days among subjects in clinical remission at the end of the induction treatment in U-ACHIEVE induction or U-ACCOMPLISH induction studies 4) Proportion of subjects with endoscopic improvement at Week 52 among subjects with endoscopic improvement in U-ACHIEVE induction or U-ACCOMPLISH induction studies 5) Proportion of subjects with endoscopic remission at Week 52 6) Proportion of subjects who maintained clinical response per Adapted Mayo score at Week 52 7) Proportion of subjects achieving histologic-endoscopic mucosal improvement at Week 52 8) Change from Baseline in IBDQ at Week 52 9) Proportion of subjects with mucosal healing at Week 52 10) Proportion of subjects who reported no bowel urgency at Week 52 11) Proportion of subjects who reported no abdominal pain at Week 52 12) Change from Baseline in FACIT-F score at Week 8

†Outcomes marked in bold are used in the model. ‡Friability describes the ease with which the mucosa is damaged by contact with the endoscope or biopsy instrument.
Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ, inflammatory bowel disease questionnaire.

Table 8. Definition of disease-specific endpoints in the U-ACHIEVE induction, U-ACCOMPLISH induction, and U-ACHIEVE maintenance studies

Endpoint	Definition of measure
Clinical remission	Per Adapted Mayo score, defined as SFS ≤1 and not greater than Baseline, an RBS of 0, and endoscopic subscore ≤1
	Per Full Mayo score defined as Full Mayo score ≤2 with no subscore >1
Clinical response	Per Adapted Mayo score, defined as decrease from baseline in the Adapted Mayo score ≥2 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1
	Per Partial Adapted Mayo score, defined as decrease from Baseline ≥1 points and ≥30% from Baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1
Endoscopic remission	Defined as an endoscopic subscore of 0
Endoscopic improvement	Defined as an endoscopic subscore ≤1
Histologic-endoscopic mucosal improvement	Defined as endoscopic subscore ≤1 and Geboes score ≤3.1
Histologic improvement	Defined as a decrease from baseline in Geboes score
Change IBDQ total score	Change from Baseline in IBDQ total score at Week 8 or Week 52
Mucosal healing	Defined as endoscopic subscore = 0 and Geboes score <2
Change in FACIT-F score	Change from Baseline in FACIT-F score at Week 8 or Week 52

Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ, inflammatory bowel disease questionnaire; RBS, rectal bleeding score; SFS, stool frequency subscore.

Table 9. Description of endpoint measurements/disease activity index in the U-ACHIEVE induction, U-ACCOMPLISH induction, and U-ACHIEVE maintenance studies

Endpoint	Definition of measure
Mayo score	Comprises SFS, RBS, Physician's Global Assessment, and endoscopic appearance (endoscopic subscore) categories all assessed on a scale of 0–3 The individual categories are summed to give a total score on a scale of 0–12 with a higher score indicating increased severity of disease
Adapted Mayo score	Comprises SFS, RBS, and endoscopic appearance (endoscopic subscore) categories all assessed on a scale of 0–3 The individual categories are summed to give a total score on a scale of 0–9 with a higher score indicating increased severity of disease
Partial Mayo score	Comprises SFS, RBS, and Physician's Global Assessment categories all assessed on a scale of 0–3 The individual categories are summed to give a total score on a scale of 0–9 with a higher score indicating increased severity of disease
Partial Adapted Mayo score	Comprises SFS and RBS categories all assessed on a scale of 0–3 The individual categories are summed to give a total score on a scale of 0–6 with a higher score indicating increased severity of disease

Endpoint	Definition of measure
SFS	Assessed on a scale of 0–3, with a higher score indicating increased severity of disease
RBS	
Physician's Global Assessment	
Endoscopic subscore	
Geboes score	Assessed on a scale of Grade 0–5, with additional subgrades indicating various histological criteria/features of disease
IBDQ	A 32-item measure with each item scored on a 7-point Likert scale, ranging from 1 (worst health) to 7 (best health) Each item score is summed to give a total score, with higher scores reflecting better HRQoL
FACIT-F	A 40-item measure with each item scored on a 5-point Likert scale, ranging from 0 (not at all) to 4 (very much so) Each item score is summed to give a total score, with higher scores reflecting higher levels of fatigue and a greater impact of disease on daily activities and functioning

Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HRQoL, health-related quality of life; IBDQ, inflammatory bowel disease questionnaire; RBS, rectal bleeding score; SFS, stool frequency subscore.

B.2.3.3 Baseline characteristics and demographics

The baseline demographics and clinical characteristics of subjects were well balanced between the treatment groups in each trial and were generally similar across trials (Table 10).

For the U-ACHIEVE and U-ACCOMPLISH induction studies, the mean age of patients ranged from 42.1 to 44.4 years and mean disease duration ranged from 7.3 to 9.1 years, across treatments arms. Similar baseline characteristics were observed for the U-ACHIEVE maintenance study; the mean age of patients ranged from 42.6 to 43.3 years and mean disease duration ranged from 8.2 to 8.9 years across treatment arms.

Across the U-ACHIEVE and U-ACCOMPLISH induction studies, disease severity baseline characteristics were reflective of moderately to severely active UC; approximately 40% of subjects were considered to have more severe disease based on a baseline Adapted Mayo score >7. Disease severity baseline characteristics were broadly similar for the U-ACHIEVE maintenance study.

Approximately 50% of subjects entering the trials were classed as having had prior biological treatment failure (Bio-IR), defined as inadequate response or intolerance to biologic therapies. The remainder had failed on oral aminosalicylate, immunomodulators, or corticosteroids (non-Bio-IR).

The proportion of subjects with baseline use of corticosteroids and aminosalicylates across the U-ACHIEVE and U-ACCOMPLISH induction studies ranged between 35.2 and 41.4% and between 66.9 and 69.0%, respectively. Furthermore, 81.2% of patients had previously used 5-ASAs (both arms) and 85.1–87.1% had used corticosteroids in U-ACHIEVE, and 69.0–78.3% and 83.9–84.5% had previously used 5-ASAs and corticosteroids in U-ACCOMPLISH, respectively (Table 11).

The percentage of subjects who had received ≥1 immunomodulator ranged between 49.9 and 58.0% across the two induction studies. For the U-ACHIEVE maintenance study, similar results were observed. However, as immunomodulator use was prohibited (specifically azathioprine and mercaptopurine) within 10 days prior to Baseline and during the study (Table 6 disallowed medications), baseline use of immunomodulators was minimal (0.3 to 1.9% of subjects). The percentage of subjects who had received ≥1 biologic, including TNF-α inhibitors ranged between 50.7 and 54.5% across the two induction studies. For the U-ACHIEVE maintenance study, similar results were observed.

Table 10: Baseline demographics and clinical characteristics of participants across treatment groups in U-ACHIEVE induction and U-ACCOMPLISH induction (ITT1 population) studies, and U-ACHIEVE maintenance (ITT_A population) study

Characteristic	U-ACHIEVE induction study		U-ACCOMPLISH induction study		U-ACHIEVE maintenance study		
	UPA 45 mg QD (n=319)	Placebo QD (n=154)	UPA 45 mg QD (n=341)	Placebo QD (n=174)	UPA 15 mg QD (n=148)	UPA 30 mg QD (n=154)	Placebo QD (n=149)
Sex, n (%)							
Female	121 (37.9)	57 (37.0)	127 (37.2)	67 (38.5)	53 (35.8)	68 (44.2)	64 (43.0)
Male	198 (62.1)	97 (63.0)	214 (62.8)	107 (61.5)	95 (64.2)	86 (55.8)	85 (57.0)
Age, mean years (SD)	43.6 (14.04)	44.4 (14.63)	42.1 (14.74)	42.2 (14.35)	42.6 (14.10)	42.6 (14.75)	43.3 (14.37)
Age group, n (%)							
<18 years	0 (0.0)	0 (0.0)	6 (1.8)	3 (1.7)	0 (0.0)	1 (0.6)	1 (0.7)
≥18–<40 years	133 (41.7)	64 (41.6)	158 (46.3)	79 (45.4)	67 (45.3)	69 (44.8)	68 (45.6)
≥40–<65 years	161 (50.5)	73 (47.4)	144 (42.2)	79 (45.4)	68 (45.9)	69 (44.8)	68 (45.6)
≥65 years	25 (7.8)	17 (11.0)	33 (9.7)	13 (7.5)	13 (8.8)	15 (9.7)	12 (8.1)
Ethnicity, n (%)							
Hispanic or Latino	28 (8.8)	12 (7.8)	26 (7.6)	16 (9.2)	13 (8.8)	9 (5.8)	7 (4.7)
not Hispanic or Latino	291 (91.2)	142 (92.2)	315 (92.4)	158 (90.8)	135 (91.2)	145 (94.2)	142 (95.3)
Race, n (%)							
White	206 (64.6)	100 (64.9)	234 (68.6)	124 (71.3)	97 (65.5)	101 (65.6)	93 (62.4)
Black or African American	12 (3.8)	4 (2.6)	11 (3.2)	6 (3.4)	7 (4.7)	3 (1.9)	6 (4.0)
Asian	95 (29.8)	46 (29.9)	94 (27.6)	41 (23.6)	42 (28.2)	44 (29.7)	48 (31.2)
American Indian or Alaska Native	0 (0.0)	2 (1.3)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or other Pacific Islander	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.6)	1 (0.7)
Multiple	5 (1.6)	2 (1.3)	2 (0.6)	1 (0.6)	0 (0.0)	1 (0.6)	7 (4.7)
BMI (kg/m^2), mean (SD)	24.7 (5.10)	25.7 (6.68)	25.1 (5.33)	25.4 (5.94)	25.5 (5.93)	25.3 (6.52)	25.0 (5.35)

Characteristic	U-ACHIEVE induction study		U-ACCOMPLISH induction study		U-ACHIEVE maintenance study		
	UPA 45 mg QD (n=319)	Placebo QD (n=154)	UPA 45 mg QD (n=341)	Placebo QD (n=174)	UPA 15 mg QD (n=148)	UPA 30 mg QD (n=154)	Placebo QD (n=149)
BMI group, n (%)							
<25 kg/m^2	194 (61.0)	84 (54.9)	195 (57.2)	96 (55.2)	88 (59.5)	83 (54.2)	89 (59.7)
≥25–30 kg/m^2	77 (24.2)	38 (24.8)	100 (29.3)	45 (25.9)	30 (20.3)	43 (28.1)	36 (24.2)
≥30 kg/m^2	47 (14.8)	31 (20.3)	46 (13.5)	33 (19.0)	30 (20.3)	27 (17.6)	24 (16.1)
Missing	1 (0.3)	1 (0.6)	NR	NR	0 (0.0)	1 (0.6)	0 (0.0)
Disease duration (years), mean (SD)	8.6 (7.17)	9.1 (8.76)	7.3 (6.45)	7.4 (7.20)	8.9 (8.10)	8.2 (7.62)	8.7 (8.00)
Disease duration group, n (%)							
≤3 years	88 (27.6)	43 (27.9)	105 (30.8)	51 (29.3)	42 (28.4)	53 (34.4)	41 (27.5)
>3 years	231 (72.4)	111 (72.1)	236 (69.2)	123 (70.7)	106 (71.6)	101 (65.6)	108 (72.5)
Bio-IR status, n (%)							
Bio-IR	168 (52.7)	78 (50.6)	172 (50.4)	89 (51.1)	71 (48.0)	73 (47.4)	81 (54.4)
Non-Bio-IR	151 (47.3)	76 (49.4)	169 (49.6)	85 (48.9)	77 (52.0)	81 (52.6)	68 (45.6)
Baseline corticosteroid use, n (%)							
Yes	124 (38.9)	61 (39.6)	120 (35.2)	72 (41.4)	55 (37.2)	57 (37.0)	60 (40.3)
No	195 (61.1)	93 (60.4)	221 (64.8)	102 (58.6)	93 (62.8)	97 (63.0)	89 (59.7)
Baseline immunomodulator use, n (%)							
Yes	2 (0.6)	3 (1.9)	1 (0.3)	3 (1.7)	1 (0.7)	1 (0.6)	0 (0.0)
No	317 (99.4)	151 (98.1)	340 (99.7)	171 (98.3)	147 (99.3)	153 (99.4)	149 (100)
Baseline aminosalicylates use, n (%)							
Yes	220 (69.0)	103 (66.9)	233 (68.3)	120 (69.0)	99 (66.9)	106 (68.8)	99 (66.4)

Characteristic	U-ACHIEVE induction study		U-ACCOMPLISH induction study		U-ACHIEVE maintenance study		
	UPA 45 mg QD (n=319)	Placebo QD (n=154)	UPA 45 mg QD (n=341)	Placebo QD (n=174)	UPA 15 mg QD (n=148)	UPA 30 mg QD (n=154)	Placebo QD (n=149)
No	99 (31.0)	51 (33.1)	108 (31.7)	54 (31.0)	49 (33.1)	48 (31.2)	50 (33.6)
Baseline adapted Mayo score, n (%)							
≤7	195 (61.3)	94 (61.0)	205 (60.3)	103 (59.2)	89 (60.1)	88 (57.9)	87 (58.4)
>7	123 (38.7)	60 (39.0)	135 (39.7)	71 (40.8)	59 (39.9)	64 (42.1)	62 (41.6)
Missing	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)
Baseline full Mayo score, n (%)							
≤9	162 (50.9)	79 (51.3)	160 (47.1)	86 (49.4)	75 (50.7)	73 (48.0)	74 (49.7)
>9	156 (49.1)	75 (48.7)	180 (52.9)	88 (50.6)	73 (49.3)	79 (52.0)	75 (50.3)
Missing	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	2 (1.2)	0 (0.0)
hsCRP (mg/L), mean (SD)	9.412 (15.26)	12.223 (21.23)	9.283 (15.31)	10.782 (19.94)	8.362 (12.44)	8.626 (14.75)	9.827 (15.89)
Baseline hsCRP - n (%)							
≤5 mg/L	178 (55.8)	80 (51.9)	193 (56.6)	89 (51.1)	84 (56.8)	88 (57.1)	81 (54.4)
>5 mg/L	141 (44.2)	74 (48.1)	148 (43.4)	85 (48.9)	64 (43.2)	66 (42.9)	68 (45.6)
Faecal calprotectin (mg/kg), mean (SD)	3910.1 (5698.72)	3135.5 (3986.79)	3130.5 (4719.82)	3126.7 (4742.09)	3141.7 (4694.00)	2737.3 (4326.71)	3620.3 (5222.27)
IBDQ score – Total, mean (SD)	122.2 (36.50)	121.5 (30.96)	122.8 (34.52)	122.7 (37.66)	125.8 (35.93)	121.3 (34.95)	122.6 (33.44)
FACIT-F, mean (SD)	30.5 (11.73)	31.6 (10.88)	29.8 (11.76)	31.4 (12.64)	31.4 (11.54)	29.9 (11.75)	30.2 (11.12)

Abbreviations: BMI, body mass index; Bio-IR, biologic therapy-intolerant or inadequate responder; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; hs-CRP, high sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; ITT, intention-to-treat; NR, not reported; QD, once-daily dosing; SD, standard deviation; UPA, upadacitinib.

Table 11: Number of previous UC-related medications in U-ACHIEVE induction and U-ACCOMPLISH induction studies (ITT1 population), and U-ACHIEVE maintenance study (ITT_A population)

Characteristic	U-ACHIEVE induction study		U-ACCOMPLISH induction study		U-ACHIEVE maintenance study		
	UPA 45 mg QD (n=319)	Placebo QD (n=154)	UPA 45 mg QD (n=341)	Placebo QD (n=174)	UPA 15 mg QD (n=148)	UPA 30 mg QD (n=154)	Placebo QD (n=149)
Aminosalicylates							
1	217 (68.0)	108 (70.1)	234 (68.6)	101 (58.0)	114 (77.0)	124 (80.5)	118 (79.2)
2	41 (12.9)	17 (11.0)	31 (9.1)	16 (9.2)	27 (18.2)	23 (14.9)	21 (14.1)
3	1 (0.3)	0	2 (0.6)	3 (1.7)	0 (0.0)	1 (0.6)	1 (0.7)
≥4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
At least one medication	259 (81.2)	125 (81.2)	267 (78.3)	120 (69.0)	141 (95.3)	148 (96.1)	140 (94.0)
Antibiotics							
1	21 (6.6)	15 (9.7)	25 (7.3)	17 (9.8)	5 (3.4)	14 (9.1)	15 (10.1)
2	14 (4.4)	8 (5.2)	15 (4.4)	9 (5.2)	10 (6.8)	9 (5.8)	6 (4.0)
3	1 (0.3)	0	1 (0.3)	1 (0.6)	2 (1.4)	2 (1.3)	0 (0.0)
≥4	0	1 (0.6)	3 (0.9)	0	3 (2.0)	0 (0.0)	0 (0.0)
At least one medication	36 (11.3)	24 (15.6)	44 (12.9)	27 (15.5)	20 (13.5)	25 (16.2)	21 (14.1)
Biologics (Including TNF-α inhibitors)							
1	64 (20.1)	29 (18.8)	64 (18.8)	39 (22.4)	30 (20.3)	34 (22.1)	30 (20.1)
2	64 (20.1)	31 (20.1)	67 (19.6)	36 (20.7)	32 (21.6)	24 (15.6)	34 (22.8)
3	35 (11.0)	18 (11.7)	34 (10.0)	15 (8.6)	10 (6.8)	16 (10.4)	16 (10.7)
≥4	11 (3.4)	4 (2.6)	8 (2.3)	3 (1.7)	1 (0.7)	3 (1.9)	4 (2.7)
At least one medication	174 (54.5)	82 (53.2)	173 (50.7)	93 (53.4)	73 (49.3)	77 (50.0)	84 (56.4)

Characteristic	U-ACHIEVE induction study		U-ACCOMPLISH induction study		U-ACHIEVE maintenance study		
	UPA 45 mg QD (n=319)	Placebo QD (n=154)	UPA 45 mg QD (n=341)	Placebo QD (n=174)	UPA 15 mg QD (n=148)	UPA 30 mg QD (n=154)	Placebo QD (n=149)
Corticosteroids							
1	165 (51.7)	62 (40.3)	162 (47.5)	83 (47.7)	73 (49.3)	84 (54.5)	75 (50.3)
2	83 (26.0)	55 (35.7)	87 (25.5)	48 (27.6)	50 (33.8)	42 (27.3)	44 (29.5)
3	27 (8.5)	12 (7.8)	33 (9.7)	16 (9.2)	15 (10.1)	11 (7.1)	16 (10.7)
≥4	3 (0.9)	2 (1.3)	4 (1.2)	0	1 (0.7)	3 (1.9)	2 (1.3)
At least one medication	278 (87.1)	131 (85.1)	286 (83.9)	147 (84.5)	139 (93.9)	140 (90.9)	137 (91.9)
Immunomodulators							
1	149 (46.7)	72 (46.8)	139 (40.8)	77 (44.3)	59 (39.9)	71 (46.1)	63 (42.3)
2	35 (11.0)	13 (8.4)	27 (7.9)	17 (9.8)	14 (9.5)	14 (9.1)	17 (11.4)
3	1 (0.3)	2 (1.3)	3 (0.9)	1 (0.6)	1 (0.7)	1 (0.6)	2 (1.3)
≥4	0	0	1 (0.3)	0	1 (0.7)	0 (0.0)	0 (0.0)
At least one medication	185 (58.0)	87 (56.5)	170 (49.9)	95 (54.6)	75 (50.7)	86 (55.8)	82 (55.0)

Abbreviations: ITT, intention-to-treat; QD, once-daily dosing; TNF-α, tumour necrosis factor-alpha; UPA, upadacitinib.

B.2.3.4 Expert elicitation/opinion

UK clinical and health economic expert opinion was sought to support the submission for upadacitinib in patients with moderately to severely active UC, with expert opinion collected at a face-to-face advisory board meeting, via round table discussions, in [redacted]. AbbVie approached eight experts (five clinicians and three health economic experts), of which all eight experts participated.

Experts were provided with pre-read material prior to the advisory board which contained UC disease overview and UK epidemiological data, methods for assessing disease severity and activity, the current UK treatment landscape, upadacitinib product information and clinical trial data, and UPA health economic model information. All information provided to the experts was consistent with the evidence provided in the submission.

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

B.2.4.1 Definitions of patient population analysis sets

Definitions of the patient population analysis sets of the U-ACHIEVE induction and U-ACCOMPLISH induction, and U-ACHIEVE maintenance studies are provided in Table 12 and Table 13, respectively. The patient numbers comprising each data set are presented in Section B.2.4.3.

Table 12. Definitions of analysis sets in U-ACHIEVE induction and U-ACCOMPLISH induction studies

Analysis set	Definition
ITT1	The ITT population for the 8-week double-blinded induction period (Part 1) that includes all randomised subjects who received ≥1 dose of double-blinded study drug in Part 1
ITT2	The ITT population for the 8-week open-label extended treatment period (Part 2) that includes all subjects who received ≥1 dose of UPA 45 mg in Part 2
SA1	The safety population for Part 1 that includes all randomised subjects who received ≥1 dose of study drug in Part 1
SA2	The safety population for Part 2 that includes all subjects who received ≥1 dose of UPA 45 mg in Part 2
SA-UPA	The all UPA treated safety population (denoted by SA-UPA) that includes all subjects who received at least one dose of UPA in Part 1 or Part 2

Abbreviations: ITT, intention-to-treat; SA, safety analysis; SA-UPA, safety analysis-upadacitinib; UPA, upadacitinib.

Table 13. Definitions of analysis sets in U-ACHIEVE maintenance study

Analysis set	Definition
ITT	The ITT population for the 52-week maintenance treatment period that includes all randomised subjects who received ≥1 dose of study drug
ITT_A	The ITT_A population is the primary analysis population in Cohort 1 for efficacy endpoints ITT_A is the subset of the ITT population who were the first 451 randomised UPA 45 mg QD 8-week induction responders and who were enrolled under the protocol for the 52-week maintenance treatment period in Cohort 1[†]
SA	The safety population that includes all randomised subjects who received ≥1 dose of study drug in the maintenance study
SA_A	The subset of the SA safety population who were the first 451 randomised UPA 45 mg QD 8-week induction responders and who were enrolled under the protocol for the 52-week maintenance treatment period in Cohort 1
SA-UPA	The all UPA treated safety population (denoted by SA-UPA) that includes all subjects who received at least one dose of UPA in the maintenance study

[†]The planned number of subjects in the ITT_A population was 450; however, the actual number of subjects was 451 due to the tie in enrolment date of subjects #450 and #451.
Abbreviations: ITT, intention-to-treat; SA, safety analysis; SA-UPA, safety analysis-upadacitinib; UPA, upadacitinib.

B.2.4.2 Statistical analysis

A summary of the statistical analysis plan for each of the U-ACHIEVE induction, U-ACCOMPLISH induction, and U-ACHIEVE maintenance studies is provided in Table 14.

Table 14. Summary of statistical analysis approach in U-ACHIEVE induction, U-ACCOMPLISH induction, and U-ACHIEVE maintenance studies

	U-ACHIEVE induction study	U-ACCOMPLISH induction study	U-ACHIEVE maintenance study
Hypothesis objective	The primary hypothesis was the proportion of subjects achieving clinical remission per Adapted Mayo score treated with UPA 45 mg QD is greater than those treated with placebo at Week 8.		The primary hypothesis was the proportion of subjects achieving clinical remission per Adapted Mayo score treated with UPA 15 mg QD and UPA 30 mg QD is greater than those treated with placebo at Week 52.
Statistical analysis	Efficacy endpoints in Part 1 were analysed based on the ITT1 population and in Part 2 were based on the ITT2 population. All significance tests were planned at the α level of 0.05 (two-sided). The overall type I error rate of the primary and the ranked secondary endpoints were controlled using the fixed-sequence multiple testing procedure. Specifically, testing was performed in the sequence of the primary and ranked secondary endpoints specified in Table 7 at the α level of 0.05 (two-sided). Unless otherwise stated, categorical efficacy endpoints were assessed using the CMH test stratified by bio-IR status (Bio-IR versus non-Bio-IR), baseline corticosteroid use (yes versus no) and baseline Adapted Mayo score (≤7 versus >7). Continuous variables collected longitudinally were analysed using the MMRM method. Continuous variables collected at only one post-baseline visit (such as Mayo score) were analysed using an ANCOVA model.		Efficacy endpoints in Cohort 1 were analysed based on the ITT_A population. All significance tests were planned at the α level of 0.05 (two-sided). The overall type I error rate of the primary and the ranked secondary endpoints were tested with graphical multiplicity adjustment. Specifically, testing was performed in the sequence of the primary and ranked secondary endpoints specified in Table 7 at the α level of 0.05 (two-sided). Unless otherwise stated, categorical efficacy endpoints were assessed using the CMH test stratified by bio-IR status (Bio-IR versus non-Bio-IR) at the Baseline of induction study, clinical remission status at Week 0 (yes versus no), and corticosteroid use at Week 0 (yes versus no). Continuous variables collected longitudinally were analysed using the MMRM method. Continuous variables collected at only one post-baseline visit (such as Mayo score) were analysed using an ANCOVA model.
Sample size, power calculation	A total sample of 462 subjects randomised in a 2:1 ratio to UPA 45 mg QD (n=308) or placebo (n=154) was planned to achieve at least 95% power to assess clinical remission with a treatment difference of 13% at Week 8, using a two-sided Fisher's exact test at a significance level of 0.05.		A total sample of 1,046 subjects were enrolled into four Cohorts (Cohorts 1–4). In Cohort 1, 847 subjects were re-randomised in a 1:1:1 ratio to UPA 15 mg QD (n=289), UPA 30 mg QD (n=276), or placebo (n=282). A sample size of 150 subjects in each of the three treatments arms was planned to achieve at least 95% power to assess clinical remission with a treatment difference of 28% at Week 52, using a two-sided Fisher's exact test at a significance level of 0.025.

	U-ACHIEVE induction study	U-ACCOMPLISH induction study	U-ACHIEVE maintenance study
Data management, patient withdrawals	**For categorical endpoints:** The primary approach for handling missing data was non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19 (termed NRI-C). **For continuous endpoints:** The primary approach for handling missing data was MMRM. **For sensitivity analyses for the primary endpoint:** NRI with no special data handling for missing due to COVID-19 (termed NRI-NC), hybrid multiple imputation (termed HMI), and as observed (termed AO) analysis was performed. **NRI-C:** The NRI-C categorised any subject who did not have an evaluation during a pre-specified visit window (either due to missing assessment or due to early withdrawal from the study) as a non-responder for the visit. The only exception was that missing data due to COVID-19 infection or logistical restrictions related to the COVID-19 pandemic was handled by MI. At each visit, subjects will be characterised as responders or non-responders based on MI imputed values if missing due to COVID-19; otherwise, subjects were considered as non-responders for missing due to other reasons in the NRI-C approach. In addition, subjects were considered as non-responders at or after the occurrence of the UC-related corticosteroids intercurrent event. **NRI-NC:** NRI-NC was performed in the same way as NRI-C without the exception of missing due to COVID-19. Missing due to COVID-19 or COVID-19 logistical restriction were counted as non-responders. **HMI:** Sensitivity analysis was performed for the primary endpoint using the HMI method. Subjects who discontinued study drug prior to Week 8 due to lack of efficacy or AEs and had no available measurements were considered as non-responders. Subjects who discontinued for other reasons and had no available measurements were categorised according to the data from MI. **AO:** The AO analysis did not impute values for missing evaluations, and therefore a subject who did not have an evaluation on a scheduled visit was excluded from the AO analysis		**For categorical endpoints:** The primary approach for handling missing data was non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C). **For continuous endpoints:** The primary approach for handling missing data was RTB-MI. **For sensitivity analyses for the primary endpoint:** NRI with no special data handling for missing due to COVID-19 (NRI-NC), hybrid multiple imputation (termed HMI), and as observed (AO) analysis was performed. **NRI-C:** The NRI-C categorised any subject who did not have an evaluation during a pre-specified visit window (either due to missing assessment or due to early withdrawal from the study) as a non-responder for the visit. The only exception was that missing data due to COVID-19 infection or logistical restrictions related to the COVID-19 pandemic was handled by MI. At each visit, subjects will be characterised as responders or non-responders based on MI imputed values if missing due to COVID-19; otherwise, subjects were considered as non-responders for missing due to other reasons in the NRI-C approach. In addition, subjects were considered as non-responders at or after the occurrence of the UC-related corticosteroids intercurrent event. **NRI-NC:** NRI-NC was performed in the same way as NRI-C without the exception of missing due to COVID-19. Missing due to COVID-19 or COVID-19 logistical restriction were counted as non-responders. **HMI:** Sensitivity analysis was performed for the primary endpoint using the HMI method. Subjects who discontinued study drug prior to Week 52 due to lack of efficacy or AEs and had no available measurements were considered as non-responders. Subjects who discontinued for other reasons and had no available measurements were categorised according to the data from MI. **AO:** The AO analysis did not impute values for missing evaluations, and therefore a subject who did not have an evaluation on a scheduled visit was excluded from the AO analysis for that visit. AO included all values collected in the study. **RTB-MI:** Assumes that subjects who received UC-related rescue

	U-ACHIEVE induction study	U-ACCOMPLISH induction study	U-ACHIEVE maintenance study
	for that visit. AO included all values collected in the study. **MMRM:** Conducted using the mixed model including observed measurements at all visits, except for measurements at or after the occurrence of UC-related corticosteroids intercurrent event.		medication will have a washout 'return to baseline' of any potential treatment effect.

Abbreviations: ANCOVA, Analysis of Covariance; AO, as observed; Bio-IR, biologic therapy-intolerant or inadequate responder; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; HMI, hybrid multiple imputation method; ITT, intention-to-treat; MI, multiple imputation; MMRM, mixed effect model repeated measurement; NRI, non-responder information; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; NRI-NC, NRI with no special data handling for missing due to COVID-19; QD, once-daily dosing; RTB-MI, multiple imputation incorporating return to baseline; UPA, upadacitinib.

B.2.4.3 Participant flow in the relevant randomised controlled trials

B.2.4.3.1 U-ACHIEVE induction study

Approximately 462 subjects were planned for U-ACHIEVE induction study. Non-Bio-IR subjects enrolled were planned to be at least 25% and not to exceed 50% of the total number of subjects enrolled, with approximately 52% Bio-IR subjects and 48% non-Bio-IR subjects enrolled in the trial (Table 10).

A total of 474 subjects were randomised and treated in U-ACHIEVE induction study Part 1 (n=319 upadacitinib 45 mg; n=155 placebo) (Table 15). A total of 443 subjects completed treatment in Part 1 (n=307 upadacitinib 45 mg; n=136 placebo); 12 subjects discontinued active treatment compared with 19 in the placebo group. Lack of efficacy was the most frequent primary reason for study drug discontinuation in the placebo arm compared with AEs in the upadacitinib 45 mg arm (ITT1 population; Table 16).

In U-ACHIEVE induction study Part 2 (the open-label, 8-week extended induction period for clinical non-responders from U-ACHIEVE induction study Part 1), 144 subjects were treated (n=85 placebo/upadacitinib 45 mg; n=59 upadacitinib 45 mg/upadacitinib 45 mg). Twenty-one subjects discontinued study drug in Part 2 across the two treatment groups (n=10 placebo/upadacitinib 45 mg; n=11 upadacitinib 45 mg/upadacitinib 45 mg).

Table 15: U-ACHIEVE induction study subject accountability

	Randomised n	Treated n	Study drug		Study discontinued n
			Completed n	Discontinued n	
Part 1 (n=474)					
Placebo	155	155	136	19	20
UPA 45 mg	319	319	307	12	13
Total	474	474	443	31	33
Part 2 (n=144)					
Placebo/ UPA 45 mg	-	85	75	10	11
UPA 45 mg/ UPA 45 mg	-	59	48	11	12
Total	-	144	123	21	23

Abbreviations: UPA, upadacitinib.

Table 16: U-ACHIEVE induction study subject disposition (ITT1 and ITT2 populations)

Characteristic	Part 1		Part 2	
	UPA 45 mg QD (n=319), n (%)	Placebo QD (n=154), n (%)	Placebo/UPA 45 mg QD (n=84), n (%)	UPA 45 mg QD/ UPA 45 mg QD (n=59), n (%)
Discontinuation of study drug due to				
Primary Reason†	12 (3.8)	19 (12.3)	9 (10.7)	11 (18.6)
Adverse event	7 (2.2)	7 (4.5)	2 (2.4)	0
Withdrew consent	1 (0.3)	2 (1.3)	3 (3.6)	1 (1.7)
Lack of efficacy	2 (0.6)	9 (5.8)	3 (3.6)	7 (11.9)
Lost to follow-up	1 (0.3)	0 (0.0)	0 (0.0)	1 (1.7)
COVID-19 infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19 logistical restrictions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.3)	1 (0.6)	1 (1.2)	2 (3.4)
Discontinuation of study due to				
Primary Reason†	13 (4.1)	20 (13.0)	10 (11.9)	12 (20.3)
Adverse event	6 (1.9)	9 (5.8)	3 (3.6)	0
Withdrew consent	2 (0.6)	3 (1.9)	3 (3.6)	1 (1.7)
Lost to follow-up	1 (0.3)	1 (0.6)	0	1 (1.7)
COVID-19 infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19 logistical restrictions	1 (0.3)	0 (0.0)	0 (0.0)	2 (3.4)
Other	3 (0.9)	7 (4.5)	4 (4.8)	8 (13.6)

†Subjects who discontinued are counted under each reason given for discontinuation, therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations.
Abbreviations: COVID-19, coronavirus disease 2019; ITT, intention-to-treat; QD, once-daily dosing; UPA, upadacitinib.

B.2.4.3.2 U-ACCOMPLISH induction study

Approximately 462 subjects were planned for U-ACCOMPLISH induction study. Non-Bio-IR subjects enrolled were planned to be at least 25% and not to exceed 50% of the total number of subjects enrolled, with approximately 51% Bio-IR subjects and 49% non-Bio IR subjects enrolled in the trial (Table 10).

A total of 522 subjects were randomised in U-ACCOMPLISH induction study Part 1 (n=345 upadacitinib 45 mg; n=177 placebo) (Table 17). One subject was randomised to upadacitinib 45 mg but did not receive treatment. A total of 497 subjects completed treatment in Part 1 (n=333 upadacitinib 45 mg; n=164 placebo); 11 subjects discontinued active treatment compared with 13 in the placebo group. Adverse event was the most

frequent primary reason for study drug discontinuation in the placebo arm compared with withdrawal of consent in the upadacitinib 45 mg arm (ITT1 population; Table 18).

In U-ACCOMPLISH induction study Part 2 (the open-label, 8-week extended treatment period for clinical non-responders from Part 1), 184 subjects were treated (n=116 placebo/upadacitinib 45 mg; n=68 upadacitinib 45 mg/ upadacitinib 45 mg). Nine subjects discontinued study drug in Part 2 across the two treatment groups (n=5 placebo/upadacitinib 45 mg; n=4 upadacitinib 45 mg/upadacitinib 45 mg).

Table 17: U-ACCOMPLISH induction study subject accountability

	Randomised n	Treated n	Study drug		Study discontinued n
			Completed n	Discontinued n	
Part 1 (n=522)					
Placebo	177	177	164	13	13
UPA 45 mg	345	344	333	11	12
Total	522	521	497	24	25
Part 2 (n=184)					
Placebo/ UPA 45 mg	-	116	111	5	5
UPA 45 mg/ UPA 45 mg	-	68	64	4	3
Total	-	184	175	9	8

Abbreviations: UPA, upadacitinib.

Table 18: U-ACCOMPLISH induction study subject disposition (ITT1 and ITT2 populations)

Characteristic	Part 1		Part 2	
	UPA 45 mg QD (n=341) n (%)	Placebo QD (n=174) n (%)	Placebo/UPA 45 mg QD (n=113) n (%)	UPA 45 mg QD/ UPA 45 mg QD (n=66) n (%)
Discontinuation of study drug due to				
Primary Reason†	11 (3.2)	13 (7.5)	5 (4.4)	4 (6.1)
Adverse event	5 (1.5)	5 (2.9)	2 (1.8)	2 (3.0)
Withdrew consent	6 (1.8)	4 (2.3)	2 (1.8)	1 (1.5)
Lack of efficacy	0 (0.0)	4 (2.3)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19 infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19 logistical restrictions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.5)

Characteristic	Part 1		Part 2	
	UPA 45 mg QD (n=341) n (%)	Placebo QD (n=174) n (%)	Placebo/UPA 45 mg QD (n=113) n (%)	UPA 45 mg QD/ UPA 45 mg QD (n=66) n (%)
Discontinuation of study due to				
Primary Reason†	11 (3.2)	13 (7.5)	5 (4.4)	3 (4.5)
Adverse event	5 (1.5)	6 (3.4)	1 (0.9)	1 (1.5)
Withdrew consent	6 (1.8)	4 (2.3)	2 (1.8)	1 (1.5)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19 infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19 logistical restrictions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	3 (1.7)	2 (1.8)	1 (1.5)

†Subjects who discontinued are counted under each reason given for discontinuation, therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations.
Abbreviations: COVID-19, coronavirus disease 2019; ITT, intention-to-treat; QD, once-daily dosing; UPA, upadacitinib.

B.2.4.3.3 U-ACHIEVE maintenance study

A total of 1,046 subjects were enrolled in U-ACHIEVE maintenance study across Cohorts 1–4. Of these, 847 subjects who achieved clinical response per Adapted Mayo score in U-ACHIEVE induction or U-ACCOMPLISH induction studies comprised Cohort 1 which was the only cohort that was placebo controlled and included both upadacitinib 15 mg QD and upadacitinib 30 mg QD study arms (n=289 upadacitinib 15 mg QD; n=276 upadacitinib 30 mg; n=282 placebo) (Table 19). The primary analysis population in Cohort 1 for efficacy endpoints was the ITT_A population which was the subset of the ITT population who were the first 451 randomised upadacitinib 45 mg QD 8-week induction responders and who were enrolled under the protocol for the 52-week maintenance treatment period in Cohort 1 (Table 13).

A total of 370 subjects completed treatment in Cohort 1 (n=144 upadacitinib 15 mg; n=155 upadacitinib 30 mg; n=71 placebo); 88 and 53 subjects discontinued active treatment in the upadacitinib 15 mg and upadacitinib 30 mg arms, respectively, compared with 180 in the placebo group, with 154 ongoing on study drug at the time of the data cut-off date (Table 19). Lack of efficacy was the most frequent primary reason for study drug discontinuation in the active treatment and placebo arms (ITT_A population; Table 20).

Table 19: U-ACHIEVE maintenance study subject accountability (Cohort 1)

	Enrolled n	Treated n	Study drug			Study		
			Completed n	Discont. n	Ongoing n	Completed n	Discont. n	Ongoing n
Placebo	282	281	71	180	30	71	181	30
UPA 15 mg	289	288	144	88	56	144	89	56
UPA 30 mg	276	276	155	53	68	155	52	69
Total	847	845	370	321	154	370	322	155

Abbreviations: Discont, discontinued; UPA, upadacitinib.

Table 20: U-ACHIEVE maintenance study subject disposition (Cohort 1; ITT_A population)

Characteristic	UPA 15 mg QD (n=148) n (%)	UPA 30 mg QD (n=154) n (%)	Placebo QD (n=149) n (%)
Discontinuation of study drug due to			
Primary reason	49 (33.1)	33 (21.4)	98 (65.8)
Adverse event	4 (2.7)	8 (5.2)	14 (9.4)
Withdrew consent	1 (0.7)	4 (2.6)	1 (0.7)
Lack of efficacy	35 (23.6)	12 (7.8)	74 (49.7)
Lost to follow-up	0 (0.0)	1 (0.6)	0 (0.0)
COVID-19 infection	0 (0.0)	1 (0.6)	0 (0.0)
COVID-19 logistical restrictions	0 (0.0)	1 (0.6)	0 (0.0)
Other	9 (6.1)	6 (3.9)	9 (6.0)
Discontinuation of study due to			
Primary reason	49 (33.1)	33 (21.4)	98 (65.8)
Adverse event	5 (3.4)	10 (6.5)	13 (8.7)
Withdrew consent	1 (0.7)	5 (3.2)	4 (2.7)
Lost to follow-up	0 (0.0)	1 (0.6)	0 (0.0)
COVID-19 infection	0 (0.0)	0 (0.0)	0 (0.0)
COVID-19 logistical restrictions	0 (0.0)	1 (0.6)	0 (0.0)
Other	43 (29.1)	16 (10.4)	81 (54.4)

†Subjects who discontinued are counted under each reason given for discontinuation, therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations.
Abbreviations: COVID-19, coronavirus disease 2019; ITT, intention-to-treat; QD, once-daily dosing; UPA, upadacitinib.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

U-ACHIEVE induction, U-ACCOMPLISH induction, and U-ACHIEVE maintenance studies were large, randomised, double-blind, placebo-controlled, well-conducted, and methodologically robust Phase 3 studies. The study protocols and amendments were approved by an independent ethics committee or institutional review board, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Randomisation to study drugs was achieved via a web-based interactive response technology (IRT), and an Independent Data Monitoring Committee was established to monitor data on an ongoing basis to ensure the continuing safety of the study patients.

A summary of quality assessment results is provided in Table 21.

A complete quality assessment and risk of bias assessment for each trial is provided in Appendix D.

Table 21: Quality assessment results for parallel group RCTs

Trial number (acronym)	M14-234 (U-ACHIEVE induction study)	M14-675 (U-ACCOMPLISH induction study)	M14-234 (U-ACHIEVE maintenance study)
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	Yes	Yes	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes

B.2.6 Clinical effectiveness results of the relevant trials

Efficacy results for the upadacitinib clinical trial programme

The clinical benefits of upadacitinib versus placebo have been demonstrated in two pivotal induction studies (U-ACHIEVE induction study and U-ACCOMPLISH induction study) and one pivotal maintenance study (U-ACHIEVE maintenance study). All primary and ranked secondary endpoints were met for both the induction and maintenance phases of the clinical trial programme.

In the U-ACHIEVE induction and U-ACCOMPLISH induction studies, statistically significant improvements in disease activity were observed as early as Week 2 and improvements in endoscopic and histologic outcomes observed at Week 8, following treatment with upadacitinib 45 mg QD. In addition, a post-hoc analysis of improvements in stool frequency and rectal bleeding were observed as early as Day 1 post-treatment (53). Results from the U-ACHIEVE maintenance study demonstrated that upadacitinib 15 mg QD and upadacitinib 30 mg QD provided effective maintenance treatment in subjects achieving a clinical response to upadacitinib 45 mg QD induction treatment.

Key results for the U-ACHIEVE induction and U-ACCOMPLISH induction studies

- The primary objective of the pivotal U-ACHIEVE induction and U-ACCOMPLISH induction studies was met. A significantly greater proportion of patients achieved clinical remission per Adapted Mayo score at Week 8 compared with placebo in U-ACHIEVE induction [redacted] and U-ACCOMPLISH induction studies [redacted]
- Upadacitinib 45 mg QD further demonstrated beneficial treatment effects in Bio-IR and non-Bio-IR patients, irrespective of prior biologic use.
  - Improvements in disease activity were observed as early as Week 2 with statistically significant improvements in clinical response in patients receiving upadacitinib 45 mg QD compared with placebo in U-ACHIEVE induction [redacted] and U-ACCOMPLISH induction studies [redacted]
- Upadacitinib 45 mg QD was superior compared with placebo for all ranked secondary endpoints evaluated, providing statistically significant improvements in objective measures of disease activity such as endoscopic assessment, histologic assessment, disease activity and symptoms, as well as improvements in important QoL indices

such as fatigue with 8-week induction treatment.

Key results for the U-ACHIEVE maintenance study

- The primary objective of the pivotal U-ACHIEVE maintenance study was met. Patients who received either upadacitinib 15 mg QD or upadacitinib 30 mg QD after 8-week induction on upadacitinib 45 mg QD demonstrated a sustained response for clinical remission per Adapted Mayo score compared with placebo over 52 weeks. A significantly greater proportion of patients achieved clinical remission per Adapted Mayo score at Week 52 compared with placebo in those receiving upadacitinib 15 mg QD [redacted] and upadacitinib 30 mg QD [redacted]
- Upadacitinib 15 mg QD and upadacitinib 30 mg QD were superior compared with placebo for all ranked secondary endpoints evaluated and delivered sustained improvements in objective measures of disease activity such as endoscopic improvement, endoscopic remission, histologic endoscopic improvement, and mucosal healing through 52 weeks of treatment, as well as improvements in important QoL indices such as fatigue.
- A statistically significantly greater proportion of subjects in the upadacitinib 15 mg QD and upadacitinib 30 mg QD arms achieved clinical remission and were corticosteroid free for ≥90 days compared with placebo.
- Upadacitinib 15 mg QD and upadacitinib 30 mg QD maintenance treatment further demonstrated beneficial treatment effects for Bio-IR or non-Bio-IR subjects for clinical remission and endoscopic response.

B.2.6.1 U-ACHIEVE induction and U-ACCOMPLISH induction studies

In U-ACHIEVE induction and U-ACCOMPLISH induction studies, the primary endpoint (clinical remission per Adapted Mayo score at Week 8) and all ranked secondary endpoints were met for upadacitinib 45 mg QD when compared with placebo.

B.2.6.1.1 Primary efficacy outcome: Clinical remission per Adapted Mayo score at Week 8

The primary efficacy endpoint (clinical remission per Adapted Mayo score compared with the placebo arm) in both U-ACHIEVE induction study Part 1 and U-ACCOMPLISH induction study Part 1 was analysed for the ITT1 population. Clinical remission was defined as SFS ≤1 and not greater than Baseline, RBS of 0, and endoscopic subscore ≤1 (see Table 8 and Table 9).

Overall population

In both U-ACHIEVE induction and U-ACCOMPLISH induction studies, upadacitinib 45 mg QD met the primary efficacy endpoint. A statistically significantly greater proportion of subjects in the upadacitinib 45 mg QD arm achieved clinical remission per Adapted Mayo score compared with the placebo arm at Week 8 (Table 22).

- U-ACHIEVE induction study:
  [redacted]
- U-ACCOMPLISH induction study:
  [redacted]

Inadequate treatment response subgroups

Analysis of clinical remission per Adapted Mayo score by prior biologic failure status demonstrated that upadacitinib 45 mg QD led to high rates of remission irrespective of prior failure on CT (non-Bio-IR) or biologics (Bio-IR) (CIs for the treatment difference between upadacitinib 45 mg QD versus placebo excluded zero in favour of the upadacitinib 45 mg dose group) at Week 8 (Table 22):

- U-ACHIEVE induction study:
  - [redacted]
- U-ACCOMPLISH induction study:
  - [redacted]

Table 22: Clinical remission per Adapted Mayo score at Week 8 in U-ACHIEVE induction and U-ACCOMPLISH induction studies– overall population and by prior treatment failure (NRI-C†) (Part 1; ITT1 population)

Endpoint, n (%)	U-ACHIEVE induction study				U-ACCOMPLISH induction study			
	UPA 45 mg QD	Placebo	Adjusted treatment diff, % (95% CI)‡	p-value‡	UPA 45 mg QD	Placebo	Adjusted treatment diff, % (95% CI)‡	p-value‡
Clinical remission per Adapted Mayo score at Week 8, n (%)								
Overall population								
	[redacted]							
Prior biologic failure								
Bio-IR	[redacted]							
Non-Bio-IR	[redacted]							

†NRI-C is non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
‡For the overall population, response rate difference based on the CMH test adjusted for baseline stratification factors. For bio subgroups, response rate difference is calculated based on normal approximation to the binomial distribution.
§Achieved statistical significance based on the pre-specified multiple testing procedure controlling the overall type I error rate at the 0.05 level.
Abbreviations: Bio-IR, biologic therapy-intolerant or inadequate responder; CI, confidence interval; CMH, Cochran Mantel-Haenszel; diff, difference; Non-Bio-IR, inadequate response, loss of response, or intolerance to conventional therapy but not failed biologic therapy; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; QD, once daily dosing; UPA, upadacitinib.

B.2.6.1.2 Ranked secondary outcomes

Secondary endpoints were ranked (see Table 7) and were analysed in a fixed-sequence multiple testing procedure in U-ACHIEVE induction study Part 1 and U-ACCOMPLISH induction study Part 1 for the ITT1 population.

B.2.6.1.2.1 Overview of secondary outcome results

Overall population

Analysis of the overall population demonstrated that upadacitinib 45 mg QD was statistically significantly superior for all ranked secondary endpoints compared with placebo, including clinical response per Adapted Mayo score at both Weeks 2 and 8. Compared with placebo, patients receiving upadacitinib 45 mg QD were significantly more likely to experience symptomatic improvement, clinical remission, endoscopic and histologic remission, and improvement in important QoL indices such as fatigue (Table 23).

Table 23: Ranked secondary efficacy endpoints at Week 2 (clinical response per Partial Adapted Mayo score only) and Week 8 (all other outcomes) in U-ACHIEVE induction and U-ACCOMPLISH induction studies – overall population (NRI-C[†]/MMRM[‡]) (Part 1; ITT1 population)

Endpoint, n (%) or LS mean	U-ACHIEVE induction study				U-ACCOMPLISH induction study			
	UPA 45 mg QD	Placebo	Adjusted treatment diff, % (95% CI)[§]	p-value	UPA 45 mg QD	Placebo	Adjusted treatment diff, % (95% CI)[§]	p-value
Endoscopic improvement at Week 8, n (%)[†]								
	[redacted]							
Endoscopic remission at Week 8, n (%)[‡]								
	[redacted]							
Clinical response per Adapted Mayo score at Week 8, n (%)[†]								
	[redacted]							
Clinical response per Partial Adapted Mayo score at Week 2, n (%)[†]								
	[redacted]							
Histologic-endoscopic mucosal improvement at Week 8, n (%)[†]								
	[redacted]							
No reported bowel urgency at Week 8, n (%)[†]								
	[redacted]							
No reported abdominal pain at Week 8, n (%)[†]								
	[redacted]							
Histologic improvement at Week 8, %[†]								
	[redacted]							
Change from Baseline in IBDQ Total score at Week 8, LS mean[‡]								
	[redacted]							
Mucosal healing at Week 8, %[†]								
	[redacted]							
Change from Baseline in FACIT-F score at Week 8, LS mean[‡]								
	[redacted]							

[†]NRI-C is non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19. [‡]MMRM approach. [§]For the overall population, response rate difference based on the CMH test adjusted for baseline stratification factors.

Abbreviations: Bio-IR, biologic therapy-intolerant or inadequate responder; CI, confidence interval; CMH, Cochran Mantel-Haenszel; diff, difference; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ, Inflammatory Bowel Disease Questionnaire; LS, least square; MMRM, mixed effect model repeated measurement; Non-Bio-IR, inadequate response, loss of response, or intolerance to conventional therapy but not failed biologic therapy; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID 19; QD, once-daily dosing; UPA, upadacitinib.

Inadequate treatment response subgroups

Analysis of key secondary endpoints by prior biologic failure demonstrated similar results to those observed for the overall population irrespective of prior failure on CT (non-Bio IR) or biologics (Bio-IR) (CIs for the treatment difference between upadacitinib 45 mg QD versus placebo excluded zero in favour of the upadacitinib 45 mg dose group) in both induction trials at Week 8 (Table 24). Patients receiving upadacitinib 45 mg QD had improvements in endoscopic assessment and disease activity, with patients more likely to experience improvements in clinical response and endoscopic remission, compared with placebo.

Table 24: Ranked secondary efficacy endpoints at Week 8 in U-ACHIEVE induction and U-ACCOMPLISH induction studies – by prior treatment failure (NRI-C†) (Part 1; ITT1 population)

Endpoint, n (%)	U-ACHIEVE induction study				U-ACCOMPLISH induction study			
	UPA 45 mg QD	Placebo	Adjusted treatment diff, % (95% CI)‡	p-value	UPA 45 mg QD	Placebo	Adjusted treatment diff, % (95% CI)‡	p-value
Endoscopic improvement at Week 8, n (%)†								
[redacted]								
[redacted]								
Endoscopic remission at Week 8, n (%)†								
[redacted]								
[redacted]								
Clinical response per Adapted Mayo score at Week 8, n (%)†								
[redacted]								
[redacted]								

†NRI-C is non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19. ‡For bio subgroups, response rate difference is calculated based on normal approximation to the binomial distribution.
Abbreviations: Bio-IR, biologic therapy-intolerant or inadequate responder; CI, confidence interval; diff, difference; Non-Bio-IR, inadequate response, loss of response, or intolerance to conventional therapy but not failed biologic therapy; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; QD, once daily dosing; UPA, upadacitinib.

Additional detailed secondary outcome results are presented in Appendix N.

B.2.6.1.3 Efficacy analysis in Part 2 of U-ACHIEVE induction and U-ACCOMPLISH induction studies at Week 16 (Extended induction)

Approximately [redacted] of patients who received upadacitinib 45 mg QD during the initial 8-week induction phase in U-ACHIEVE induction and U-ACCOMPLISH induction trials were considered eligible for extended induction with upadacitinib for a further 8 weeks. Among a total of 125 subjects who received upadacitinib 45 mg QD in U-ACHIEVE induction and U-ACCOMPLISH induction studies and did not respond, 50.8% and 45.5% subsequently achieved clinical response per Adapted Mayo score at Week 16 (ITT2 population) with an additional 8 weeks of upadacitinib 45 mg QD induction treatment, respectively, demonstrating the potential benefit of extended induction treatment. This option to extend induction treatment by a further 8 weeks in patients who have not responded to the initial 8-week course is expected to be incorporated into the SmPC.

B.2.6.1.4 Conclusion

U-ACHIEVE induction and U-ACCOMPLISH induction studies demonstrated that 8-week induction treatment with upadacitinib 45 mg QD is highly effective in patients with moderate to severely active UC, irrespective of prior biologic use. In both studies, a statistically significantly higher proportion of patients achieved clinical remission per Adapted Mayo score at Week 8 compared with placebo. Furthermore, improvements in disease activity were observed as early as Week 2 with statistically significant improvements in clinical response per Partial Adapted Mayo score at Week 2 in patients receiving upadacitinib 45 mg QD compared with placebo.

Upadacitinib 45 mg QD also provided improvements in objective measures of disease activity such as endoscopic assessment, histologic assessment, disease activity and symptoms, and QoL with 8-Week induction treatment, compared with placebo. Long-term mucosal healing has been identified as an important treatment target in patients with UC and is considered a central therapeutic goal (44). Mucosal endpoints are therefore considered clinically meaningful as they highlight objective improvements in tissue and are associated with long-term benefit (12, 54); however, achieving mucosal endpoints in an 8-week period is considered challenging. Despite this, improvements in endoscopic and histologic outcomes were observed at Week 8 following treatment with upadacitinib 45 mg QD compared with placebo, as well as improvements in important QoL indices such as fatigue.

Finally, extended induction treatment with upadacitinib 45 mg QD to Week 16 demonstrated the benefit of additional 8 weeks of induction in patients who had an inadequate response to an initial 8-week course of treatment.

B.2.6.2 U-ACHIEVE maintenance study

In U-ACHIEVE maintenance study the primary endpoint (clinical remission per Adapted Mayo score at Week 52) and all ranked secondary endpoints were met for upadacitinib 15 mg QD and upadacitinib 30 mg QD when compared with placebo.

B.2.6.2.1 Primary efficacy outcome: Clinical remission per Adapted Mayo score at Week 52

The primary efficacy endpoint (clinical remission per Adapted Mayo score at Week 52 compared with the placebo arm) of U-ACHIEVE maintenance study Cohort 1 was analysed for the ITT_A population. Clinical remission was defined as SFS ≤1 and not greater than Baseline, RBS of 0, and endoscopic subscore ≤1 (see Table 8 and Table 9).

Overall population

In U-ACHIEVE maintenance study, upadacitinib 15 mg QD and upadacitinib 30 mg QD met the primary efficacy endpoint. A statistically significantly greater proportion of subjects in the upadacitinib 15 mg QD and upadacitinib 30 mg QD arms achieved clinical remission per Adapted Mayo score compared with the placebo arm at Week 52 (Table 25):

[redacted]

Inadequate treatment response subgroups

Analysis of clinical remission per Adapted Mayo score by prior biologic failure status demonstrated that upadacitinib 15 mg QD and upadacitinib 30 mg QD led to high rates of remission irrespective of prior failure on CT (non-Bio-IR) or biologics (Bio-IR) (CIs for the treatment difference between upadacitinib 15 mg QD and upadacitinib 30 mg QD versus placebo excluded zero in favour of the upadacitinib 15 mg and upadacitinib 30 mg dose groups) at Week 52 (Table 25):

[redacted]

[redacted]

Table 25: Clinical remission per Adapted Mayo score at Week 52 in U-ACHIEVE maintenance study – overall population and by prior treatment failure (NRI-C†) (Cohort 1; ITT_A population)

Endpoint, n (%)	U-ACHIEVE maintenance study						
	UPA 15 mg QD	UPA 30 mg QD	Placebo	Adjusted treatment diff vs placebo, % (95% CI)§		p-value‡	
				UPA 15 mg QD	UPA 30 mg QD	UPA 15 mg QD	UPA 30 mg QD
Clinical remission per Adapted Mayo score at Week 52, n (%)							
[redacted]							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†NRI-C is non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
‡For the overall population, response rate difference based on the CMH test adjusted for baseline stratification factors. For bio subgroups, response rate difference is calculated based on normal approximation to the binomial distribution.
§Achieved statistical significance based on the pre-specified multiple testing procedure controlling the overall type I error rate at the 0.05 level.
Abbreviations: Bio-IR, biologic therapy-intolerant or inadequate responder; CI, confidence interval; CMH, Cochran Mantel-Haenszel; diff, difference; Non-Bio-IR, inadequate response, loss of response, or intolerance to conventional therapy but not failed biologic therapy; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; QD, once daily dosing; UPA, upadacitinib.

B.2.6.2.2 Ranked secondary outcomes

Secondary endpoints were ranked (see Table 7) and were analysed with a graphical multiplicity adjustment procedure in U-ACHIEVE maintenance study for the ITT_A population.

B.2.6.2.2.1 Overview of secondary outcome results

Overall population

Analysis of the overall population demonstrated that upadacitinib 15 mg QD and upadacitinib 30 mg QD were statistically significantly superior for all ranked secondary endpoints compared with placebo at Week 52 and demonstrated superiority for improvement in endoscopic and histologic assessment, disease activity and symptoms, and QoL (Table 26). Compared with placebo, patients receiving upadacitinib 15 mg QD and upadacitinib 30 mg QD were significantly more likely to experience symptomatic improvement, clinical remission, endoscopic and histologic remission, and improvement in important QoL indices such as fatigue.

Table 26: Ranked secondary efficacy endpoints at Week 52 in U-ACHIEVE maintenance study – overall population (NRI-C[†]/RTB-MI[‡]) (Cohort 1; ITT_A population)

Endpoint, n (%) or LS mean	U-ACHIEVE maintenance study						
	UPA 15 mg QD	UPA 30 mg QD	Placebo	Adjusted treatment diff vs placebo, % (95% CI)[§]		p-value	
				UPA 15 mg QD	UPA 30 mg QD	UPA 15 mg QD	UPA 30 mg QD
Endoscopic improvement at Week 52, n (%)[†]							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission per Adapted Mayo score at Week 52 among subjects who achieved clinical remission per Adapted Mayo score in U-ACHIEVE induction or U-ACCOMPLISH induction studies, n (%)[†]							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission per Adapted Mayo score and corticosteroid free for ≥90 days at Week 52 among subjects who achieved clinical remission per Adapted Mayo score in U-ACHIEVE induction or U-ACCOMPLISH induction studies, n (%)[†]							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endoscopic improvement at Week 52 among subjects with endoscopic improvement in U-ACHIEVE induction or U-ACCOMPLISH induction studies, n (%)[†]							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endoscopic remission at Week 52, n (%)[†]							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response per Adapted Mayo score at Week 52, n (%)[†]							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histologic-endoscopic mucosal improvement at Week 52, n (%)[†]							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline in IBDQ Total score at Week 52, LS mean[‡]							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mucosal healing at Week 52, %[†]							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No reported bowel urgency at Week 52, n (%)[†]							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No reported abdominal pain at Week 52, n (%)[†]							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Endpoint, n (%) or LS mean	U-ACHIEVE maintenance study						
	UPA 15 mg QD	UPA 30 mg QD	Placebo	Adjusted treatment diff vs placebo, % (95% CI)[§]		p-value	
				UPA 15 mg QD	UPA 30 mg QD	UPA 15 mg QD	UPA 30 mg QD
Change from Baseline in FACIT-F score at Week 52, LS mean[‡]							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[†]NRI-C is non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19. [‡]RTB-MI approach. [§]For the overall population, response rate difference based on the CMH test adjusted for baseline stratification factors.
Abbreviations: Bio-IR, biologic therapy-intolerant or inadequate responder; CI, confidence interval; CMH, Cochran Mantel-Haenszel; diff, difference; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ, Inflammatory Bowel Disease Questionnaire; LS, least square; Non-Bio-IR, inadequate response, loss of response, or intolerance to conventional therapy but not failed biologic therapy; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID 19; QD, once-daily dosing; RTB-MI, multiple imputation incorporating return to baseline; UPA, upadacitinib.

Inadequate treatment response subgroups

Analysis of key secondary endpoints by prior biologic failure demonstrated similar results to those observed for the overall population irrespective of prior failure on CT (non-Bio IR) or biologics (Bio-IR) at Week 52. The CIs for treatment differences between upadacitinib 15 mg QD and upadacitinib 30 mg QD versus placebo excluded zero in favour of the upadacitinib 15 mg and upadacitinib 30 mg dose groups for the majority of endpoints evaluated apart from three outcomes evaluated in non-Bio-IR subjects in the upadacitinib 15 mg QD arm for which upadacitinib 15 mg QD was numerically better compared with placebo (Table 27):

- Clinical remission per Adapted Mayo score at Week 52 among subjects who achieved clinical remission per Adapted Mayo score in U-ACHIEVE induction or U-ACCOMPLISH induction studies
- Clinical remission at Week 52 per Adapted Mayo score and corticosteroid free for ≥90 days among subjects in clinical remission at the end of U-ACHIEVE induction or U-ACCOMPLISH induction studies
- Mucosal healing at Week 52

Additional detailed secondary outcome results are presented in Appendix N.

Table 27: Ranked secondary efficacy endpoints at Week 52 in U-ACHIEVE maintenance study – by prior treatment failure (NRI-C[†]) (Cohort 1; ITT_A population)

Endpoint, n (%)	U-ACHIEVE maintenance study						
	UPA 15 mg QD	UPA 30 mg QD	Placebo	Adjusted treatment diff vs placebo, % (95% CI)[‡]		p-value	
				UPA 15 mg QD	UPA 30 mg QD	UPA 15 mg QD	UPA 30 mg QD
Endoscopic improvement at Week 52, n (%)[†]							
[redacted]							
[redacted]							
Clinical remission per Adapted Mayo score at Week 52 among subjects who achieved clinical remission per Adapted Mayo score in U-ACHIEVE induction or U-ACCOMPLISH induction studies, n (%)[†]							
[redacted]							
[redacted]							
Clinical remission per Adapted Mayo score and corticosteroid free for ≥90 days at Week 52 among subjects who achieved clinical remission per Adapted Mayo score in U-ACHIEVE induction or U-ACCOMPLISH induction studies, n (%)[†]							
[redacted]							
[redacted]							
Endoscopic improvement at Week 52 among subjects with endoscopic improvement in U-ACHIEVE induction or U-ACCOMPLISH induction studies, n (%)[†]							
[redacted]							
[redacted]							
Endoscopic remission at Week 52, n (%)[†]							
[redacted]							
[redacted]							
Clinical response per Adapted Mayo score at Week 52, n (%)[†]							
[redacted]							
[redacted]							

Endpoint, n (%)	U-ACHIEVE maintenance study						
	UPA 15 mg QD	UPA 30 mg QD	Placebo	Adjusted treatment diff vs placebo, % (95% CI)‡		p-value	
				UPA 15 mg QD	UPA 30 mg QD	UPA 15 mg QD	UPA 30 mg QD
Histologic-endoscopic mucosal improvement at Week 52, n (%)†							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mucosal healing at Week 52, n (%)†							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†NRI-C is non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19. ‡For bio subgroups, response rate difference is calculated based on normal approximation to the binomial distribution.
Abbreviations: Bio-IR, biologic therapy-intolerant or inadequate responder; CI, confidence interval; diff, difference; Non-Bio-IR, inadequate response, loss of response, or intolerance to conventional therapy but not failed biologic therapy; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; QD, once daily dosing; UPA, upadacitinib.

B.2.6.2.3 Conclusion

U-ACHIEVE maintenance study demonstrated that 52-week maintenance treatment with upadacitinib 15 mg QD and upadacitinib 30 mg QD is highly effective in patients with moderate to severely active UC, and in patients irrespective of prior biologic use, with a statistically significantly higher proportion of patients achieving clinical remission per Adapted Mayo score compared with placebo at Week 52. As observed with induction treatment, upadacitinib 15 mg QD and upadacitinib 30 mg QD also provided statistically significant improvements in highly stringent objective measures of disease activity such as endoscopic assessment, assessment, disease activity and symptoms, and QoL indices such as fatigue with 52-Week maintenance treatment, compared with placebo. As long-term mucosal healing has been identified as an important treatment target in patients with UC (12, 44), mucosal endpoints are therefore considered clinically meaningful as they highlight objective improvements in tissue and are associated with long-term benefit (12, 54). Improvements in endoscopic and histologic outcomes were observed at Week 52 following treatment with upadacitinib 15 mg QD and upadacitinib 30 mg QD compared with placebo. Maintenance treatment with upadacitinib 15 mg QD and upadacitinib 30 mg QD delivered sustained clinical remission and endoscopic improvement through 52 weeks, indicating that upadacitinib provides durable efficacy and that patients who enter early remission are therefore likely to maintain remission for at least 52 weeks.

Finally, upadacitinib is effective in reducing steroid use in patients with UC; a statistically significant proportion of patients receiving upadacitinib 15 mg QD or upadacitinib 30 mg QD achieved clinical remission and were corticosteroid free for ≥90 days. Reduction in steroid use is considered important for patients and their QoL as steroids are associated with several AEs, including risk of serious infection (55).

B.2.7 Subgroup analysis

Across the upadacitinib induction and maintenance studies, several pre-planned subgroup analyses of the primary efficacy outcome (clinical remission per Adapted Mayo score) were conducted to assess treatment differences between pre-specified subgroups (Table 28). Apart from Bio-IR status, these pre-planned subgroups are not used in the model (see Section B.3), and so have not been described in detail in the submission.

A summary of the subgroup analyses results is provided in Appendix E.

Table 28: Pre-planned subgroup analyses in U-ACHIEVE induction, U-ACCOMPLISH induction, and U-ACHIEVE maintenance studies

Analysis	U-ACHIEVE induction study	U-ACCOMPLISH induction study	U-ACHIEVE maintenance study
Pre-planned subgroups	• Sex (male, female) • Age (≤ median, > median) • Race (white, non-white) • Bio-IR status (Bio-IR, non-Bio-IR) • Baseline corticosteroid use (yes, no) • Baseline Adapted Mayo score (≤7, >7) • Baseline Full Mayo score (≤9, >9) • Prior TNF-α exposure (yes, no) for non-Bio-IR • Prior biological therapy exposure (yes, no) for non-Bio-IR • Baseline weight (≥ median, > median) • Pancolitis at baseline (yes, no) • Disease duration at baseline (≥ median, > median) • Baseline hs-CRP (≥5 mg/mL and >5 mg/mL) • Region (US versus non-US)		As per U-ACHIEVE induction and U-ACCOMPLISH induction studies plus: • Baseline aminosalicylate use (yes, no)

Abbreviations: Bio-IR, biologic therapy-intolerant or inadequate responder; hs-CRP, high sensitivity C-reactive protein; non-Bio-IR, inadequate response, loss of response, or intolerance to conventional therapy but not failed biologic therapy; TNF-α, tumour necrosis factor-alpha; US, United States.

B.2.8 Meta-analysis

U-ACHIEVE induction, U-ACCOMPLISH induction, and U-ACHIEVE maintenance studies all provide placebo-controlled estimates of upadacitinib effectiveness. All three trials have been incorporated into a network meta-analysis (NMA) to enable generation of relative treatment effects versus relevant comparators, as described in Section B.2.9.

B.2.9 Indirect and mixed treatment comparisons

Please note: The following populations are used in the submission from this point forward:

- Bio-naïve: Patients that have had no previous exposure to biologic therapies (considered equivalent to the non-Bio-IR population of the upadacitinib trials)†
- Bio-exposed: Patients who had an inadequate response or intolerance to CT or a biologic treatment, and those who have received biologic therapy in the past but stopped therapy based on reasons other than inadequate response or intolerance (considered equivalent to the Bio-IR population of the upadacitinib trials)†

To keep the NMA comparable with previous trial populations, patient-level data from the upadacitinib trials was used to separate the patients into the bio-naïve and bio-exposed cohorts.

†In the upadacitinib trials (Section B.2.3) the non-Bio-IR population is considered equivalent to the bio-naïve population; only 2% of the non-Bio-IR population had previously been exposed to a biologic treatment.

Full Mayo score and adapted Mayo score have been used to assess clinical outcomes, the NMA includes both and details on outcomes and definitions can be found in Appendix D.1.3.1.2 and Appendix D.1.3.1.3.1.

B.2.9.1 Analysis scope

In the absence of head-to-head randomised controlled trials (RCTs) between all comparators specified in the NICE scope, network meta-analyses (NMAs) were performed to assess the relative efficacy of upadacitinib compared with the relevant comparators (adalimumab, infliximab, golimumab, tofacitinib, ustekinumab, vedolizumab) in adults with moderately to severely active UC who have had an inadequate response, loss of response or were intolerant to either CT or a biologic agent. The methodology of the systematic literature review (SLR) that identified studies used in the NMAs is described in Appendix D.

B.2.9.2 Study selection for the NMA

As described in Appendix D, a total of 293 records met the inclusion criteria of the global clinical SLR, reporting on 48 original studies. After applying the inclusion/exclusion criteria (outlined in Appendix D), 20 unique trials reported by 46 records were included for analysis in the NMA. A list of all studies excluded from the NMA (including reason for exclusion) is available in Appendix D.

The interventions and doses of interest included in the NMAs for the induction and maintenance phases are presented in Appendix D. For each of the interventions included in the NMAs, only licensed doses were included in the analysis. However, a maintenance dose of 10 mg/kg infliximab (unlicensed) was included, with the rationale for its inclusion presented in Appendix D. A summary of the trials used to conduct the NMA is presented in Table 29.

Table 29: Summary of the trials used to carry out the NMA

Study	Phase	UC severity	Bio-experience	Asian study population	Induction Phase			Maintenance Phase						Primary (bolded) and secondary publication(s)
					Duration (weeks)	Total N	Included regimen(s) (+PBO)	RCT design	Induction treatment	Induction status	Duration (weeks)	Total N	Included regimen(s) (+PBO)	
ACT-1 (NCT00036439)	3	FM6/12; EMS2	Naïve		8	364	IFX10 IFX5	TT	IFX10 IFX5 PBO	All	46	364	IFX10 IFX5	**Rutgeerts 2005 (56)**
ACT-2 (NCT00096655)	3	FM6/12; EMS2	Naïve		8	364	IFX10 IFX5	*Excluded: Duration <40 weeks*						
Japic CTI-060298	3	FM6/12; EMS2	Naïve	X	8	208	IFX5	*Excluded: Duration <40 weeks*						**Kobayashi 2016 (57)**
Jiang 2015	NR	FM6/12; EMS2	Naïve	X	8	123	IFX5 (IFX3.5 excluded)	*Excluded: Duration <40 weeks*						**Jiang 2015 (58)**
NCT01551290	3	FM6/12; EMS2	Naïve	X	8	99	IFX5	*Excluded: Duration <40 weeks*						**REMICADEUCO3001 CSR (59)**
ULTRA-1 (NCT00385736)	3	FM6/12; EMS2	Naïve		8	390	ADA160/80 (ADA80/40 excluded)	*No maintenance*						**Reinisch 2011 (60)**
ULTRA-2 (NCT00408629)	3	FM6/12; EMS2	Mixed		8	518	ADA160/80	TT	ADA160/80 PBO	All	44	518	ADA40Q2W	**Sandborn 2012 (61);** Ghosh 2013 (62); Colombel 2013; Sandborn 2011 (63); D'Haens 2012 (64); Sandborn 2013 (65); Panaccione 2015 (66)
M10-447 (NCT00853099)	2/3	FM6/12; EMS2	Naïve	X	8	274	ADA160/80 (ADA80/40 excluded)	TT	ADA160/80 ADA80/40 PBO	All	44	274	ADA40Q2W (ADA160/80 and ADA80/40 combined)	**Suzuki 2014 (67)**
SERENE-UC (NCT02065622)	3	FM6/12; EMS2	Mixed		*Excluded: Intervention ADA HIR*			RR	ADA HIR ADA160/80	All (efficacy evaluated in FM responders)	44	371	ADA40Q2W ADA40QW (ADA TDM excluded; no PBO)	**Panes 2019 (68)**; Colombel 2020 (47)
PURSUIT-J (NCT01863771)	3	FM6/12; EMS2	Naïve	X	*Excluded: Open-label*			RR	GOL200/100	FM response	54	63	GOL100	**Hibi 2017 (69)**
PURSUIT-M (NCT00488631)	3	FM6/12; EMS2	Naïve		*Induction in PURSUIT-SC*			RR	GOL400/200 GOL200/100	FM response	54	464	GOL100 GOL50	**Sandborn 2014a (70)**
PURSUIT-SC (NCT00487539)	3	FM6/12; EMS2	Naïve		6	774	GOL200/100 (GOL400/200 excluded)	*Maintenance in PURSUIT-M*						**Sandborn 2014b (71)**
GEMINI 1 (NCT00783718)	3	FM6/12; EMS2	Mixed		6	374	VEZ300	RR	VED300	FM response	46	373	VED300Q8W VED300Q4W	**Feagan 2013 (72);** Sandborn 2019 (73); Feagan 2017 (74)
NCT02039505	3	FM6/12;	Mixed	X	10	246	VED300	RR	VED300	FM	50	83	VED300Q8W	**Motoya 2019 (75);** Nagahori 2021

Study	Phase	UC severity	Bio-experience	Asian study population	Induction Phase			Maintenance Phase						Primary (bolded) and secondary publication(s)
					Duration (weeks)	Total N	Included regimen(s) (+PBO)	RCT design	Induction treatment	Induction status	Duration (weeks)	Total N	Included regimen(s) (+PBO)	
		EMS2								response				(76)
UNIFI (NCT02407236)	3	FM6/12; EMS2	Mixed		8	961	UST6 (UST130 excluded)	RR	UST130 UST6	FM response	44	523	UST90Q12W UST90Q8W	**Sands 2019 (39);** Van Assche 2019 (77); Sands 2019 (78); Alcala 2020 (79); Danese 2019 (80); Panaccione 2019 (81)
OCTAVE 1 (NCT01465763)	3	FM6/12; EMS2; RBS1	Mixed		8	598	TOF10	*Maintenance in OCTAVE Sustain*						**Sandborn 2017 (82);** Lichtenstein 2019 (83); Dubinsky 2017 (84); Sandborn 2020 (85); Sandborn 2021 (86); D'Haens 2016 (87); Hanauer 2019 (88); Chiorean 2018 (89); Danese 2017 (90); Sands 2021 (91); Vavricka 2021 (92); Reinisch 2019 (93); Feagan 2017 (94); Lichtenstein 2019 (95); Hudesman 2021 (96)
OCTAVE 2 (NCT01458951)	3	FM6/12; EMS2; RBS1	Mixed		8	541	TOF10	*Maintenance in OCTAVE Sustain*						
OCTAVE Sustain (NCT01458574)	3	FM6/12; EMS2; RBS1	Mixed		*Induction in OCTAVE 1 and OCTAVE 2*			RR	TOF10 TOF15 PBO	FM response	52	593	TOF10 TOF5	
U-ACCOMPLISH (NCT03653026)	3	AFM5/9; EMS2	Mixed		8	522	UPA45	*Induction in U-ACHIEVE Study 3*						**CSR Tables**
U-ACHIEVE Study 2, 3 (NCT02819635)	3	AFM5/9; EMS2	Mixed		8	474	UPA45	RR	UPA45	AM response	52	451	UPA30 UPA15	**CSR Tables**

Abbreviations: ADA, adalimumab; AFM, abbreviated full Mayo score; AMS, adapted Mayo score; AM response, decrease in AMS ≥2 points and ≥30% from baseline, and a decrease in RBS ≥1 or an absolute RBS ≤1; AM2 remission, SFS≤1 and ≥1-point decrease from baseline, RBS=0, and EMS≤1; EMS, endoscopic Mayo subscore; EMS2, EMS≥2; FMS, full Mayo score; FM response, decrease in FMS ≥3 points and ≥30% from baseline, and a decrease in RBS ≥1 or an absolute RBS ≤1; GOL, golimumab; HIR, higher induction dosing regimen; IFX, infliximab; NMA, network meta-analysis; NR, not reported; PBO, placebo; PGA, physician's global assessment subscore; PGA2, PGA≥2; RBS, rectal bleeding subscore; RBS1, RBS≥1; RCT, randomised clinical trial; RR, re-randomised responder; SFS, stool frequency subscore; SFS1, SFS≥1; TDM, therapeutic drug monitoring; TOF, tofacitinib; TT, treat-through; UC, ulcerative colitis; UST, ustekinumab; VED, vedolizumab.

The outcomes of interest for the NMA included clinical remission (Full Mayo score [FMS] ≤2 with no subscore >1), clinical response (decrease from baseline in FMS ≥3 points and ≥30%, accompanied by a decrease in rectal bleeding subscore [RBS] of ≥1 or an absolute RBS ≤1), discontinuation due to adverse events (AEs), serious adverse events (SAEs) and serious infections (see Appendix D for more details). In general, outcomes were assessed after an induction phase of 6 to 10 weeks and a maintenance phase of 40 to 54 weeks (see Appendix D for more details). An overview of the studies which reported the efficacy and safety outcomes used in the NMA is presented in Table 30, Table 31, and Table 32.

Table 30: Trials reporting clinical remission outcomes used in the NMA

Treatment population	Bio-naïve		Bio-exposed	
Treatment phase	**Induction**	**Maintenance**	**Induction**	**Maintenance**
Studies reporting clinical remission	• ACT-1 (NCT00036439) • ACT-2 (NCT00096655) • GEMINI 1 (NCT00783718) • Japic CTI-060298 • Jiang 2015 • M10-447 (NCT00853099) • NCT01551290 • NCT02039505 • OCTAVE 1 (NCT01465763) • OCTAVE 2 (NCT01458951) • PURSUIT-SC (NCT0048753) • U-ACCOMPLISH (Study M14-675; NCT03653026) • U-ACHIEVE Study 2 (Study M14-234; NCT02819635) • ULTRA-1 (NCT00385736) • ULTRA-2 (NCT00408629) • UNIFI (NCT02407236)	• ACT-1 (NCT00036439) • GEMINI 1 (NCT00783718) • NCT02039505 • PURSUIT-J (NCT01863771) • PURSUIT-M (NCT00488631) • U-ACHIEVE Study 3 (Study M14-234; NCT02819635) • ULTRA-2 (NCT00408629) • UNIFI (NCT02407236)	• NCT02039505 • OCTAVE 1 (NCT01465763) • OCTAVE 2 (NCT01458951) • U-ACCOMPLISH (Study M14-675; NCT03653026) • U-ACHIEVE Study 2 (Study M14-234; NCT02819635) • ULTRA-2 (NCT00408629) • UNIFI (NCT02407236)	• NCT02039505 • U-ACHIEVE Study 3 (Study M14-234; NCT02819635) • ULTRA-2 (NCT00408629) • UNIFI (NCT02407236)

Abbreviations: NMA, network meta-analysis.

Table 31: Trials reporting clinical response outcomes used in the NMA

Treatment population	Bio-naïve		Bio-exposed	
Treatment	**Induction**	**Maintenance**	**Induction**	**Maintenance**

Treatment population	Bio-naïve		Bio-exposed	
phase				
Studies reporting clinical response	• ACT-1 (NCT00036439) • ACT-2 (NCT00096655) • GEMINI 1 (NCT00783718) • Japic CTI-060298 • Jiang 2015 • M10-447 (NCT00853099) • NCT01551290 • NCT02039505 • OCTAVE 1 (NCT01465763) • OCTAVE 2 (NCT01458951) • PURSUIT-SC (NCT0048753) • U-ACCOMPLISH (Study M14-675; NCT03653026) • U-ACHIEVE Study 2 (Study M14-234; NCT02819635) • ULTRA-1 (NCT00385736) • ULTRA-2 (NCT00408629) • UNIFI (NCT02407236)	• ACT-1 (NCT00036439) • GEMINI 1 (NCT00783718) • NCT02039505 • PURSUIT-J (NCT01863771) • PURSUIT-M (NCT00488631) • U-ACHIEVE Study 3 (Study M14-234; NCT02819635) • ULTRA-2 (NCT00408629) • UNIFI (NCT02407236)	• NCT02039505 • OCTAVE 1 (NCT01465763) • OCTAVE 2 (NCT01458951) • U-ACCOMPLISH (Study M14-675; NCT03653026) • U-ACHIEVE Study 2 (Study M14-234; NCT02819635) • ULTRA-2 (NCT00408629)	• NCT02039505 • U-ACHIEVE Study 3 (Study M14-234; NCT02819635) • ULTRA-2 (NCT00408629)

Abbreviations: NMA, network meta-analysis.

Table 32: Trials reporting serious infection outcomes used in the NMA

Treatment phase	Induction	Maintenance
Studies reporting serious infections	• GEMINI 1 (NCT00783718) • Japic CTI-060298 • M10-447 (NCT00853099) • NCT02039505 • OCTAVE 1 (NCT01465763) • OCTAVE 2 (NCT01458951) • PURSUIT-SC (NCT00487539) • U-ACCOMPLISH • (Study M14-675; NCT03653026) • U-ACHIEVE Study 2 • (Study M14-234; NCT02819635) • ULTRA-1 (NCT00385736) • ULTRA-2 (NCT00408629) • UNIFI (NCT02407236)	• ACT-1 (NCT00036439) • GEMINI 1 (NCT00783718) • NCT02039505 • OCTAVE Sustain (NCT01458574) • PURSUIT-M (NCT00488631) • SERENE-UC (NCT02065622) • U-ACHIEVE Study 3 (Study M14-234; NCT02819635) • ULTRA-2 (NCT00408629) • UNIFI (NCT02407236)

Abbreviations: NMA, network meta-analysis.

B.2.9.3 Summary of trials included in the NMA

A summary of the trials included in the NMAs is presented in Table 29, for a full description of each included trial see Appendix D. The reporting of outcomes from each study considered for inclusion is also detailed in Appendix D.

B.2.9.4 Overview of NMA methodology

A Bayesian NMA approach was used, with the NMA developed based on methods considered valid by NICE (see Appendix D for further details). For each feasible network, NMAs were conducted in a Generalised Linear Model (GLM) framework using Bayesian Markov Chain Monte Carlo (MCMC) simulations and three chains with 100,000 runs each, with a burn-in that was half of the convergence sequence (set size of 10,000). Convergence was assessed with the Brooks-Gelman-Rubin method using the Potential Scale Reduction Factor (PSRF). All binary response outcomes were modelled with a binomial likelihood and logit link function. The feasibility of the NMAs based on the included RCTs was assessed as described in Cope et al. (2014) (97) (see Appendix D for further details).

Two different maintenance study designs (specifically treat-through and re-randomised responder designs) were used in the UC studies identified for the NMA. Consequently, a standard NMA for maintenance outcomes is inappropriate. To make outcomes between studies with different designs more comparable, the data from studies with a treat-through design were re-calculated to mimic a re-randomised responder study design (see Appendix D for further details). Model selections were made after comparing the fit statistics, leverage plots, and density plots of posterior standard deviation (SD) for each set of four possible models: fixed effects (FE), fixed effects with baseline-risk adjustment (FEA), random effects (RE), and random effects with baseline-risk adjustment (REA) (see Appendix D for model details). An RE model was selected as base-case to account for the expected heterogeneity in outcomes, study design, and study populations across included studies in the NMA. A baseline risk-adjusted version of the RE model was performed to adjust for differences in mean placebo effects across studies.

For each combination of outcome and NMA, the following results are presented:

- Relative effect estimates of each intervention versus placebo

- Surface under the cumulative ranking curve (SUCRA) values for each treatment
- Predicted absolute outcomes for each treatment

Full details of the methodology for the NMAs are provided in Appendix D.

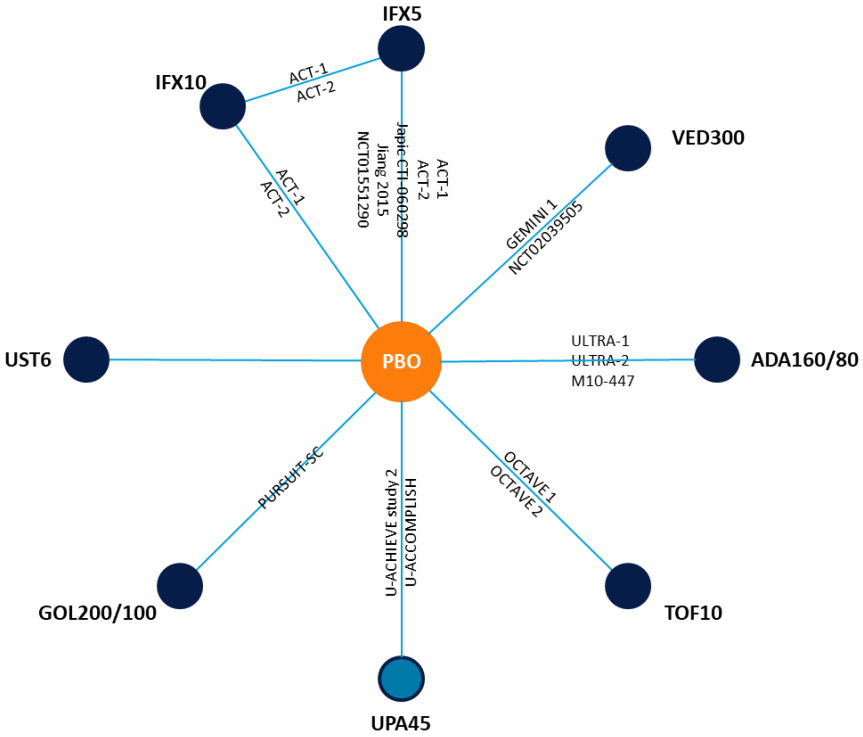
B.2.9.5 Network diagrams

The treatment networks for the studies included in the base case analyses for the bio-naïve and bio-exposed populations are presented in the following sections. In all networks, placebo was included as the common comparator.

B.2.9.5.1 Induction phase

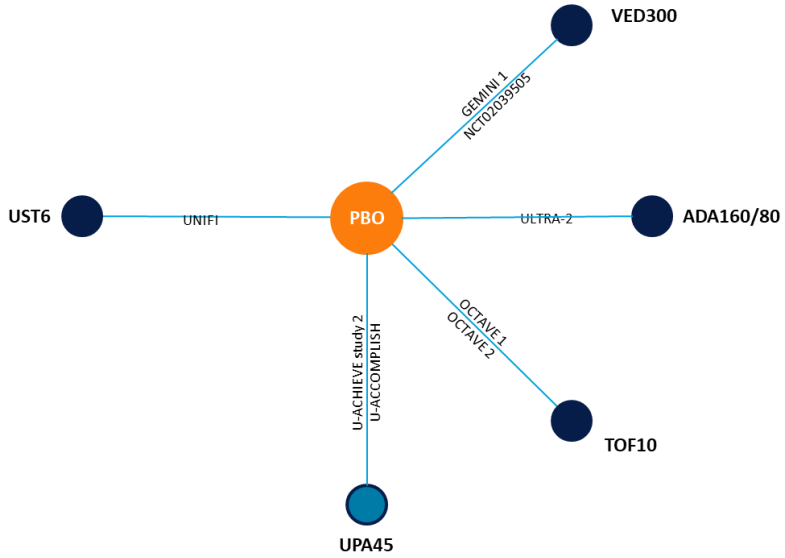
The same network was used for clinical remission and clinical response in the induction phase and is presented for both outcomes in Figure 4 for the bio-naïve population and in Figure 5 for the bio-exposed population.

Figure 4: Network plot for clinical remission and clinical response in bio-naïve induction NMA



Abbreviations: ADA, adalimumab; GOL, golimumab; IFX, infliximab; PBO, placebo; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Figure 5: Network plot for clinical remission and clinical response in bio-exposed induction NMA

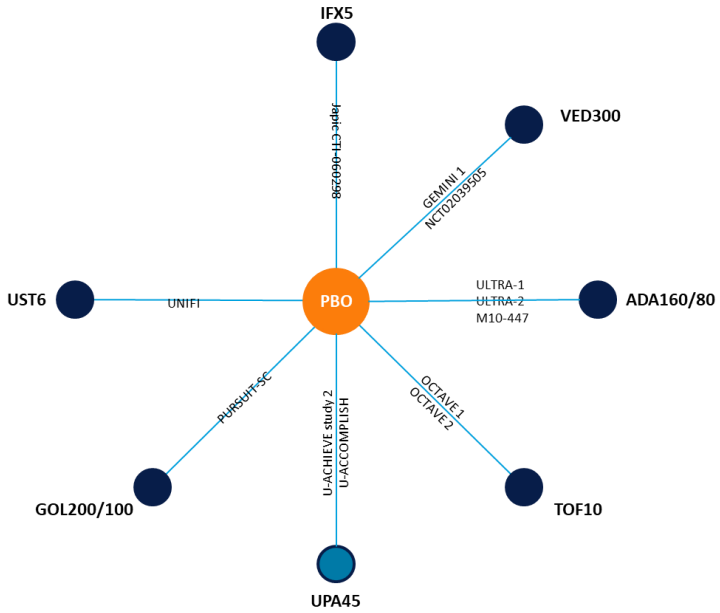


Abbreviations: ADA, adalimumab; PBO, placebo; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Serious infections – overall population

The network diagram for serious infections in the induction phase is presented in Figure 6.

Figure 6: Network plot for serious infections in overall induction NMA

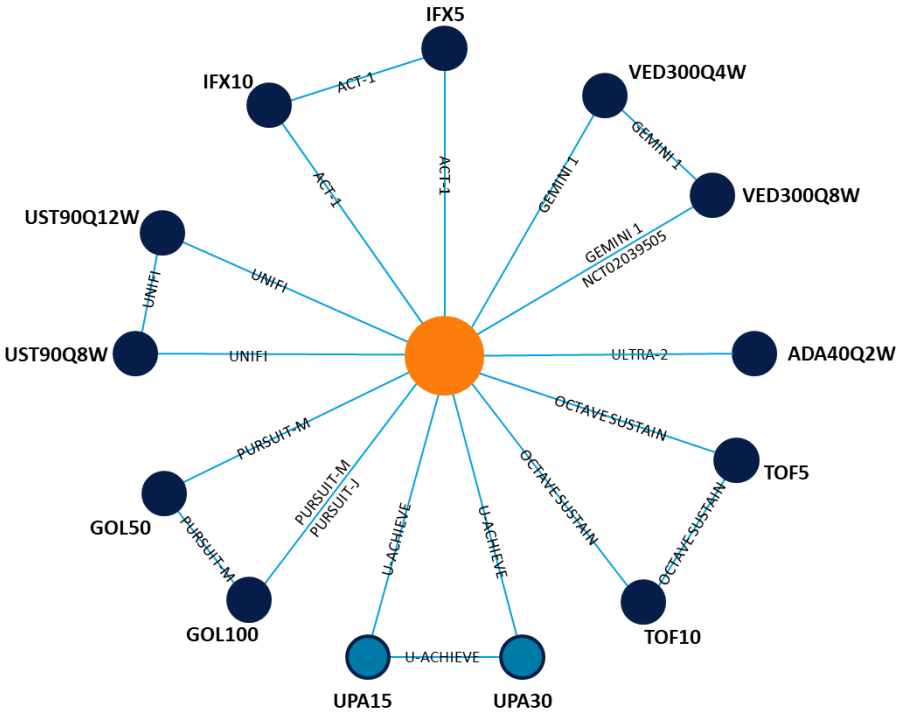


Abbreviations: ADA, adalimumab; GOL, golimumab; IFX, infliximab; PBO, placebo; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.2.9.5.2 Maintenance phase

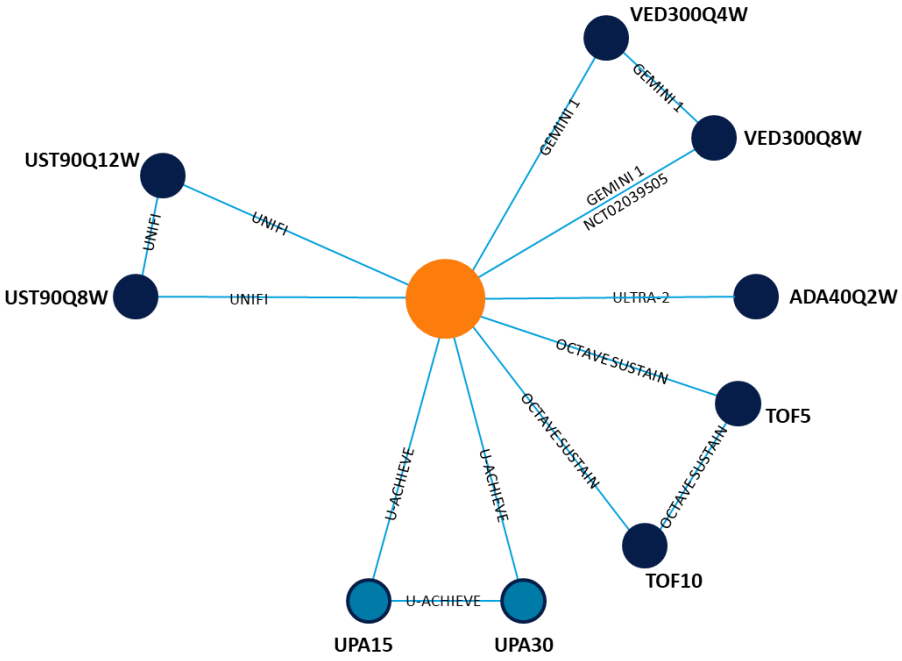
The same network was used for clinical remission and clinical response in the maintenance phase and is presented for both outcomes in Figure 7 for the bio-naïve population and in Figure 8 for the bio-exposed population.

Figure 7: Network plot for clinical response and remission in bio-naïve maintenance NMA



Abbreviations: ADA, adalimumab; GOL, golimumab; IFX, infliximab; PBO, placebo; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Figure 8: Network plot for clinical response and remission in bio-exposed maintenance NMA



Abbreviations: ADA, adalimumab; PBO, placebo; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.2.9.6 Results

B.2.9.6.1 Base-case analyses

Model fit statistics determined the selection between FE and RE models; all else equal, the RE model was selected over the FE model. Therefore, for all analyses presented in this section, aside from one, the RE results have been selected. The one exception was the clinical response in the bio-naïve population in induction, where the FEA model results were presented.

Induction phase – clinical remission

The base-case NMA clinical remission results for induction with upadacitinib versus comparators in the bio-naïve and bio-exposed populations are presented in Table 33 and Table 34, respectively (upadacitinib results are presented in bold).

In the bio-naïve population (Table 33), all comparators were statistically superior to placebo on the outcome of clinical remission, except for adalimumab and ustekinumab. Upadacitinib was associated with the highest predicted probability of clinical remission ([redacted] compared with [redacted] for the next best treatment, infliximab 5 mg/kg). Upadacitinib was associated with the highest SUCRA score ([redacted]) and was statistically superior to placebo and adalimumab.

Table 33: Results for clinical remission in bio-naïve induction NMA (RE model)

Treatment	Odds ratio vs. PBO Median (95% CrI)	SUCRA score	Predicted absolute outcome rate, median (95% CrI)
UPA45	[redacted]	[redacted]	[redacted]
IFX5	[redacted]	[redacted]	[redacted]
VED300	[redacted]	[redacted]	[redacted]
GOL200/100	[redacted]	[redacted]	[redacted]
IFX10	[redacted]	[redacted]	[redacted]
TOF10	[redacted]	[redacted]	[redacted]
UST6	[redacted]	[redacted]	[redacted]
ADA160/80	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ADA160/80, adalimumab 160/80 mg induction; CrI, credible interval; GOL200/100, golimumab 200/100 mg induction; IFX5/IFX10, infliximab 5 mg/kg body weight/10 mg/kg body weight; PBO, placebo; RE, random effects; SUCRA, surface under the cumulative ranking curve; TOF10, tofacitinib 10 mg; UPA45, upadacitinib 45 mg; UST6, ustekinumab 6 mg/kg body weight; VED300, vedolizumab 300 mg.

In the bio-exposed population (Table 34), upadacitinib was again associated with the highest probability of clinical remission ([redacted]% compared with [redacted]% for the next best treatment, ustekinumab). Upadacitinib was associated with the highest SUCRA score ([redacted]%) and was statistically superior to placebo.

Table 34: Results for clinical remission in bio-exposed induction NMA (RE model)

Treatment	Odds ratio vs. PBO Median (95% CrI)	SUCRA score	Predicted absolute outcome rate, median (95% CrI)
UPA45	[redacted]	[redacted]	[redacted]
UST6	[redacted]	[redacted]	[redacted]
TOF10	[redacted]	[redacted]	[redacted]
VED300	[redacted]	[redacted]	[redacted]
ADA160/80	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ADA160/80, adalimumab 160/80 mg induction; CrI, credible interval; PBO, placebo; RE, random effects; SUCRA, surface under the cumulative ranking curve; TOF10, tofacitinib 10 mg; UPA45, upadacitinib 45 mg; UST6, ustekinumab 6 mg/kg body weight; VED300, vedolizumab 300 mg.

Induction phase – clinical response

The base-case NMA clinical response results for induction with upadacitinib versus comparators in the bio-naïve and bio-exposed populations are presented in Table 35 and Table 36, respectively (upadacitinib results are presented in bold).

In the bio-naïve population (Table 35), all comparators were statistically superior to placebo on the outcome of clinical response. Upadacitinib was associated with the highest predicted probability of clinical response ([redacted]% compared with [redacted]% for the next best treatment, ustekinumab). Upadacitinib was associated with the highest SUCRA score ([redacted]%) and was statistically superior to all comparators apart from ustekinumab.

Table 35: Results for clinical response in bio-naïve induction NMA (FEA model)

Treatment	Odds ratio vs. PBO Median (95% CrI)	SUCRA score	Predicted absolute outcome rate, median (95% CrI)
UPA45	[redacted]	[redacted]	[redacted]
UST6	[redacted]	[redacted]	[redacted]
IFX10	[redacted]	[redacted]	[redacted]
IFX5	[redacted]	[redacted]	[redacted]
TOF10	[redacted]	[redacted]	[redacted]
ADA160/80	[redacted]	[redacted]	[redacted]
VED300	[redacted]	[redacted]	[redacted]
GOL200/100	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ADA160/80, adalimumab 160/80 mg induction; CrI, credible interval; FEA, fixed effects with baseline-risk adjustment; GOL200/100, golimumab 200/100 mg induction; IFX5/IFX10, infliximab 5 mg/kg body weight/10 mg/kg body weight; PBO, placebo; SUCRA, surface under the cumulative ranking curve; TOF10, tofacitinib 10 mg; UPA45, upadacitinib 45 mg; UST6, ustekinumab 6 mg/kg body weight; VED300, vedolizumab 300 mg.

In the bio-exposed population (Table 36), upadacitinib was associated with the highest predicted probability of clinical response ([redacted]% compared with [redacted]% for the next best treatment, tofacitinib). Upadacitinib was associated with a SUCRA score of [redacted]% and was statistically superior to placebo, adalimumab, and vedolizumab.

Table 36: Results for clinical response in bio-exposed induction NMA (RE model)

Treatment	Odds ratio vs. PBO Median (95% CrI)	SUCRA score	Predicted absolute outcome rate Median (95% CrI)
UPA45	[redacted]	[redacted]	[redacted]
TOF10	[redacted]	[redacted]	[redacted]
UST6	[redacted]	[redacted]	[redacted]
VED300	[redacted]	[redacted]	[redacted]

Treatment	Odds ratio vs. PBO Median (95% CrI)	SUCRA score	Predicted absolute outcome rate Median (95% CrI)
ADA160/80	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ADA160/80, adalimumab 160/80 mg induction; CrI, credible interval; PBO, placebo; RE, random effects; SUCRA, surface under the cumulative ranking curve; TOF10, tofacitinib 10 mg; UPA45, upadacitinib 45 mg; UST6, ustekinumab 6 mg/kg body weight; VED300, vedolizumab 300 mg.

Induction phase – serious infections

Table 37 presents the base-case NMA serious infection results for upadacitinib versus comparators in an overall induction population, ranked from low to high (upadacitinib results are presented in bold).

The predicted probability of serious infections was low in all active treatment arms (≤1%). Upadacitinib was associated with a probability of serious infections of [redacted]% and a SUCRA score of [redacted]%. Golimumab and ustekinumab were associated with the lowest probability of serious infection ([redacted]%).

Table 37: Results for serious infections in overall induction NMA (RE model)

Treatment	Odds ratio vs. PBO Median (95% CrI)	SUCRA score	Predicted absolute outcome rate, median (95% CrI)
GOL200/100	[redacted]	[redacted]	[redacted]
UST6	[redacted]	[redacted]	[redacted]
VED300	[redacted]	[redacted]	[redacted]
IFX5	[redacted]	[redacted]	[redacted]
TOF10	[redacted]	[redacted]	[redacted]
UPA45	[redacted]	[redacted]	[redacted]
ADA160/80	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ADA160/80, adalimumab 160/80 mg induction; CrI, credible interval; GOL200/100, golimumab 200/100 mg induction); IFX5, infliximab 5 mg/kg body weight; PBO, placebo; RE, random effects; SUCRA, surface under the cumulative ranking curve; TOF10, tofacitinib 10 mg; UPA45, upadacitinib 45 mg; UST6, ustekinumab 6 mg/kg body weight; VED300, vedolizumab 300 mg.

Maintenance phase – clinical remission

The base-case NMA clinical remission results for maintenance with upadacitinib versus comparators in the bio-naïve and bio-exposed populations are presented in Table 38 and Table 39, respectively (upadacitinib results are presented in bold).

In the bio-naïve population, upadacitinib 15 mg and upadacitinib 30 mg were associated with probabilities of clinical remission of [redacted]% and [redacted]%, and a SUCRA ranking of 6 and 3 out of 14, respectively (Table 38). Tofacitinib was associated with the highest probability of clinical remission during maintenance in the bio-naïve population with a probability of [redacted]% for the 10 mg/kg regimen.

Table 38: Results for clinical remission in bio-naïve maintenance NMA (RE model)

Treatment	Odds ratio vs. PBO Median (95% CrI)	SUCRA score	Predicted absolute outcome rate, median (95% CrI)
TOF10	[redacted]	[redacted]	[redacted]
TOF5	[redacted]	[redacted]	[redacted]
UPA30	[redacted]	[redacted]	[redacted]
VED300Q4W	[redacted]	[redacted]	[redacted]
VED300Q8W	[redacted]	[redacted]	[redacted]
UPA15	[redacted]	[redacted]	[redacted]
GOL100	[redacted]	[redacted]	[redacted]
GOL50	[redacted]	[redacted]	[redacted]
UST90Q8W	[redacted]	[redacted]	[redacted]
UST90Q12W	[redacted]	[redacted]	[redacted]
IFX10	[redacted]	[redacted]	[redacted]
IFX5	[redacted]	[redacted]	[redacted]
ADA40Q2W	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ADA40Q2W, adalimumab 40 mg every other week; CrI, credible interval; GOL50/GOL100, golimumab 50 mg/100 mg; IFX5/IFX10, infliximab 5 mg/kg body weight/10 mg/kg body weight; PBO, placebo; RE, random effects; SUCRA, surface under the cumulative ranking curve; TOF5/TOF10, tofacitinib 5 mg/10 mg; UPA15 or UPA30, upadacitinib 15 mg/30 mg; UST90Q8W/UST90Q12W, ustekinumab 90 mg every 8 weeks/every 12 weeks; VED300QW/VED300Q8W, vedolizumab 300 mg every 4 weeks/every 8 weeks.

In the bio-exposed population, upadacitinib 15 mg and upadacitinib 30 mg were associated with probabilities of clinical remission of [redacted]% and [redacted]%, respectively, and were ranked highest in terms of SUCRA score (Table 39). The next best treatment (vedolizumab Q8W) was associated with a probability of clinical remission of [redacted]%. Upadacitinib 15 mg and upadacitinib 30 mg were both statistically superior to placebo, as were vedolizumab (Q4W and Q8W), tofacitinib 10 mg/kg, and ustekinumab Q8W.

Adalimumab, tofacitinib 5 mg/kg and ustekinumab Q12W were not statistically superior to placebo.

Table 39: Results for clinical remission in bio-exposed maintenance NMA (RE model)

Treatment	Odds ratio vs. PBO Median (95% CrI)	SUCRA score	Predicted absolute outcome rate, median (95% CrI)
UPA30	[redacted]	[redacted]	[redacted]
UPA15	[redacted]	[redacted]	[redacted]
VED300Q8W	[redacted]	[redacted]	[redacted]
VED300Q4W	[redacted]	[redacted]	[redacted]
TOF10	[redacted]	[redacted]	[redacted]
UST90Q8W	[redacted]	[redacted]	[redacted]
ADA40Q2W	[redacted]	[redacted]	[redacted]
TOF5	[redacted]	[redacted]	[redacted]
UST90Q12W	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ADA40Q2W, adalimumab 40 mg every other week; CrI, credible interval; PBO, placebo; RE, random effects; SUCRA, surface under the cumulative ranking curve; TOF5/TOF10, tofacitinib 5 mg/10 mg; UPA15 or UPA30, upadacitinib 15 mg/30mg; UST90Q8W/UST90Q12W, ustekinumab 90 mg every 8 weeks/every 12 weeks; VED300Q4W/VED300Q8W, vedolizumab 300 mg every 4 weeks/every 8 weeks.

Maintenance phase – clinical response

The base-case NMA clinical response results for maintenance with upadacitinib versus comparators in the bio-naïve and bio-exposed populations are presented in Table 40 and Table 41, respectively (upadacitinib results are presented in bold).

In the bio-naïve population, upadacitinib 15 mg and upadacitinib 30 mg were associated with predicted probabilities of clinical response of [redacted]% and [redacted]%, respectively, and were both statistically superior to placebo (Table 40). Most comparators were also statistically significant to placebo, except for infliximab (5 mg/kg and 10 mg/kg regimens) and adalimumab. Upadacitinib 30 mg ranked highest of all treatment in terms of SUCRA score ([redacted]%), while upadacitinib 15 mg raked fourth of 14 with a SUCRA score of [redacted]%.

Table 40: Results for clinical response in bio-naïve maintenance NMA (RE model)

Treatment	Odds ratio vs. PBO Median (95% CrI)	SUCRA score	Predicted absolute outcome rate, median (95% CrI)
UPA30	[redacted]	[redacted]	[redacted]
TOF10	[redacted]	[redacted]	[redacted]
VED300Q8W	[redacted]	[redacted]	[redacted]
UPA15	[redacted]	[redacted]	[redacted]
TOF5	[redacted]	[redacted]	[redacted]
VED300Q4W	[redacted]	[redacted]	[redacted]
UST90Q8W	[redacted]	[redacted]	[redacted]
UST90Q12W	[redacted]	[redacted]	[redacted]
GOL100	[redacted]	[redacted]	[redacted]
IFX10	[redacted]	[redacted]	[redacted]
GOL50	[redacted]	[redacted]	[redacted]
IFX5	[redacted]	[redacted]	[redacted]
ADA40Q2W	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ADA40Q2W, adalimumab 40 mg every other week; CrI, credible interval; GOL50/GOL100, golimumab 50 mg/100 mg; IFX5/IFX10, infliximab 5 mg/kg body weight/10 mg/kg body weight; PBO, placebo; RE, random effects; SUCRA, surface under the cumulative ranking curve; TOF5/TOF10, tofacitinib 5 mg/10 mg; UPA15 or UPA30, upadacitinib 15 mg/30 mg; UST90Q8W/UST90Q12W, ustekinumab 90 mg every 8 weeks/every 12 weeks; VED300Q4W/VED300Q8W, vedolizumab 300 mg every 4 weeks/every 8 weeks.

In the bio-exposed population, upadacitinib 15 mg and upadacitinib 30 mg were associated with predicted probabilities of clinical response of [redacted]% and [redacted]%, respectively, and were both statistically superior to placebo Table 41. Most comparators were also statistically significant to placebo, except for adalimumab and ustekinumab Q12W. Upadacitinib 30 mg ranked highest of all treatment in terms of SUCRA score ([redacted]%), while upadacitinib 15 mg raked third of 10 with a SUCRA score of [redacted]%.

Table 41: Results for clinical response in bio-exposed maintenance NMA (RE model)

Treatment	Odds ratio vs. PBO Median (95% CrI)	SUCRA score	Predicted absolute outcome rate, median (95% CrI)
UPA30	[redacted]	[redacted]	[redacted]
TOF10	[redacted]	[redacted]	[redacted]
UPA15	[redacted]	[redacted]	[redacted]
TOF5	[redacted]	[redacted]	[redacted]
VED300Q8W	[redacted]	[redacted]	[redacted]
VED300Q4W	[redacted]	[redacted]	[redacted]
UST90Q8W	[redacted]	[redacted]	[redacted]
ADA40Q2W	[redacted]	[redacted]	[redacted]

Treatment	Odds ratio vs. PBO Median (95% CrI)	SUCRA score	Predicted absolute outcome rate, median (95% CrI)
UST90Q12W	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

Abbreviations: ADA40Q2W, adalimumab 40 mg every other week; CrI, credible interval; PBO, placebo; RE, random effects; SUCRA, surface under the cumulative ranking curve; TOF5/TOF10, tofacitinib 5 mg/10 mg; UPA15 or UPA30, upadacitinib 15 mg/30 mg; UST90Q8W/UST90Q12W, ustekinumab 90 mg every 8 weeks/every 12 weeks; VED300Q4W/VED300Q8W, vedolizumab 300 mg every 4 weeks/every 8 weeks.

B.2.9.6.2 Sensitivity analyses

As an extension of baseline risk adjustment, additional risk difference (RD) NMAs were conducted as needed to generate corresponding ITT efficacy estimates in sensitivity analysis; these did not materially change the results.

B.2.9.7 Conclusion

Overall, the NMA results indicated that upadacitinib induction and maintenance treatment compared favourably with all comparators in both bio-naïve and bio-exposed populations for the outcomes of relevance.

Upadacitinib 45 mg QD induction treatment was associated with the highest predicted probability of clinical remission versus all comparators in both bio-naïve and bio-exposed populations and was statistically superior to placebo and adalimumab in bio-naïve patients, and to placebo in bio-exposed patients. A similar trend was observed for clinical response with upadacitinib 45 mg induction treatment demonstrating the highest predicted probability of clinical response in both patient populations and was statistically superior to all comparators apart from ustekinumab in bio-naïve patients. In the bio-exposed population upadacitinib 45 mg was statistically superior to placebo, adalimumab, and vedolizumab.

Maintenance treatment with upadacitinib 30 mg QD was ranked third for the highest predicted probability of clinical remission versus all comparators in the bio-naïve population with upadacitinib 30 mg and upadacitinib 15 mg associated with the highest predicted probability of clinical remission in the bio-exposed population. Upadacitinib 15 mg and 30 mg was superior compared with placebo in bio-exposed patients. A similar trend was observed for clinical response with upadacitinib 30 mg maintenance treatment demonstrating the highest predicted probability of clinical response in both patient populations and both upadacitinib 15 mg and 30mg were statistically superior compared with placebo in both bio-naïve and bio-exposed patients.

B.2.9.8 Uncertainties in the indirect and mixed treatment comparisons

Model fit was robustly analysed in the NMA. Results presented within this analysis were all drawn from models that met convergence criteria and displayed successful updating of the prior distribution assumptions in the posterior distributions. There was little evidence of inconsistency in the networks analysed. Furthermore, to account for differences in the baseline (PBO) risk across RCTs, baseline risk-adjusted models were considered (and selected in the case of clinical response in the bio-naïve induction analysis).

One general limitation of the NMA is that assumptions underlying it, network connectivity, homogeneity, and transitivity or consistency, must be carefully considered, because if any one of them are violated, the conclusions of the NMA may be invalid. Furthermore, similar to a traditional pairwise meta-analysis, conclusions from the NMA are susceptible to the methodological quality of included studies, as well as to reporting biases and choices of study eligibility criteria.

B.2.10 Adverse reactions

Safety results for the upadacitinib clinical trial programme

Across the upadacitinib induction (U-ACHIEVE induction and U-ACCOMPLISH induction) and maintenance (U-ACHIEVE maintenance) studies, no new safety risks were observed versus placebo, and the overall safety profile was consistent with the known safety profile of upadacitinib.

Induction phase

- For both induction studies, the rates of serious adverse events (SAEs), severe adverse events and adverse events (AEs) leading to discontinuation were numerically lower for upadacitinib 45 mg QD arm compared with the placebo arm, with most events related to gastrointestinal (GI) disorders and infections and manifestations.

Maintenance phase

- In U-ACHIEVE maintenance study, the rates of SAEs, severe AEs and AEs leading to discontinuation were numerically lower in the upadacitinib 15 mg QD and upadacitinib 30 mg QD arms compared with the placebo arm, with most events also related to GI disorders and infections and manifestations.

B.2.10.1 Studies identified in Section 2.2

B.2.10.1.1 U-ACHIEVE induction and U-ACCOMPLISH induction studies

For both induction studies, the rates of serious adverse events (SAEs), severe adverse events and adverse events (AEs) leading to discontinuation were numerically higher in the placebo arm versus the upadacitinib 45 mg QD arm, with most events related to gastrointestinal (GI) disorders and infections and manifestations.

Adverse event data were recorded in U-ACHIEVE induction and U-ACCOMPLISH induction studies. All AEs are treatment-emergent unless specified. An overview of AEs is provided for the SA1 population (which included all subjects who received at least 1 dose of upadacitinib 45 mg QD in Part 1 of both U-ACHIEVE induction and U-ACCOMPLISH induction studies) is presented in Table 42, with a summary of AEs reported by ≥2% of patients in either arm of either trial presented in Table 43.

Serious adverse events are presented in Table 44, with AESI presented in Table 45.

A summary of AEs leading to discontinuation of study drug is presented in Table 46.

Table 42: Overview of AEs and deaths during induction treatment (Part 1;SA1 populations)

Category, n (%)	U-ACHIEVE induction study		U-ACCOMPLISH induction study	
	UPA 45 mg QD (n=319)	Placebo (n=155)	UPA 45 mg QD (n=344)	Placebo (n=177)
Any AE	[redacted]	[redacted]	[redacted]	[redacted]
AE with reasonable possibility of being related to study drug according to the investigator	[redacted]	[redacted]	[redacted]	[redacted]
Severe AE†	[redacted]	[redacted]	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to death	[redacted]	[redacted]	[redacted]	[redacted]
All deaths‡	[redacted]	[redacted]	[redacted]	[redacted]

†Severe AEs are those Grade 3 or above based on the CTCAE version 5.0. ‡Includes non-treatment-emergent deaths

Abbreviations: AE, adverse event; CTCAE, common terminology criteria for AEs; QD, once daily dosing; SA1, safety analysis population in Part 1; UPA, upadacitinib.

Table 43: AEs reported in ≥2% of patients during induction treatment in either arm of either U-ACHIEVE induction or U-ACCOMPLISH induction studies (Part 1; SA1 populations)

AE, n (%)	U-ACHIEVE induction study		U-ACCOMPLISH induction study	
	UPA 45 mg QD (n=319)	Placebo QD (n=155)	UPA 45 mg QD (n=344)	Placebo QD (n=177)
Blood creatine phosphokinase increased	[redacted]	[redacted]	[redacted]	[redacted]
Acne	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Folliculitis	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract	[redacted]	[redacted]	[redacted]	[redacted]

AE, n (%)	U-ACHIEVE induction study		U-ACCOMPLISH induction study	
	UPA 45 mg QD (n=319)	Placebo QD (n=155)	UPA 45 mg QD (n=344)	Placebo QD (n=177)
infection				
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Ulcerative colitis	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]
Arthropathy	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; QD, once-daily dosing; SA1, safety population in Part 1; UPA, upadacitinib.

Table 44: SAEs reported in patients during induction treatment (Part 1; SA1 populations)

SAE, n (%)	U-ACHIEVE induction study		U-ACCOMPLISH induction study	
	UPA 45 mg QD (n=319)	Placebo QD (n=155)	UPA 45 mg QD (n=344)	Placebo QD (n=177)
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]	[redacted]
Diaphragmatic hernia	[redacted]	[redacted]	[redacted]	[redacted]
Large intestine perforation	[redacted]	[redacted]	[redacted]	[redacted]
Ulcerative colitis	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Appendicitis	[redacted]	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]	[redacted]

SAE, n (%)	U-ACHIEVE induction study		U-ACCOMPLISH induction study	
	UPA 45 mg QD (n=319)	Placebo QD (n=155)	UPA 45 mg QD (n=344)	Placebo QD (n=177)
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Dengue fever	[redacted]	[redacted]	[redacted]	[redacted]
Enterococcal infection	[redacted]	[redacted]	[redacted]	[redacted]
Escherichia infection	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis norovirus	[redacted]	[redacted]	[redacted]	[redacted]
Muscle abscess	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Viral infection	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal stoma necrosis	[redacted]	[redacted]	[redacted]	[redacted]
Hand fracture	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypoalbuminaemia	[redacted]	[redacted]	[redacted]	[redacted]
Malnutrition	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Acute psychosis	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Pyoderma gangrenosum	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Pelvic venous thrombosis	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QD, once daily dosing; SA1, safety population in Part 1; SAE, serious adverse event; UPA, upadacitinib.

Table 45: AESI in patients during induction treatment (Part 1; SA1 populations)

AE, n (%)	U-ACHIEVE induction study		U-ACCOMPLISH induction study	
	UPA 45 mg QD (n=319)	Placebo QD (n=155)	UPA 45 mg QD (n=344)	Placebo QD (n=177)
Any serious infection	[redacted]	[redacted]	[redacted]	[redacted]

AE, n (%)	U-ACHIEVE induction study		U-ACCOMPLISH induction study	
	UPA 45 mg QD (n=319)	Placebo QD (n=155)	UPA 45 mg QD (n=344)	Placebo QD (n=177)
Opportunistic infection excluding tuberculosis and herpes	[redacted]	[redacted]	[redacted]	[redacted]
Active tuberculosis	[redacted]	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
CPK elevation	[redacted]	[redacted]	[redacted]	[redacted]
Malignancy	[redacted]	[redacted]	[redacted]	[redacted]
Malignancies excluding NMSC	[redacted]	[redacted]	[redacted]	[redacted]
NMSC	[redacted]	[redacted]	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]	[redacted]	[redacted]
Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic disorder	[redacted]	[redacted]	[redacted]	[redacted]
Adjudicated GI perforations	[redacted]	[redacted]	[redacted]	[redacted]
Adjudicated MACE†	[redacted]	[redacted]	[redacted]	[redacted]
Adjudicated VTE‡	[redacted]	[redacted]	[redacted]	[redacted]

†MACE defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke ‡VTE includes deep vein thrombosis and pulmonary embolism.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; CPK, creatinine phosphokinase; GI, gastrointestinal; MACE, major adverse cardiac event; NMSC, non-melanoma skin cancer; QD, once-daily dosing; SA1, safety population in Part 1; UPA, upadacitinib; VTE, venous thromboembolism.

Table 46: AEs leading to discontinuation of study drug during induction treatment (Part 1; SA1 populations)

AE, n (%)	U-ACHIEVE induction study		U-ACCOMPLISH induction study	
	UPA 45 mg QD (n=319)	Placebo QD (n=155)	UPA 45 mg QD (n=344)	Placebo QD (n=177)
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]
Tinnitus	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]	[redacted]	[redacted]

AE, n (%)	U-ACHIEVE induction study		U-ACCOMPLISH induction study	
	UPA 45 mg QD (n=319)	Placebo QD (n=155)	UPA 45 mg QD (n=344)	Placebo QD (n=177)
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]	[redacted]
Large intestine perforation	[redacted]	[redacted]	[redacted]	[redacted]
Rectal dysplasia	[redacted]	[redacted]	[redacted]	[redacted]
Ulcerative colitis	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Asthma	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Enterococcal infection	[redacted]	[redacted]	[redacted]	[redacted]
Escherichia infection	[redacted]	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]
Muscle abscess	[redacted]	[redacted]	[redacted]	[redacted]
Viral infection	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal stoma necrosis	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Decreased haemoglobin	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Arthritis	[redacted]	[redacted]	[redacted]	[redacted]
Trigger finger	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Burning sensation	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Migraine	[redacted]	[redacted]	[redacted]	[redacted]

AE, n (%)	U-ACHIEVE induction study		U-ACCOMPLISH induction study	
	UPA 45 mg QD (n=319)	Placebo QD (n=155)	UPA 45 mg QD (n=344)	Placebo QD (n=177)
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Chronic kidney disease	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Pelvic venous thrombosis	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; QD, once-daily dosing; SA1, safety population in Part 1; UPA, upadacitinib.

B.2.10.1.2 U-ACHIEVE maintenance study

In U-ACHIEVE maintenance study, the rates of SAEs, severe AEs and AEs leading to discontinuation were numerically higher in the placebo arm versus the upadacitinib 15 mg QD and upadacitinib 30 mg QD arms, with most events related to GI disorders and infections and manifestations.

Adverse event data were recorded in U-ACHIEVE maintenance study. All AEs are treatment-emergent unless specified. An overview of AEs is provided for the SA_A population (the subset of the SA population who were the first 451 randomised upadacitinib 45 mg QD 8-week induction responders and who were enrolled under the protocol for the 52-week maintenance treatment period in Cohort 1) is presented in Table 42, with a summary of AEs reported by ≥2% of patients in any arm presented in Table 43. Serious adverse events are presented in Table 44, with AESI presented in Table 45. A summary of AEs leading to discontinuation of study drug is presented in Table 46.

Table 47: Overview of treatment-emergent AEs and deaths during maintenance treatment (SA_A population)†

Category, n (%)	U-ACHIEVE maintenance study

[SSA%]	UPA 15 mg QD (n=148)	UPA 30 mg QD (n=154)	Placebo (n=149)
Any AE	[redacted]	[redacted]	[redacted]
AE with reasonable possibility of being related to study drug according to the investigator	[redacted]	[redacted]	[redacted]
Severe AE‡	[redacted]	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]	[redacted]
AE leading to discontinuation	[redacted]	[redacted]	[redacted]
AE leading to death	[redacted]	[redacted]	[redacted]
All deaths§	[redacted]	[redacted]	[redacted]

†TEAEs are defined as events that begin either on or after the first dose of the study drug in U-ACHIEVE maintenance study and within 30 days after the last dose administration of the study drug for subjects who do not participate in the long-term extension U-ACTIVATE or until first dose of study drug in U-ACTIVATE if the subject is enrolled into U-ACTIVATE. ‡Severe AEs are those Grade 3 or above based on the CTCAE version 4.03.
§Includes non-treatment-emergent deaths.
Abbreviations: AE, adverse event; CTCAE, common terminology criteria for AEs; QD, once daily dosing; SA_A, safety analysis population for Cohort 1; SSA, study size adjusted; TEAE, treatment-emergent AE; UPA, upadacitinib.

Table 48: Treatment-emergent AEs reported in ≥2% of subjects during maintenance treatment (SA_A population)†

AE, n (%)	U-ACHIEVE maintenance study		
	UPA 15 mg QD (n=148)	UPA 30 mg QD (n=154)	Placebo (n=149)
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Ulcerative colitis	[redacted]	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]
Acne	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]
Increased alanine aminotransferase	[redacted]	[redacted]	[redacted]
Increased aspartate aminotransferase	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]

AE, n (%)	U-ACHIEVE maintenance study		
	UPA 15 mg QD (n=148)	UPA 30 mg QD (n=154)	Placebo (n=149)
Pyrexia	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Folliculitis	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]
Hypercholesterolaemia	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]
Abdominal distension	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Blood cholesterol increased	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Demodicidosis	[redacted]	[redacted]	[redacted]
Eczema	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Cystitis	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Low density lipoprotein increased	[redacted]	[redacted]	[redacted]
Nephrolithiasis	[redacted]	[redacted]	[redacted]

[†]TEAEs are defined as events that begin either on or after the first dose of the study drug in U-ACHIEVE maintenance study and within 30 days after the last dose administration of the study drug for subjects who do not participate in the long-term extension U-ACTIVATE or until first dose of study drug in U-ACTIVATE if the subject is enrolled into U-ACTIVATE.
Abbreviations: AE, adverse event; QD, once-daily dosing; SA_A, safety analysis population for Cohort 1; TEAE, treatment-emergent AE; UPA, upadacitinib.

Table 49: Treatment-emergent SAEs reported in subjects during maintenance treatment (SA_A population)[†]

SAE, n (%)	U-ACHIEVE maintenance study		
	UPA 15 mg QD (n=148)	UPA 30 mg QD (n=154)	Placebo (n=149)
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]
Acute myocardial infarction	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Anal fistula	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]
Ulcerative colitis	[redacted]	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Abdominal abscess	[redacted]	[redacted]	[redacted]
Acute endocarditis	[redacted]	[redacted]	[redacted]
Arthritis bacterial	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]
Bursitis infective	[redacted]	[redacted]	[redacted]
Clostridium difficile infection	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]
Large intestine infection	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Tonsillitis	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	[redacted]	[redacted]	[redacted]
Adenocarcinoma of	[redacted]	[redacted]	[redacted]

SAE, n (%)	U-ACHIEVE maintenance study		
	UPA 15 mg QD (n=148)	UPA 30 mg QD (n=154)	Placebo (n=149)
colon			
Invasive breast carcinoma	[redacted]	[redacted]	[redacted]
Small cell carcinoma	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]
Mental disorder	[redacted]	[redacted]	[redacted]
Suicidal ideation	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]	[redacted]
Chronic obstructive pulmonary disease	[redacted]	[redacted]	[redacted]
Interstitial lung disease	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Erythema nodosum	[redacted]	[redacted]	[redacted]
Panniculitis	[redacted]	[redacted]	[redacted]
Surgical and medical procedures	[redacted]	[redacted]	[redacted]
Induced abortion	[redacted]	[redacted]	[redacted]

[†]TEAEs are defined as events that begin either on or after the first dose of the study drug in U-ACHIEVE maintenance study and within 30 days after the last dose administration of the study drug for subjects who do not participate in the long-term extension U-ACTIVATE or until first dose of study drug in U-ACTIVATE if the subject is enrolled into U-ACTIVATE.
Abbreviations: AE, adverse event; QD, once-daily dosing; SA_A, safety analysis population for cohort 1; SAE, serious adverse event; UPA, upadacitinib.

Table 50: Treatment-emergent AESI in subjects during maintenance treatment (SA_A population)[†]

AE, n (%) [SSA%]	U-ACHIEVE maintenance study		
	UPA 15 mg QD (n=148)	UPA 30 mg QD (n=154)	Placebo (n=149)
Any serious infection	[redacted]	[redacted]	[redacted]
Opportunistic infection excluding tuberculosis and herpes	[redacted]	[redacted]	[redacted]
Active tuberculosis	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]

AE, n (%) [SSA%]	U-ACHIEVE maintenance study		
	UPA 15 mg QD (n=148)	UPA 30 mg QD (n=154)	Placebo (n=149)
Neutropenia	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]
CPK elevation	[redacted]	[redacted]	[redacted]
Malignancy	[redacted]	[redacted]	[redacted]
Malignancies excluding NMSC	[redacted]	[redacted]	[redacted]
NMSC	[redacted]	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]	[redacted]
Renal dysfunction	[redacted]	[redacted]	[redacted]
Hepatic disorder	[redacted]	[redacted]	[redacted]
Adjudicated GI perforations	[redacted]	[redacted]	[redacted]
Adjudicated MACE‡	[redacted]	[redacted]	[redacted]
Adjudicated VTE¶	[redacted]	[redacted]	[redacted]

†TEAEs are defined as events that begin either on or after the first dose of the study drug in U-ACHIEVE maintenance study and within 30 days after the last dose administration of the study drug for subjects who do not participate in the long-term extension U-ACTIVATE or until first dose of study drug in U-ACTIVATE if the subject is enrolled into U-ACTIVATE. ‡MACE defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke ¶VTE includes deep vein thrombosis and pulmonary embolism.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; CPK, creatinine phosphokinase; GI, gastrointestinal; MACE, major adverse cardiac event; NMSC, non-melanoma skin cancer; QD, once-daily dosing; SA_A, safety analysis population for Cohort 1; UPA, upadacitinib; VTE, venous thromboembolism.

Table 51: Treatment-emergent AEs leading to discontinuation of study drug during maintenance treatment (SA_A population)†

AE, n (%)	U-ACHIEVE maintenance study		
	UPA 15 mg QD (n=148)	UPA 30 mg QD (n=154)	Placebo (n=149)
Cardiac disorders	[redacted]	[redacted]	[redacted]
Acute myocardial infarction	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Ulcerative colitis	[redacted]	[redacted]	[redacted]
Large intestine perforation	[redacted]	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]	[redacted]

AE, n (%)	U-ACHIEVE maintenance study		
	UPA 15 mg QD (n=148)	UPA 30 mg QD (n=154)	Placebo (n=149)
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]
Drug-induced liver injury	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Abdominal abscess	[redacted]	[redacted]	[redacted]
Acute endocarditis	[redacted]	[redacted]	[redacted]
Arthritis bacterial	[redacted]	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Increased blood creatine phosphokinase	[redacted]	[redacted]	[redacted]
Decreased haemoglobin	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	[redacted]	[redacted]	[redacted]
Invasive breast carcinoma	[redacted]	[redacted]	[redacted]
Small cell carcinoma	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]
Renal impairment	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Interstitial lung disease	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Erythema	[redacted]	[redacted]	[redacted]
Erythema nodosum	[redacted]	[redacted]	[redacted]
Panniculitis	[redacted]	[redacted]	[redacted]
Seborrhoeic dermatitis	[redacted]	[redacted]	[redacted]

AE, n (%)	U-ACHIEVE maintenance study		
	UPA 15 mg QD (n=148)	UPA 30 mg QD (n=154)	Placebo (n=149)
Vascular disorders	[redacted]	[redacted]	[redacted]
Deep vein thrombosis	[redacted]	[redacted]	[redacted]

†TEAEs are defined as events that begin either on or after the first dose of the study drug in U-ACHIEVE maintenance study and within 30 days after the last dose administration of the study drug for subjects who do not participate in the long-term extension U-ACTIVATE or until first dose of study drug in U-ACTIVATE if the subject is enrolled into U-ACTIVATE.
Abbreviations: AE, adverse event; QD, once-daily dosing; SA_A, safety analysis population for Cohort 1; UPA, upadacitinib.

B.2.10.2 Additional studies

There are no additional studies for upadacitinib besides those presented in Section B.2.2.

B.2.10.3 Overview of safety from the pivotal induction and maintenance trials

B.2.10.3.1 Pooled safety

B.2.10.3.1.1 Induction treatment

The placebo-controlled induction (PC_IND) analysis set provides a safety assessment through 8 weeks of induction treatment with upadacitinib 45 mg QD versus placebo. It includes subjects who received upadacitinib 45 mg QD or placebo during the 8-week placebo-controlled induction period from the U-ACHIEVE induction and U-ACCOMPLISH induction studies.

In the PC_IND analysis set, the proportion of subjects with any treatment-emergent adverse event (TEAE) was similar across the upadacitinib 45 mg QD and placebo groups (Table 52). The proportion of subjects with SAEs, TEAEs leading to discontinuation of study drug, and severe TEAEs were lower in the upadacitinib 45 mg QD group compared with the placebo group. The proportion of subjects with TEAEs with reasonable possibility of being related to study drug was higher in the upadacitinib 45 mg QD group compared with the placebo group. No deaths were reported.

Table 52: Overview of subjects with TEAEs during induction treatment (PC_IND analysis set)

TEAE, n (%) [SSA%]	UPA 45 mg QD N=719	Placebo N=378

TEAE, n (%) [SSA%]	UPA 45 mg QD N=719	Placebo N=378
Any TEAE	[redacted]	[redacted]
COVID-19 infection-related AE	[redacted]	[redacted]
Any SAE	[redacted]	[redacted]
Any AE leading to discontinuation of study drug	[redacted]	[redacted]
Any severe AE	[redacted]	[redacted]
Any AE with reasonable possibility of being related to study drug†	[redacted]	[redacted]
Any AE leading to death	[redacted]	[redacted]
Deaths‡	[redacted]	[redacted]

†As assessed by investigator. ‡Includes both treatment-emergent and non-treatment-emergent deaths.
Abbreviations: AE, adverse event; SAE, serious AE, SSA, study size adjusted; QD, once daily dosing; TEAE, treatment-emergent AE; UPA, upadacitinib.

In the PC_IND analysis set, the most frequently reported TEAEs (≥5% of subjects) were acne and increased blood creatine phosphokinase (CPK) in the upadacitinib 45 mg group and UC in the placebo group (Table 53). The frequency of TEAEs of acne, increased blood CPK, neutrophil count decreased, rash, and folliculitis were higher in the upadacitinib 45 mg QD group compared with placebo, while TEAEs of UC were more frequent in the placebo group compared with the upadacitinib 45 mg QD group. Of note, TEAEs of anaemia, a common complication associated with UC, were reported in a numerically greater percentage of subjects in the placebo group compared with the upadacitinib 45 mg QD group. All the TEAEs of neutrophil count decreased were reported in the upadacitinib 45 mg QD group.

Table 53: TEAEs reported in ≥2% of subjects in any group by decreasing frequency during induction treatment, by preferred term (PC_IND Analysis Set)

TEAE, n (%) [SSA%]	UPA 45 mg QD N=719	Placebo N=378
Any TEAE	[redacted]	[redacted]
Acne	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]

TEAE, n (%) [SSA%]	UPA 45 mg QD N=719	Placebo N=378
Rash	[redacted]	[redacted]
Folliculitis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Ulcerative colitis	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Nausea	[redacted]	[redacted]

Abbreviations: QD, once-daily dosing; SSA, study size adjusted; TEAE, treatment-emergent adverse event; UPA, upadacitinib.

The frequency of treatment-emergent adverse events of special interest (TEAESI) in U-ACHIEVE induction and U-ACCOMPLISH induction studies were generally low in both the upadacitinib 45 mg QD and placebo groups (Table 54). Anaemia was reported in a numerically greater percentage of subjects in the placebo group compared with the upadacitinib 45 mg QD group. Neutropenia, lymphopenia, increased blood CPK, and hepatic disorders were reported in a numerically greater percentage of subjects in the upadacitinib 45 mg QD group compared with the placebo group (Table 54).

Table 54: Overview of subjects with TEAESI during induction treatment (PC_IND analysis set)

TEAESI, n (%) [SSA%]	UPA 45 mg QD N=719	Placebo N=378
Serious infection	[redacted]	[redacted]
Opportunistic infection excluding tuberculosis and herpes zoster	[redacted]	[redacted]
Active tuberculosis	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]
Adjudicated gastrointestinal perforations	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]
Hepatic disorder	[redacted]	[redacted]
Renal dysfunction	[redacted]	[redacted]
Malignancy	[redacted]	[redacted]
Malignancies excluding NMSC	[redacted]	[redacted]
NMSC	[redacted]	[redacted]

TEAESI, n (%) [SSA%]	UPA 45 mg QD N=719	Placebo N=378
Lymphoma	[redacted]	[redacted]
Adjudicated MACE	[redacted]	[redacted]
Adjudicated VTE	[redacted]	[redacted]

Abbreviations: MACE. Major adverse cardiovascular event; NMSC, non-melanoma skin cancer; QD, once-daily dosing; SSA, study size adjusted; TEAESI, treatment-emergent adverse event of special interest; UPA, upadacitinib; VTE, venous thromboembolism.

B.2.10.3.1.2 Maintenance treatment

Pooled safety data for maintenance treatment with upadacitinib 15 mg QD and upadacitinib 30 mg QD is presented in Appendix F.

B.2.10.3.2 Induction trial safety

Individual trial safety data for the U-ACHIEVE induction and U-ACCOMPLISH induction studies is presented in Appendix F.

B.2.10.3.3 Maintenance trial safety

B.2.10.3.3.1 Overall safety

Additionally, upadacitinib 15 mg QD or upadacitinib 30 mg QD maintenance treatment (U-ACHIEVE maintenance study) for 52 weeks was generally well tolerated. The rates of SAEs, severe AEs and AEs leading to discontinuation were numerically higher in the placebo arm versus the upadacitinib 15 mg QD and upadacitinib 30 mg QD arms, with most events related to GI disorders and infections and manifestations.

B.2.10.3.3.2 Frequently-reported adverse events

The majority of frequently-reported AEs were mild or moderate in severity with few leading to discontinuation of study drug (Table 51). The most frequently-reported AEs reported in ≥2% of subjects with moderately to severely active UC in the placebo arm were UC itself, nasopharyngitis, arthralgia, back pain, anaemia, headache, acne, and upper respiratory tract infection (Table 48). Increased blood creatine phosphokinase, rash, herpes zoster, increased alanine aminotransferase, back pain, gastroenteritis, and urinary tract infection were also reported in the upadacitinib 15 mg QD arm; however, the frequency of these AEs was low with no dose-dependent pattern between treatment arms (Table 48). The most frequently reported AEs in subjects in the upadacitinib 30 mg QD arm over and above those

reported in the placebo and upadacitinib 15 mg arms were influenza and COVID-19. The AE rates for nasopharyngitis, increased blood CPK, and upper respiratory tract infection were greater in the upadacitinib 15 mg QD and upadacitinib 30 mg QD arms compared with placebo (Table 48). Of note, the AE rate for UC was lower in the upadacitinib 15 mg QD and upadacitinib 30 mg QD arms compared with placebo (upadacitinib 15 mg [redacted] versus upadacitinib 30 mg [redacted] vs placebo [redacted] (Table 48). A similar trend was observed for arthralgia (upadacitinib 15 mg [redacted] versus upadacitinib 30 mg [redacted] vs placebo [redacted] (Table 48).[redacted]

B.2.10.3.3.3 Adverse events of special interest

Lower rates of serious infection were observed in the upadacitinib 15 mg QD and upadacitinib 30 mg QD treatment arms compared with placebo (upadacitinib 15 mg [redacted] versus upadacitinib 30 mg [redacted] versus placebo [redacted] (Table 50). Higher rates of herpes zoster were observed with upadacitinib 15 mg QD and upadacitinib 30 mg QD compared with placebo, with similar rates reported in both upadacitinib treatment arms, and no events were reported in the placebo arm (upadacitinib 15 mg [redacted] versus upadacitinib 30 mg [redacted] versus placebo [redacted] Overall, however, most herpes zoster cases were considered mild or moderate in severity and discontinuation of upadacitinib due to herpes zoster was low [redacted]) (Table 50). Malignancy excluding non-melanoma skin cancer (NMSC) was reported infrequently across all treatment arms (upadacitinib 15 mg [redacted] versus upadacitinib 30 mg [redacted] versus placebo [redacted] NMSC was the most common type of malignancy reported with more events reported in the upadacitinib 30 mg QD arm compared with upadacitinib 15 mg QD and placebo arms [redacted] versus [redacted] versus [redacted] (Table 50). No adjudicated GI perforation due to study drug was reported in subjects receiving upadacitinib (Table 50). [redacted] of adjudicated venous thromboembolism (VTE) were reported in the upadacitinib 30 mg QD arm, with [redacted] leading to study drug discontinuation, compared with no events reported in the upadacitinib 15 mg QD and placebo arms; however, all subjects who experienced VTE receiving upadacitinib 30 mg QD had at least one risk factor identified for thrombosis (Table 50). Consistent with other indications, the events of neutropenia and increased blood CPK were reported more frequently in subjects receiving upadacitinib than those

receiving placebo, with most considered mild or moderate in severity, and only [redacted] of increased blood CPK leading to study drug discontinuation in the upadacitinib 30 mg QD arm (Table 50).

B.2.11 Ongoing studies

A long-term extension study of the U-ACHIEVE (M14-234) maintenance study in patients with UC is ongoing (U-ACTIVATE [M14-533]).

U-ACTIVATE is a multicentre, long-term extension study to evaluate the safety, tolerability, and efficacy of upadacitinib in patients with UC up to Week 288. The study population includes patients who previously participated in completed or ongoing trials, including U-ACHIEVE (M14-234) induction, U-ACCOMPLISH (M14-675) induction, and U-ACHIEVE (M14-234) maintenance studies.

U-ACTIVATE is expected to complete in Q3 2024 when final efficacy and safety data will be available, with interim results expected in October 2022.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

The clinical benefits of upadacitinib versus placebo have been demonstrated in two pivotal induction studies (U-ACHIEVE induction and U-ACCOMPLISH induction studies) and one pivotal maintenance study (U-ACHIEVE maintenance study).

B.2.12.1.1 Efficacy

In UK clinical practice, adult patients with moderately to severely active UC will typically go through a sequence of treatments and switch to advanced therapies following treatment failure, where upon they will continue to cycle through different therapies to control their disease. A substantial proportion of the subjects enrolled in the U-ACHIEVE and U-ACCOMPLISH induction studies were treatment refractory, with approximately 50% of subjects entering the trials having prior biological treatment failure, and approximately 30% of subjects having had ≥2 biological treatments. Despite the substantial proportion of patients having failed multiple biologics, evidence from across the pivotal UC trials indicated that upadacitinib had a

durable treatment effect which was consistent irrespective of prior treatment failure (i.e., in Bio-IR and non-Bio-IR subjects), with treatment effects higher in the non-Bio-IR population as expected due to the treatment-refractory nature of the Bio-IR population. Some patients will therefore benefit from switching to a Janus kinase (JAK) inhibitor and upadacitinib offers statistically significant improvements in clinical remission compared with placebo.

All primary and ranked secondary endpoints were met for both the induction (U-ACHIEVE induction and U-ACCOMPLISH induction studies) and maintenance (U-ACHIEVE maintenance study) phases of the clinical trial programme. In both induction studies, a statistically significantly greater proportion of patients achieved clinical remission with upadacitinib 45 mg QD compared with placebo.

All key ranked secondary endpoints were statistically significantly superior for upadacitinib 45 mg QD induction treatment versus placebo, with improvements in clinical response per Partial Adapted Mayo score observed as early as Week 2. Rapid control of symptoms is considered important by patients with UC as they suffer from unpredictable relapses of GI symptoms, such as diarrhoea, abdominal pain, and bowel urgency, which reduce their QoL (98), and where disease flares can lead to hospitalisation and surgery. Furthermore, despite the availability of biologic therapies, approximately 15% of patients develop acute severe UC (ASUC), a life-threating condition where hospitalisation and inpatient treatment is advised and where a fast onset of response is crucial (99). However, for some biologic therapies, improvement in symptoms can be slow and can take over 3 months to achieve maximal efficacy (50-52). Analysis of upadacitinib 45 mg QD induction treatment demonstrated that the onset of upadacitinib action was rapid, as shown by the achievement of clinical response per partial Mayo score at Week 2 (50, 51). The rapid control of symptoms achieved with upadacitinib 45 mg induction therapy, aligns with a reduction of inflammatory biomarkers by Week 2 which was maintained through Week 8 (50, 51). Statistically significant improvements in objective measures of disease activity such as mucosal outcomes and endoscopic outcomes were observed at Week 8 in the upadacitinib 45 mg QD arm versus placebo. Long-term mucosal healing has been identified as an important treatment target in patients with

UC by the BSG (12, 45, 46) with induction and subsequent maintenance of mucosal healing considered one of the central therapeutic goals (44).

The results from the U-ACHIEVE maintenance study support continued maintenance treatment with upadacitinib 15 mg QD and upadacitinib 30 mg QD in subjects with clinical response to upadacitinib 45 mg QD induction treatment. Treatment with upadacitinib met the primary efficacy endpoint with a statistically significantly greater proportion of subjects in the upadacitinib 15 mg QD and upadacitinib 30 mg QD arms achieving clinical remission per Adapted Mayo score compared with the placebo arm at Week 52. Maintenance treatment with upadacitinib 15 mg QD and upadacitinib 30 mg QD also delivered sustained improvements in endoscopic and histologic assessment, disease activity and symptoms, and important QoL indices such as fatigue with 52-Week maintenance treatment, compared with placebo, indicating that upadacitinib provides durable efficacy as far as Week 52. As long-term mucosal healing has been identified as an important treatment target in patients with UC (44), mucosal endpoints are considered clinically meaningful as they highlight objective improvements in tissue and are associated with long-term benefits (12, 54). Improvements in objective measures of disease activity such as endoscopic outcomes and histologic outcomes were observed at Week 52 following treatment with upadacitinib 15 mg QD and upadacitinib 30 mg QD compared with placebo.

Furthermore, upadacitinib is effective in reducing steroid use in patients with UC; a statistically significant proportion of patients receiving upadacitinib 15 mg QD or upadacitinib 30 mg QD achieved clinical remission and were corticosteroid free for ≥90 days. Reduction in steroid use is considered important for patients and their QoL as steroids are associated with several AEs, including risk of serious infection (55).

Additionally, subgroup analyses revealed robust upadacitinib treatment responses in the induction and maintenance phase for the primary endpoint across all subgroups in U-ACHIEVE induction, U-ACCOMPLISH induction, and U ACHIEVE maintenance studies were consistent with results for the overall trial populations. Importantly, subgroup analyses confirmed a consistent benefit in favour of upadacitinib regardless of baseline characteristics suggesting a broad range of patients could benefit from upadacitinib treatment.

B.2.12.1.2 Safety

Across the induction and maintenance studies, upadacitinib demonstrated a comparable AE profile with placebo, with no new safety concerns or risks identified compared with the known safety profile of upadacitinib in other indications (100).

Induction treatment with upadacitinib 45 mg QD for 8 weeks (Part 1) and extended induction with upadacitinib 45 mg QD for an additional 8 weeks (Part 2) was generally well tolerated. In both induction studies, the overall incidence of AEs during the initial induction period was similar among treatment arms. The rates of SAEs, severe AEs, and AEs leading to discontinuation were numerically higher in the placebo arm, with most events related to GI disorders and infections and manifestations. Specifically, the frequency of TEAEs of acne, increased blood CPK, neutrophil count decreased, rash, and folliculitis were higher in the upadacitinib 45 mg QD group compared with placebo (Table 53).

Additionally, upadacitinib 15 mg QD and upadacitinib 30 mg QD maintenance treatment administered for 52 weeks was generally well tolerated. As observed in the induction studies, the rates of SAEs, severe AEs, and AEs leading to discontinuation were numerically higher in the placebo arm compared with the upadacitinib 15 mg QD and upadacitinib 30 mg QD arms, with most AEs related to GI disorders and infections and manifestations. Specifically, the AE rates for nasopharyngitis, increased blood CPK, and upper respiratory tract infection were greater in the upadacitinib 15 mg QD and upadacitinib 30 mg QD arms compared with placebo (Table 48).

B.2.12.2 Strengths and limitations of the clinical evidence base for the technology

B.2.12.2.1.1 Trial design

U-ACHIEVE induction, U-ACCOMPLISH induction, and U-ACHIEVE maintenance studies were large, multinational, placebo-controlled, well-conducted and methodologically robust studies. The study entry criteria were relevant and appropriate. The upadacitinib UC clinical trial programme enrolled a total of 14 subjects across UK centres, with UK subjects representing approximately 1% of the study populations in U-ACHIEVE induction, U-ACCOMPLISH induction, and U-ACHIEVE maintenance studies.

B.2.12.2.1.2 Intervention and comparators

The upadacitinib UC trials included treatment arms with different doses of upadacitinib; however, only results for the upadacitinib doses which are expected to be used in UK clinical practice (upadacitinib 45 mg QD induction and both upadacitinib 15 mg QD and upadacitinib 30 mg QD maintenance doses) are presented in this submission.

The studies were all placebo-controlled, with the placebo design similar to other recently approved biologics for moderately to severely active UC. This trial design facilitates indirect treatment comparison with multiple other comparator treatments through the respective placebo arms. CT was permitted comprising 5-ASA and corticosteroids which partly reflects CT in UK clinical practice. However, immunomodulators also form part of CT in UK clinical practice and the immunosuppressants azathioprine and mercaptopurine were not permitted within 10 days of baseline or during trials such that overall baseline immunomodulator use was low. Despite this, clinical expert opinion obtained at an advisory board meeting (see section B.2.3.4) concluded that the low levels of baseline immunomodulator was not a limitation of the trial design and would not likely impact on the applicability of the trial results to UK clinical practice (101).

B.2.12.2.1.3 Patient characteristics

Patient characteristics in the upadacitinib clinical trials were representative of the moderately to severely active UC patient population in the UK. The baseline demographics and clinical characteristics of subjects were well balanced between the treatment groups in each trial and were generally similar across studies. Across studies, the disease severity baseline characteristics were reflective of patients with moderately to severely active UC.

Some patient groups were excluded from the clinical trials who would otherwise be treated for UC in UK clinical practice (patients with proctitis, patients of childbearing potential, patients aged >75 years, and patients with comorbidities) (101). However, the overall subject populations of the U-ACHIEVE induction, U-ACCOMPLISH induction, and U-ACHIEVE maintenance studies were similar with regard to demographic and key disease characteristics, and considered to be representative of the UK UC patient population who would be treated with upadacitinib in the UK according to expert clinical opinion (101). Additionally, based on expert clinical opinion (101), the Bio-IR population is considered to be aligned with the NICE recommendation for ustekinumab (102).

B.2.12.2.1.4 Outcomes

U-ACHIEVE induction, U-ACCOMPLISH induction, and U-ACHIEVE maintenance studies provide efficacy and safety data of direct relevance to the anticipated licence for upadacitinib. The trials evaluated several secondary endpoints where mucosal healing (absence of macroscopic mucosal inflammation or ulceration), a target assessed through endoscopic endpoints which is associated with improved long-term outcomes (e.g., reduced risk of relapse, decreased hospitalisations rates, steroid-free remission, and fewer bowel resections) is now considered a major treatment objective in clinical trials and clinical practice (47, 48). In addition, current guidance by the BSG recognises the importance of different treatment goals, with a recent focus on endoscopic outcomes, in addition to controlling clinical symptoms (12). According to expert clinical opinion, endoscopic remission is the best predictor of long-term patient outcomes, providing positive predictive value compared with clinical improvement alone (102). However, it is acknowledged by clinicians that UK clinical practice remains driven by clinical remission (102). The endpoints assessed within, and the subsequent results obtained from, U-ACHIEVE induction,

U-ACCOMPLISH induction, and U-ACHIEVE maintenance studies, align with these emerging treatment goals.

B.2.12.2.1.5 Limitations

A limitation of the U-ACHIEVE maintenance study is the re-randomised responder-withdrawal design where subjects with previous exposure to upadacitinib 45 mg QD induction treatment could be randomised to the placebo arm of Cohort 1 in U-ACHIEVE maintenance study (Figure 3). Consequently, the placebo arm in Cohort 1 contains subjects who achieved clinical response to upadacitinib 45 mg QD induction treatment but were subsequently treated with placebo in U-ACHIEVE maintenance study (Figure 3) and is considered a withdrawal placebo arm rather than a true placebo arm. However, the trial design of U-ACHIEVE maintenance study is in line with previous trials that have evaluated treatments for UC (82, 103) which have been evaluated by NICE (34, 35), and is in accordance with ethical considerations and Good Clinical Practice, as well as the expected trial design requirements by regulatory authorities.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A global systematic literature review (SLR) was conducted on 06 January 2022 to identify available economic evaluations, appraise cost-effectiveness evaluations, and examine cost and resource use in moderately to severely active UC. The SLR was conducted as per guidance from the Cochrane Handbook for Systematic Reviews of Interventions, Centre for Reviews and Dissemination (CRD)'s Guidance for Undertaking Reviews in Healthcare, and Methods for the Development of NICE Public Health Guidance (104-106). Full details of the SLR search strategy, study selection process, and results are presented in Appendix G.

In total, 10 records were identified which reported cost-effectiveness analyses conducted from a United Kingdom (UK) healthcare system perspective and are therefore considered to be relevant to clinical practice in England. Of the studies identified and reported, five used a Markov model, three used hybrid models (a decision tree for induction and a Markov model for maintenance), and one used a cost per response analysis. Three studies used a lifetime horizon, while the remainder of the studies used shorter time horizons (1-year, 30 months, 10 years) These studies are summarised in Table 55; for complete details and other studies identified in the global SLR, see Appendix G.

Table 55: Summary list of published UK perspective cost-effectiveness studies

Study	Summary of model	Population	Total QALYs / response measure *Intervention vs comparator*	Total costs *Intervention vs comparator*	ICER/ICUR *Intervention vs comparator*
Ali_AJGC_2012 (abstract)	CEA (Markov model) Comparison 1: ADA vs SoC Comparison 2: ADA vs surgery Country: UK Currency (cost year): GBP (2010) Perspective: UK NHS Time horizon: 1 year and 5 years	People with moderate to severe active UC	NR	NR	**Comparison 1** 1 year time horizon: £96,733/QALY gained 5-year time horizon: £22,087/QALY gained DSA: £18,933 - £30,292/QALY gained **Comparison 2** 1-year time horizon: Dominant 5-year time horizon: Dominant
Arebi_ECCO_2013 (abstract)	CEA (model NR) comparing surgery vs IFX Country: UK Currency (cost year): GBP (2013) Perspective: NR Time horizon: NR	People with refractory UC undergoing surgery Median age (Range): 38.4 (18-75)	50% vs 63% good surgical outcome 28.8 vs 15.8 days in hospital	£22,920 vs £12,723	£784/good surgical outcome £784/day in hospital
Borsi_ISPOR_2020 (abstract)	Cost per response/remission analysis comparing UST vs comparators (IFX, IFX-B, ADA, ADA-B, VDZ, GOL, TOF) Country: UK Currency (cost year): GBP (2020) Perspective: Payer perspective in the UK Time horizon: 1 year	Moderate-to-severe UC with biologic-failure and non-biologic-failure	NR	NR	**Non-bio-failure (per responder):** £17,729.53 (UST Q12W) vs £16,021.78 (ADA-B) vs £18,310.46 (ADA Q2W) vs £25,052.00 (VDZ Q8W) vs £24,514.85 (UST Q8W) vs £41,943.80 (VDZ Q4W) vs £33,820.41 (GOL Q4W) vs £28,130.21 (TOF). **Bio-failure (per responder):** £24,771.90/ (UST Q12W) vs £29,670.87 (UST Q8W) vs £33,800.60 (VDZ Q8W) vs £52,635.86 (VDZ Q4W)

Study	Summary of model	Population	Total QALYs / response measure *Intervention vs comparator*	Total costs *Intervention vs comparator*	ICER/ICUR *Intervention vs comparator*
Lohan_BMJOG_2019	CEA (Markov model) comparing TOF vs VDZ vs IFX vs GOL vs ADA vs CT Country: UK Currency (cost year): GBP (2016-2017) Perspective: UK NHS Time horizon: Lifetime	Adults with moderately to severely active UC with or without prior exposure to TNF inhibitor therapies Mean age: Mean 41	**ITT** (TOF vs VDZ vs CT): 9.397 vs 9.301 vs 8.948 QALY **TNFi-naïve**: 9.536 vs 9.462 vs 9.346 vs 9.286 vs 9.191 vs 8.991 QALY **TNFi-exposed**: 9.240 vs 9.146 vs 9.051 vs 9.051 vs 9.051 vs 8.903 QALY	**ITT** (TOF vs VDZ vs CT): £141,500 vs £147,822 vs £132,508 **TNFi-naïve**: £143,963 vs £152,694 vs £145,660 vs £141,360 vs £138,534 vs £132,349 **TNFi-exposed:** £140,399 vs £145,380 vs £140,661 vs £138,088 vs £137,035 vs £132,712	**ITT population** TOF vs CT: £20,038/QALY gained VDZ vs CT: £43,485/QALY gained **TNFi-naïve subgroup** TOF vs CT: £21,388/QALY gained VDZ vs CT: £43,205/QALY gained IFX vs CT: £37,495/QALY gained GOL vs CT: £30,602/QALY gained ADA vs CT: £30,982/QALY gained **TNFi-exposed subgroup** TOF vs CT: £22,816/QALY gained VDZ vs CT: £52,275/QALY gained IFX vs CT: £53,831/QALY gained GOL vs CT: £36,403/QALY gained ADA vs CT: £29,284/QALY gained WTP: £30,000/QALY
Punekar_EJHE_2010	CEA (Decision analytic model for one year and Markov model years 2-10 (sensitivity analysis only)) comparing IFX vs SoC vs CIC vs surgery Country: UK Currency (cost year): GBP (2006-2007) Perspective: NHS in England and Wales Time horizon: 12 months	People with acute severe UC	0.80 vs 0.68 vs 0.70 vs 0.58 QALY	£19,847 vs £18,524 vs £18,122 vs £17,067	CIC vs SUR: £9,032/QALY gained SOC vs CIC: Dominated IFX vs SOC: £18,388/QALY gained CE acceptability curves presented by WTP threshold
Tsai_APT_2008	CA (Markov model) comparing IFX vs SoC Country: UK Currency (cost year): GBP (2006-2007) Perspective: NHS in England and Wales Time horizon: 10 years	People with moderate to severe UC	Responder only: 4.591 vs 3.838 QALY Remission only: 4.154 vs 3.767 QALY	Responder only: £66,460 vs £45,798 Remission only: £53,874 vs £46,259	**Responders only**: £27,424/QALY gained DSA: £21,066 - £86,320/QALY gained **Remission only**: £19,696/QALY DSA: £14,728 - £46,765/QALY gained
Williams_HTA_2016	CUA (Markov Model) comparing CIC vs IFX Country: UK Currency (cost year): GBP (2012-2013)	People with steroid-resistant acute severe UC	**Mean** (SD): 1.921 (0.18) vs 1.900 (0.16) QALY	Mean (SD): £14,609 (£593) vs £20,241	Dominant

Study	Summary of model	Population	Total QALYs / response measure *Intervention vs comparator*	Total costs *Intervention vs comparator*	ICER/ICUR *Intervention vs comparator*
	Perspective: NHS and PSS Time horizon: 30 months	Mean age (SD): 40.6 (15.31)	**Incremental QALY**: 0.021 (95% CI: -0.032, 0.0096, p=0.350)	(£695) Incremental cost: -£5,632 (95% CI: -£8,305, -£2,773, p=0.000)	CE acceptability curves presented by WTP threshold
Wilson_CEOR_2017	CEA (Markov decision analytic model [induction decision tree and long-term Markov]) comparing VDZ vs CT Country: UK Currency (cost year): GBP (2013-2014) Perspective: NHS and PSS Time horizon: Lifetime	People with moderate to severe UC Mean age: 40.25	**ITT**: 10.516 vs 10.181 QALY; 21.606 vs 21.606 LY **TNFi-naive**: 10.549 vs 10.186 QALY; 21.606 vs 21.606 LY **TNFi-failure**: 10.416 vs 10.150 QALY; 21.606 vs 21.606 LY	**ITT:** £205,361.83 vs £203,991.36 **TNFi-naive**: £205,520.82 vs £203,917.05 **TNFi-failure**: £206,133.38 vs £204,546.71	ITT population: £4,095/QALY gained TNFi-naive population: £4,423/QALY gained TNFi-failure: £5,972/QALY gained CE acceptability curves presented by WTP threshold
Wilson_EJHE_2017	CEA (induction decision tree and Markov maintenance) comparing VDZ vs IFX vs ADA vs GOL Country: UK Currency (cost year): GBP (2012-2013) Perspective: NHS and PSS Time horizon: Lifetime	People with moderate-to-severe UC, who have had an inadequate response with, loss of response to, or are intolerant to a CT and switched to a treatment with a TNFi Mean age: 40.36	21.607 vs 21.607 vs 21.607 vs 21.607 LY 14.077 vs 13.788 vs 13.872 vs 13.809 QALY	£199,431.15 vs £206,065.90 vs £194,764.73 vs £200,018.31	VDZ vs IFX: VDZ dominates VDZ vs ADA: £22,775/QALY gained VDZ vs GOL: VDZ dominates WTP: £30,000/QALY
Yang_UEGJ_2014 (abstract)	CEA (Markov model) comparing ADA vs SoC Country: UK Currency (cost year): GBP (2013) Perspective: UK NHS Time horizon: 10 years	People with moderately to severely active UC (sub-acute) who have an inadequate response to SoC in	NR	NR	£34,417/QALY gained DSA: £29,437- £38,073/QALY gained CE acceptability curves presented by WTP threshold

Study	Summary of model	Population	Total QALYs / response measure *Intervention vs comparator*	Total costs *Intervention vs comparator*	ICER/ICUR *Intervention vs comparator*
		the UK			

Abbreviations: ADA, adalimumab; ADA-B, adalimumab biosimilar; CE, cost effectiveness; CEA, cost-effectiveness analysis; CI, confidence interval; CIC, ciclosporin; CT, conventional therapy; CUA, cost-utility analysis; DSA, deterministic sensitivity analysis; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IFX-B, infliximab biosimilar; ITT, intention to treat; LY, life year; NHS, National Health Service; NR, not reported; PSS, Personal Social Services; QALY, quality-adjusted life year; SD, standard deviation; SoC, standard of care; TNFi, tumour necrosis factor inhibitor; TOF, tofacitinib; UC, ulcerative colitis; VDZ, vedolizumab; WTP, willingness-to-pay.

B.3.2 Economic analysis

Please note: The following populations are used in B3, aligned with the network meta-analysis (NMA) populations:

- Bio-naïve: Patients that have had no previous exposure to biologic therapies
- Bio-exposed: Patients who had an inadequate response or intolerance to conventional therapy (CT), and those who have received biologic therapy in the past but stopped therapy based on reasons other than inadequate response or intolerance

To keep the NMA comparable with previous trial populations, patient-level data from the UPA trials was used to separate the patients into the bio-naïve and bio-exposed cohorts. In the upadacitinib induction and maintenance trials (Section B.2.3) the non-Bio-IR population is considered equivalent to the bio-naïve population; only 2% of the non-Bio-IR population had previously been exposed to a biologic treatment.

None of the cost-effectiveness analyses (CEAs) identified in the economic SLR (Appendix G) included upadacitinib as a comparator. It was therefore necessary to develop a *de novo* economic model for this submission. Previous NICE technology appraisals (TAs) of treatments for UC (TA329, TA342, TA547, and TA633), along with published cost-effectiveness analyses identified in the economic SLR, were used to inform the model structure, assumptions, and data sources.

The objective of the economic evaluation was to assess the cost-effectiveness of upadacitinib for the treatment of people with moderately to severely active UC versus all relevant comparators listed in the NICE scope.

The CEA was conducted considering a National Health Service (NHS) and personal social services (PSS) perspective over a life-time horizon (100 years), consistent with the NICE reference case. The cost-effectiveness analysis is based on data from the upadacitinib clinical trials (see Section B.2.6), an NMA conducted to estimate comparative efficacy and safety for upadacitinib versus comparators (see Section B.2.9), and information obtained from previous NICE technology appraisals and the

published literature. The model is described in greater detail in the following sections.

B.3.2.1 Patient population

In line with the anticipated marketing authorisation for upadacitinib and the NICE scope for this appraisal, the analysis considered [redacted].

In line with previous technology appraisals in this patient population, patients were divided into two subgroups in the upadacitinib clinical trials:

- **Bio-naïve**: Patients that have had no previous exposure to biologic therapies
- **Bio-exposed**: Patients who had an inadequate response or intolerance to conventional therapy/treatment (CT), and those who have received biologic therapy in the past but stopped therapy based on reasons other than inadequate response or intolerance

These patient groups formed the base-case populations which aligned with the base-case population for the ustekinumab economic analysis in TA633 (35) and the patient population in the upadacitinib clinical trials (see Section B.2.2)

B.3.2.2 Model structure

The cost-effectiveness model (CEM) was developed in Microsoft® Excel (Microsoft, Washington, USA, 2022), using Visual Basic for Applications (VBA) functionality to determine the cost-effectiveness of upadacitinib versus relevant comparator treatments in the management of moderately to severely active UC over a lifetime horizon. The model structure was consistent with the previously published technology appraisal for ustekinumab (TA633) (35), this model structure has remained largely consistent over recent submissions to NICE for UC treatments (34, 36, 37).

In line with TA633 (ustekinumab), TA329 (adalimumab, golimumab, infliximab) and TA342 (vedolizumab) a hybrid decision-analytical modelling approach was implemented where:

- A decision tree was used to model the initial induction phase of treatment (described in B.3.2.2.1)
- A Markov model was used to evaluate subsequent long-term (lifetime, until 100 years of age) outcomes during maintenance treatment and surgery.

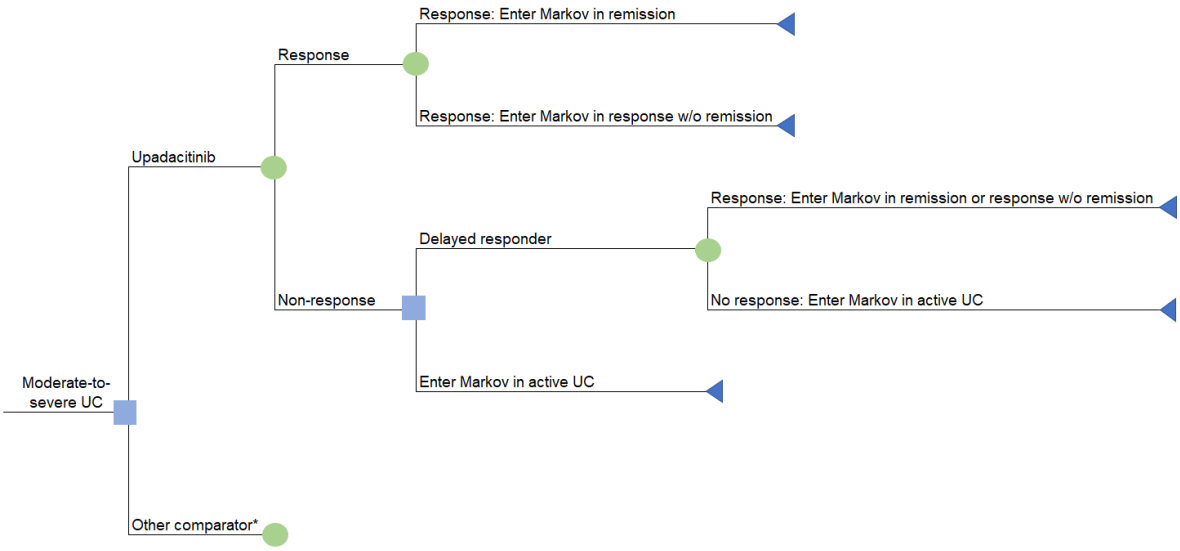
The model structure was selected to represent clinical practice wherein patients are prescribed higher doses of treatments to assess response, followed by lower maintenance doses for responders. This modelling approach has been deemed appropriate by NICE committees in past UC appraisals and was found to be acceptable by clinical and economic advisors at an advisory board meeting held for upadacitinib (See section B.2.3.4).

B.3.2.2.1 Induction period decision tree

The induction phase is replicated within a decision tree, where patients with moderately to severely active UC who were refractory to CT entered the model and were treated with either upadacitinib or an alternative biologic (the full list of comparators is detailed in Section B.1.1) (Figure 9). The decision tree governs the proportion of patients that move into remission, response without remission, active UC and death health states at the end of the induction phase for each treatment. The definitions of remission and response without remission are provided in Table 56. At the end of Week 6 (golimumab) and Week 8 induction treatment (upadacitinib, ustekinumab, vedolizumab, infliximab, infliximab biosimilar, adalimumab, adalimumab biosimilar and tofacitinib), were distributed to one of three starting Markov health states: remission, response without remission, or active UC.

The standard induction duration for vedolizumab was derived from an average of that reported in GEMINI 1 (107) and NCT02039505 (108).

Figure 9: Induction phase decision tree



*As per the decision tree structure for patients on upadacitinib.
Note: Extended induction (delayed responder) is not included in the base case of the model but is captured within a scenario analysis.
Abbreviations: UC, ulcerative colitis; w/o, without.

Patients who respond to induction treatment, consisting of both clinical remission and response without remission, enter the Markov model in the remission and response without remission health states. Within these states, patients continue on the same treatment and receive maintenance dosing of the previously-received induction treatment for the duration of their response. Patients who do not respond to induction therapy enter the Markov model in an active UC health state. In a scenario analysis, patients who do not achieve a response during the initial induction period remain on extended induction therapy for a further 4-8 weeks to allow for a delayed response. Response is then re-assessed at the end of the extended induction period. Patients who have not responded to treatment enter the Markov model in the active UC health state.

As previously described, in the base case, it is assumed that patients who do not achieve a response discontinue treatment after the induction period. This is aligned with expert clinical opinion collected from an advisory board meeting (See section B.2.3.4), which indicated that the evolution of the treatment landscape and the availability of alternative therapeutic options mean that there is little cause to continue patients on a treatment that is not effective. Furthermore, this approach was

aligned with the Evidence Review Group's (ERG's) feedback in TA633 (ustekinumab), where it was agreed that there is high uncertainty over the direct trial estimates for response and remission for extended induction (denoted as delayed induction in TA633 [ustekinumab]) and loss of response rates for delayed responders. However, extended induction is captured within a scenario analysis to reflect product Summary of Product Characteristics (SmPCs), which state that patients who do not have an adequate response to treatment may receive extended induction to assess for a delayed response. Patients who do not achieve a response after initial induction (or extended induction in the scenario analysis) enter the Markov model in the active UC health state on CT alone. CT is based on the treatment regimens prescribed for the placebo arm across the relevant trials as per the approach adopted in TA633 and comprises mercaptopurine, methotrexate, 5-ASA, prednisone, azathioprine and budesonide (see Table 62). A scenario wherein patients experiencing treatment failure receive a further line of (non-CT) treatment is considered in a scenario analysis.

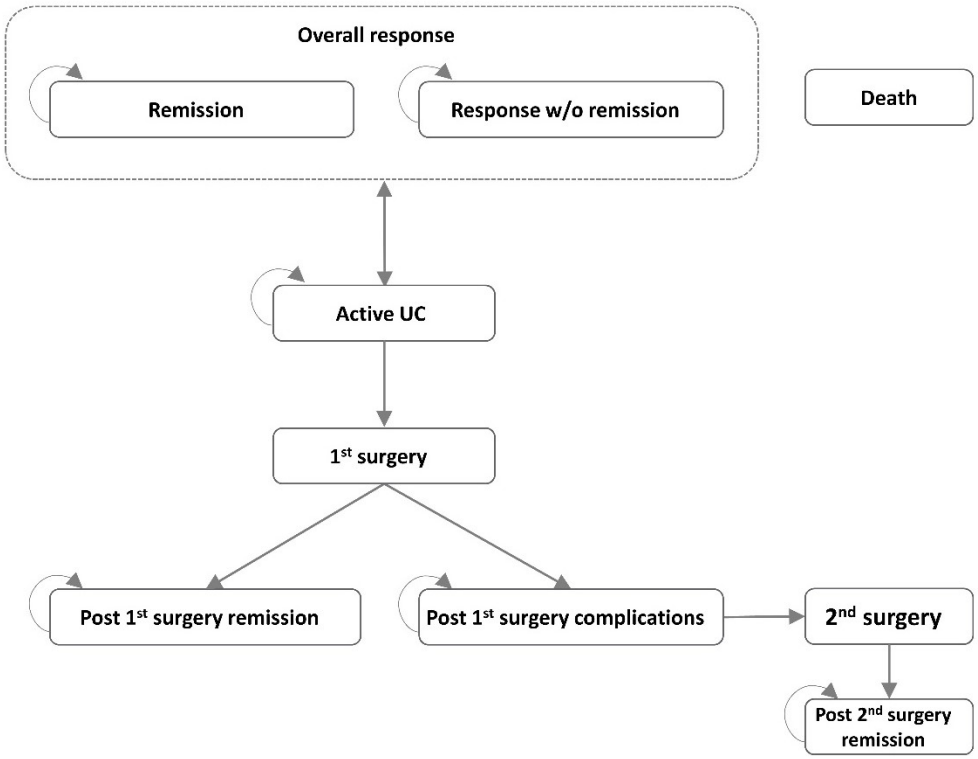
Finally, a background mortality rate is applied to all patients in the decision tree (not shown for simplicity) based on the 2018–2020 National Life Tables for the UK (109). The modelling of mortality is described in detail in Section B.3.3.4.

B.3.2.2.2 Markov model (maintenance)

The Markov model structure presented in Figure 10 is aligned with the structure used in TA633 for ustekinumab (35), and is comprised of nine health states: remission, response without remission, active UC, first surgery, post-first surgery remission, post-first surgery complications, second surgery, post-second surgery remission, and death. Please note that first surgery refers to the surgical intervention to resolve UC (with an assumed duration of 6 months) and second surgery refers to an intervention due to pouch failure (with an assumed duration of 6 months). It is estimated that 33.5% of patients incur post-surgery chronic complications, derived from TA633 reported via Royal College of Physicians (RCP) National clinical audit (2014) of inpatient care for adults with UC. Both first and second surgery can include acute complications. Post-first surgery chronic complications include wound infection, bowel obstruction, intra-abdominal abscess, or anastomotic leak. No chronic

complications are assumed for second surgery with all patients assumed to enter the post second surgery remission health state.

Figure 10: Long-term maintenance phase Markov model



Note: Health states are categorised by treatment response. Arrows represent permissible transitions between states while loops represent no transition. Death is possible from any health state.
Abbreviations: UC, ulcerative colitis; w/o, without.

The health states were adopted to illustrate the natural history of the disease, and, where possible, to align with the definitions used in the upadacitinib U-ACHIEVE induction, U-ACCOMPLISH induction, and U-ACHIEVE maintenance studies. A description of the model health states is provided in Table 56.

Table 56: Description of model health states

Health State	Definition
Remission	Full Mayo score of 0–2 with no individual subscore >1
Response without remission	A decrease from baseline in the Full Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1, but not meeting remission definition
Active UC	Full Mayo score of 6–12 (remission or response without remission not achieved)
First surgery	First surgical intervention to resolve UC (assumed duration of 6

Health State	Definition
	months); could include acute complications
Post-first surgery remission	No chronic complications from first surgery
Post-first surgery complications	Chronic complications from first surgery such as wound infection, bowel obstruction, intra-abdominal abscess, or anastomotic leak
Second surgery	Second surgical intervention due to pouch failure (assumed duration of 6 months); could include acute complications
Post-second surgery remission	No chronic complications from second surgery
Death	Absorbing state

Abbreviations: UC, ulcerative colitis.

At the end of each cycle in the Markov model, responders either remain on maintenance treatment (in remission or response without remission health states), lose response and transition to active UC (where they receive CT), or die (Figure 10). A situation wherein patients experiencing treatment failure receive a further line of (non-CT) treatment is considered in a scenario analysis. Patients are assumed to continue receiving maintenance treatment until loss of response (35) at which point they enter the active UC health state where they receive CT (Figure 10). Patients in the active UC health state can remain in that health state, have surgery, or die. Spontaneous remission is not considered in the base-case, in line with the preferred base-case for TA633; however, spontaneous remission has been considered in a scenario analysis.

Each Markov cycle is 4 weeks, and a lifetime horizon is considered, defined as patients reaching 100 years of age. No half cycle correction was applied in the Markov trace given the short cycle length of 4 weeks.

B.3.2.2.3 Surgery and surgery complications

Surgery is included as an option for patients in the active UC health state who are assumed to have exhausted all treatment options. Modelling surgery is in line with clinical practice and previous NICE TAs (TA342 [vedolizumab], TA547 [tofacitinib], and TA633 [ustekinumab]).

The model assumes that patients remain in the surgical health state for a total of 6 months, before transitioning into either the post-first surgery remission or post-first

surgery complications health states. To reflect patients spending 6 months in this health state, the first surgery health state was programmed as a sequence of six tunnel health states, each with a duration of 4 weeks (in line with the Markov model cycle length). In the surgery states, patients are assumed to stop all drug treatments (including CT) for the remaining time horizon.

The model allows patients to either remain in the post-first surgery remission health state, or transition into post-first surgery complications health state, where patients experience long-term chronic complications; patients either remain in this health state or undergo a second surgery. Patients remain in the second surgery health state for a total of 6 months, after which they are assumed to enter a post-second surgery remission health state for the remainder of the time horizon. Reflecting the first surgery health state, the second surgery health state is modelled as a sequence of six tunnel health states, each with a 4-week duration. It was assumed that patients can undergo up to two surgical interventions, following which no further complications occur.

As with TA633 (ustekinumab), inputs for the probability of surgery in the active UC health state and for surgery complications were taken from literature. An annual probability of first and second surgery of 0.47% was derived from Misra (2016) (110) and the proportion of surgeries that resulted in post-surgery complications (33.5%) was taken from the UK-based clinical audit, used in both TA547 (tofacitinib) and TA633 (ustekinumab).

Patients can die at any time over the modelled time horizon and remain in this absorbing state until the end of the time horizon.

Model outcomes

The model estimates total lifetime costs and total lifetime quality-adjusted life year (QALY) gains for each treatment arm. Incremental values are calculated (incremental costs and QALYs) as well as the incremental cost-effectiveness ratio (ICER), in line with the NICE reference case. Costs and QALYs accrued after the first year are discounted at an annual rate of 3.5% (111).

The model was developed following good modelling practices (112, 113) and aligns with NICE guidance (111). Key features of the economic analysis compared with previous UC appraisals are presented in Table 57.

Table 57: Features of the economic analysis compared with previous UC appraisals

Factor	Previous appraisals				Current appraisal	
	TA329 AG	TA342	TA547	TA633	Chosen values	Justification
Time horizon	Lifetime	10 years	Lifetime	Lifetime	Lifetime (100 years of age)	Adopted to capture all important differences in costs and outcomes between the technologies being compared per NICE reference case and aligned with previous TAs
Model structure	State-transition Markov cohort model – assessment group	Hybrid decision tree- Markov model	Markov model	Hybrid decision tree- Markov model	Hybrid decision tree- Markov model	Captures induction and maintenance phases. Consistent with previous appraisals
Cycle length	2 weeks	6 weeks (induction), 8 weeks (maintenance)	8 weeks	2 weeks	4 weeks	Short enough to capture changes in health state occupancy, and to address the concern in TA633 regarding the short (2 week) cycle length.
Treatment waning effect?	No	No	No	No	No	Consistent with previous appraisals
Source of utilities	Woehl et al.	GEMINI 1 (VED) and Punekar and Hawkins et al., utility decrements for adverse events were taken from	Woehl et al.	Woehl et al. and Arseneau et al.	Woehl et al. and Arseneau et al.	Aligned with TA633 (UST)

Factor	Previous appraisals				Current appraisal	
	TA329 AG	TA342	TA547	TA633	Chosen values	Justification
		clinical trials.				
Source of costs	Published literature	NHS list price and BNF, December 2013	2016/12 NHS reference costs, (eMIT), (MIMs), (PSSRU)	2017/18 NHS reference cost, BNF, MIMS, previous submissions, published literature	2019/20 NHS reference costs, BNF, published literature	Consistent with previous appraisals
Pharmacological treatment adverse events	No AEs were considered	Serious infection, tuberculosis, lymphoma, hypersensitivity and injection site reaction	Serious infection	Serious infection	Serious infection	Consistent with previous appraisals
Stopping rule	Yes	Yes	No	No	No	Consistent with recent appraisals
Spontaneous remission	No	No	No	No	No	Consistent with previous appraisals

Abbreviations: AG, assessment group; BNF, British National Formulary; eMIT, electronic Market Information Tool; HRQoL, health-related quality of life; MIMS, Monthly Index Medical Specialties; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year; QoL, quality of life; RCT, randomised controlled trial; TA, technology appraisal; UC, ulcerative colitis; UST, ustekinumab; VED, vedolizumab.

B.3.2.3 Intervention technology and comparators

The intervention in the analysis is upadacitinib 45 mg QD (induction dose), and upadacitinib 15 mg QD and upadacitinib 30 mg QD ('standard' and 'high' maintenance doses, respectively), in line with the anticipated European Medicines Agency (EMA) marketing authorisation and the NICE scope. The dosages used are those assessed in the U-ACHIEVE (50) and U-ACCOMPLISH (51)) induction studies, as well as the U-ACHIEVE maintenance study (52)).

Details of the intervention and comparator dose regimens are presented in Table 58. All comparators included are listed in the NICE final scope for this appraisal, except filgotinib, ozanimod, and CT. Both filgotinib and ozanimod are excluded from the analysis, despite being listed in the final scope, as they are both currently being evaluated by NICE and are not yet approved for use in, or considered standard of care for, patients with moderately to severely active UC. Similarly, CT is not considered an appropriate comparator for upadacitinib in the submission and is excluded from the analysis as CT would typically be given earlier in the treatment pathway, compared with biological treatment, and prior to where upadacitinib will be placed.

Adalimumab and infliximab biosimilars have been included, reflecting previous precedence in TA633 (ustekinumab), by assuming an equal efficacy and safety profile compared with the original products. Vedolizumab subcutaneous (SC) formulation is included alongside vedolizumab intravenous (IV) formulation. The efficacy and safety data for vedolizumab IV are leveraged as VISIBLE 1 did not present data for the bio-naïve and bio-exposed populations separately for inclusion in the network meta-analysis (NMA). Both infliximab and golimumab are excluded from the bio-exposed population as their respective studies exclude those with previous biologic treatment.

Table 58: Comparators included in the economic model for upadacitinib in patients with UC

Comparator	Bio-naïve population	Bio-exposed population
ADA (and biosimilar)	Included	Included
GOL	Included	Excluded
IFX (and biosimilar)	Included	Excluded
TOF	Included	Included
UST	Included	Included
VED†	Included	Included

Abbreviations: ADA, adalimumab; GOL, golimumab; IFX, infliximab; IV, intravenous; NMA, network meta-analysis; SC, subcutaneous; TOF, tofacitinib; UC, ulcerative colitis; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

[†]The efficacy and safety data for vedolizumab IV are applied to vedolizumab SC since the VISIBLE 1 trial did not present data for the bio-naïve and bio-exposed populations separately for inclusion in the NMA.

For maintenance therapy, both standard (15 mg QD) and high (30 mg QD) doses of upadacitinib are explored in separate analyses. This approach is taken to provide estimates of the cost-effectiveness of both doses versus the comparators.

For comparators, consistent with NICE TA633 (ustekinumab) (35), high dose maintenance is assumed for a proportion of patients which serves to reflect the patients who require a higher dose or more frequent treatment to maintain response. This has been incorporated as a separate parameter for specific therapies, i.e., the percent of patients receiving high dose maintenance. Consistent with NICE TA633 (ustekinumab), a dose mix is assumed, where a proportion of patients are treated with the standard maintenance dose, and the remaining patients treated with a higher maintenance dose. In the base-case it is assumed that 30% of patients on comparator treatments are on a higher maintenance dose (where relevant). This assumption is in line with TA633 for ustekinumab and is based on retrospective studies (114-117).

Details on the intervention and comparator dose regimens for the induction, extended induction (scenario analysis), and maintenance phases are presented in Table 59, Table 60, and Table 61, respectively.

Table 59: Dose regimen for intervention treatment and comparators for the induction phase

Treatment	Route of administration	Initial induction phase	Dosage
UPA	Oral	Duration: 8 weeks	45 mg QD
ADA	SC	Duration: 8 weeks	160 mg at Week 0, 80 mg at Week 2, then 40 mg every other week
GOL	SC	Duration: 6 weeks	Initial dose of 200 mg, followed by 100 mg at week 2
IFX 5 mg	IV	Duration: 8 weeks	5 mg/kg at Weeks 0, 2, 6
TOF	Oral	Duration: 8 weeks	10 mg BID for 8 weeks
UST	IV	Duration: 8 weeks	Single dose based on body weight (~6 mg/kg: ≤55 kg=260 mg; >55 kg to ≤85 kg=390 mg; >85 kg=520 mg) at Week 0
VED	IV	Duration: 8 weeks	300mg at Weeks 0, 2, 6
VED	SC	Duration: 8 weeks	300 mg at Weeks 0, 2, 6

Abbreviations: ADA, adalimumab; BID, twice daily; GOL, golimumab; IFX, infliximab; IV, intravenous; mg, milligram; QD, once daily; SC, subcutaneous; TOF, tofacitinib; UC, ulcerative colitis; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 60 Dose regimen for intervention treatment and comparators for the extended induction phase

Treatment	Route of administration	Extended induction duration	Dosage
UPA	Oral	Duration: 8 weeks	45 mg QD
GOL	SC	Duration: 8 weeks	200 mg
TOF	Oral	Duration: 8 weeks	10 mg BID for 8 weeks
UST	SC	Duration: 8 weeks	90 mg
VED	IV	Duration: 4 weeks	300 mg

Abbreviations: BID, twice daily; GOL, golimumab; IV, intravenous; mg, milligram; QD, once daily; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 61: Dose regimen for intervention treatment and comparators for the maintenance phase

Treatment	Route of administration	Standard Dosage	High Dosage
UPA	Oral	15 mg QD	30 mg QD
ADA	SC	40 mg Q2W	40 mg QW
GOL	SC	50 mg Q4W	100 mg Q4W
IFX 5 mg	IV	5 mg/kg Q8W	10 mg/kg Q8W
TOF	Oral	5 mg BID	10 mg BID
UST	IV	90 mg Q12W	90 mg Q8W
VED	IV	300 mg Q8W	300 mg Q4W
VED	SC	108 mg Q2W	108 mg Q2W

Abbreviations: ADA, adalimumab; BID, twice daily; GOL, golimumab; IFX, infliximab; IV, intravenous; QD, once daily; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

The assumed composition of CT used to determine costs of CT in the model is presented in Table 62. The proportion of use of each component part of CT has been derived from TA342. The methodology applied is consistent with TA633. The impact of change in these inputs on the model is minimal given the magnitude of the costs.

Table 62. Recommended dose regimen and assumed patient usage inputs for CT

Treatment	Dose	Utilisation
Azathioprine	2.5 mg/kg/day	39%
Mercaptopurine	1.5 mg/kg/day	15%
Methotrexate	17 mg/week	9%
5-aminosalicylate	2 g/week	13%
Prednisone	20 mg/day for 2 weeks	36%
Budesonide	3 mg/3 x day for 8 weeks	1%

Abbreviations: CT, conventional therapy; g, gram; kg, kilogram; mg, milligram.

B.3.3 Clinical parameters and variables

B.3.3.1.1 Patient characteristics

The model utilised data from the upadacitinib clinical trials for several model inputs and were split into the bio-naïve and bio-exposed patient populations (general model settings and baseline characteristics that were used in the model are described in Table 63 and Table 64). Data from the pooled (U-ACHIEVE induction and U-ACCOMPLISH induction) induction trials were used throughout the CEM for baseline characteristics and safety data.

Table 63: General model settings used in the economic model

Parameter	Mean	SE	DSA (Low; high values)	Source
Time horizon (years)	100	N/A	5; 100	Base: Assumption per NICE reference case.
Discount rate, costs	3.5%	N/A	0%; 6%	Base: NICE reference case. Low/ high: NICE recommended scenarios
Discount rate, utilities	3.5%	N/A	0%; 6%	

Abbreviations: DSA, deterministic sensitivity analysis; N/A, not applicable; NICE, National Institute for Health and Care Excellence; SE, standard error.

Table 64: Patient baseline characteristics (Induction trials [pooled ISE1 population])

Characteristic	Bio-naïve population	Bio-exposed population
Mean age, years (SE)	42.99 (0.79)	42.69 (0.79)
Number of male patients, n (%)	209 (66.8)	203 (58.5)
Mean weight, kg (SE)	73.09 (1.06)	72.3 (0.94)
Number of patients <55kg, n (%)	53 (16.9)	56 (16.1)

Characteristic	Bio-naïve population	Bio-exposed population
Proportion of patients 55–85kg, n (%)	194 (62.0)	221 (63.7)
Proportion of patients >85kg, n (%)	66 (21.1)	70 (20.2)

Abbreviations: kg, kilogram; n, number; SE, standard error.
Source: Data from UPA induction trials (pooled ISE1 population).

B.3.3.1.2 Efficacy inputs

Clinical remission in the upadacitinib trials was defined as Full Mayo score of 0–2, with no individual subscore >1.

Clinical response in the upadacitinib trials was defined as a decrease from baseline in the Full Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1, but not meeting remission definition.

The proportion of patients achieving clinical remission and response (without remission) during induction was informed by Phase 3 clinical trials.

The efficacy inputs in the model are as follows:

- Percentage of responders and percentage of remitters at Week 8 (initial induction)
- Percentage of responders and percentage of remitters at Week 16, among Week 8 non-responders (extended induction)
- Percentage of responders and percentage of remitters who maintain a response during maintenance treatment

B.3.3.1.3 Induction phase patient transitions

The proportion of patients achieving remission and response at the end of the induction period was obtained from evidence synthesised via an NMA (see Section B.2.9). The treatment efficacy was derived from an SLR and synthesised via an NMA. Two separate networks were formed for the bio-naïve and bio-exposed populations.

For each treatment, the proportion of patients achieving overall response and remission were estimated in the NMA. The proportion of patients in response without remission was calculated as the difference between the proportion of patients with overall response and proportion of patients in remission.

The proportions of patients achieving remission or response without remission at the end of induction treatment in the-base case, estimated using a binary response model (118), for bio-naïve and bio-exposed populations are presented in Table 65 and Table 66, respectively.

Table 65: Clinical remission and response at the end of induction in the base-case: bio-naïve population NMA – random and fixed effects adjusted models

Treatment	Remission	Response without remission
UPA 45	[redacted]	[redacted]
ADA 160/80	[redacted]	[redacted]
ADA 160/80 biosimilar	[redacted]	[redacted]
GOL 200/100	[redacted]	[redacted]
IFX 5	[redacted]	[redacted]
IFX 5 biosimilar	[redacted]	[redacted]
TOF 10	[redacted]	[redacted]
UST 6	[redacted]	[redacted]
VED 300	[redacted]	[redacted]
VED 108	[redacted]	[redacted]
Model	Random effects	Fixed effects adjusted

Abbreviations: ADA, adalimumab; GOL, golimumab; IFX, infliximab; NMA, network meta-analysis; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 66: Clinical remission and response at the end of induction in the base-case: bio-exposed population NMA – random effects models

Treatment	Remission	Response without remission
UPA 45	[redacted]	[redacted]
ADA 160/80	[redacted]	[redacted]
ADA 160/80 biosimilar	[redacted]	[redacted]
TOF 10	[redacted]	[redacted]
UST 6	[redacted]	[redacted]
VED 300	[redacted]	[redacted]
VED 108	[redacted]	[redacted]
Model	Random effects	Random effects

Abbreviations: Abbreviations: ADA, adalimumab; GOL, golimumab; IFX, infliximab; NMA, network meta-analysis; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

In a scenario analysis, an extended induction response was allowed based on data from clinical trials. The proportions of patients achieving remission or response without remission in the base case, for the bio-naïve and bio-exposed populations, are presented

in Table 67 and Table 68, respectively, for extended induction for treatments where there was evidence available.

Table 67: Clinical remission and response at the end of extended induction in the base-case: bio-naïve population

Treatment	Remission	Response without remission	Reference
UPA 45	[redacted]	[redacted]	Pooled upadacitinib trials: Proportion of Subjects with Clinical Remission /Response per Adapted Mayo Score at Week 16
GOL 200/100	15.50%	12.60%	TA633
IFX 5	15.50%	12.60%	TA633
IFX 5 biosimilar	15.50%	12.60%	TA633
TOF 10	12.50%	27.90%	TA633
UST 6	13.50%	51.90%	TA633
VED 300	16.00%	20.00%	TA633
VED 108	16.00%	20.00%	TA633

Abbreviations: GOL, golimumab; IFX, infliximab; NMA, network meta-analysis; TA, technology appraisal; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 68: Clinical remission and response at the end of extended induction in the base-case: bio-exposed population

Treatment	Remission	Response without remission	Reference
UPA 45	[redacted]	[redacted]	Pooled upadacitinib trials: Proportion of Subjects with Clinical Remission /Response per Adapted Mayo Score at Week 16
TOF 10	5.90%	31.80%	TA633
UST 6	1.40%	45.10%	TA633
VED 300	6.70%	19.70%	TA633
VED 108	6.70%	19.70%	TA633

Abbreviations: NMA, network meta-analysis; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

The proportion of patients not responding to treatment (moving to active UC) at the end of the delayed response phase was estimated as the difference between the proportion of patients alive and those who responded to treatment. This methodology was used for both early induction responders and delayed responders.

B.3.3.1.4 Maintenance phase patient transition

The following section describes the approach taken to calculate the transition probabilities for patients on maintenance treatment. Patients who are defined as responders after the

initial induction period remain on treatment moving into the Markov element of the economic model. This reflects clinical practice where, following a response to induction treatment, the same active treatment would be given during the maintenance phase.

The probability that a patient remains in the states of remission or response without remission at 52 weeks, based on NMA results for each comparator for the bio-naïve and bio-exposed populations, is presented in Table 69 and Table 70, respectively, for those who received the 'standard' maintenance dose.

Table 69: Probability of remission or response without remission at 52 weeks conditional on response at induction on the 'standard' maintenance dose for bio-naïve patients

Treatment	Remission	Response without remission
UPA 15 QD	[redacted]	[redacted]
ADA 40 Q2W	[redacted]	[redacted]
ADA 40 Q2W biosimilar	[redacted]	[redacted]
GOL100 Q4W	[redacted]	[redacted]
IFX 5 Q8W	[redacted]	[redacted]
IFX 5 Q8W biosimilar	[redacted]	[redacted]
TOF 5 BID	[redacted]	[redacted]
UST 90 Q12W	[redacted]	[redacted]
VED 300 Q8W	[redacted]	[redacted]
VED 108 Q2W	[redacted]	[redacted]
Model	Random effects	Random effects

Abbreviations: ADA, adalimumab; BID, twice a day; GOL, golimumab; IFX, infliximab; QD, every day; Q2W, every other week; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 70: Probability of remission or response without remission at 52 weeks conditional on response at induction on the 'standard' maintenance dose for the bio-exposed patients

Treatment	Remission	Response without remission
UPA 15 QD	[redacted]	[redacted]
ADA 40 Q2W	[redacted]	[redacted]
ADA 40 Q2W biosimilar	[redacted]	[redacted]
TOF 5 BID	[redacted]	[redacted]
UST 90 Q12W	[redacted]	[redacted]
VED 300 Q8W	[redacted]	[redacted]
VED 108 Q2W	[redacted]	[redacted]
Model	Random effects	Random effects

Abbreviations: ADA, adalimumab; BID, twice a day; QD, every day; Q2W, every other week; Q8W, every 8 weeks; Q12W, every 12 weeks; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

The probability that a patient remains in the states of remission or response without remission at 52 weeks based on NMA results for each comparator for the bio-naïve and bio-exposed populations, is presented in Table 71 and Table 72, respectively, for those patients who received the 'high' maintenance dose.

Table 71: Probability of remission or response without remission at 52 weeks conditional on response at induction on the 'high' maintenance dose for the bio-naive patients

Treatment	Remission	Response without remission
UPA 30 QD	[redacted]	[redacted]
ADA 40 QW	[redacted]	[redacted]
ADA 40 QW biosimilar	[redacted]	[redacted]
GOL100 Q4W	[redacted]	[redacted]
IFX 10 Q8W	[redacted]	[redacted]
IFX 10 Q8W biosimilar	[redacted]	[redacted]
TOF 10 BID	[redacted]	[redacted]
UST 90 Q8W	[redacted]	[redacted]
VED 300 Q4W	[redacted]	[redacted]
VED 108 Q2W	[redacted]	[redacted]
Model	Random effects	Random effects

ADA, adalimumab; BID, twice a day; GOL, golimumab; IFX, infliximab; QD, every day; QW, every week; Q2W, every other week; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 72: Probability of remission or response without remission at 52 weeks conditional on response at induction on the 'high' maintenance dose for the bio-exposed patients

Treatment	Remission	Response without remission
UPA 30 QD	[redacted]	[redacted]
ADA 40 QW	[redacted]	[redacted]
ADA 40 QW biosimilar	[redacted]	[redacted]
TOF 10 BID	[redacted]	[redacted]
UST 90 Q8W	[redacted]	[redacted]
VED 300 Q4W	[redacted]	[redacted]
VED 108 Q2W	[redacted]	[redacted]
Model	Random effects	Random effects

Abbreviations: ADA, adalimumab; GOL, golimumab; IFX, infliximab; N/A, not applicable; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.3.1.4.1 Modelling loss of response in maintenance

During the maintenance phase of the model, a constant probability of loss of remission/response is applied to patients in the remission and response without remission health states. This is based on the probability of loss of remission/response calculated for each active comparator in the maintenance NMA and is based on published clinical trial

results. The same probability of loss of remission/response is applied to both 'remission' and 'response without remission' health states throughout the model's time horizon.

The probability of loss of response per cycle was derived as 1 minus the ratio of the proportion of patients responding to treatment at the end of the maintenance phase and those responding to treatment at the end of the induction phase and adjusting for the length of the maintenance period. The maintenance length was calculated by subtracting the duration of the induction phase from the total trial duration (Table 73).

Patients who maintain overall response in each cycle are split between the 'remission' and 'response without remission' health states based on a fixed proportion, namely, the 'remission' and 'response without remission' probabilities from the maintenance NMA.

The approach described for modelling loss of remission/response is aligned with that adopted in TA547 (tofacitinib), reflecting the lack of availability of mid-maintenance period response and remission data for comparators that may permit a more complex approach. A scenario analysis was run considering a lower probability of loss of response beyond 12 months.

Table 73: Duration of induction and maintenance phase

Treatment	Standard induction (Weeks)	Extended induction (Weeks)	Maintenance phase for responders at standard induction (Weeks)
UPA 45	8	8	52
ADA 160/80	8	-	44
ADA 160/80 biosimilar	8	-	44
GOL 200/100	6	8	54
IFX 5	8	6	46
IFX 5 biosimilar	8	6	46
TOF 10	8	8	52
UST 6	8	8	44
VED 300	8	4	46
VED 108	8	4	46

Abbreviations: ADA, adalimumab; GOL, golimumab; IFX, infliximab; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.3.2 Surgery and surgery complications

As it was assumed that surgery-related inputs do not vary between the bio-naïve and bio-exposed populations, one set of inputs was therefore used for both subgroups.

The model included two phases of surgery, each lasting 6months to account for the possibility of staged procedures. This approach is different to TA547 (tofacitinib) and TA342 (vedolizumab), in which surgery was treated as a one-off event. However, it is consistent with TA633 (ustekinumab), to better reflect the usual process of staged procedures including phase 1: colectomy with ileostomy followed by either ileal pouch-anal anastomosis (IPAA) (pouch) surgery or permeant ileostomy; and phase 2: potential revision surgery due to pouch failure. Within the model, it is assumed that all patients within both subgroups who have revision (second) surgery incur no chronic complications following remission. It is expected that the number of patients affected would be small, and therefore have a minimal impact on the overall costs and QALYs.

B.3.3.2.1 First and second surgery

In the base-case, the annual probability of first and second surgery was taken from Misra (2016) (110) as a recent UK study with a large population which has been used in previous submissions (TA547 [tofacitinib] and TA633 [ustekinumab]). Based on a targeted literature review, a total of eight studies were identified for first surgery (Table 74). The model estimated the proportion of patients having first surgery at each cycle by applying the derived probability of first surgery to the proportion of patients in the active UC health state.

For the second surgery, an assumption was made that the probability was equal to the probability of first surgery which aligns with the approach taken in TA633 (ustekinumab).

Table 74: First surgery literature review results

Author/ year	Sample size	Country	Follow-up duration	Converted to annual rate
Base-case				
Misra 2016	73,318	UK	15 years	0.47%
Alternative sources				
Actis 2007	34	Italy	7 years	13.93%
Gower-Rousseau 2009	113	France	Median 6.4 years	4.18%
Molnar 2011	183	Hungary	Mean 4.4 years	6.22%
Mocciaro 2012	65	Italy	Mean 4.6 years	11.69%
Gustavsson 2007	158	Sweden	Mean 14.4 years	5.21%
Solberg 2009	843	Norway	10 years	1.03%
Chhaya 2015	1,766	UK	20 years	0.59%

Abbreviations: UK, United Kingdom.

B.3.3.2.2 Post-first surgery complications

The proportion of surgeries that resulted in post-surgery complications was derived from the UK-based clinical audit used by both TA547 (tofacitinib) and TA633 (ustekinumab) (Table 75). Two alternative publications were identified but not used in past submissions as they were not conducted in the UK, with the data used in previous appraisals being selected due to their UK setting. The proportion was applied to the patients alive at the end of the first surgery to estimate the proportion of patients entering the post first surgery complications state following surgery.

Table 75: Post-first surgery complications

Author/ year	Country	% of patients with chronic complications
Base case		
TA547 and TA633 (based on the National clinical audit of 2013 for inpatient care for adults with UC)	UK	33.5% (average of 32% for elective and 35% for non-elective surgery)
Alternative sources		
Mahadevan et al. 2002	US	32%
Ferrante et al. 2008	US	27%

Abbreviations: TA, technology appraisal; UC, ulcerative colitis; UK, United Kingdom; US, United States.

B.3.3.2.3 Post-first surgery remission to chronic complications

For the annual probability of delayed chronic complications post-surgery, four publications were identified which had a minimum of one year of follow-up. These studies, along with a calculated annualised risk of complications, are presented in Table 76; estimates range from 1.85% to 9.04% suggesting significant heterogeneity. Within TA633 (ustekinumab), the publication by Segal et al. 2018 (119) was selected due to it being the only publication from the UK; however, for the current appraisal the annual probability of achieving delayed chronic complications for post-surgery was estimated as a weighted average across the four studies, rather than choosing an estimate from one small study alone. The model estimated the proportion of patients transitioning from the post first surgery health state to post first surgery complications state at each cycle by applying the estimated probability of post first surgery complications to the patients in the post-first surgery health state.

Table 76: Post-first surgery complications following post-first surgery remission literature review results

Author/ year	Sample size	Country	Follow-up duration	Risk of complications per year (calculated)
Segal et al (2018)	39	UK	6 years	3.25%
Gonzalez et al (2014)	60	Argentina	10 years	1.85%
Ferrante et al (2008)	173	Belgium	6.5 years	9.04%
Suzuki et al (2012)	284	Japan	10 years	4.70%
Weighted average	**556**			**5.64%**

Abbreviations: UK, United Kingdom.

B.3.3.2.4 Post second surgery complications

For simplicity, and to align with TA633 (ustekinumab), it was assumed that following a second surgery, all patients transition to the post-second surgery remission health state and no further surgical complications are modelled.

B.3.3.3 Treatment safety: adverse events

Consistent with the two most recent NICE appraisals in UC (TA547 and TA633), the model considered only serious infections adverse events (AEs). These were selected for inclusion due to their high cost. Adverse events were modelled during the induction period only. Discontinuation due to AEs is not explicitly modelled and serious infection is treated as a one-time event during induction. The probability of serious infections for each treatment was taken from the induction NMA (See Section B.2.9). The probability of serious infection was low (<1%) in each treatment arm.

Table 77: Probability of serious infections during the induction phase

Treatment	8-week probability
UPA 45	1.01%
ADA 160/80	1.02%
ADA biosimilar	1.02%
GOL 200/100	0.19%
IFX 5	0.65%
IFX 5 biosimilar	0.65%
TOF	0.74%
UST	0.21%
VED 300	0.40%
VED 108	0.40%

Treatment	8-week probability
Model	Random effects

Abbreviations: ADA, adalimumab; GOL, golimumab; IFX, infliximab; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.3.4 Mortality

Patients in the model are at risk of death in each cycle. In most health states, the risk of death is modelled in line with UK general population mortality based on data presented in the Office for National Statistics (ONS) National Life Tables for 2018-20 and weighted according to the model's baseline male to female ratio. An excess risk of death due to surgery of 30% was applied to the surgery health states, based on published data (120), and in line with the assumption in TA633 (ustekinumab).

B.3.4 Measurement and valuation of health effects

Health effects in the model are expressed as QALYs.

The utility data from U-ACHIEVE induction, U-ACCOMPLISH induction, and U-ACHIEVE maintenance studies are described in B.3.4.1.

The base-case model incorporates utilities taken from the literature, which is consistent with previous submissions to NICE (TA633 [ustekinumab], TA329 [adalimumab, golimumab, infliximab] and TA547 [tofacitinib]). A summary of the utility data identified is provided in B.3.4.3.

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

In the upadacitinib clinical trials, EuroQol 5-dimension-5-level (EQ-5D-5L) utility data were collected at baseline (Week 0), Week 2, Week 8, and Week 16 during the induction period, and at baseline (Week 0) and Week 52 in the maintenance period.

Apart from the EQ-5D-5L, data were collected using a series of patient questionnaires:

- Inflammatory Bowel Disease Questionnaire (IBDQ)
- Short Form 36 (SF-36)
- Work Productivity and Activity Impairment (WPAI)
- Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)
- Patient Global Impression of Severity (PGIS)
- UC Symptoms Questionnaire (UC-SQ)

B.3.4.2 Mapping

Not applicable as literature data EuroQol 5-dimension-3-level (EQ-5D-3L) were used in the model. Data presented in Appendix H (changes in utilities in upadacitinib trials) were collected as EQ-5D-5L and mapped using the Hernandez-Alava algorithm (Hernández Alava et al. 2017) as per NICE reference case.

B.3.4.3 Health-related quality of life studies

An SLR was conducted on 06 January 2022 to identify studies reporting on the health-related quality of life (HRQoL) of patients with moderately to severely active UC. Full details of the methodology and results of included studies are presented in Appendix H.

B.3.4.4 Adverse reactions

Aligning with TA633 (ustekinumab), a disutility for serious infection (0.156) was calculated from Stevenson et al. (2016) (121) and applied to patients experiencing this adverse event during the induction period. The disutility was adjusted for the expected duration of symptoms during the induction phase (8-week probability). This adapted duration reflects an adjustment made in TA329 (adalimumab, golimumab, infliximab), in which the duration of symptoms was associated with 28 days.

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

Utility values for most health states were obtained from Woehl et al. (2008) (122) and represent values which have previously been used in NICE appraisals in UC (TA140, TA262, TA342, TA547, TA633). Woehl et al. (2008) (122) used the EQ-5D-3L questionnaire to collect responses from patients with active UC in the UK (n=180), generating utility scores for patients in remission, mild disease, moderately to severely active disease, and post-colectomy (without complications). These values were used to inform the utility values for the following health states: remission, response without remission, active UC, first and second surgery remission. The availability of utility values for most health states in the model is a benefit of the Woehl et al. (2008) data (122).

The utility values derived from the literature were deemed the most appropriate as they are the most reflective of patients treated in clinical practice. Collecting utility values from real-world clinical practice can provide more appropriate values than those in clinical trials, as real-world data is more representative of the population who would receive the

intervention being evaluated. The Hawthorne Effect can impact the generalisability of clinical research to routine practice, as it is the inclination of people who are part of an experiment to change or improve their behaviour due to being studied, rather than direct changes in the experiment. The effect has been shown to have a significant impact on quality of life (QoL) estimates (123). Literature suggests that more intense researcher contact may lead to a better recognition of patient needs, due to a greater awareness of the diagnosis (and resulting disability), therefore impacting the perception of QoL. The Hawthorne effect can be mitigated if patients are not aware they are being observed (103).

For the utility values not reported in Woehl et al. (2008) (122), utility values for first surgery, second surgery, and post-first-surgery complications from Arseneau et al. 2006 (124) were used. Arseneau et al. (2006) obtained utility values from 48 active UC patients using both a TTO and VAS methods (124). To be consistent with the NICE reference case, utility weights derived from the time trade-off (TTO) method were preferred over the visual analogue scale (VAS) scores.

To obtain the utility for first and second surgery, a weighted average of the utility values for ileostomy (0.57) and IPAA (0.68) was calculated by assuming 60% of patients had an ileostomy and 40% had IPAA (125). The weighted average was calculated as 0.61.

The utility value of the post-first-surgery complications health state was obtained by estimating the weighted average of the utilities for chronic pouchitis (0.40), obstruction (0.21) and post-colectomy UC (0.41) and their respective weights (54.82%, 32.14%, and 13.04%) to give a utility value of 0.34.

Utility values used for all health states in the model are presented in Table 78. Scenario analyses explored alternative utility values for remission, response without remission, active UC, and post-surgery remission derived from Swinburn et al. (2012) (126) and Vaizey et al. (2014) (127).

Table 78: Utility values used in the base-case and scenario analysis model

Health state	Base-case value	Scenario 1: Swinburn et al. (2012) analysis	Scenario 2: Vaizey et al. (2013) analysis	Base-case reference
Active UC	0.410	0.55	0.66	Woehl et al. (2008)
Remission	0.870	0.91	0.86	Woehl et al. (2008)
Response (no remission)	0.760	0.80	0.77	Woehl et al. (2008)
Surgery (1st and 2nd)	0.610	-	-	Arseneau et al. (2006)
Post-surgery remission (1st and 2nd)	0.720	0.59	-	Woehl et al. (2008)
Post-surgery complications	0.340	-	-	Arseneau et al. (2006)

Abbreviations: UC, ulcerative colitis.

B.3.4.5.1 Utility adjustments based on age

Considering the lifetime horizon of the analysis, a general decline in HRQoL with age was modelled in the base-case by applying the method described in Ara and Brazier (2010) (128). Specifically, the utility values are adjusted to account for the natural decline in utility as patients age, using the baseline age and proportion of males in the model. The regression model was based on EQ-5D data from the Health and Survey for England in 2003 and 2006:

U_base (age,gender) = 0.9508566 + 0.0212126 * Male - 0.0002587 * Age - 0.0000332 * (Age)^2

Age and gender were derived from the induction arm from the U-ACHIEVE induction and U-ACCOMPLISH induction studies (pooled ISE1 population).

Table 79: Summary of utility values used in the cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Active UC	0.410	[0.385 to 0.435]	B.3.4.5, page 149	Aligned with past appraisals and representative of patients with moderate-to-severe UC in the UK
Remission	0.870	[0.859 to 0.881]	B.3.4.5, page 149	
Response (no remission)	0.760	[0.747 to 0.773]	B.3.4.5, page 149	
Surgery (1st and 2nd)	0.610	[0.599 to 0.621]	B.3.4.5, page 149	
Post-surgery remission (1st and 2nd)	0.720	[0.696 to 0.744]	B.3.4.5, page 149	
Post-surgery complications	0.340	[0.329 to 0.351]	B.3.4.5, page 149	

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Serious infection	-0.156	[-0.187 to -0.125]	B.3.4.4, page 149	

Abbreviations: UC, ulcerative colitis; UK, United Kingdom

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

An SLR was conducted on 06 January 2022 to identify studies reporting on the cost and healthcare resource use (HCRU) data of patients with moderately to severely active UC. Full details of the methodology and results are presented in Appendix I.

Cost and HCRU inputs considered in the base-case analysis comprised of direct medical costs including drug acquisition costs, administration costs, costs associated with the management of AEs, the cost of surgery, and background disease management cost. Costs were collected from published literature, previous NICE submissions (TA342, TA547 and TA633), NHS Reference Costs for 2019/20 and the British National Formulary (BNF) (2022).

Drug acquisition costs were calculated for the whole induction duration and per year of maintenance treatment. Total maintenance costs were derived by calculating the cost for each treatment dosing regimen (either standard or high dose), and then applying the proportion of patients who were on the ‘standard’ or ‘high’ maintenance dose, respectively.

Cost details of each treatment, including the upadacitinib, all relevant comparators and concomitant treatments are provided in Appendix K.

B.3.5.1 Intervention and comparators’ costs and resource use

B.3.5.1.1 Drug acquisition costs

Total induction and annual maintenance costs are presented in Table 80 (induction bio-naïve), Table 81 (induction bio-exposed), Table 82 (maintenance bio-naïve), and Table 83 (maintenance bio-exposed).

For infliximab, costs were based on an average weight of 73.09 kg for bio-naïve and 72.30 kg for bio-exposed patients based on data from the U-ACHIEVE induction and U-ACCOMPLISH induction studies (pooled ISE1 population). For the ustekinumab IV

dose, the proportion of patients in each weight category (based on the upadacitinib trials) is multiplied by the corresponding number of vials, in line with the product SmPC. Specifically, two vials for patients with body weight ≤55 kg, three vials for patients with body weight of 55–85 kg, and four vials for patients with a body weight of >85 kg.

Drug acquisition costs for comparators were taken from the BNF for comparators while the PAS price was used for upadacitinib. Dosing regimens used to calculate the total drug cost were obtained from the SmPCs for each comparator treatment, while the draft SmPC was used for upadacitinib. When multiple options were available, the lowest price was used. The net (PAS) price for upadacitinib was used in the analysis.

Table 80: Treatment costs for the induction phase (bio-naïve)

Treatment/ Dosing	Total used during induction	Unit price (£)	Total induction cost (£)[†]
UPA 45 mg	56	[redacted]	[redacted]
ADA (160/80/40 mg)	8	352.14	2,817.12
ADA biosimilar (160/80/40 mg)	8	316.80	2,534.40
GOL (200/100 mg)[‡]	3	762.97	2,288.91
IFX IV (5 mg/kg)	11	419.62	4,600.57
IFX biosimilar (Flixabi) (5 mg/kg)	11	377.00	4,133.30
TOF (10 mg)	112	24.64	2,767.70
UST (6 mg/kg)	3	2,147.00	6,530.17
VED (300 mg)	3	2,050.00	6,150.00

[†]For weight-based drugs, displayed costs are based on an average weight of 73.09 kg for bio-naïve and 72.30 kg for bio-exposed patients.
[‡]Golimumab was approved by NICE under a PAS by which the cost of the 100 mg/1 mL dose is available at the same price as the 50 mg/0.5 mL dose.
Abbreviations: ADA, adalimumab; GOL, golimumab; IFX, infliximab; IV, intravenous; PAS, patient access scheme; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 81: Treatment costs for the induction phase (bio-exposed)

Treatment/ Dosing	Total used during induction	Unit price (£)	Total induction cost (£)†
[redacted]	[redacted]	[redacted]	[redacted]
ADA (160/80/40 mg)	8	352.14	2,817.12
ADA biosimilar (169/ 80/40 mg)	8	316.80	2,534.40
TOF (10 mg)	112	24.64	2,767.70
UST (6 mg/kg)	3	2,147.00	6,527.62
VED (300 mg)	3	2,050.00	6,150.00

†For weight-based drugs, displayed costs are based on an average weight of 73.09 kg for bio-naïve and 42.69 kg for bio-exposed patients.
Abbreviations: ADA, adalimumab; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 82: Treatment costs for the maintenance phase (bio-naïve)

Treatment	Dosing	Maintenance phase dosage	Total maintenance annual cost (£)†
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
ADA	Standard dose	40 mg Q2W	9,155.64
	High dose	40 mg QW	18,311.28
ADA biosimilar	Standard dose	40 mg Q2W	8,236.80
	High dose	40 mg QW	16,473.60
GOL	Standard dose	50 mg Q4W	9,918.61
	High dose	100 mg Q4W	9,918.61
IFX	Standard dose	5 mg/kg Q8W	10,734.66
	High dose	10 mg/kg Q8W	21,469.31
IFX biosimilar	Standard dose	5 mg/kg Q8W	9,644.36
	High dose	10 mg/kg Q8W	9,644.36
TOF	Standard dose	5 mg BID	8,970.39
	High dose	10 mg BID	17,940.78
UST	Standard dose	90 mg Q12W	10,735.00
	High dose	90 mg Q8W	15,029.00
VED	Standard dose	300 mg Q8W	14,350.00
	High dose	300 mg Q4W	26,650.00
VED SC	Standard dose	108 mg Q2W	13,325.00

†For weight-based drugs, displayed costs are based on an average weight of 73.09kg for bio-naïve patients.
Abbreviations: BID, twice daily; kg, kilogram; mg, milligram; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; QD, once-daily.
Abbreviations: Abbreviations: ADA, adalimumab; GOL, golimumab; IFX, infliximab; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 83: Treatment costs for the maintenance phase (bio-exposed)

Treatment	Dosing	Maintenance phase dosage	Total maintenance annual cost (£)*
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
ADA	Standard dose	40 mg Q2W	9,155.64
	High dose	40 mg QW	18,311.28
ADA biosimilar	Standard dose	40 mg Q2W	8,236.80
	High dose	40 mg QW	16,473.60
TOF	Standard dose	5 mg BID	8,970.39
	High dose	10 mg BID	17,940.78
UST	Standard dose	90 mg Q12W	10,735.00
	High dose	90 mg Q8W	15,029.00
VED	Standard dose	300 mg Q8W	14,350.00
	High dose	300 mg Q4W	26,650.00
VED SC	Standard dose	108 mg Q2W	13,325.00

†For weight-based drugs, displayed costs are based on an average weight of 73.09 kg for bio-naïve and 72.30 kg for bio-exposed patients.
Abbreviations: ADA, adalimumab; BID, twice daily; mg, milligram; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; QD, every day; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.5.1.2 Administration costs

The administration cost for IV drugs were assumed to equal the cost of a non-admitted face-to-face follow-up outpatient visit (Healthcare Resource Group [HRG] code: WF01A). The unit costs were taken from 2019/20 NHS Reference Costs value and estimated to be £125.44.

Subcutaneous injections had zero costs associated with administration, as patients are assumed to self-administer their medication. This assumption is consistent with TA633 (ustekinumab).

B.3.5.2 Health-state unit costs and resource use

Disease management resource use included outpatient (consultant visit, blood test, and elective endoscopy) and inpatient (emergency endoscopy, care without colectomy and stoma care) visits. Resource use data was derived from Tsai et al. 2008 (129), a UK cost-effectiveness model (CEM), which reported the annual resource use for each of the model's health states as determined by a panel of UK gastroenterologists. Costs were updated based on the 2019-20 NHS Reference Costs where possible.

As Tsai et al. 2008 (129) did not include resource use for surgery health states, the cost of surgery was calculated based on Buchanan et al. (2011) (125) in line with TA633 (ustekinumab). The total cost assumed 40% of the costs were derived from restorative IPAA surgery and 60% was attributed to ileostomy surgery, with one acute complication included to the total cost of surgery. Costs were inflated to 2020/21 prices using the NHS Cost Inflation Index (NHSCII) in PSSRU 2021, resulting in a total cost for the first surgery of £15,783. The second surgery was assumed to be the same cost as ileostomy, which was inflated to 2020/21 prices using the NHSCII index in PSSRU 2021, resulting in a cost of £11,337.

Unit costs and annual resource use for all health states are presented in Table 84, with annual costs per health states reported in Table 85. The model assumes that the same costs apply to both bio-naïve and bio-exposed patients.

Table 84: Health care resource use by health state

	Resource use per year, by health state							
Resource item	**HRG code**	**Unit Cost (NHS reference costs)**	**Remission**	**Response without remission**	**Active UC**	**first/second surgery‡**	**Post-first/second surgery remission**	**Post-first surgery complications**
Outpatient visit								
Consultant visit	WF01A; WF01B	£148.12	2	4.5	6.5	6.5	1.5	1.75
Blood test	DAPS05	£2.53	3.25	3.9	6.5	6.5	1.5	3.25
Elective endoscopy	FE32Z (outpatient procedure)	£332.89	0.2	0.5	2	2	1.25	0.65
Inpatient visit								
Emergency endoscopy	FE32Z (non-elective inpatient short stay)	£621.69	0	0.25	0.75	0.75	0.5	0.13
Care without colectomy	FD02E; FD02F; FD02G, FD02H (elective inpatient)	£1,780.97	0	0	0.15	0.15	0	3.25
Stoma care (post-colectomy)	-	£449.21†	-	-	-	1	-	-

Abbreviations: HRG, healthcare resource group; NHS, National Health Service; UC, ulcerative colitis.
All unit costs are based on NHS reference costs 2019/20, unless otherwise stated. All resource use per year reported in the table are from Tsai et al. 2008 (129), unless otherwise stated.
†Stoma care costs are derived from cost estimates by Buchanan et al. 2011 and uprated for nurse costs (PSSRU 2017) and HCHS inflation for consumables. The original cost included as per TA547 is £426.36 per person in post-surgery assuming 40% have a stoma.
‡Assume the same resource use as active UC with the addition of stoma care

Table 85: Total annual cost of resource use by health state

Health state	Cost per health state (£), per year	SE (£)	DSA (low; high values)	Reference
Remission	371.05	74.21	297; 445	TA633 (UST) via Tsai et al. (2008) (129) for outpatient visits, blood tests, emergency and elective endoscopies and care without colectomy. Costs based on NHS reference cost 2019-20.
Response (without remission)	998.29	199.66	799; 1,198	TA633 (UST) via Tsai et al. (2008) (129) for outpatient visits, blood tests, emergency and elective endoscopies and care without colectomy. Costs based on NHS reference cost 2019-20.
Active UC	2,378.44	475.69	1,903; 2,854	TA633 (UST) via Tsai et al. (2008) (129) for outpatient visits, blood tests, emergency and elective endoscopies and care without colectomy. Costs based on NHS reference cost 2019-20.
Surgery	2,827.64	565.53	2,262; 3,393	Assumed equal resource use as Active UC with the addition of stoma care. Stoma care cost inflated to 2020/21 prices using value in TA547 and the NHSCII index in PSSRU 2021.
Post-surgery remission	952.93	190.58	762; 1,144	TA633 (UST) via Tsai et al. (2008) (129). Outpatient visits, blood tests, emergency and elective endoscopies NHS reference costs 2019-20.
Post-surgery complications	6,352.79	1,270.56	5,082; 7,623	TA633 (UST) via Tsai et al. (2008) (129). NHS reference costs 2019-

Health state	Cost per health state (£), per year	SE (£)	DSA (low; high values)	Reference
				20.
First phase surgery	15,782.58	3,156.58	12,626; 18,939	Base source: TA633 (UST) via Buchanan et al 2011 (125) assuming 40% IPAA and 60% ileostomy, with one acute complication. Inflated to 2020/21 prices using the NHSCII index in PSSRU 2021.
Second surgery for pouch failure	11,336.74	2,267.38	9,069; 13,604	Base source: TA633 (UST) via assumed same cost as ileostomy. Inflated to 2020/21 prices using the NHSCII index in PSSRU 2021.

Please note: Similar to TA633 (UST), the SE of the total annual cost of resource use by health state was assumed to be 20%.
Abbreviations: DSA, deterministic sensitivity analysis; HRG, healthcare resource group; IPAA, ileal pouch-anal anastomosis; NHS, National Health Service; NHSCII, National Health Service Cost Inflation Index; PSSRU, Personal Social Services Research Unit; SE, standard error; TA, technology appraisal; UC, ulcerative colitis.

B.3.5.3 Adverse reaction unit costs and resource use

The cost associated with each AE included in the model is an average of five different types of serious infections**:** sepsis, pneumonia, urinary tract infection, respiratory infection, and bronchitis. The composite of AEs included are aligned with TA633 (ustekinumab). The average AE cost of £2,685 was derived from the NHS Reference Costs 2019-20. A breakdown of the serious infection cost calculation is provided in Table 86.

Table 86: Derivation of serious infection cost

Adverse reactions	Cost (£)	HRG code	Assumption
Sepsis	3,307	WJ06A-WJ06J	Sepsis with or without interventions. Non-elective inpatient long stay. Weighted average calculation
Pneumonia	2,842	DZ11K-DZ11V and DZ23H - DZ23N	Lobar, Atypical or Viral Pneumonia with or without interventions. Bronchopneumonia with or without interventions. Non-elective inpatient long stay. Weighted average calculation.
Urinary tract infection	2,810	LA04H-LA04S	Kidney or Urinary Tract Infections with or without interventions. Non-elective inpatient long stay. Weighted average calculation.
Respiratory infection	2,302	DZ22K-Q	Unspecified Acute Lower Respiratory Infection with and without interventions. Non-elective inpatient long stay. Weighted average calculation.
Bronchitis	2,163	DZ65A-K	Chronic Obstructive Pulmonary Disease or Bronchitis with or without interventions. Non-elective inpatient long stay. Weighted average calculation.
Mean AE cost	2,685		

Abbreviations: AE, adverse event; HRG, heath resource group.

B.3.5.4 Miscellaneous unit costs and resource use

No additional miscellaneous costs are considered in the CEM.

B.3.6 Severity

UC has a significant burden on patients in terms of QoL as discussed in B.1.3.1.3. No impact on survival for people with UC was considered in the model (apart from a risk of death associated with surgery), with mortality of a person with UC therefore assumed to be equivalent to that of the general population. The QALY shortfall calculator developed by Schneider et al., 2022 (130) was used to generate results. The key inputs for the QALY shortfall analysis are presented in Table 87.

Table 87: Summary features of QALY shortfall analysis

Factor	Bio-naïve population	Bio- exposed population	Reference to section/table in submission
Sex distribution, male	66.8%	58.5%	B.3.3.1.1
Starting age, years	42.99	42.69	
EQ-5D dataset used	Hernandez Alava et al., EQ-5D-5L to 3L mapping + HSE 2017-2018		B.3.4.2

Abbreviations: ED-5D-5L, EuroQol-5 Dimension-5 Level; Health Survey for England.

It was not possible to calculate the QALY shortfall for previous NICE TAs in appraisals for biologic treatments in UC, as total QALY values were redacted (TA342 [vedolizumab], TA547 [tofacitinib] and TA633 [ustekinumab]).

The disaggregated utilities and life years used in the model for conventional care are presented in Table 88.

Table 88: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (confidence interval)	Undiscounted life years	
		Bio-naive	Bio-exposed
Remission	0.870 (0.783; 0.957)	0.07	0.02
Response w/o remission	0.760 (0.684; 0.836)	0.03	0.02
Active UC	0.410 (0.639; 0.451)	28.27	28.42
Surgery (first and second)	0.610 (0.549; 0.671)	0.06	0.06
Post-surgery remission (first and second)	0.720 (0.648; 0.792)	1.00	1.01
Post first surgery complications	0.340 (0.306; 0.374)	1.62	1.64

Abbreviations: QALY, quality-adjusted life year; UC, ulcerative colitis; w/o, without.

The summary of QALY shortfall for the general population, with the same age and sex distribution as those with UC, and patients living with UC are presented in Table 89. The absolute QALY shortfall range for the bio-naïve population and bio-exposed population was between [redacted] and [redacted], and [redacted] and [redacted], respectively. This accounted for a proportional QALY shortfall for bio-naïve and bio-exposed population to range between [redacted] and [redacted], and [redacted] and [redacted], respectively. This illustrates that UC has a significant burden on patients.

Table 89: Summary of QALY shortfall analysis

Treatment	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall (absolute)	QALY shortfall (proportional)
Bio-naïve population				
UPA 15 mg maintenance dose	[redacted]	[redacted]	[redacted]	[redacted]
UPA high maintenance dose	[redacted]	[redacted]	[redacted]	[redacted]
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]
GOL	[redacted]	[redacted]	[redacted]	[redacted]
VED	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]
TOF	[redacted]	[redacted]	[redacted]	[redacted]
Bio-exposed population				
UPA 15 mg maintenance dose	[redacted]	[redacted]	[redacted]	[redacted]
UPA high maintenance dose	[redacted]	[redacted]	[redacted]	[redacted]
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]
VED	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]
TOF	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; GOL, golimumab; IFX, infliximab; QALY, quality-adjusted life year; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.7 Uncertainty

The principal areas of uncertainty in the analysis may be summarised as follows:

- The absence of treatment sequencing-based data to allow for the accurate modelling of patients cycling through different biologics necessitates a simpler modelling approach, whereby all patients discontinuing their initial therapy move to CT. This may not reflect clinical practice where patients would likely receive further line(s) of treatment. Treatment sequencing has been explored in a scenario analysis
- The CEM is populated with clinical efficacy and safety data from an NMA. Indirect treatment comparisons, by their nature, are associated with greater uncertainty than head-to-head comparisons. To address this, the base case analysis considered a probabilistic model in which efficacy values were sampled from NMA CODA across 5,000 simulations
- These is uncertainty associated with the long-term probability of loss of treatment response. To address this uncertainty, the submission includes a scenario wherein the probability of loss of response for each treatment is reduced by 25% from Year 2 onwards to reflect the opinion that loss of response is most likely to occur during the first year
- Methodological and reporting limitations of the Woehl et al. (2008) study (122) have been raised in previous appraisals. The study is reported only in abstract form, providing limited information on its design and on the patients recruited. Despite uncertainties, the NICE committee have generally considered the utility values from Woehl et al. (2008) (122) to be appropriate. Scenario analyses were run considering alternative sources of utility values.

B.3.8 Managed access proposal

Not applicable – upadacitinib is not a candidate for managed access in UC.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

Base-case results are presented for both the bio-naïve and bio-exposed populations. Results are shown using list prices for all treatments, except UPA where the PAS price is used. Several comparators have a confidential PAS; results are therefore presented using list prices for all comparators. GOL was approved by NICE under a

PAS by which the cost of the 100 mg/1 mL dose is available at the same price as the 50 mg/0.5 mL dose; this is reflected in the analysis.

Results are reported below based on probabilistic analysis using the following settings in Table 90 and variables reported in Table 91.

Table 90: Base-case setting

Setting	Base-case setting	Reference to section in submission
Perspective	UK publicly funded health care payer	B.3.2
Time horizon	100 years of age	B.3.2.2
Annual probability of surgery	0.47%	B.3.2.2.3
Main source of efficacy data	U-ACHIEVE, U-ACCOMPLISH trials	B.2.6
Spontaneous remission	No	B.3.2.2.2
Delayed response	No	B.3.2.2.1
Utility values	Based on values from Woehl et al (2008) (122) and Arseneau et al. (2006) (124)	B.3.4.5
Age/gender utility adjustment	Yes	B.3.4.5.1

Abbreviations: UK, United Kingdom.

Table 91: Summary of variables applied in the economic model

Parameter	Variable	Value (reference to appropriate table or figure in submission)	Precision around the mean/median	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model parameters					
Model settings	Discount rate (effects and costs)	3.5%	Fixed	N/A	B.3.3.1.1B.3.3.1.1
Patient characteristics bio-naive population	Age	42.99	(41.44 to 44.55)	Normal distribution	
	Proportion male	66.8%	(61.6% to 72.0%)	Beta distribution	
	Weight (kg)	73.09	(71.02 to 75.16)	Normal distribution	
	Weight (<55kg)	16.9%		Dirichlet distribution	
	Weight (>55kg and <85 kg)	62.0%			
	Weight (>85kg)	21.1%			

Parameter	Variable	Value (reference to appropriate table or figure in submission)	Precision around the mean/median	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Patient characteristics bio-exposed population	Age	42.69	(41.13 to 44.24)	Normal distribution	B.3.3.1.1
	Proportion male	58.5%	(53.3% to 63.7%)	Beta distribution	
	Weight (kg)	72.3	(70.43 to 74.11)	Normal distribution	
	Weight (<55kg)	16.1%		Dirichlet distribution	
	Weight (>55kg and <85 kg)	63.7%			
	Weight (>85kg)	20.2%			
Efficacy and safety					
Induction remission bio-naïve population	Upadacitinib	50.67%	(29.68% to 71.62%)	NMA CODA	B.3.3.1.3
	Adalimumab	15.59%	(9.05% to 25.11%)		
	Adalimumab biosimilar	15.59%	(9.05% to 25.11%)		
	Golimumab	25.30%	(11.83% to 46.35%)		
	Infliximab	29.03%	(19.65% to 40.35%)		
	Infliximab biosimilar	29.03%	(19.65% to 40.35%)		
	Tofacitinib	19.33%	(9.92% 35.95%)		
	Ustekinumab	17.85%	(7.55% to 37.07%)		
	Vedolizumab IV	25.46%	(12.88% to 45.75%)		
	Vedolizumab SC	25.46%	(12.88% to 45.75%)		
Induction response without remission bio-naive	Upadacitinib	28.38%	(33.63% to 47.69%)	NMA CODA	B.3.3.1.3

Parameter	Variable	Value (reference to appropriate table or figure in submission)	Precision around the mean/median	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	Adalimumab	38.89%	(28.88% to 46.57%)		
	Adalimumab biosimilar	38.89%	(28.88% to 46.57%)		
	Golimumab	26.30%	(18.07% to 43.81%)		
	Infliximab	35.75%	(26.86% to 40.61%)		
	Infliximab biosimilar	35.75%	(26.68% to 40.61%)		
	Tofacitinib	43.82%	(30.38% to 50.29%)		
	Ustekinumab	48.67%	(35.50% to 59.51%)		
	Vedolizumab IV	28.32%	(16.72% to 39.96%)		
	Vedolizumab SC	28.32%	(16.72% to 39.96%)		
Induction remission bio-exposed population	Upadacitinib	22.53%	(10.88% to 42.39%)	NMA CODA	B.3.3.1.3
	Adalimumab	6.88%	(1.93% to 19.29%)		
	Adalimumab biosimilar	6.88%	(1.93% to 19.29%)		
	Tofacitinib	13.30%	(6.04% to 30.62%)		
	Ustekinumab	14.61%	(5.93% to 35.86%)		
	Vedolizumab IV	8.23%	(3.06% to 19.70%)		
	Vedolizumab SC	8.23%	(3.06% to 19.70%)		
Induction response	Upadacitinib	57.61%	(45.08%	NMA CODA	B.3.3.1.3

Parameter	Variable	Value (reference to appropriate table or figure in submission)	Precision around the mean/median	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
without remission bio-exposed population			to 66.30%)		
	Adalimumab	23.00%	(8.19% to 43.62%)		
	Adalimumab biosimilar	23.00%	(8.19% to 43.62%)		
	Tofacitinib	39.87%	(24.19% to 55.37%)		
	Ustekinumab	36.82%	(17.86% to 55.47%)		
	Vedolizumab IV	23.64%	(10.14% to 40.82%)		
	Vedolizumab SC	23.64%	(10.14% to 40.82%)		
Maintenance remission bio-naïve (standard dose)	Upadacitinib	44.34%	(18.40% to 74.11%)	NMA CODA	B.3.3.1.4
	Adalimumab	23.31%	(8.13% to 51.36%)		
	Adalimumab biosimilar	23.31%	(8.13% to 51.36%)		
	Golimumab	37.43%	(17.72% to 65.90%)		
	Infliximab	27.45%	(9.49% to 58.74%)		
	Infliximab biosimilar	27.45%	(9.49% to 58.74%)		
	Tofacitinib	61.01%	(31.96% to 84.57%)		
	Ustekinumab	33.54%	(13.57% to 62.01%)		
	Vedolizumab IV	44.66%	(22.74% to 68.37%)		
	Vedolizumab SC	44.66%	(22.74% to		

Parameter	Variable	Value (reference to appropriate table or figure in submission)	Precision around the mean/median	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
			68.37%)		
Maintenance response without remission bio-naïve (standard dose)	Upadacitinib	25.35%	(1.37% to 41.98%)	NMA CODA	B.3.3.1.4
	Adalimumab	15.80%	(0.00% to 39.91%)		
	Adalimumab biosimilar	15.80%	(0.00% to 39.91%)		
	Golimumab	14.51%	(0.00% to 34.50%)		
	Infliximab	23.73%	(0.00% to 47.27%)		
	Infliximab biosimilar	23.73%	(0.00% to 47.27%)		
	Tofacitinib	5.28%	(0.00% to 22.09%)		
	Ustekinumab	26.52%	(2.99% to 46.23%)		
	Vedolizumab IV	25.38%	(5.45% to 39.71%)		
	Vedolizumab SC	25.38%	(5.45% to 39.71%)		
Maintenance remission bio-naïve (high dose)	Upadacitinib	52.61%	(24.01% to 69.01%)	NMA CODA	B.3.3.1.4
	Adalimumab	23.31%	(8.13% to 51.36%)		
	Adalimumab biosimilar	23.31%	(8.13% to 51.36%)		
	Golimumab	43.85%	(24.59% to 71.04%)		
	Infliximab	28.35%	(9.81% to 60.01%)		
	Infliximab biosimilar	28.35%	(9.81% to 60.01%)		
	Tofacitinib	63.45%	(34.12% to 85.85%)		
	Ustekinumab	36.46%	(15.02% to 65.36%)		

Parameter	Variable	Value (reference to appropriate table or figure in submission)	Precision around the mean/median	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	Vedolizumab IV	48.80%	(22.92% to 75.44%)		
	Vedolizumab SC	48.80%	(22.92% to 75.44%)		
Maintenance response without remission bio-naïve (high dose)	Upadacitinib	30.99%	(11.72% to 41.11%)	NMA CODA	B.3.3.1.4
	Adalimumab	15.80%	(0.00% to 39.91%)		
	Adalimumab biosimilar	15.80%	(0.00% to 39.91%)		
	Golimumab	13.19%	(0.00% to 31.06%)		
	Infliximab	27.10%	(2.08% to 49.68%)		
	Infliximab biosimilar	27.10%	(2.08% to 49.68%)		
	Tofacitinib	9.84%	(0.00% to 23.98%)		
	Ustekinumab	24.17%	(0.18% to 44.05%)		
	Vedolizumab IV	13.71%	(0.00% to 32.13%)		
	Vedolizumab SC	13.71%	(0.00% to 32.13%)		
Maintenance remission bio-exposed (standard dose)	Upadacitinib	64.80%	(34.48% to 89.01%)	NMA CODA	B.3.3.1.4
	Adalimumab	23.89%	(6.22% to 65.05%)		
	Adalimumab biosimilar	23.89%	(6.22% to 65.05%)		
	Tofacitinib	23.48%	(9.41% to 48.13%)		
	Ustekinumab	18.60%	(7.56% to 39.37%)		
	Vedolizumab IV	51.03%	(23.83% to 80.39%)		
	Vedolizumab	51.03%	(23.83%		

Parameter	Variable	Value (reference to appropriate table or figure in submission)	Precision around the mean/median	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	SC		to 80.39%)		
Maintenance response without remission bio-exposed (standard dose)	Upadacitinib	2.56%	0.00% to 22.74%)	NMA CODA	B.3.3.1.4
	Adalimumab	20.44%	(0.00% to 54.99%)		
	Adalimumab biosimilar	20.44%	(0.00% to 54.99%)		
	Tofacitinib	33.91%	(5.46% to 58.36%)		
	Ustekinumab	17.39%	(0.00% to 45.56%)		
	Vedolizumab IV	3.95%	(0.00% to 29.86%)		
	Vedolizumab SC	3.95%	(0.00% to 29.86%)		
Maintenance remission bio-exposed (high dose)	Upadacitinib	70.03%	(40.04% to 91.22%)	NMA CODA	B.3.3.1.4
	Adalimumab	23.89%	(6.22% to 65.05%)		
	Adalimumab biosimilar	23.89%	(6.22% to 65.05%)		
	Tofacitinib	35.95%	(16.55% to 62.33%)		
	Ustekinumab	27.48%	(12.38% to 51.07%)		
	Vedolizumab IV	50.41%	(20.66% to 82.62%)		
	Vedolizumab SC	50.41%	(20.66% to 82.62%)		
Maintenance response without remission bio-exposed (high dose)	Upadacitinib	7.34%	(0.00% to 22.24%)	NMA CODA	B.3.3.1.4
	Adalimumab	20.44%	(0.00% to 54.99%)		
	Adalimumab biosimilar	20.44%	(0.00% to 54.99%)		
	Tofacitinib	35.04%	(6.64% to		

Parameter	Variable	Value (reference to appropriate table or figure in submission)	Precision around the mean/median	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
			53.06%)		
	Ustekinumab	17.80%	(0.00% to 44.61%)		
	Vedolizumab IV	1.29%	(0.00% to 30.67%)		
	Vedolizumab SC	1.29%	(0.00% to 30.67%)		
Utility					
Non-surgical health states	Remission	0.87	(0.78 to 0.96)	Beta distribution	B.3.4.5.1
	Response without remission	0.76	(0.68 to 0.84)		
	Active UC	0.41	(0.37 to 0.45)		
Adverse events and surgery health states	1st/ 2nd surgery	0.61	(0.55 to 0.67)		
	Post-1st and 2nd surgery remission	0.72	(0.65 to 0.79)		
	Chronic or late pouch failure complications	0.34	(0.31 to 0.37)		
	Serious infection disutility	-0.156	(-0.172 to -0.140)	Normal	
Costs and resource use					
Drug costs 1st induction (bio-naïve)	[redacted]	[redacted]	Fixed	N/A	B.3.5.1.1
	ADA	£2,817.12			
	ADA biosimilar	£2,534.40			
	GOL	£2,288.91			
	IFX	£4,600.57			
	IFX biosimilar	£4,133.30			
	TOF	£2,767.70			
	UST	£6,530.17			
	VED IV	£6,150.00			
	VED SC	£6,150.00			
Drug costs 1st induction (bio-	[redacted]	[redacted]	Fixed	N/A	B.3.5.1.1
	ADA	£2,817.12			

Parameter	Variable	Value (reference to appropriate table or figure in submission)	Precision around the mean/median	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
exposed)	ADA biosimilar	£2,534.40			
	GOL	£2,288.91			
	IFX	£4,548.85			
	IFX biosimilar	£4,086.84			
	TOF	£2,767.70			
	UST	£6,527.62			
	VED IV	£6,150.00			
	VED SC	£6,150.00			
Drug costs maintenance standard dose (bio-naïve)	[redacted]	[redacted]	Fixed	N/A	B.3.5.1.1
	ADA	£9,155.64			
	ADA biosimilar	£8,236.80			
	GOL	£9,918.61			
	IFX	£10,734.66			
	IFX biosimilar	£9,644.36			
	TOF	£8,970.39			
	UST	£10,735.00			
	VED IV	£14,350.00			
	VED SC	£13,325.00			
Drug costs maintenance standard dose (bio-exposed)	[redacted]	[redacted]	Fixed	N/A	B.3.5.1.1
	ADA	£9,155.64			
	ADA biosimilar	£8,236.80			
	TOF	£8,970.39			
	UST	£10,735.00			
	VED IV	£14,350.00			
	VED SC	£13,325.00			
Drug costs maintenance high dose (bio-naïve)	[redacted]	[redacted]	Fixed	N/A	B.3.5.1.1
	ADA	£18,311.28			
	ADA biosimilar	£16,473.60			
	GOL	£9,918.61			
	IFX	£21,469.31			
	IFX biosimilar	£19,288.72			
	TOF	£17,940.78			
	UST	£15,029.00			

Parameter	Variable	Value (reference to appropriate table or figure in submission)	Precision around the mean/median	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	VED IV	£26,650.00			
	VED SC	£13,325.00			
Drug costs maintenance high dose (bio-exposed)	[redacted]	[redacted]	Fixed	N/A	B.3.5.1.1
	ADA	£18,311.28			
	ADA biosimilar	£16,473.60			
	TOF	£17,940.78			
	UST	£15,029.00			
	VED IV	£26,650.00			
	VED SC	£13,325.00			
Administration costs	IV administration	£125.44	Fixed	N/A	B.3.5.1.2
Inpatient healthcare resource use costs	Inpatient care without colectomy	£1,780.97	Fixed	N/A	B.3.5.2
	Emergency endoscopy	£621.69			
	Elective endoscopy	£332.89			
	Stoma care (post-colectomy)	£449			
Outpatient	Consultant visit	£148.12	Fixed	N/A	B.3.5.2
	Blood test	£2.53			
Resource use (per year) remission	Outpatient consultant visit	2	Fixed	N/A	B.3.5.2
	Inpatient care without colectomy	0			
	Outpatient blood test	3.25			
	Emergency endoscopy	0			
	Elective endoscopy	0.2			
Resource use (per year) active UC	Outpatient consultant visit	6.5	Fixed	N/A	B.3.5.2
	Inpatient care without colectomy	0.15			

Parameter	Variable	Value (reference to appropriate table or figure in submission)	Precision around the mean/median	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	Outpatient blood test	6.5			
	Emergency endoscopy	0.75			
	Elective endoscopy	2			
Resource use (per year) response (without remission)	Outpatient consultant visit	4.5	Fixed	N/A	B.3.5.2
	Inpatient care without colectomy	0			
	Outpatient blood test	3.9			
	Emergency endoscopy	0.25			
	Elective endoscopy	0.5			
Resource use (per year) surgery ($1^{st}/2^{nd}$)	Outpatient consultant visit	6.5	Fixed	N/A	B.3.5.2
	Inpatient care without colectomy	0.15			
	Outpatient blood test	6.5			
	Emergency endoscopy	0.75			
	Elective endoscopy	2			
Resource use (per year) post-$1^{st}/2^{nd}$ surgery remission	Outpatient consultant visit	1.5	Fixed	N/A	B.3.5.2
	Inpatient care without colectomy	0			
	Outpatient blood test	1.5			
	Emergency endoscopy	0.5			
	Elective endoscopy	1.25			
Resource use (per year) post-1^{st}	Outpatient consultant visit	1.75	Fixed	N/A	B.3.5.2

Parameter	Variable	Value (reference to appropriate table or figure in submission)	Precision around the mean/median	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
surgery complications	Inpatient care without colectomy	3.5			
	Outpatient blood test	3.25			
	Emergency endoscopy	0.13			
	Elective endoscopy	0.65			
Adverse event costs (per event)	Serious infection cost	£2,684.53	(£2,148 to £3,221	Gamma distribution	B.3.5.3
Annual direct medical costs based on health state	Remission	£371.05	(£297 to £445)	Gamma distribution	B.3.5.2
	Response (without remission)	£998.29	(£799 to £1,198)		
	Active UC	£2,378.44	(£1,903 to £2,854)		
	Surgery	£2,827.64	(£2,262 to £3,393)		
	Post-surgery remission	£952.93	(£762 to £1,144)		
	Post-surgery complications	£6,352.79	(£5,082 to £7,623)		
Surgery procedure costs	First surgery	£15,782.58	(£12,626 to £18,939)	Gamma distribution	B.3.5.2
	Second surgery	£11,336.74	(£9,069 to £13,604)		
Surgery events	Annual probability of first surgery	0.47%	(0.45% to 0.49%)	Beta distribution	B.3.3.2.1
	Proportion of post-surgery chronic conditions	33.50%	(31.83% to 35.18%)		B.3.3.2.2
	Annual probability from post-surgery remission to chronic complications	5.64%	(5.36% to 5.92%)		B.3.3.2.3
	Annual	0.47%	(0.45% to		B.3.3.2.1

Parameter	Variable	Value (reference to appropriate table or figure in submission)	Precision around the mean/median	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	probability of second (revision) surgery		0.49%)		

Abbreviations: ADA, adalimumab; CI, confidence interval; GOL, golimumab; IFX, infliximab; TOF, tofacitinib; UC, ulcerative colitis; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.9.2 Assumptions

The main assumptions of the economic model alongside supporting justification are presented in Table 92.

Table 92: Assumptions and justifications of the economic model

Parameter	Assumption	Justification
Modelled decision problem		
Population	Results are reported for two subgroups: moderately to severely active UC patients who are bio-naïve or bio-exposed.	Aligned with TA633 and the NICE scope.
Comparators	Infliximab and adalimumab biosimilars are included in the model, with the same assumed clinical effects and safety profiles as the originator products.	Aligned with TA633.
	Vedolizumab SC is included as a comparator, assuming equal efficacy and safety as vedolizumab IV	VISIBLE 1 did not present data for the bio-naïve and bio-exposed populations separately for inclusion of vedolizumab SC in the NMA
	Infliximab and golimumab are not included as comparators in the bio exposed population.	RCTs for infliximab and golimumab excluded patients with previous biologic treatment. Further, clinical input at an advisory board confirmed that these treatments would not be considered in the bio exposed population.
Assumptions about treatment		
Extended induction for delayed response	The model assumes no extended induction in the base case but includes extended induction in the scenario analysis.	Clinicians consulted at an advisory board did not see extended induction as reflective of clinical practice given the current availability of treatment options for UC.

Parameter	Assumption	Justification
Dose escalation during the maintenance phase of treatment	Separate analyses are provided for the standard (15 mg daily) and high (30 mg daily) maintenance doses of UPA. For comparators where a high maintenance dose is available, it is assumed that 30% of patients would be on the high dose. A scenario analysis is run considering 30% of UPA patients on the high dose, with the remaining 70% on the 15 mg dose.	Aligned with TA633 and published retrospective studies. Individual scenario analyses are provided for UPA 15 mg and 30 mg doses to aid decision making.
Constant loss of response	The probability of loss of response from the remission and response without remission health states is assumed to be constant over time.	This is in line with previous appraisals (TA329, TA342, TA547, TA633), and reflects the lack of data to estimate changes in loss of response over time. In the absence of interim response/ remission data for the trials or longer-term follow-up it is difficult to predict how the relative or absolute risks of loss of response change over time. A scenario analysis was run considering a 25% lower probability of loss of response after year 1.
Treatment continuation	The model does not consider a treatment stopping rule for responders and remitters.	This is aligned with TA547 and TA633. Furthermore, clinical advisors during an ad board stated that if a drug is effective, patients will stay on treatment. Treatment discontinuation in UC is associated with a high risk of flare and would therefore be avoided wherever possible.
Treatment sequencing	No modelling of treatment sequencing. Patients discontinuing treatment are assumed to receive CT.	This is aligned with previous submissions in UC including TA633. In this appraisal, it was agreed that while sequential use of therapies is common in practice, treatment sequences are variable, and the choice can impact interpretation of cost-effectiveness. Data to robustly model treatment sequencing in UC are also lacking. A scenario analysis was run considering treatment sequences.
Model structure and framework		
Model type	Hybrid model with a decision tree to reflect induction outcomes and a Markov model for maintenance, subsequent treatment, and surgery.	The model structure is consistent with previous appraisals (i.e., TA633, TA329 and TA342) and published economic evaluations. The model structure was found to be

Parameter	Assumption	Justification
		acceptable at an advisory board for upadacitinib.
Cycle length	4 weeks	Short enough to capture changes in patient health states. Addresses concerns about the short (2 week) cycle length in TA633.
Half cycle correction	Half cycle correction was not applied.	Half cycle correction was excluded given the short cycle length (4 weeks).
Time horizon	Lifetime - 100 years of age	Consistent with a lifetime horizon in previous appraisals, including TA329, TA547 and TA633. In line with the NICE reference case. Scenario analyses considered shorter time horizons (10 years and 50 years).
Surgery	Surgery is included as an option for patients with active UC after failure of initial therapy. Two phases of surgery are modelled, each allowing for a six-month staged procedure. If the first surgery is successful, patients remain in remission until death. However, if a patient has a chronic complication following surgery, a second phase of surgery for revision is required. The model assumes that all patients achieve remission after the second surgery.	Consistent with TA633, the model reflected current practice with staged procedures (phase 1 and 2), following unsuccessful surgery. The assumption of remission after second surgery is aligned with TA633 and reflects the lack of data on complications following a second surgery. This health state has a minimal impact on the results of the analysis.
Mortality	The model uses general population all-cause mortality rates adjusted for age and gender from the most recent UK Life tables. Excess mortality for UC was a 30% relative risk for surgery, which was applied during the six-month surgery health states.	This approach is consistent with TA633.
Clinical parameters		
Response and remission rates	The probability of remission and response without remission at the end of the induction phase of treatment was taken from a company NMA. Maintenance phase conditional probability of remission and response without remission estimates were taken from a company NMA.	NMA permits the indirect comparison of upadacitinib and relevant comparators.
Adverse events	Adverse events were a weighted average of five serious infections. Adverse events were modelled during the induction period.	This approach is aligned with TA633. It may be reasonable to assume that adverse events would occur early during

Parameter	Assumption	Justification
		treatment and that patients not tolerating treatment would discontinue.
Incidence of surgery and complications	The source of the probability of 1st and 2nd surgery (0.47%) was derived from Misra et al. (2016). Chronic complications of first surgery (33.5%) were derived from a national report 2014. The rate of late chronic complications (5.64%) is based on a weighted average of values derived by Segal et al 2018, Gonzalez et al 2014, Ferrante et al 2008, Suzuki et al 2012). Loftus et al 2008 was excluded as an outlier.	The source of incidence of 1st and 2nd surgery was used in TA547 and TA633. Chronic complications of first surgery were based on TA633 via national clinical audit of inpatient care for adults with UC, National report 2014. It was assumed that the rate of late chronic complications (3.25%, Segal et al. 2018) was based on a small sample size (39 patients).
Utilities		
Health state utilities	Health state utility values were derived from the literature using two primary sources: Woehl et al. (2008) and Arseneau et al. (2006).	The utility values align with those utility values used in TA329, TA342, TA547 and TA633 and have been selected given the perceived limitations of trial-based utility data (see Section B.3.4.5)
Disutility for serious infection	A disutility associated with serious infection was derived from TA329, as reported by Stevenson et al. The disutility value was applied as an on-off decrement, adjusted for the cycle duration.	Aligned with previous appraisals.
Costs and resource use		
Drug acquisition costs	Drugs are costed according to their licensed regimens, with unit costs derived from the BNF. The agreed PAS price is used for UPA.	Aligned with the NICE manual.
Administration costs	Administration costs for intravenous administration were included, with a cost associated with an outpatient visit based on 2019/20 NHS Refence Costs. No administration cost was included for self-injection.	Consistent with current practice and aligned with previous appraisals.
Other health care costs	Health state resource use was based primarily on data from Tsai et al. 2008. Costs of surgery were based on Buchanan et al (2011).	The estimates are consistent with previous appraisals, including TA547 and TA633.
Adverse event costs	The cost of serious infection included the composite of five types of infection: sepsis, pneumonia, urinary tract infection, respiratory infection and bronchitis. The cost of adverse events	This aligned with TA547 and TA633.

Parameter	Assumption	Justification
	was estimated as a weighted average of HRG costs for the five types of infection using NHS Reference Costs 2019/20.	

Abbreviations: BNF, British National Formulary; CT, conventional therapy; HRG, healthcare resource group; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; RCT, randomised, controlled trial; TA, technology appraisal, TTO, time trade-off; UC, ulcerative colitis; UK, United Kingdom.

B.3.10 Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results

Incremental analyses are shown for the bio-naïve (upadacitinib 15 mg and 30 mg maintenance doses) and bio-exposed (upadacitinib 15 mg and 30 mg maintenance doses) populations in Table 93 and Table 94, respectively. In all analyses, 30% of patients in the comparator arms are assumed to be receiving the high maintenance dose of treatment (where applicable), with the remaining 70% receiving the standard maintenance dose. A probabilistic scenario was run considering the same distribution of upadacitinib maintenance dosing (see Section B.3.11.3.1.7).

An incremental analysis compares multiple mutually exclusive treatments against each other to find the most cost-effective treatment option out of all of the available comparators. This is implemented in a stepwise approach following the steps below:

- Comparators are ordered from the least to most expensive
- Comparators are compared for strong dominance. Comparators are dominated if they are both more costly and less effective than other comparators included in the analysis
- Comparators are compared for extended dominance. Comparators are extendedly dominated if an alternative comparator can provide more QALYs for a lower cost per QALY

All base-case analyses were run using the probabilistic model and running 5,000 simulations following an assessment of convergence in line with the methodology proposed by Hatswell et al (2018) (131).

B.3.10.1.1 Bio-naïve patients

The fully incremental analysis for bio-naive patients in the upadacitinib 15 mg and 30 mg maintenance doses are presented in Table 93 and Table 94, respectively. In the bio-naïve population and considering the upadacitinib 15 mg maintenance dose, upadacitinib is associated with the highest QALYs and lowest costs. As such, upadacitinib strictly dominates all comparators.

Table 93: Base-case results for bio-naïve standard UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total discounted LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
GOL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
IFX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; GOL, golimumab; IV, intravenous; LYG, life years gained; QALYs, quality-adjusted life years; SC, subcutaneous therapy; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

In the bio-naïve population and considering the upadacitinib 30 mg maintenance dose, upadacitinib is associated with the highest QALYs and the highest costs. In a fully incremental analysis, the cost-effectiveness frontier is comprised of adalimumab biosimilar, golimumab and upadacitinib. Upadacitinib is associated with an incremental cost-effectiveness ratio (ICER) of £15,333 versus golimumab (Table 94).

Table 94: Base-case results for bio-naïve UPA 30 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total discounted LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
GOL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,969	14,969
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,119	Dominated
IFX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	63,419	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	45,063	Dominated
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,497	Extendedly dominated
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,122	Dominated
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	70,055	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,264	15,333

Abbreviations: ADA, adalimumab; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; LYG, life years gained; QALYs, quality-adjusted life years; SC, subcutaneous therapy; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

The expected NHBs are also presented for bio-exposed and bio-naïve populations in Table 95 and Table 96, respectively. The NHBs are informative when there are several comparators. Upadacitinib is associated with the highest NHB at cost-effectiveness willingness-to-pay thresholds of both £20,000 and £30,000.

Table 95: NHB for bio-naïve UPA 15 mg maintenance dose

Technologies	NHB at £20,000	NHB at £30,000
ADA biosimilar	5.08	6.18
ADA	5.04	6.16
GOL	5.14	6.30
IFX 5 biosimilar	4.83	6.06
IFX	4.73	6.00
TOF	5.01	6.32
UST	4.78	6.06
UPA 15	5.80	6.89
VED SC	4.72	6.04
VED IV	4.34	5.78

Abbreviations: ADA, adalimumab; GOL, golimumab; IFX, infliximab; IV, intravenous; NHB, net health benefit; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

In the bio-naïve population and considering the upadacitinib 30 mg maintenance dose, upadacitinib is also associated with the highest NHB at willingness-to-pay thresholds of £20,000 and £30,000 (Table 96).

Table 96: NHB for bio-naïve UPA 30 mg maintenance dose

Technologies	NHB at £20,000	NHB at £30,000
ADA biosimilar	5.08	6.18
ADA	5.03	6.15
GOL	5.15	6.31
IFX biosimilar	4.84	6.07
IFX	4.74	6.01
TOF	5.01	6.32
UST	4.78	6.06
UPA 30	5.40	6.85
VED SC	4.70	6.02
VED IV	4.35	5.79

Abbreviations: ADA, adalimumab; GOL, golimumab; IFX, infliximab; IV, intravenous; NHB, net health benefit; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.10.1.2 Bio-exposed patients

The fully incremental analysis for bio-exposed patients in the upadacitinib 15 mg and 30 mg maintenance doses are presented in Table 97 and Table 98, respectively. In the bio-exposed population and considering the upadacitinib 15 mg maintenance dose, upadacitinib is associated with the highest QALYs. Upadacitinib dominates ustekinumab, vedolizumab (SC and IV), and tofacitinib. Adalimumab is extendedly dominated by a combination of adalimumab biosimilar and upadacitinib. The cost-effectiveness frontier is comprised of adalimumab biosimilar and upadacitinib. Upadacitinib is associated with an ICER of £1,186 versus adalimumab biosimilar (Table 97).

Table 97: Base-case results for bio-exposed UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total discounted LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	114,500	Extendedly dominated
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,186	1,186
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	116,854	Dominated
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	66,556	Dominated
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,583	Dominated
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	112,615	Dominated

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG, life years gained; SC, subcutaneous therapy; QALYs, quality-adjusted life years; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

In the bio-exposed population and considering the upadacitinib 30 mg maintenance dose, upadacitinib is associated with the highest costs and QALYs. All other comparators are strictly dominated, or extendedly dominated by a combination of upadacitinib and adalimumab biosimilar. Upadacitinib is associated with an ICER of £14,146 versus adalimumab biosimilar (Table 98).

Table 98: Base case results for bio-exposed UPA 30 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total discounted LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	-	-	-	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	118,563	Extendedly dominated
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	76,532	Extendedly dominated
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,828	Extendedly dominated
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	105,952	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,146	14,146

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG, life years gained; SC, subcutaneous therapy; QALYs, quality-adjusted life years; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

The expected NHBs are also presented for bio-exposed population; upadacitinib 15 mg and 30 mg maintenance doses in Table 99 and Table 100, respectively. The NHBs are informative when there are several comparators. For both the upadacitinib 15 mg and 30 mg maintenance regimens, upadacitinib is associated with the highest NHB at willingness-to-pay thresholds of both £20,000 and £30,000.

Table 99: NHB for bio-exposed UPA 15 mg maintenance dose

Technologies	NHB at £20,000	NHB at £30,000
ADA biosimilar	5.11	6.20
ADA	5.09	6.18
UPA 15	6.02	7.12
UST	4.88	6.06
VED IV	4.67	5.94
TOF	5.02	6.23
VED SC	4.86	6.07

Abbreviations: ADA, adalimumab; IV, intravenous; NHB, net health benefit; SC, subcutaneous therapy; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 100: NHB for bio-exposed UPA 30 maintenance dose

Technologies	NHB at £20,000	NHB at £30,000
ADA biosimilar	5.12	6.21
ADA	5.07	6.17
UST	4.89	6.06
VED SC	4.86	6.06
TOF	5.02	6.24
VED IV	4.68	5.94
UPA 30	5.51	6.91

Abbreviations: ADA, adalimumab; IV, intravenous; NHB, net health benefit; SC, subcutaneous therapy; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Clinical outcomes from the model and disaggregated results of the base-case cost-effectiveness analyses are provided in Appendix J.

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

The base-case analyses used a probabilistic model and 5,000 simulations. Parameters varied in the PSA were:

- Baseline patient characteristics
- Health state utilities
- Surgery inputs
- Efficacy inputs (probability of remission and response without remission)
- Costs (direct medical costs, AE costs, and indirect costs)

For induction and maintenance treatment efficacy, the model used Convergence Diagnostic and Output Analysis (CODA) samples to reflect uncertainty over NMA results. The PSA therefore reflects the joint posterior distribution, with correlations across treatments. A total of 5,000 simulations were included and selected at random with replacement over the 5,000 PSA simulations. The number of NMA simulations (5,000) was selected by comparing the NMA point estimates and 95% credible intervals (CrIs) to the random CODA sample that were representative of the full CODA sample.

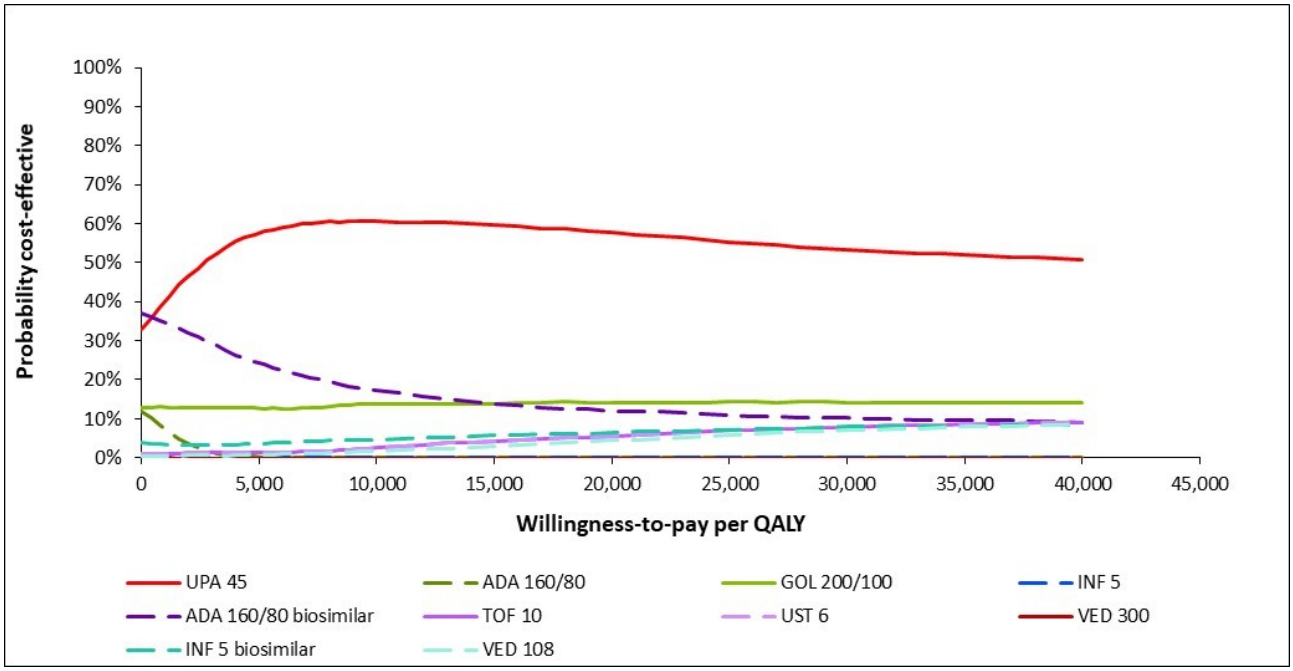
A normal distribution is used for baseline age and weight. Health utilities were modelled using beta distributions, except for response without remission and active UC, which were modelled as log-normal to preserve the relative ordering among the health states. The distribution of patients by weight category is modelled as a Dirichlet distribution. The proportion of male, AE rates, and extended induction efficacy rates are all assumed to have a beta distribution. Gamma distributions are used for all cost parameters.

PSA results are included in the form of multiple cost-effectiveness curves (multiple cost-effectiveness acceptability curves [CEACs]). The probability of upadacitinib being the most cost-effective treatment options at willingness-to-pay thresholds of £20,000 and £30,000 is presented.

B.3.11.1.1 Bio-naïve population, upadacitinib 15 mg maintenance dose

In the bio-naïve patient population, the 15 mg maintenance dose of upadacitinib was associated with the highest probability of having the highest NMB at values of the ICER willingness-to-pay threshold above £1,000. Upadacitinib was associated with a 57.6% and 53.3% probability of being the most cost-effective treatment at a threshold of £20,000 per QALY and £30,000 per QALY, respectively (Figure 11).

Figure 11: Cost-effectiveness acceptability curve, bio-naïve population, UPA 15 mg maintenance dose

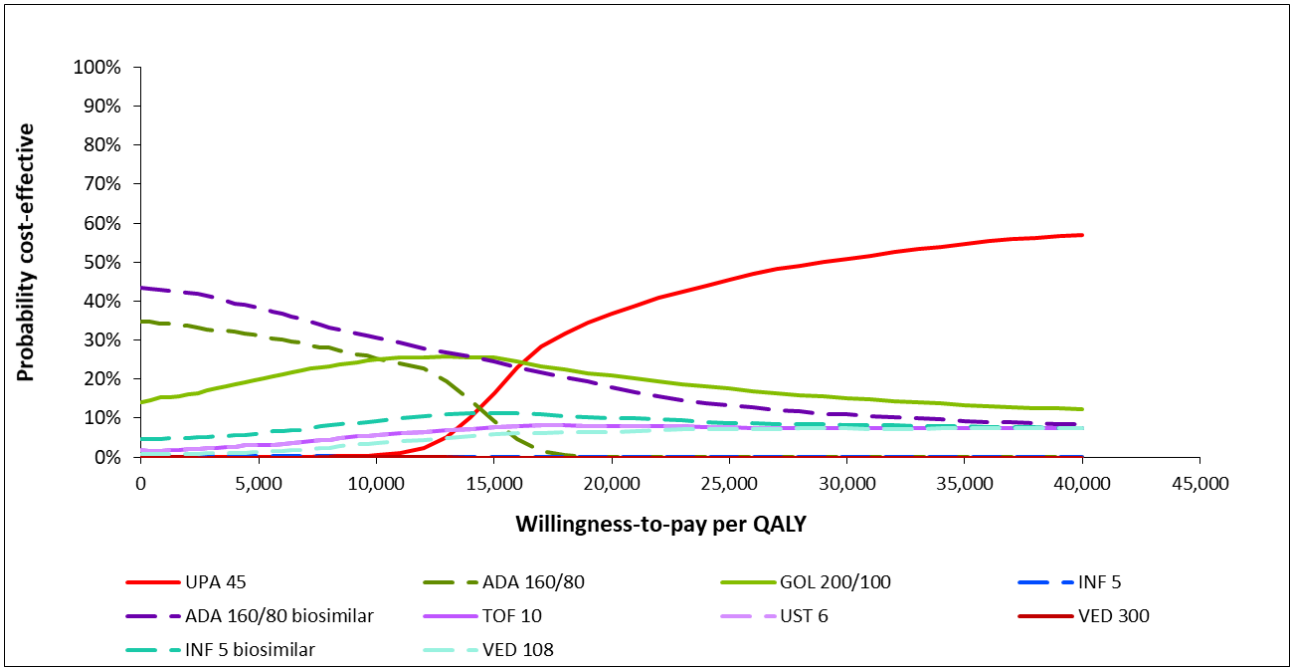


Abbreviations: ADA, adalimumab; GOL, golimumab; INF, infliximab; QALY, quality-adjusted life year; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.11.1.2 Bio-naive population, upadacitinib 30 mg maintenance dose

In the bio-naïve patient population, the 30 mg maintenance dose of upadacitinib was associated with the highest probability of having the highest NMB at values of the ICER willingness-to-pay threshold above £17,000. Upadacitinib was associated with a 36.8% and 50.8% probability of being the most cost-effective treatment at a threshold of £20,000 and £30,000 per QALY, respectively (Figure 12).

Figure 12: Cost-effectiveness acceptability curve, bio-naïve population, UPA 30 mg maintenance dose

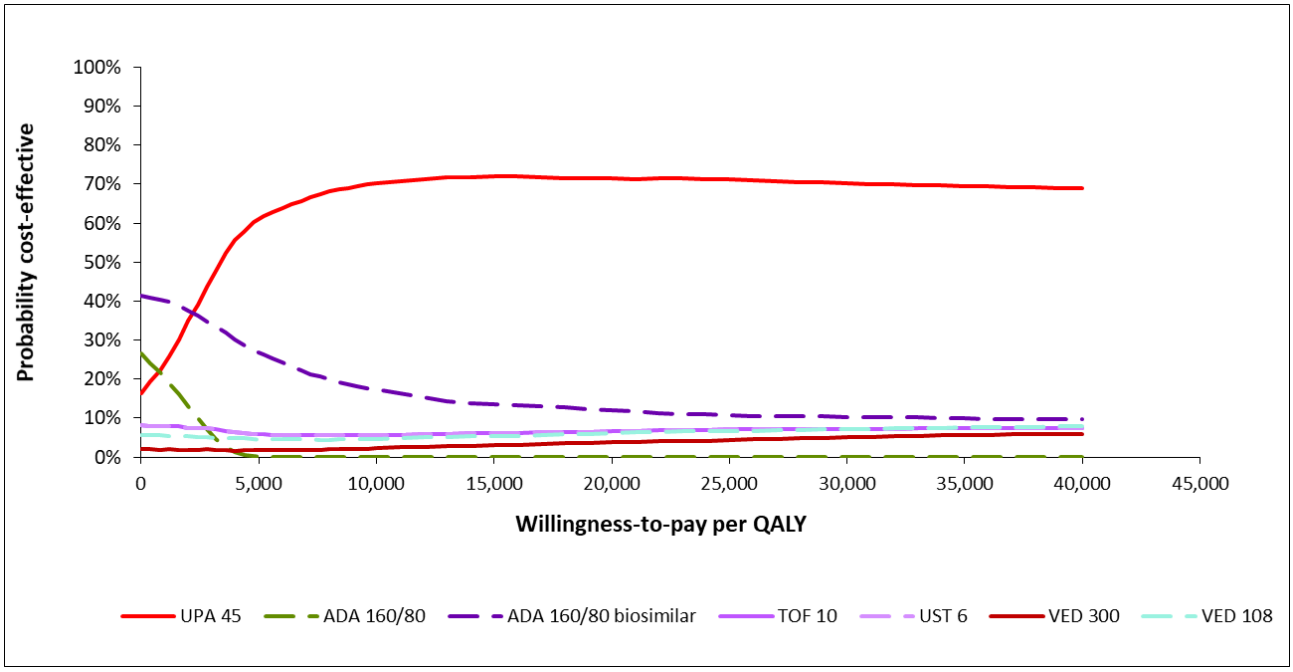


Abbreviations: ADA, adalimumab; GOL, golimumab; INF, infliximab; QALY, quality adjusted life year; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.11.1.3 Bio-exposed population, upadacitinib 15 mg maintenance dose

In the bio-exposed patient population, the 15 mg maintenance dose of upadacitinib was associated with the highest probability of having the highest NMB at values of the ICER willingness-to-pay threshold above £2,000. Upadacitinib was associated with a 71.6% and 70.3% probability of being the most cost-effective treatment at a threshold of £20,000 and £30,000 per QALY, respectively (Figure 13).

Figure 13: Cost-effectiveness acceptability curve, bio-exposed population, UPA 15 mg maintenance dose

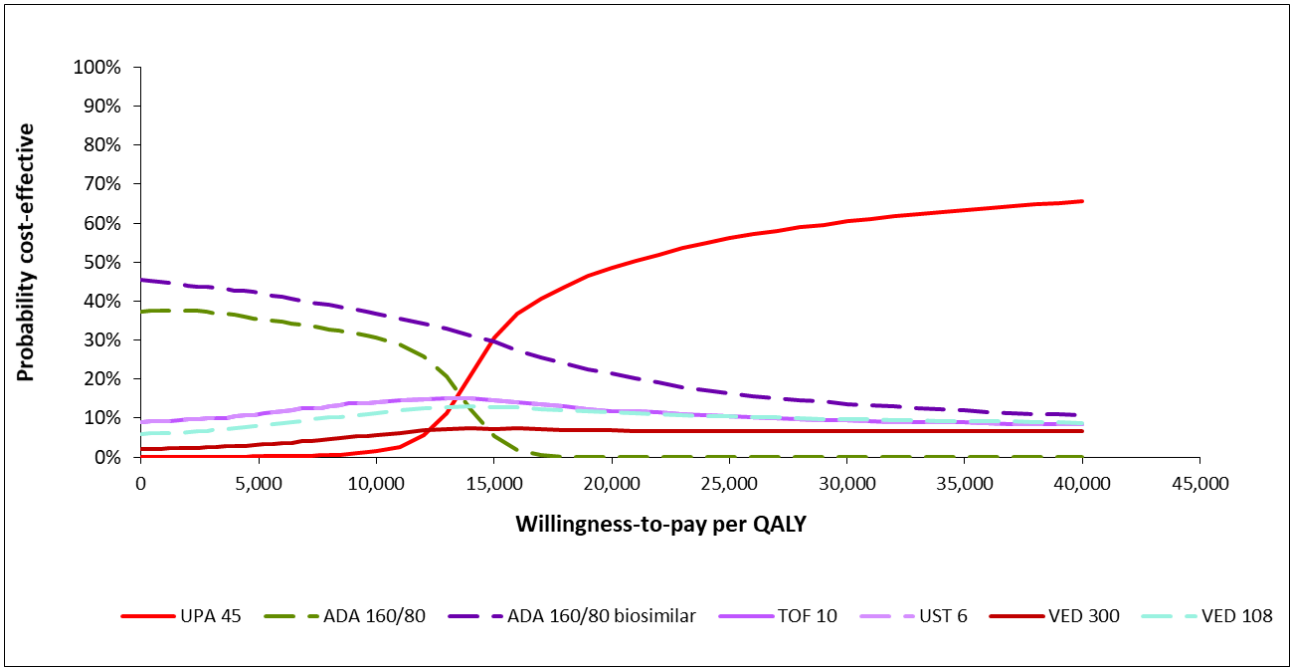


Abbreviations: ADA, adalimumab; QALY, quality adjusted life year; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.11.1.4 Bio-exposed population, upadacitinib 30 mg maintenance dose

In the bio-exposed patient population, the 30 mg maintenance dose of upadacitinib was associated with the highest probability of having the highest NMB at values of the ICER willingness-to-pay threshold above £15,000. Upadacitinib was associated with a 48.5% and 60.4%probability of being the most cost-effective treatment at a threshold of £20,000 and £30,000 per QALY, respectively.

Figure 14: Cost-effectiveness acceptability curve, bio-exposed population, UPA 30 mg maintenance dose



Abbreviations: ADA, adalimumab; QALY, quality adjusted life year; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.11.2 Deterministic sensitivity analysis

Parameters varied in the deterministic sensitivity analysis (DSA) include:

- Time horizon
- Discount rates
- Baseline patient characteristics
- Efficacy and safety parameters
- Health state utilities
- Costs (direct medical costs, AE costs, indirect costs)

The time horizon was varied from 5 years to lifetime whereas discount rates were set to 0% and 6%. Baseline characteristics (age, proportion of male, and weight) were varied by ±1.96 standard error (SE) around the base case value. Health utilities were varied by ±10% as confidence intervals were available from published literature, without raising concerns regarding uncertainty.

Efficacy response at Week 8 for each treatment was varied using 95% CrIs estimated by the NMA. The maintenance response was also varied using 95% CrIs, while the proportion of patients on “high dose” maintenance regimens was varied ±20%. Adverse event rates were varied ±10%.

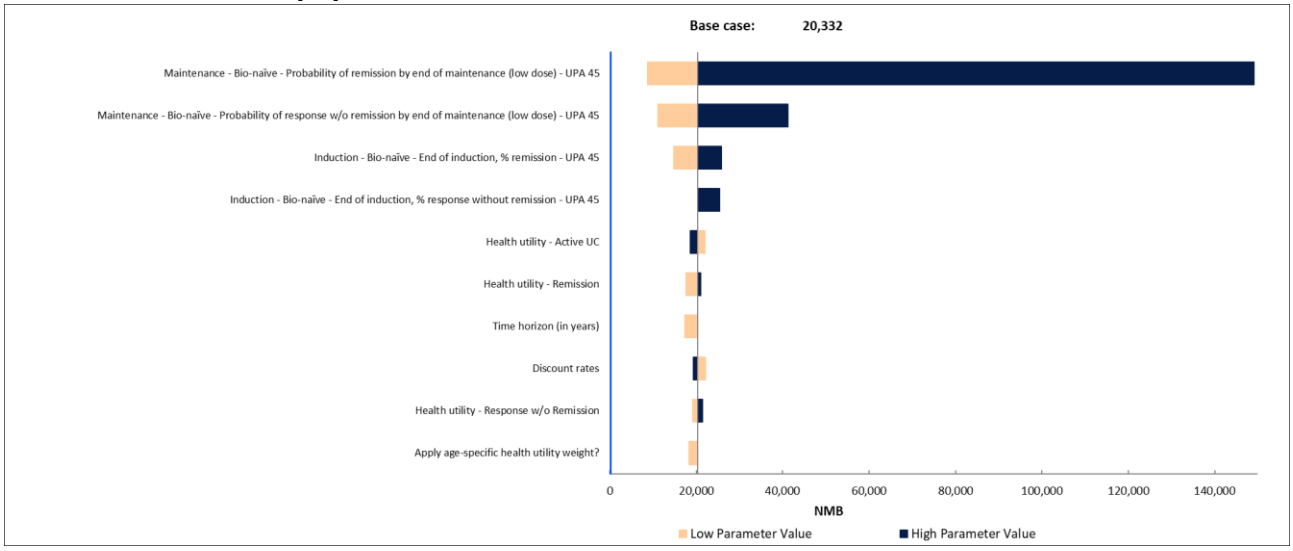
Drug acquisition costs were not varied. All other cost items were varied ±20%, consistent with TA633 (ustekinumab). Finally, background mortality rate was based on large national samples with little measurement error, with no variation therefore included.

Considering the number of comparators which are dominated by upadacitinib in the base-case analysis, the DSA has generally focused on the comparators on the cost-effectiveness frontier. The analyses were run using the deterministic model; as such, the net monetary benefits (NMB) will not match those of the base case (probabilistic) results.

B.3.11.2.1 Bio-naïve population, upadacitinib 15 mg maintenance dose

In the base-case analysis for the upadacitinib 15 mg maintenance dose in the bio-naïve population, upadacitinib dominates all comparators. The DSA considers adalimumab biosimilar as the comparator with the lowest costs apart from upadacitinib. The results are presented in terms of the NMB. All relevant parameters were varied as part of the analysis; the top ten parameters influencing the NMB are presented in Figure 15 and Table 101. The NMB remained positive (indicating that upadacitinib would be considered cost effective at a willingness-to-pay threshold of £30,000 per QALY) with all changes in parameters. Varying the efficacy parameters for upadacitinib (probability of remission and response without remission) had the biggest impact on the NMB.

Figure 15: Results of univariate analysis: UPA 15 mg maintenance dose versus adalimumab biosimilar, bio-naïve population



Abbreviations: NMB, net monetary benefit; UC, ulcerative colitis; UPA, upadacitinib; w/o, without.

Table 101: Results of univariate analysis: UPA 15 mg maintenance dose versus adalimumab biosimilar, bio-naïve population

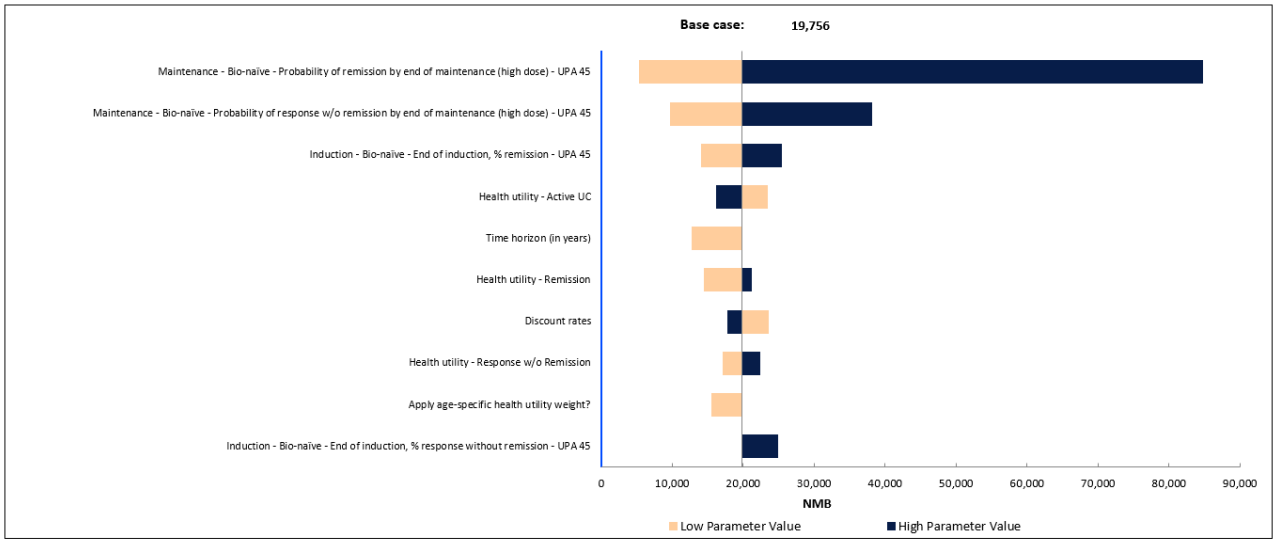
Parameter	NMB with lower bound (£)	NMB with upper bound (£)
Maintenance – Bio-naïve – Probability of remission by end of maintenance (UPA 15 mg)	8,682	149,048
Maintenance – Bio-naïve – Probability of response w/o remission by end of maintenance (UPA 15 mg)	11,053	41,233
Induction – Bio-naïve – End of induction, % remission - UPA 45	14,799	25,855
Induction – Bio-naïve – End of induction, % response without remission - UPA 45	21,693	25,342
Health utility – Active UC	22,052	18,612
Health utility – Remission	17,679	21,019
Time horizon (in years)	17,388	20,332
Discount rates	22,153	19,313
Health utility – Response w/o Remission	19,180	21,485
Apply age-specific health utility weight?	18,285	20,332

Abbreviations: NMB, net monetary benefit; UC, ulcerative colitis; UPA, upadacitinib; w/o, without.

B.3.11.2.2 Bio-naïve population, upadacitinib 30 mg maintenance dose

In the-base case analysis for the upadacitinib 30 mg maintenance dose in the bio-naïve population, upadacitinib is on the cost-effectiveness frontier alongside adalimumab biosimilar and golimumab. All relevant parameters were varied as part of the analysis; the top ten parameters influencing the NMB are presented in Figure 16 and Table 102 for the comparison versus adalimumab biosimilar, and in Figure 17 and Table 103 for the comparison versus golimumab. The NMB remained positive with variations in all parameters. Varying the efficacy parameters (probability of remission and response without remission) had the biggest impact on the NMB.

Figure 16: Results of univariate analysis: UPA 30 mg maintenance dose versus adalimumab biosimilar, bio-naïve population



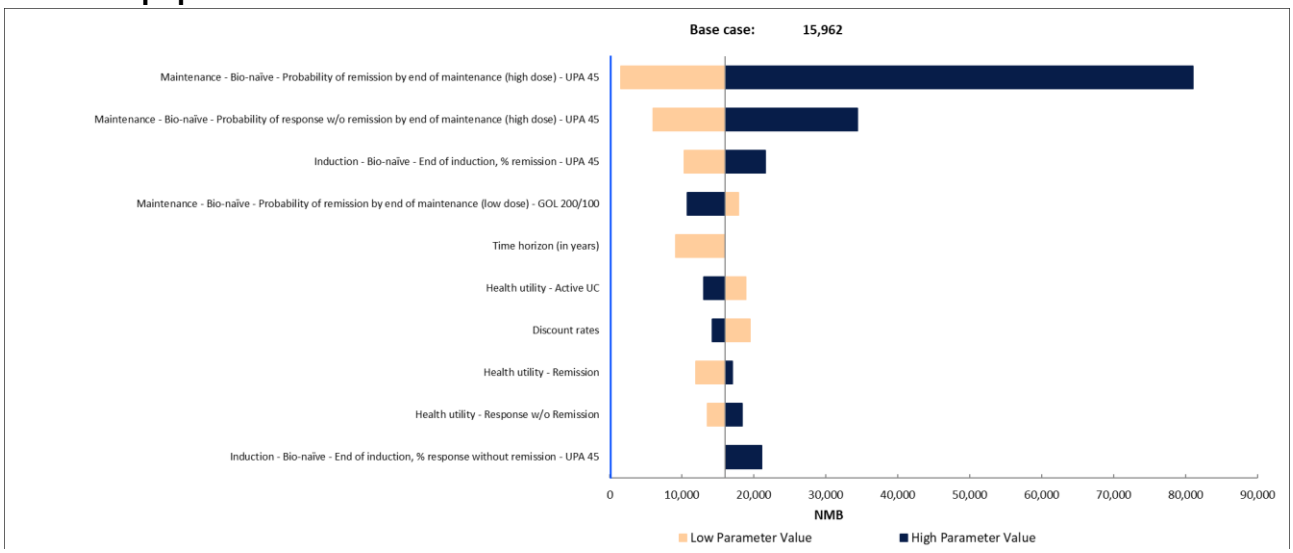
Abbreviations: NMB, net monetary benefit; UC, ulcerative colitis; UPA, upadacitinib; w/o, without.

Table 102: Results of univariate analysis: UPA 30 mg maintenance dose versus adalimumab biosimilar, bio-naïve population

Parameter	NMB with lower bound (£)	NMB with upper bound (£)
Maintenance - Bio-naïve - Probability of remission by end of maintenance (UPA 30 mg)	5,316	84,758
Maintenance - Bio-naïve - Probability of response w/o remission by end of maintenance (UPA 30 mg)	9,752	38,135
Induction - Bio-naïve - End of induction, % remission - UPA 45	14,146	25,354
Health utility - Active UC	23,339	16,172
Time horizon (in years)	12,726	19,756
Health utility - Remission	14,443	21,130
Discount rates	23,502	17,872
Health utility - Response w/o Remission	17,186	22,326
Apply age-specific health utility weight?	15,529	19,756
Induction - Bio-naïve - End of induction, % response without remission - UPA 45	21,139	24,847

Abbreviations: NMB, net monetary benefit; UC, ulcerative colitis; UPA, upadacitinib; w/o, without.

Figure 17: Results of univariate analysis: UPA 30 mg maintenance dose versus golimumab, bio-naïve population



Abbreviations: GOL, golimumab; NMB, net monetary benefit; UC, ulcerative colitis; UPA, upadacitinib; w/o, without.

Table 103: Results of univariate analysis: UPA 30 mg maintenance dose versus golimumab, bio-naïve population

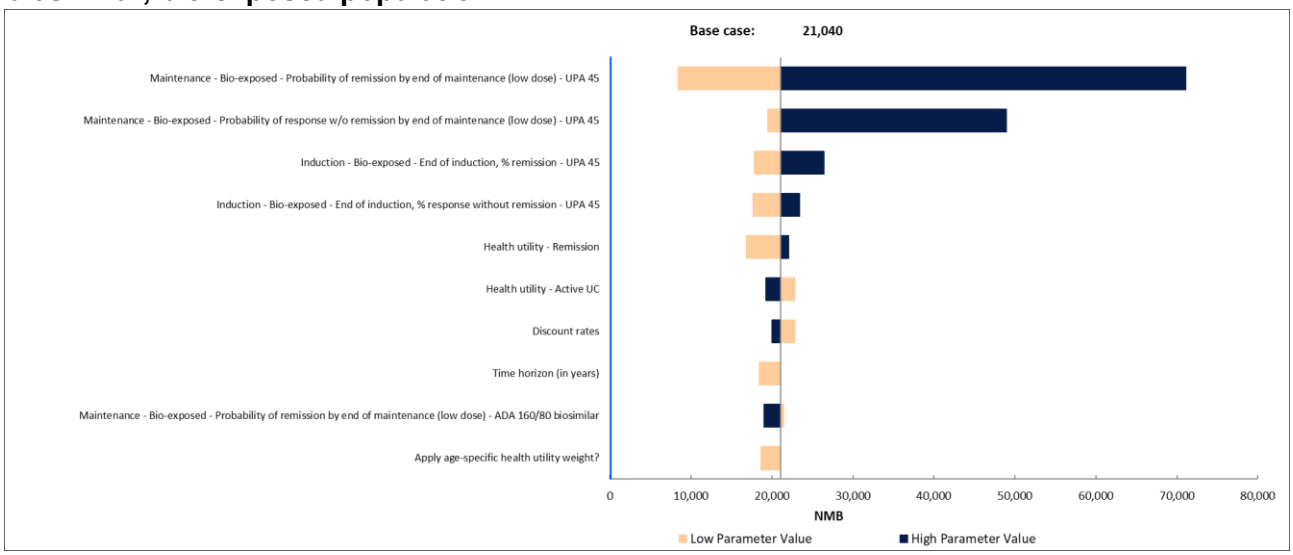
Parameter	NMB with lower bound (£)	NMB with upper bound (£)
Maintenance - Bio-naïve - Probability of remission by end of maintenance (UPA 30 mg)	1,522	80,965
Maintenance - Bio-naïve - Probability of response w/o remission by end of maintenance (UPA 30 mg)	5,958	34,341
Induction - Bio-naïve - End of induction, % remission - UPA 45	10,352	21,561
Maintenance - Bio-naïve - Probability of remission by end of maintenance (low dose) - GOL 200/100	17,823	10,754
Time horizon (in years)	9,164	15,962
Health utility - Active UC	18,916	13,008
Discount rates	19,442	14,218
Health utility – Remission	11,919	17,008
Health utility - Response w/o Remission	13,554	18,370
Induction - Bio-naïve - End of induction, % response without remission - UPA 45	17,345	21,054

Abbreviations: GOL, golimumab; NMB, net monetary benefit; UC, ulcerative colitis; UPA, upadacitinib; w/o, without.

B.3.11.2.3 Bio-exposed population, upadacitinib 15 mg maintenance dose

In the base-case analysis for the upadacitinib 15 mg maintenance dose in the bio-exposed population, the cost-effectiveness frontier is comprised of adalimumab biosimilar and upadacitinib. Results for the univariate analysis are presented in terms of changes in the NMB benefit for upadacitinib versus adalimumab biosimilar at a maximum willingness-to-pay threshold of £30,000 per QALY. All relevant parameters were varied as part of the analysis; the top ten parameters influencing the NMB are presented in Figure 18 and Table 104. The NMB remained positive with variations in all parameters. Varying the efficacy parameters (probability of remission and response without remission) for upadacitinib had the biggest impact on the NMB.

Figure 18: Results of univariate analysis: UPA 15 mg maintenance dose versus adalimumab biosimilar, bio-exposed population



Abbreviations: ADA, adalimumab; NMB, net monetary benefit; UC, ulcerative colitis; UPA, upadacitinib; w/o, without.

Table 104: Results of univariate analysis: UPA 15 mg maintenance dose versus adalimumab biosimilar, bio-exposed population

Parameter	NMB with lower bound (£)	NMB with upper bound (£)
Maintenance - Bio-exposed - Probability of remission by end of maintenance (UPA 15 mg)	8,407	71,060
Maintenance - Bio-exposed - Probability of response w/o remission by end of maintenance (UPA 15 mg)	19,528	48,968
Induction - Bio-exposed - End of induction, % remission - UPA 45	17,864	26,451
Induction - Bio-exposed - End of induction, % response without remission - UPA 45	17,681	23,370
Health utility – Remission	16,846	22,040

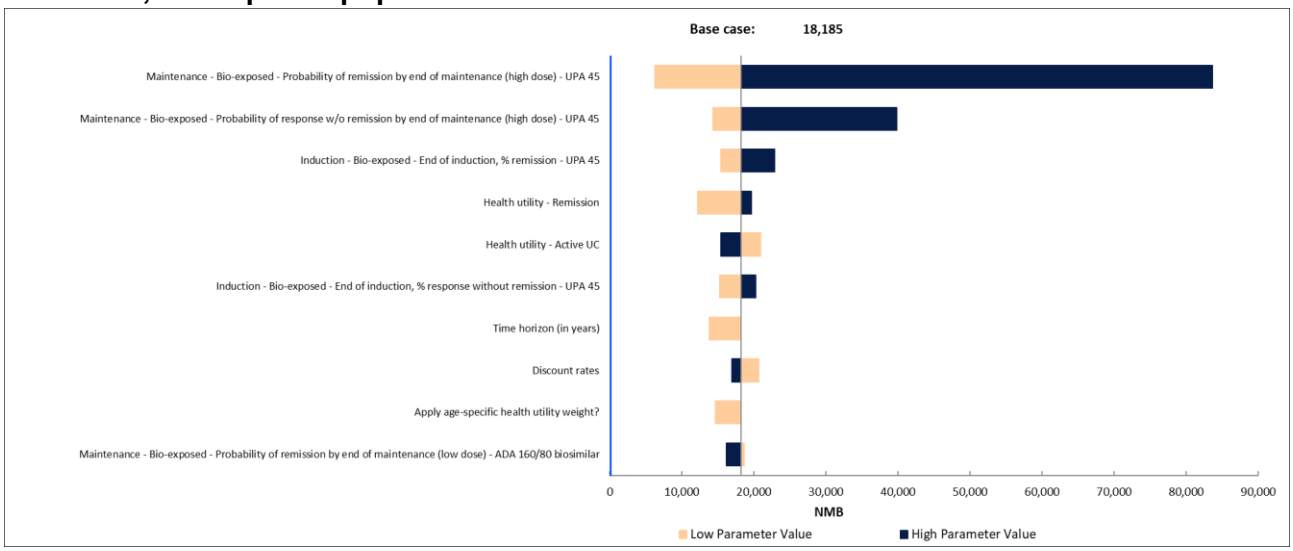
Parameter	NMB with lower bound (£)	NMB with upper bound (£)
Health utility - Active UC	22,824	19,255
Discount rates	22,793	20,054
Time horizon (in years)	18,399	21,040
Maintenance - Bio-exposed - Probability of remission by end of maintenance (low dose) - ADA 160/80 biosimilar	21,470	19,004
Apply age-specific health utility weight?	18,681	21,040

Abbreviations: ADA, adalimumab; NMB, net monetary benefit; UC, ulcerative colitis; UPA, upadacitinib; w/o, without.

B.3.11.2.4 Bio-exposed population, upadacitinib 30 mg maintenance dose

In the base-case analysis for the upadacitinib 30 mg maintenance dose in the bio-exposed population, the cost-effectiveness frontier is comprised of adalimumab biosimilar and upadacitinib. Results of a univariate analysis are presented for upadacitinib versus adalimumab biosimilar and for upadacitinib versus tofacitinib, a treatment which is extendedly dominated in the fully incremental analysis, but which is the next most effective treatment following upadacitinib. Results for the univariate analysis are presented in terms of changes in the NMB. All relevant parameters were varied as part of the analysis; the top ten parameters influencing the NMB are presented in Figure 19 and Table 105 for the comparison versus adalimumab biosimilar, and in Figure 20 and Table 106 for the comparison versus tofacitinib. The NMB remained positive with variations in all parameters. Varying the efficacy parameters (probability of remission and response without remission) for upadacitinib had the biggest impact on the NMB. The health state utility value for remission was the fourth largest driver of the NMB.

Figure 19: Results of univariate analysis: UPA 30 mg maintenance dose versus adalimumab biosimilar, bio-exposed population



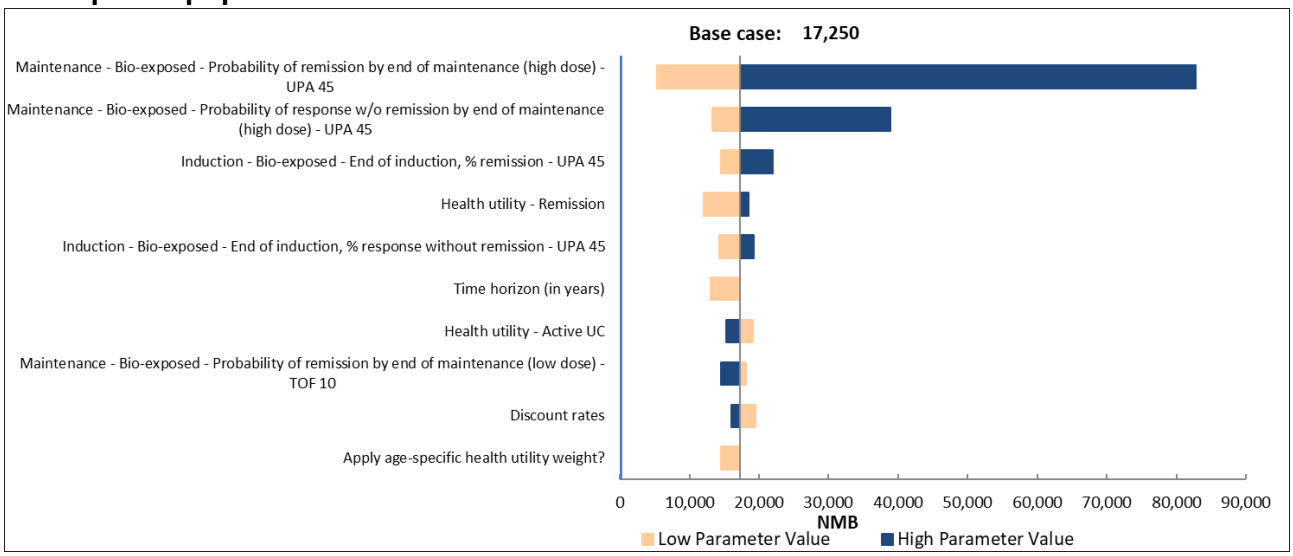
Abbreviations: ADA, adalimumab; NMB, net monetary benefit; UC, ulcerative colitis; UPA, upadacitinib; w/o, without.

Table 105: Results of univariate analysis: UPA 30 mg maintenance dose versus adalimumab biosimilar, bio-exposed population

Parameter	ICER with lower bound (£)	ICER with upper bound (£)
Maintenance - Bio-exposed - Probability of remission by end of maintenance (UPA 30 mg)	11,041	14,978
Health utility – Remission	16,345	12,802
Maintenance - Bio-exposed - Probability of response w/o remission by end of maintenance (high dose) - UPA 45	12,383	15,196
Maintenance - Bio-exposed - Percent of patients on high dose maintenance - UPA 30 mg	10,922	13,360
Health utility - Active UC	12,321	14,591
Annual direct medical costs based on health state - Active UC	14,346	12,375
Apply age-specific health utility weight?	14,999	13,360
Maintenance - Bio-exposed - Probability of response w/o remission by end of maintenance (low dose) - ADA 160/80 biosimilar	13,699	12,067
Maintenance - Bio-exposed - Probability of remission by end of maintenance (low dose) - ADA 160/80 biosimilar	13,534	12,106
Induction - Bio-exposed - End of induction, % response without remission - ADA 160/80 biosimilar	13,808	12,647

Abbreviations: ADA, adalimumab; NMB, net monetary benefit; UC, ulcerative colitis; UPA, upadacitinib; w/o, without.

Figure 20: Results of univariate analysis: UPA 30 mg maintenance dose versus tofacitinib, bio-exposed population



Abbreviations: NMB, net monetary benefit; TOF, tofacitinib; UC, ulcerative colitis; UPA, upadacitinib; w/o, without.

Table 106: Results of univariate analysis: UPA 30 mg maintenance dose versus tofacitinib, bio-exposed population

Parameter	NMB with lower bound (£)	NMB with upper bound (£)
Maintenance - Bio-exposed - Probability of remission by end of maintenance (UPA 30 mg)	5,345	82,746
Maintenance - Bio-exposed - Probability of response w/o remission by end of maintenance (UPA 30 mg)	13,331	38,904
Induction - Bio-exposed - End of induction, % remission - UPA 45	14,493	21,947
Health utility – Remission	12,030	18,495
Induction - Bio-exposed - End of induction, % response without remission - UPA 45	14,336	19,272
Time horizon (in years)	13,021	17,250
Health utility - Active UC	19,194	15,306
Maintenance - Bio-exposed - Probability of remission by end of maintenance (low dose) - TOF 10	18,094	14,507
Discount rates	19,497	16,048
Apply age-specific health utility weight?	14,594	17,250

Abbreviations: NMB, net monetary benefit; TOF, tofacitinib; UC, ulcerative colitis; UPA, upadacitinib; w/o, without.

B.3.11.3 Scenario analysis

An overview of the scenario analyses run is presented in Table 107. Scenario analysis included variations in the model's time horizon, the inclusion of extended induction or treatment sequencing, consideration of alternative sources of data for health state utility values, consideration of mixed maintenance dosing for upadacitinib, the possibility of spontaneous remission, and a non-constant probability of loss of response.

All scenarios were run using the deterministic model, except for scenario 7 (mixed upadacitinib maintenance dosing), for which the probabilistic model was run with 5,000 simulations in line with the base case analyses.

Table 107: Scenario analysis settings

Aspect	UPA model base case	Scenario analysis
Time horizon	Lifetime (100 years of age)	**Scenario 1**: 10 years (based on TA342) **Scenario 2**: 50 years (based on TA633)
Extended induction (delayed responder)	No	**Scenario 3**: Yes
Treatment sequencing	No	**Scenario 4**: Consideration of ustekinumab as subsequent therapy
Source of utility data	Woehl et al. (2008) (122) and Arseneau et al. (2006) (124)	**Scenario 5**: Swinburn et al. (2012) (126) **Scenario 6**: Vaizey et al. (2013) (127)
Maintenance dose assumptions	**UPA**: 15 mg maintenance dose **Comparators**: 70% standard dose, 30% high dose **UPA**: 30 mg maintenance dose **Comparators**: 70% standard dose, 30% high dose	**Scenario 7: UPA**: 70% 15 mg, 30% 30 mg **Comparators**: 70% standard dose, 30% high dose
Spontaneous remission from active UC	0%	**Scenario 8:** 1% probability per cycle
Probability of loss of response	Constant treatment-specific probability applied for model time horizon	**Scenario 9:** 25% reduction in the probability of loss of response after 12 months

Abbreviations: TA, technology appraisal; UC, ulcerative colitis; UPA, upadacitinib.

B.3.11.3.1 Results from scenario analysis

The direction of change for the base-case ICER in each scenario analysis for the bio-naïve population, upadacitinib 15 mg and 30 mg, and bio-exposed population upadacitinib 15 mg and 30 mg, are presented in Table 108, Table 109, Table 110, and Table 111, respectively. Scenario analyses were run using the deterministic model. Deterministic base case ICERs are provided for comparison. ICERs are not presented when a comparator is dominated.

In the scenario analysis for the bio-naïve patient population considering the upadacitinib 15 mg maintenance dose, upadacitinib remains cost effective (or dominant) compared with all comparators across all scenarios

Table 108. Scenario analyses: Incremental results UPA 15 mg maintenance dose vs comparator (ICER as cost per QALY, £), bio-naive

Scenario	Description	ADA biosimilar	ADA	GOL	IFX biosimilar	IFX	TOF	UST	VED SC	VED IV
Base case		Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 1: Time horizon (10 years)	Time horizon is updated to 10 years (based on TA342)	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 2: Time horizon (50 years)	Time horizon is updated to 50 years (based on TA633)	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 3: Extended induction	Delayed responders are included in the analysis	N/A	N/A	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 4: Treatment sequencing	Upon loss of response, a second treatment is	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA

Scenario	Description	ADA biosimilar	ADA	GOL	IFX biosimilar	IFX	TOF	UST	VED SC	VED IV
	initiated for each comparator (UST)									
Scenario 5: Utility data from Swinburn et al.	Utilities for active UC, remission, response, post-surgery remission	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 6: Utility data from Vaizey et al.	Utilities for active UC, remission, and response	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 7: Maintenance dose of UPA 70%:30% split (15 mg/30 mg)	UPA maintenance dosing is 70% 15 mg and 30% 30 mg	4,433	3,297	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 8: Spontaneous remission from active UC	Spontaneous remission is 1% probability per cycle	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 9: Loss of response	Probability of loss of response is reduced by 25% after year 1	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA

Abbreviations: ADA, adalimumab; GOL, golimumab: ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A not applicable; SC, subcutaneous; TOF, tofacitinib, UC, ulcerative colitis; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 109. Scenario analyses: Incremental results UPA 30 mg maintenance dose vs comparator (ICER as cost per QALY, £), bio-naive

Scenario	Description	ADA biosimilar	ADA	GOL	IFX biosimilar	IFX	TOF	UST	VED SC	VED IV
Base case		14,927	14,254	15,019	10,320	8,844	11,033	8,440	6,798	241
Scenario 1: Time horizon (10 years)	Time horizon is updated to 10 years (based on TA342)	14,844	14,076	14,877	9,440	7,723	9,986	7,131	5,195	Dominated by UPA
Scenario 2: Time horizon (50 years)	Time horizon is updated to 50 years (based on TA633)	14,929	14,256	15,021	10,322	8,846	11,035	8,442	6,800	243
Scenario 3: Extended induction	Delayed responders are included in the analysis	N/A	N/A	14,960	10,563	9,033	9,607	7,465	2,454	Dominated by UPA
Scenario 4: Treatment sequencing	Upon loss of response, a second treatment is initiated for each comparator (UST)	14,178	13,493	14,252	9,481	7,978	10,154	N/A	5,887	Dominated by UPA
Scenario 5: Utility data from Swinburn et al.	Utilities for active UC, remission, response, post-surgery remission	19,449	18,573	19,602	13,443	11,520	14,460	10,996	8,868	314

Scenario	Description	ADA biosimilar	ADA	GOL	IFX biosimilar	IFX	TOF	UST	VED SC	VED IV
Scenario 6: Utility data from Vaizey et al.	Utilities for active UC, remission, and response	34,133	32,595	34,781	23,505	20,143	26,526	19,235	15,674	555
Scenario 7: Maintenance dose of UPA 70%:30% split (15 mg/30 mg)	UPA maintenance dosing is 70% 15 mg and 30% 30 mg	4,433	3,297	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 8: Spontaneous remission from active UC	Spontaneous remission is 1% probability per cycle	14,699	13,876	14,860	9,663	7,984	10,481	7,925	6,055	Dominated by UPA
Scenario 9: Loss of response	Probability of loss of response is reduced by 25% after year 1	15,158	14,559	15,200	10,966	9,607	11,317	9,421	7,707	1,189

Abbreviations: ADA, adalimumab; GOL, golimumab: ICER, incremental cost effectiveness ratio; IFX, infliximab; IV, intravenous; N/A not applicable; SC, subcutaneous; TOF, tofacitinib, UC, ulcerative colitis; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 110: Scenario analyses: Incremental results UPA 15 mg maintenance dose vs comparator (ICER as cost per QALY, £), bio-exposed

Scenario	Description	ADA biosimilar	ADA	UST	VED SC	VED IV	TOF
Base case		761	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 1: Time horizon (10 years)	Time horizon is updated to 10 years (based on TA342)	969	44	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 2: Time horizon (50 years)	Time horizon is updated to 50 years (based on TA633)	763	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA

Scenario	Description	ADA biosimilar	ADA	UST	VED SC	VED IV	TOF
Scenario 3: Extended induction	Delayed responders are included in the analysis	N/A	N/A	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 4: Treatment sequencing	Upon loss of response, a second treatment is initiated for each comparator (UST)	Dominated by UPA	Dominated by UPA	N/A	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 5: Utility data from Swinburn et al.	Utilities for active UC, remission, response, post-surgery remission	987	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 6: Utility data from Vaizey et al.	Utilities for active UC, remission, and response	1,608	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 7: Maintenance dose of UPA 70%:30% split (15 mg/30 mg)	UPA maintenance dosing is 70% 15 mg and 30% 30 mg	5,244	4,413	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 8: Spontaneous remission from active UC	Spontaneous remission is 1% probability per cycle	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 9: Loss of response	Probability of loss of response is reduced by 25% after year 1	13,548	13,016	9,360	9,164	6,688	9,035

Abbreviations: ADA, adalimumab; GOL, golimumab: ICER, incremental cost effectiveness ratio; IFX, infliximab; IV, intravenous; N/A not applicable; SC, subcutaneous; TOF, tofacitinib, UC, ulcerative colitis; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 111: Scenario analyses: Incremental results UPA 30 mg maintenance dose vs comparator (ICER as cost per QALY, £), bio-exposed

Scenario	Description	ADA biosimilar	ADA	UST	VED SC	VED IV	TOF
Base case		13,360	12,758	8,306	8,216	5,638	8,711
Scenario 1: Time horizon (10 years)	Time horizon is updated to 10 years (based on TA342)	13,452	12,815	8,079	7,987	5,252	8,421
Scenario 2: Time horizon (50 years)	Time horizon is updated to 50 years (based on TA633)	13,362	12,760	8,308	8,218	5,640	8,713
Scenario 3: Extended induction	Delayed responders are included in the analysis	N/A	N/A	7,330	4,530	-1,034	6,074
Scenario 4: Treatment sequencing	Upon loss of response, a second treatment is initiated for each comparator (UST)	12,674	12,061	N/A	7,433	4,810	7,976
Scenario 5: Utility data from Swinburn et al.	Utilities for active UC, remission, response, post-surgery remission	17,354	16,572	10,785	10,683	7,331	11,276
Scenario 6: Utility data from Vaizey et al.	Utilities for active UC, remission, and response	28,673	27,381	17,737	17,800	12,214	17,991
Scenario 7: Maintenance dose of UPA 70%:30% split (15mg/30mg)	UPA maintenance dosing is 70% 15 mg and 30% 30 mg	5,244	4,413	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 8: Spontaneous remission from active UC	Spontaneous remission is 1% probability per cycle	13,142	12,405	7,894	7,646	4,369	8,266
Scenario 9: Loss of response	Probability of loss of response is reduced by 25% after year 1	13,548	13,016	9,360	9,164	6,688	9,035

Abbreviations: ADA, adalimumab; GOL, golimumab: ICER, incremental cost effectiveness ratio; IFX, infliximab; IV, intravenous; N/A not applicable; SC, subcutaneous; TOF, tofacitinib, UC, ulcerative colitis; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.11.3.1.1 Scenario 1 Time horizon (10 years)

Scenario 1 considered a shorter time horizon of 10 years aligned with TA342. The consideration of a 10-year time horizon did not change the conclusions of the analysis, with upadacitinib remaining cost effective at both upadacitinib 15 mg and 30 mg maintenance doses in the bio-naïve (Table 112 and Table 113) and bio-exposed (Table 114 and Table 115) populations.

Table 112: Scenario 1 results for bio-naïve UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
GOL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
IFX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
TOF	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
UST	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA

Abbreviations: ADA, adalimumab; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous therapy; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 113: Scenario 1 results for bio-naïve UPA 30 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
GOL	[redacted]	[redacted]	[redacted]	[redacted]	14,723	14,723
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	50,743	Dominated

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
IFX	[redacted]	[redacted]	[redacted]	[redacted]	62,148	Dominated
TOF	[redacted]	[redacted]	[redacted]	[redacted]	21,867	Extended dominance
UST	[redacted]	[redacted]	[redacted]	[redacted]	44,920	Dominated
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	45,200	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	14,844	14,877
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	69,390	Dominated by UPA

Abbreviations: ADA, adalimumab; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous therapy; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 114: Scenario 1 results for bio-exposed UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	969	969
UST	[redacted]	[redacted]	[redacted]	[redacted]	97,127	Dominated by UPA
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	84,769	Dominated by UPA
TOF	[redacted]	[redacted]	[redacted]	[redacted]	26,874	Dominated by UPA
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	120,456	Dominated by UPA

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous therapy; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 115: Scenario 1 results for bio-exposed UPA 30 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	97,127	Extended dominance
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	84,769	Extended

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
						dominance
TOF	[redacted]	[redacted]	[redacted]	[redacted]	26,874	Extended dominance
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	120,456	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	13,452	13,452

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous therapy; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.11.3.1.2 Scenario 2 Time horizon (50 years)

Scenario 2 considered a time horizon of 50 years aligned with TA633. This is a small change from the base-case which assumes a time horizon of up to 100 years of age. The consideration of a 50-year time horizon did not change the conclusions of the analysis, with upadacitinib remaining cost effective at both upadacitinib 15 mg and 30 mg maintenance doses in the bio-naïve (Table 116 and Table 117) and bio-exposed (Table 118 and Table 119) populations.

Table 116: Scenario 2 results for bio-naïve UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
GOL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
IFX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
TOF	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
UST	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA

Abbreviations: ADA, adalimumab; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 117: Scenario 2 results for bio-naïve UPA 30 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
GOL	[redacted]	[redacted]	[redacted]	[redacted]	14,527	14,527
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	50,662	Dominated
IFX	[redacted]	[redacted]	[redacted]	[redacted]	62,114	Dominated
TOF	[redacted]	[redacted]	[redacted]	[redacted]	21,716	Extended dominance
UST	[redacted]	[redacted]	[redacted]	[redacted]	44,781	Dominated
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	44,898	Dominated
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	69,074	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	14,929	15,021

Abbreviations: ADA, adalimumab; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 118: Scenario 2 results for bio-exposed UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	763	763
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	97,210	Dominated
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	84,759	Dominated
TOF	[redacted]	[redacted]	[redacted]	[redacted]	26,692	Dominated
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	120,546	Dominated

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 119: Scenario 2 results for bio-exposed UPA 30 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	97,210	Extended dominance
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	84,759	Extended dominance
TOF	[redacted]	[redacted]	[redacted]	[redacted]	26,692	Extended dominance
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	120,546	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	13,362	13,362

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.11.3.1.3 Scenario 3 Extended induction

Scenario 3 considers extended induction for relevant comparators. Adalimumab and adalimumab biosimilar were excluded from this scenario since extended induction is not an option for these treatments. Upadacitinib remained cost effective at both upadacitinib 15 mg and 30 mg maintenance doses in both bio-naïve (Table 120 and Table 121) and bio-exposed (Table 122 and Table 123) populations in this scenario.

Table 120: Scenario 3 results for bio-naïve UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
GOL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated
IFX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated
TOF	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated

Abbreviations: GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 121: Scenario 3 results for bio-naïve UPA 30 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
GOL	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
IFX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Extended dominance
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Extended dominance
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA

Abbreviations: GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; QALYs, quality-adjusted life years; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 122: Scenario 3 results for bio-exposed UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
UST	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
TOF	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA

Abbreviations: ICER, incremental cost-effectiveness ratio; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 123: Scenario 3 results for bio-exposed UPA 30 mg maintenance dose

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
UST	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
TOF	[redacted]	[redacted]	[redacted]	[redacted]	11,087	Extended dominance
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	27,279	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	7,330	7,330
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	66,921	Dominated by UPA

Abbreviations: ICER, incremental cost-effectiveness ratio; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.11.3.1.4 Scenario 4 Treatment sequencing

The base-case analysis assumed no sequencing of treatments, and that patients discontinuing treatment would move to CT. In this scenario, patients failing to respond, or experiencing subsequent loss of response, were assumed to receive a subsequent line of treatment with ustekinumab. Ustekinumab was selected as a treatment likely to be given at this point in the treatment sequence. In this scenario, upadacitinib remained cost-effective at both standard and high maintenance doses and in both bio-naïve (Table 124 and Table 125) and bio-exposed (Table 126 and Table 127) populations.

Table 124: Scenario 4 results for bio-naïve UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
GOL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
IFX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
TOF	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA

Abbreviations: ADA, adalimumab; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; QALYs, quality-adjusted life years; TOF, tofacitinib; UPA, upadacitinib; VED, vedolizumab.

Table 125: Scenario 4 results for bio-naïve UPA 30 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
GOL	[redacted]	[redacted]	[redacted]	[redacted]	13,857	13,857
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	50,620	Dominated
IFX	[redacted]	[redacted]	[redacted]	[redacted]	62,290	Dominated
TOF	[redacted]	[redacted]	[redacted]	[redacted]	21,169	Extended dominance
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	44,708	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	14,178	14,252
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	69,312	Dominated by UPA

Abbreviations: ADA, adalimumab; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; QALYs, quality-adjusted life years; TOF, tofacitinib; UPA, upadacitinib; VED, vedolizumab.

Table 126: Scenario 4 results for bio-exposed UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
TOF	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; VED, vedolizumab.

Table 127: Scenario 4 results for bio-exposed UPA 30 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	85,187	Extended dominance
TOF	[redacted]	[redacted]	[redacted]	[redacted]	26,189	Extended dominance
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	121,473	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	12,674	12,674

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; VED, vedolizumab.

B.3.11.3.1.5 Scenario 5 Utility data from Swinburn et al. (2012) (126)

In this scenario, utility data from Swinburn et al. (2012) (126) was utilised in active UC, remission, response, and post-surgery remission health states (see Table 78 for detail). This scenario resulted in higher QALYs for all treatments compared with the base case. Upadacitinib remained cost effective at both upadacitinib 15 mg and 30 mg maintenance doses in both bio-naïve (Table 128 and Table 129) and bio-exposed (Table 130 and Table 131) populations in this scenario.

Table 128: Scenario 5 results for bio-naïve UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
GOL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
IFX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
TOF	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
UST	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated by

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
					by UPA	UPA
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA

Abbreviations: ADA, adalimumab; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; QALYs, quality-adjusted life years; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 129: Scenario 5 results for bio-naïve UPA 30 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
GOL	[redacted]	[redacted]	[redacted]	[redacted]	18,790	18,790
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	66,135	Dominated
IFX	[redacted]	[redacted]	[redacted]	[redacted]	81,086	Dominated
TOF	[redacted]	[redacted]	[redacted]	[redacted]	28,008	Extended dominance
UST	[redacted]	[redacted]	[redacted]	[redacted]	58,367	Dominated
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	58,250	Dominated
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	89,618	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	19,449	19,602

Abbreviations: ADA, adalimumab; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; QALYs, quality-adjusted life years; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 130: Scenario 5 results for bio-exposed UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	987	987
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
UST	[redacted]	[redacted]	[redacted]	[redacted]	127,046	Dominated by UPA
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	108,686	Dominated by UPA

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
TOF	[redacted]	[redacted]	[redacted]	[redacted]	35,018	Dominated by UPA
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	154,575	Dominated by UPA

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 131: Scenario 5 results for bio-exposed UPA 30 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	127,046	Extended dominance
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	108,686	Extended dominance
TOF	[redacted]	[redacted]	[redacted]	[redacted]	35,018	Extended dominance
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	154,575	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	17,354	17,354

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.11.3.1.6 Scenario 6 Utility data from Vaizey et al. (2014) (127)

Scenario 6 considers utility data from Vaizey et al. (2014) (127) in active UC, remission, and the response health state (see Table 78 for detail). This scenario resulted in higher QALYs for all treatments compared with the base case and Scenario 5. Upadacitinib remained cost effective at both upadacitinib 15 mg and 30 mg maintenance doses in the bio-exposed (Table 132 and Table 133) populations and standard dose for the bio-naïve (Table 134 and Table 135) population in this scenario.

Table 132: Scenario 6 results for bio-naïve UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
GOL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
IFX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
TOF	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
UST	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA

Abbreviations: ADA, adalimumab; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; QALYs, quality-adjusted life years; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 133: Scenario 6 results for bio-naïve UPA 30 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
GOL	[redacted]	[redacted]	[redacted]	[redacted]	31,497	31,497
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	119,531	Dominated
IFX	[redacted]	[redacted]	[redacted]	[redacted]	146,553	Dominated
TOF	[redacted]	[redacted]	[redacted]	[redacted]	45,753	Extended dominance
UST	[redacted]	[redacted]	[redacted]	[redacted]	104,026	Dominated
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	99,652	Dominated
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	153,314	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	34,133	34,781

Abbreviations: ADA, adalimumab; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; QALYs, quality-adjusted life years; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 134: Scenario 6 results for bio-exposed UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	1,608	1,608
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
UST	[redacted]	[redacted]	[redacted]	[redacted]	227,311	Dominated by UPA
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	161,027	Dominated by UPA
TOF	[redacted]	[redacted]	[redacted]	[redacted]	64,526	Dominated by UPA
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	229,014	Dominated by UPA

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 135: Scenario 6 results for bio-exposed UPA 30 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	227,311	Extended dominance
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	161,027	Extended dominance
TOF	[redacted]	[redacted]	[redacted]	[redacted]	64,526	Extended dominance
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	229,014	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	28,673	28,673

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.11.3.1.7 Scenario 7 Maintenance dose of upadacitinib (70%/30% split)

This scenario considers a mix of maintenance dosing for upadacitinib, with 70% of patients receiving the 15 mg QD and the remaining 30% receiving the 30 mg QD. Upadacitinib remained cost effective both bio-naïve (Table 136) and bio-exposed (Table 137) populations in this scenario. This analysis was run probabilistically.

Table 136: Scenario 7 results for bio-naïve subgroup: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UPA	[redacted]	[redacted]	[redacted]	[redacted]	4,433	4,433
GOL	[redacted]	[redacted]	[redacted]	[redacted]	15,763	Dominated by UPA
INF biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	52,187	Dominated by UPA
INF	[redacted]	[redacted]	[redacted]	[redacted]	68,657	Dominated by UPA
UST	[redacted]	[redacted]	[redacted]	[redacted]	45,945	Dominated by UPA
TOF	[redacted]	[redacted]	[redacted]	[redacted]	22,672	Dominated by UPA
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	44,614	Dominated by UPA
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	71,712	Dominated by UPA

Abbreviations: ADA, adalimumab; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; QALYs, quality-adjusted life years; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 137: Scenario 7 results for bio-exposed subgroup: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UPA	[redacted]	[redacted]	[redacted]	[redacted]	5,244	5,244
UST	[redacted]	[redacted]	[redacted]	[redacted]	179,906	Dominated by UPA
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	72,016	Dominated by UPA
TOF	[redacted]	[redacted]	[redacted]	[redacted]	28,511	Dominated by UPA
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	118,355	Dominated by UPA

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; VED, vedolizumab.

B.3.11.3.1.8 Scenario 8 Spontaneous remission from active UC

In this scenario, spontaneous remission from active UC was assumed with a 1% probability of spontaneous remission applied per 4-week cycle. Upadacitinib remained cost effective at both upadacitinib 15 mg and 30 mg maintenance doses in both bio-naïve (Table 138 and Table 139) and bio-exposed (Table 140 and Table 141) populations in this scenario.

Table 138: Scenario 8 results for bio-naïve UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
GOL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
INF biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
INF	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
TOF	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
UST	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA

Abbreviations: ADA, adalimumab; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; QALYs, quality-adjusted life years; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 139: Scenario 8 results for bio-naïve UPA 30 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
GOL	[redacted]	[redacted]	[redacted]	[redacted]	13,999	13,999
INF biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	53,770	Dominated

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
INF	[redacted]	[redacted]	[redacted]	[redacted]	66,801	Dominated
TOF	[redacted]	[redacted]	[redacted]	[redacted]	22,041	Extended dominance
UST	[redacted]	[redacted]	[redacted]	[redacted]	45,878	Dominated
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	46,554	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	14,699	14,860
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	74,127	Dominated by UPA

Abbreviations: ADA, adalimumab; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; QALYs, quality-adjusted life years; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 140: Scenario 8 results for bio-exposed UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
UST	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
TOF	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 141: Scenario 8 results for bio-exposed UPA 30 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	100,265	Extended dominance

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	89,349	Extended dominance
TOF	[redacted]	[redacted]	[redacted]	[redacted]	27,141	Extended dominance
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	134,792	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	13,142	13,142

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.11.3.1.9 Scenario 9 Non-constant probability of loss of response

In this scenario, a non-constant probability of loss of response was assumed. The probability of loss of response was assumed to reduce by 25% after 12 months. Upadacitinib remained cost effective at both upadacitinib 15 mg and 30 mg maintenance doses in both bio-naïve (Table 142 and Table 143) and bio-exposed (Table 144 and Table 145) populations in this scenario.

Table 142: Scenario 9 results for bio-naïve UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
GOL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
INF biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
INF	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
UST	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
TOF	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by UPA	Dominated by UPA

Abbreviations: ADA, adalimumab; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; QALYs, quality-adjusted life years; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 143: Scenario 9 results for bio-naïve UPA 30 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
GOL	[redacted]	[redacted]	[redacted]	[redacted]	14,978	14,978
INF biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	47,665	Dominated
INF	[redacted]	[redacted]	[redacted]	[redacted]	58,200	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	41,268	Dominated
TOF	[redacted]	[redacted]	[redacted]	[redacted]	21,673	Extended dominance
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	41,702	Dominated
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	64,923	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	15,158	15,200

Abbreviations: ADA, adalimumab; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; QALYs, quality-adjusted life years; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 144: Scenario 9 results for bio-exposed UPA 15 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	91,460	Extended dominance
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	74,230	Extended dominance
TOF	[redacted]	[redacted]	[redacted]	[redacted]	26,526	Extended dominance
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	108,492	Dominated
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	13,548	13,548

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 145: Scenario 9 results for bio-exposed UPA 30 mg maintenance dose: fully incremental cost-effectiveness results

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference

Technologies	Total discounted costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	91,460	Extended dominance
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	74,230	Extended dominance
TOF	[redacted]	[redacted]	[redacted]	[redacted]	26,526	Extended dominance
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	108,492	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	13,548	13,548

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; QALYs, quality-adjusted life years; SC, subcutaneous; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B.3.12 Subgroup analysis

Not applicable – key subgroups relevant to the decision problem were included in the main analysis.

B.3.13 Benefits not captured in the QALY calculation

Some people with UC may have comorbidities, including arthritic or skin conditions. These extra-intestinal manifestations have not specifically been included in QALY calculations; however, upadacitinib will likely have a positive impact on these manifestations in addition to the treatment of active UC. Upadacitinib currently has marketing authorisation and NICE recommendations in relevant indications (rheumatoid arthritis and psoriatic arthritis) with several others currently undergoing appraisal (ankylosing spondylitis, non-radiographic axial spondyloarthritis, atopic dermatitis) by NICE. Additionally, there is the potential that caregiver disutility associated with caring for patients with moderate-to-severe UC has not been captured by the model, but no evidence was identified to support its inclusion, nor would the inclusion of caregiver disutility adhere to the NICE reference case.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

B.3.14.1.1 Technical and internal validation

The model was prepared according to The Professional Society for Health Economics and Outcomes Research (ISPOR) and Society for Medical Decision Making (SMDM) best practices (112, 113), and aligns with NICE guidance (111).

To verify the results of the cost-effectiveness utility model, internal quality control procedures were undertaken to ensure that the mathematical calculations were performed correctly and were consistent with the model's specifications. This validation involved an economist who did not develop the model but who reviewed the model for coding errors, inconsistencies, and the plausibility of inputs, which was performed as a thorough sheet-by-sheet (Excel tab-by-tab) check. This review included the following:

- Extreme value testing to ensure that the model yielded a logical output
- Logical relationship testing (e.g., if intervention drug acquisition costs increase, do total intervention costs increase accordingly? Does the ICER increase accordingly?)
- Consistency checks (e.g., is an input parameter value cost in one cell consistently reflected elsewhere?)
- Checking of spreadsheet calculations and VBA code for implementation errors

Validation using different routine tests yielded the expected results. Additionally, two experienced, independent modellers reviewed the model structure and parameters.

B.3.14.1.2 External validation

Comparison of model outcomes against recent submissions in UC is not possible since model outcomes (QALYs and life years) were redacted in TA547 and TA633. As an alternative approach, model outcomes are compared against the most recent publication of a submission model. Lohan et al (2019) published an economic evaluation of tofacitinib versus conventional therapy, adalimumab, golimumab, infliximab and vedolizumab (132). Data from an SLR of randomised controlled trials (RCTs) were synthesised via an NMA and used to populate a Markov model with a structure closely aligned to that adopted for UPA. A comparison of model QALY outcomes for our analysis versus Lohan et al is presented in Table 146.

Table 146: Base case costs and QALYs gained by treatment sequence in the UPA model and in published literature

Comparator	Lohan et al. total QALYs (bio-naïve)	Current model QALYs (bio-naïve)		Lohan et al. total QALYs (bio-exposed)	Current model QALYs (bio-exposed)	
		Base-case	Adjusted†		Base-case	Adjusted†
ADA	9.191	[redacted]	[redacted]	9.051	[redacted]	[redacted]
GOL	9.286	[redacted]	[redacted]			
IFX	9.346	[redacted]	[redacted]			
VED	9.462	[redacted]	[redacted]	9.146	[redacted]	[redacted]
TOF	9.536	[redacted]	[redacted]	9.240	[redacted]	[redacted]

†Disutility of serious infection to -0.0142, probability of post-surgery complication to 0.56%; starting age/sex to 41 years and 59% male, weight to 73kg, annual probability of post-surgery remission to chronic complications to 1.46% [to equate to Lohan inputs].
Abbreviations: ADA, adalimumab; GOL, golimumab; IFX, infliximab; QALY, quality-adjusted life year; TOF, tofacitinib; UPA, upadacitinib; VED, vedolizumab.

Lifetime QALYs, by treatment, are compared between the current model and Lohan (2018) (132) in Table 146, with variance between 7–9% when unadjusted. When adjusted for patient characteristics, disutility weights and probability of surgery complications, the variance dropped between 3–5%. It should be noted that an exact match was not possible as costs and prices have evolved, more studies have become available that need to be incorporated into NMA results, effectiveness inputs have changed, and mortality tables and patient characteristics may not be an exact match between models. This suggests any remaining variance is due to NMA results, mortality, or model structure, suggesting this level of variance is therefore a reasonable range of consistency within the constraints of comparison the two models.

B.3.15 Interpretation and conclusions of economic evidence

None of the CEAs identified in the economic SLR (Appendix G) included upadacitinib as a comparator. It was therefore necessary to develop a *de novo* economic model for this submission, building upon learnings from prior economic evaluations in UC.

The economic evaluation conducted provides results separately for bio-naïve and bio-exposed populations, and for the upadacitinib 15 mg QD and upadacitinib 30 mg QD maintenance doses. To support decision making, scenario analysis considered a mix of maintenance doses for upadacitinib, with 30% of patients assumed to receive the 30 mg

maintenance dose and the remaining 70% assumed to receive the 15 mg maintenance dose.

The strengths of the analysis are that it leverages an established model framework widely used and accepted in UC which was further validated by UK clinical experts. The model is populated with clinical efficacy and safety data analysed via an NMA. The base-case analysis for this submission is fully probabilistic, with efficacy parameters sampled from NMA CODA samples to fully characterise the uncertainty in the point estimates. Extensive DSAs have also been conducted (one-way and scenario analyses).

In line with UK clinical expert feedback on the clinical trial results, upadacitinib was consistently found to be associated with having the highest probability of being the most effective and have the highest QALYs in the indirect comparison and economic evaluation. The results suggest that upadacitinib is a cost-effective treatment option for adults with moderately to severely active UC, who have had an inadequate response, loss of response, or were intolerant to either CT or a biologic agent. These conclusions were consistent across patient populations and scenarios.

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B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection, and synthesis of clinical evidence

Appendix E: Subgroup analyses

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement, and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: Upadacitinib clinical trials additional methodology

Appendix N: Upadacitinib clinical trials additional results

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Upadacitinib for treating moderately to severely active ulcerative colitis [ID3953]

Clarification questions

AbbVie UK Ltd. responses

9th May 2022

File name	Version	Contains confidential information	Date
ID3953 Upadacitinib UC Clarification letter_v1.0 to PM [CIC]_Company responses_fully redacted.docx	**1**	**Yes: [redacted]**	**25th May 2022**

Notes for company

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Section A: Clarification on clinical effectiveness data

U-ACHIEVE and U-ACCOMPLISH studies

A1. Company submission (CS), Document B, section B.2.3.1.1. Patients in the Non-Bio-IR subgroup of the U-ACHIEVE and U-ACCOMPLISH studies are defined as patients who have had an inadequate response, loss of response, or intolerance to conventional therapy (CT) but had not failed biologic therapy. The Non-Bio-IR subgroup could also include patients who had discontinued biologics for reasons other than inadequate response, loss of response, or intolerance (CS, p31). Please provide details of 'other reasons' (description and frequency) for discontinuing biologics.

Company response:

Across the upadacitinib clinical trial programme, few patients (17 in total) in the non-Bio-IR (bio-naïve) subgroup discontinued treatment due to reasons other than inadequate response, loss of response, or intolerance (10 patients in the U-ACHIEVE induction study and 7 patients in the U-ACCOMPLISH induction study). These reasons for treatment discontinuation are presented in Table 1. Please note that one patient in the U-ACHIEVE induction study and one patient in the U-ACCOMPLISH induction study had multiple reasons for treatment discontinuation.

Table 1: Reasons other than inadequate response, loss of response, or intolerance for treatment discontinuation in the non-Bio-IR subgroup across the upadacitinib clinical trial programme

Trial	U-ACHIEVE induction study	U-ACCOMPLISH induction study
Reasons for treatment discontinuation	• [redacted]	• [redacted]

Abbreviations: non-Bio-IR, inadequate response, loss of response, or intolerance to conventional therapy but not failed biologic therapy. Please note that one patient in the U-ACHIEVE and one patient in the U-ACCOMPLISH study had multiple reasons for treatment discontinuation.

A2. CS, Document B, section B.2.3.1.2. The permitted concomitant therapies in the upadacitinib trials were oral corticosteroids, antibiotics, 5-ASA and methotrexate (CS, Table 6). Please explain the rationale for permitting the use of methotrexate, whilst the use of azathioprine and mercaptopurine was prohibited.

Company response:

The use of azathioprine and mercaptopurine were prohibited due to the immunosuppressive effect and the potential increased risk of certain side effects such as infection.

Methotrexate, however, is one of the most commonly used treatments in rheumatoid arthritis (RA). In the upadacitinib RA clinical programme, studies were conducted with administration of upadacitinib and methotrexate as a background therapy. No additional safety risks were identified in patients treated with upadacitinib and methotrexate. The efficacy and safety of the use of upadacitinib in combination with methotrexate was demonstrated in a Phase 3 double-blind placebo-controlled study of patients with moderate to severely active RA in 651 patients who had an inadequate response to methotrexate alone (SELECT COMPARE) (1). In addition, three other double-blind placebo-controlled Phase 3 studies evaluated the efficacy and safety of upadacitinib in combination with various conventional synthetic disease modifying anti rheumatic drugs (csDMARDs) in patients with moderate to severe RA: (SELECT NEXT) (2), SELECT BEYOND (3), and SELECT CHOICE (4).The majority (55–75% across trials and arms) of the patients within these studies received concomitant methotrexate, with or without other csDMARDs sulfasalazine, leflunomide, hydroxychloroquine, or chloroquine. The only combination of csDMARD with upadacitinib in these studies that was not permitted was methotrexate and leflunomide due to the potential for increased immunosuppression.

Based on the established safety data from the upadacitinib in RA clinical programme, methotrexate was therefore permitted as a concomitant treatment across all upadacitinib clinical programmes, including that for UC.

A3. CS, Document B, section B.2. The adapted Mayo score was used in the upadacitinib trials to assess disease activity. Please provide details of any studies that have validated the adapted Mayo scoring system.

Company response:

Currently, there is no validated scale to define disease activity in UC; however, the Mayo Score has historically been used in UC as the outcome measure for clinical trials to assess disease activity and define remission and endoscopic healing.

As discussed in the Company submission, the Full Mayo score has four components, comprising stool frequency subscore (SFS), rectal bleeding subscore (RBS,) endoscopic subscore, and Physician's Global Assessment (PGA). While the Mayo scoring system brings some uniformity in the assessment of disease activity in clinical trials, it is a subjective measure because it includes the PGA, which does not directly reflect patient-reported clinical symptoms but reflects the physician's perspective of the clinical symptoms and endoscopy findings.

In UC, clinical trial guidance released by the FDA in 2016, the agency questioned the utility of the PGA subscore because the concept it purports to measure that is distinct from the other components is not clear (5). Therefore, the use of the PGA is not recommended in endpoint measures to support a marketing authorisation. Instead, a Modified Mayo score (excluding the PGA component in the Full Mayo score) is recommended. As a result, in some newly performed clinical trials, an Adapted/Modified/Partial Mayo score was used instead of the Full Mayo score (6).

Before implementing the Adapted Mayo score in the upadacitinib UC trials, Abbvie performed an analysis to investigate the concordance between the Full Mayo score definition of moderately to severely active UC (Full Mayo Score of 6 to12, with an endoscopy subscore of 2 or 3) and the Adapted Mayo score definition (Adapted Mayo Score of 5 to 9, with an endoscopy subscore of 2 or 3), utilising the data from registrational UC studies that investigated adalimumab (Study M06-826 and study M06-827; N=1,068). The analysis demonstrated that the two scores had a high concordance of 94%; indicating that 94% of subjects enrolled using the Full Mayo

Score definition also met the Adapted Mayo Score definition of moderately to severely active UC.

In the upadacitinib Phase 3 induction studies, post-hoc analysis further demonstrated a high concordance between the Full Mayo score and Adapted Mayo score (Table 2). In both induction studies, among all of the enrolled subjects with moderately to severely active UC defined by the Adapted Mayo score, >99% of the patients also met the criteria of moderately to severely active UC defined by the Full mayo score.

Table 2: Summary of baseline Full Mayo score and endoscopic subscore in the upadacitinib U-ACHIEVE and U-ACCOMPLISH induction studies

Endpoint measure, n (%)	U-ACHIEVE induction study		U-ACCOMPLISH induction study	
	UPA 45 mg QD (n=319)	Placebo (n=154)	UPA 45 mg QD (n=341)	Placebo (n=174)
Mayo score ≥6 and Endoscopic subscore ≥2	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QD, once-daily dosing; UPA, upadacitinib.

In summary, the Adapted Mayo score was used in defining disease activity based on the recommendation by the regulatory agency. Post-hoc analysis from both adalimumab and upadacitinib UC studies demonstrated high concordance of Full Mayo score and Adapted Mayo score definitions of moderately to severely active UC.

Network Meta-Analysis (NMA)

A4. Priority question. CS, Appendices, section D.1.3.1. To assess the comparability of studies included in the NMAs, the company collated data on study design and patient baseline characteristics in an Excel spreadsheet. Please provide the tabulated data.

Company response:

Patient baseline characteristics for studies included in the induction and maintenance NMA are presented in Table 3 and Table 4, respectively. Where there were separate baseline data available for the biologic-naïve (bio-naïve) and biologic-exposed (bio-exposed) subgroups, they have both been included.

All details on study design for the included trials can be found in the original Company submission appendices; Appendix D1.3, Table 6.

Table 3: Baseline patient characteristics data of induction populations

Study (biologic exposure subgroup)	Treatment	N	Age (years)		Male (%)	Weight (kg)		Disease duration (years)		Extensive colitis or pancolitis (%)	Total Mayo score		C-reactive protein		Concurrent medication (%)	
			Mean	SE		Mean	SE	Mean	SE		Mean	SE	Mean	SE	Immuno-modulators	Steroids
ACT-1 (Naive)	IFX10	122	41.8	1.3	59.0	76.9	1.5	8.4	0.7	44.3	8.4	0.1	16.0	2.1	48.4	59.8
ACT-1 (Naive)	IFX5	121	42.4	1.3	64.5	80.0	1.6	5.9	0.5	46.3	8.5	0.2	14.0	1.7	54.5	57.9
ACT-1 (Naive)	PBO	121	41.4	1.2	59.5	76.8	1.5	6.2	0.5	44.6	8.4	0.2	17.0	2.5	43.8	65.3
ACT-2 (Naive)	IFX10	120	40.3	1.2	56.7	79.6	1.9	6.5	0.5	37.5	8.3	0.1	14.0	2.0	41.7	55.0
ACT-2 (Naive)	IFX5	121	40.5	1.2	62.8	78.4	1.6	6.7	0.5	39.7	8.3	0.1	13.0	2.1	43.0	49.6
ACT-2 (Naive)	PBO	123	39.3	1.2	57.7	76.1	1.6	6.5	0.6	40.7	8.5	0.1	16.0	2.6	43.9	48.8
GEMINI 1 (Naive)	VED	130	39.7	1.1	53.1	69.2	1.5	5.8	0.5	38.5	8.4	0.2	NA	NA	42.3	56.2
GEMINI 1 (Naive)	PBO	76	40.5	1.3	61.8	70.0	2.2	6.1	0.7	40.8	8.5	0.2	NA	NA	34.2	57.9
GEMINI 1 (Exposed/IR)	VED	82	39.7	1.4	61.0	74.9	1.9	6.4	0.6	64.6	8.7	0.2	NA	NA	22.0	52.4
GEMINI 1 (Exposed/IR)	PBO	63	41.8	1.7	55.6	74.2	2.1	8.0	1.0	55.6	8.6	0.2	NA	NA	22.2	55.6
Japic CTI (Naive)	IFX5	104	40.0	1.2	63.5	57.6	1.2	8.1	0.7	79.8	8.6	0.1	10.0	1.5	48.1	65.4
Japic CTI (Naive)	PBO	104	37.8	1.3	64.4	60.3	1.1	7.1	0.6	80.8	8.5	0.1	7.0	1.1	47.1	66.3
Jiang 2015 (Naive)	IFX5	41	34.3	2.2	63.4	62.8	2.3	4.4	0.4	61.0	NA	NA	35.8	3.5	29.3	53.7
Jiang 2015 (Naive)	PBO	41	34.5	2.3	61.0	61.2	2.5	4.4	0.4	58.5	NA	NA	35.1	2.8	31.7	51.2
M10-447 (Naive)	ADA160/80	91	42.5	1.5	67.0	60.1	1.3	7.8	0.7	69.2	8.6	0.1	2.2	3.5	45.1	62.6
M10-447 (Naive)	PBO	96	41.3	1.4	72.9	60.8	1.4	7.8	0.7	61.5	8.5	0.2	3.4	3.5	54.2	60.4
NCT01551290 (Naive)	IFX5	50	37.0	2.3	NA	NA	NA	3.7	1.0	NA	8.0	0.2	NA	NA	NA	60.0
NCT01551290 (Naive)	PBO	49	37.0	2.3	NA	NA	NA	3.7	1.0	NA	8.0	0.2	NA	NA	NA	80.0
NCT02039505	VED	164	42.3	1.1	60.4	58.6	0.9	7.2	0.5	61.6	8.3	0.1	NA	NA	48.8	31.7
NCT02039505	PBO	82	44.0	1.8	67.1	60.4	1.4	8.6	0.9	62.2	8.1	0.2	NA	NA	52.4	30.5
OCTAVE 1	TOF	476	41.3	0.6	58.2	72.9	0.8	6.5	1.0	52.9	9.0	0.1	4.4	3.5	NA	45.0
OCTAVE 1	PBO	122	41.8	1.4	63.1	72.7	1.5	6.0	1.0	54.1	9.1	0.1	4.7	3.5	NA	47.5
OCTAVE 2	TOF	429	41.1	0.7	60.4	74.4	0.8	6.0	1.0	49.2	9.0	0.1	4.6	3.5	NA	46.2
OCTAVE 2	PBO	112	40.4	1.2	49.1	73.2	1.5	6.2	1.0	50.0	8.9	0.1	5.0	3.5	NA	49.1
PURSUIT-SC (Naive)	GOL	258	39.7	0.9	54.3	NA	NA	6.4	0.4	41.5	8.7	0.1	11.5	1.0	29.5	45.3
PURSUIT-SC (Naive)	PBO	258	39.7	0.8	50.4	NA	NA	6.4	0.5	42.6	8.3	0.1	9.6	0.9	29.5	41.1
U-ACCOMPLISH	UPA	[redacted]														
U-ACCOMPLISH	PBO															
U-ACHIEVE Study 2	UPA															
U-ACHIEVE Study 2	PBO															
ULTRA-1 (Naive)	ADA160/80	130	38.2	1.2	63.8	75.5	1.2	6.1	1.0	46.2	8.8	0.1	3.3	3.5	39.2	54.6
ULTRA-1 (Naive)	PBO	130	38.9	1.1	63.1	78.7	1.5	5.4	1.0	56.2	8.7	0.1	3.2	3.5	40.0	68.5
ULTRA-2	ADA160/80	258	39.6	0.8	55.0	75.3	1.1	8.1	0.4	46.5	8.9	0.1	14.5	2.0	36.0	58.1
ULTRA-2	PBO	260	41.3	0.8	58.5	77.1	1.1	8.5	0.5	46.2	8.9	0.1	13.1	2.3	30.8	53.8
UNIFI	UST	322	41.7	0.8	60.6	73.0	1.1	8.2	0.4	47.5	8.9	0.1	4.8	0.5	27.6	52.2
UNIFI	PBO	319	41.2	0.8	61.8	72.9	0.9	8.0	0.4	47.2	8.9	0.1	4.7	0.4	27.9	49.2

Abbreviations: ADA, adalimumab; IFX, infliximab; NA, not applicable; PBO, placebo; SE, standard error; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 4: Baseline patient characteristics data of maintenance populations

Study (biologic exposure subgroup)	Treatment arm	N	Age (years)		Male (%)	Weight (kg)		Disease duration (years)		Extensive colitis or pancolitis (%)	Total Mayo score		C-reactive protein		Concurrent medication (%)	
			Mean	SE		Mean	SE	Mean	SE		Mean	SE	Mean	SE	Immuno-modulators	Steroids
ACT-1 (Naive)	INF10	122	41.8	1.3	59.0	76.9	1.5	8.4	0.7	44.3	8.4	0.1	16.0	2.1	48.4	59.8
ACT-1 (Naive)	INF5	121	42.4	1.3	64.5	80.0	1.6	5.9	0.5	46.3	8.5	0.2	14.0	1.7	54.5	57.9
ACT-1 (Naive)	PBO	121	41.4	1.2	59.5	76.8	1.5	6.2	0.5	44.6	8.4	0.2	17.0	2.5	43.8	65.3
GEMINI 1 (Naive)	VED Q8W	72	41.0	1.6	54.2	76.1	2.2	5.8	0.6	33.3	8.3	0.2	NA	NA	41.7	54.2
GEMINI 1 (Naive)	VED Q4W	73	38.3	1.5	53.4	70.3	2.0	7.0	0.7	49.3	8.2	0.2	NA	NA	39.7	60.3
GEMINI 1 (Naive)	PBO	79	39.5	1.6	57.0	71.3	2.1	6.4	0.6	44.3	8.4	0.2	NA	NA	43.0	54.4
GEMINI 1 (Exposed/IR)	VED Q8W	43	41.3	1.7	55.8	79.1	2.8	6.8	0.7	65.1	8.5	0.3	NA	NA	16.3	60.5
GEMINI 1 (Exposed/IR)	VED Q4W	40	39.9	2.9	52.5	72.7	2.8	8.1	1.2	57.5	8.4	0.3	NA	NA	32.5	47.5
GEMINI 1 (Exposed/IR)	PBO	38	41.6	2.2	55.3	81.2	3.9	9.8	1.4	57.9	8.2	0.3	NA	NA	34.2	60.5
M10-447 (Naive)	ADA Q2W	178	43.4	1.1	62.4	59.4	0.9	8.0	0.6	65.7	8.6	0.1	NA	NA	44.4	NA
M10-447 (Naive)	PBO	96	41.3	1.4	72.9	60.8	1.4	7.8	0.7	61.5	8.5	0.2	3.4	2.6	54.2	NA
NCT02039505	VED Q8W	41	43.0	2.2	51.2	NA	NA	8.6	1.2	68.3	8.1	0.2	NA	NA	53.7	31.7
NCT02039505	PBO	42	42.6	2.2	54.8	NA	NA	8.7	1.1	54.8	7.9	0.2	NA	NA	50.0	35.7
OCTAVE Sustain (Non-IR)	TOF5	115	43.6	1.2	54.8	73.4	1.3	6.7	0.5	42.6	2.9	0.2	0.7	2.6	NA	47.8
OCTAVE Sustain (Non-IR)	TOF10	104	42.2	1.4	59.6	74.6	1.1	7.3	0.6	49.0	3.0	0.2	0.9	2.6	NA	44.2
OCTAVE Sustain (Non-IR)	PBO	109	41.9	1.3	60.6	76.2	1.2	8.0	0.8	49.5	3.0	0.2	1.0	2.6	NA	48.6
OCTAVE Sustain (Exposed/IR)	TOF5	83	39.6	1.6	48.2	73.4	1.3	9.9	0.9	63.9	3.8	0.2	0.7	2.6	NA	55.4
OCTAVE Sustain (Exposed/IR)	TOF10	93	43.7	1.5	51.6	74.6	1.1	9.6	0.8	55.9	3.9	0.2	0.9	2.6	NA	49.5
OCTAVE Sustain (Exposed/IR)	PBO	89	45.2	1.6	56.2	76.2	1.2	9.3	0.7	60.7	3.6	0.2	1.0	2.6	NA	58.4
PURSUIT-J (Naive)	GOL100	32	39.3	2.1	59.4	64.6	2.6	5.4	1.4	37.5	8.0	0.3	5.3	2.6	50.0	28.1
PURSUIT-J (Naive)	PBO	31	42.9	2.6	61.3	59.5	1.7	5.7	1.4	38.7	8.0	0.3	4.1	1.4	41.9	29.0
PURSUIT-M (Naive)	GOL100	154	39.1	1.1	57.8	NA	NA	7.2	0.6	NA	8.5	0.1	8.9	1.2	31.2	53.9
PURSUIT-M (Naive)	GOL50	154	41.4	1.1	50.0	NA	NA	6.8	0.6	NA	8.1	0.1	8.5	1.0	30.5	53.9
PURSUIT-M (Naive)	PBO	156	40.2	1.1	48.1	NA	NA	6.9	0.6	NA	8.3	0.1	9.6	1.2	33.3	56.4
U-ACHIEVE Study 3	UPA30	[redacted]														
U-ACHIEVE Study 3	UPA15															
U-ACHIEVE Study 3	PBO															
ULTRA-2	ADA Q2W	258	39.6	0.8	55.0	75.3	1.1	8.1	0.4	46.5	8.9	0.1	14.5	2.0	36.0	58.1
ULTRA-2	PBO	260	41.3	0.8	58.5	77.1	1.1	8.5	0.5	46.2	8.9	0.1	13.1	2.3	30.8	53.8
UNIFI	UST Q8W	176	39.5	1.0	53.4	72.0	1.4	8.1	0.5	45.4	8.9	0.1	4.0	0.6	26.1	54.0
UNIFI	UST Q12W	172	40.7	1.0	55.8	73.3	1.4	8.6	0.6	46.5	8.9	0.1	3.3	0.5	25.6	48.3
UNIFI	PBO	175	42.0	1.0	61.1	71.7	1.1	7.5	0.5	49.1	8.7	0.1	3.4	0.5	28.0	54.3

Abbreviations: ADA, adalimumab; IFX, infliximab; NA, not applicable; PBO, placebo; QxW, every x weeks; SE, standard error; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

A5. Priority question. CS, Document B, section B.2.9.6. Please provide clinical remission and clinical NMA outputs (means and CrIs) for pairwise comparisons for the full set of treatments considered (e.g., upadacitinib versus ustekinumab, tofacitinib versus adalimumab etc). Please provide these estimates for both the bio-exposed and bio-naïve populations and for both the induction and maintenance NMAs.

Company response:

The full set of pairwise comparisons for all treatments included in the NMA are provided in Table 5 to Table 12 below. Median odds ratios and associated credible intervals are reported.

Induction phase – clinical remission

Table 5: Pairwise comparisons for clinical remission in the bio-naïve induction NMA (RE model), median odds ratio and credible interval

Column vs. row	IFX10	IFX5	VED300	ADA160/80	TOF10	GOL200/100	UPA45	UST6	PBO
PBO									
UST6									
UPA45									
GOL200/100									
TOF10									
ADA160/80									
VED300									
IFX5									
IFX10									

Abbreviations: ADA160/80, adalimumab 160/80 mg induction; GOL200/100, golimumab 200/100 mg induction; IFX5/IFX10, infliximab 5 mg/kg body weight/10 mg/kg body weight; NMA, network meta-analysis; PBO, placebo; RE, random effects; TOF10, tofacitinib 10 mg; UPA45, upadacitinib 45 mg; UST6, ustekinumab 6 mg/kg body weight; VED300, vedolizumab 300 mg.

Table 6: Pairwise comparisons for clinical remission in the bio-exposed induction NMA (RE model), median odds ratio and credible interval

Column vs. row	VED300	TOF10	UPA45	ADA160/80	UST6	PBO
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VED300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA160/80, adalimumab 160/80 mg induction; NMA, network meta-analysis; PBO, placebo; RE, random effects; TOF10, tofacitinib 10 mg; UPA45, upadacitinib 45 mg; UST6, ustekinumab 6 mg/kg body weight; VED300, vedolizumab 300 mg.

Induction phase – clinical response

Table 7: Pairwise comparisons for clinical response in the bio-naïve induction NMA (FEA model), median odds ratio and credible interval

Column vs. row	IFX10	IFX5	VED300	ADA160/80	TOF10	GOL200/100	UPA45	UST6	PBO
PBO									
UST6									
UPA45									
GOL200/100									
TOF10									
ADA160/80									
VED300									
IFX5									
IFX10									

Abbreviations: ADA160/80, adalimumab 160/80 mg induction; FEA, fixed effects with baseline-risk adjustment; GOL200/100, golimumab 200/100 mg induction; IFX5/IFX10, infliximab 5 mg/kg body weight/10 mg/kg body weight; NMA, network meta-analysis; PBO, placebo; TOF10, tofacitinib 10 mg; UPA45, upadacitinib 45 mg; UST6, ustekinumab 6 mg/kg body weight; VED300, vedolizumab 300 mg.

Table 8: Pairwise comparisons for clinical response in the bio-exposed induction NMA (RE model), median odds ratio and credible interval

Column vs. row	VED300	TOF10	UPA45	ADA160/80	UST6	PBO
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VED300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA160/80, adalimumab 160/80 mg induction; NMA, network meta-analysis; PBO, placebo; RE, random effects; TOF10, tofacitinib 10 mg; UPA45, upadacitinib 45 mg; UST6, ustekinumab 6 mg/kg body weight; VED300, vedolizumab 300 mg.

Maintenance phase – clinical remission

Table 9: Pairwise comparisons for clinical remission in the bio-naïve maintenance NMA (RE model), median odds ratio and credible interval

Column vs. row	IFX10	IFX5	VED300 Q4W	VED300 Q8W	TOF10	TOF5	GOL100	GOL50	UPA15	UPA30	ADA40 Q2W	UST90 Q12W	UST90 Q8W	PBO
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
UST90 Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
UST90 Q12W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
ADA40 Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
UPA30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
UPA15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF10	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VED300 Q8W	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VED300 Q4W	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX5	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX10		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA40Q2W, adalimumab 40 mg every other week; GOL50/GOL100, golimumab 50 mg/100 mg; IFX5/IFX10, infliximab 5 mg/kg body weight/10 mg/kg body weight; NMA, network meta-analysis; PBO, placebo; RE, random effects; TOF5/TOF10, tofacitinib 5 mg/10 mg; UPA15 or UPA30, upadacitinib 15 mg/30 mg; UST90Q8W/UST90Q12W, ustekinumab 90 mg every 8 weeks/every 12 weeks; VED300QW/VED300Q8W, vedolizumab 300 mg every 4 weeks/every 8 weeks.

Table 10: Pairwise comparisons for clinical remission in the bio-exposed maintenance NMA (RE model), median odds ratio and credible interval

Column vs. row	VED300 Q4W	VED300 Q8W	TOF10	TOF5	UPA15	UPA30	ADA40 Q2W	UST90 Q12W	UST90 Q8W	PBO
PBO										
UST90 Q8W										
UST90 Q12W										
ADA40 Q2W										
UPA30										
UPA15										
TOF5										
TOF10										
VED300 Q8W										
VED300 Q4W										

Abbreviations: ADA40Q2W, adalimumab 40 mg every other week; PBO, placebo; RE, random effects; TOF5/TOF10, tofacitinib 5 mg/10 mg; UPA15 or UPA30, upadacitinib 15 mg/30mg; UST90Q8W/UST90Q12W, ustekinumab 90 mg every 8 weeks/every 12 weeks; VED300Q4W/VED300Q8W, vedolizumab 300 mg every 4 weeks/every 8 weeks.

Maintenance phase – clinical response

Table 11: Pairwise comparisons for clinical response in the bio-naïve maintenance NMA (RE model), median odds ratio and credible interval

Column vs. row	IFX10	IFX5	VED300 Q4W	VED300 Q8W	TOF10	TOF5	GOL100	GOL50	UPA15	UPA30	ADA40 Q2W	UST90 Q12W	UST90 Q8W	PBO
PBO														

Column vs. row	IFX10	IFX5	VED300 Q4W	VED300 Q8W	TOF10	TOF5	GOL100	GOL50	UPA15	UPA30	ADA40 Q2W	UST90 Q12W	UST90 Q8W	PBO
UST90 Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST90 Q12W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA40 Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VED300 Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VED300 Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA40Q2W, adalimumab 40 mg every other week; GOL50/GOL100, golimumab 50 mg/100 mg; IFX5/IFX10, infliximab 5 mg/kg body weight/10 mg/kg body weight; NMA, network meta-analysis; PBO, placebo; RE, random effects; TOF5/TOF10, tofacitinib 5 mg/10 mg; UPA15 or UPA30, upadacitinib 15 mg/30 mg; UST90Q8W/UST90Q12W, ustekinumab 90 mg every 8 weeks/every 12 weeks; VED300Q4W/VED300Q8W, vedolizumab 300 mg every 4 weeks/every 8 weeks.

Table 12: Pairwise comparisons for clinical response in the bio-exposed maintenance NMA (RE model), median odds ratio and credible interval

Column vs. row	VED300 Q4W	VED300 Q8W	TOF10	TOF5	UPA15	UPA30	ADA40 Q2W	UST90 Q12W	UST90 Q8W	PBO
PBO										
UST90 Q8W										
UST90 Q12W										
ADA40 Q2W										
UPA30										
UPA15										
TOF5										
TOF10										
VED300 Q8W										
VED300 Q4W										

Abbreviations: ADA40Q2W, adalimumab 40 mg every other week; NMA, network meta-analysis; PBO, placebo; RE, random effects; TOF5/TOF10, tofacitinib 5 mg/10 mg; UPA15 or UPA30, upadacitinib 15 mg/30 mg; UST90Q8W/UST90Q12W, ustekinumab 90 mg every 8 weeks/every 12 weeks; VED300Q4W/VED300Q8W, vedolizumab 300 mg every 4 weeks/every 8 weeks.

A6. Priority question. CS, Document B, section B.2.9.4 and Appendix D. Please provide full details of the model selection processes underpinning the NMA analyses.

Company response:

Per the NICE DSU TSD 2, the models' global fits were assessed and compared using their overall posterior mean residual deviance ($\overline{D}_{res}$ or Dbar), effective number of parameters (p_D or pD), deviance information criteria (DIC), leverage plots, and the posterior distribution of the between-study standard deviation (σ or sd) associated with the RE model.

All else being equal between FE and RE models, the RE model was selected to account for the expected between-studies heterogeneity in outcomes, study design, and study populations across included RCTs.

For each FE and RE model tested, a baseline risk-adjusted version was also tested that adjusted for differences in mean PBO effects across studies using the code provided in NICE DSU TSD 3. This adjustment captures many characteristics that are thought to modify the treatment effect, including those unmeasured or unknown, within a single measure. A common regression term B was assumed for all adjustments (i.e., the relationship between the PBO response and the active treatment response was assumed not to depend on treatment). The model with the baseline risk covariate was selected if, because of its inclusion, the median posterior sd (for RE models) decreased and the 95% credible interval (CrI) of the regression term B excluded zero.

For networks with significant baseline (PBO) risk heterogeneity from the feasibility assessment, but baseline risk-adjustment for the selected logit model did not converge or run due to data sparsity, a FE model using risk difference (RD) link was alternatively tested. The RD link is a valid though non-canonical method to potentially minimize the impact of PBO heterogeneity.

A summary of all models run is provided in Table 13. Information on whether each model ran and converged is provided as well as model fit statistics used to determine model selection. The selected models are indicated by bold text.

Table 13: Summary of NMA models run

Phase	Outcome	Biologic exposure	PBO risk sig*	Baseline model distribution[1,3]	Model	Baseline assumption[2]	Prior distribution for SD[3]	Result	Dbar	pD	DIC	Max. Gelman-Rubic	SD	B
Induction	Clinical remission	Naïve	No	FE	FE	Independent		Converged	36.04	24.17	60.21	1.0012	-	-
					RE	**Independent**	**Uniform**	**Converged**	**33.86**	**27.48**	**61.34**	**1.0071**	**0.237**	**-**
					FEA	Independent		Converged	40.62	26.28	66.89	1.0120	-	-0.454 (-0.875, 0.211)
					REA	Independent	Uniform	Converged	35.64	30.68	66.32	1.0099	0.278	-0.609 (-1.194, 0.139)
		Exposed	No	FE	FE	Exchangeable	Half-normal	Converged	24.76	8.7	33.47	1.0047	-	-
					RE	**Exchangeable**	**Half-normal**	**Converged**	**24.55**	**9.35**	**33.9**	**1.0118**	**0.134**	**-**
					FEA	Exchangeable	Half-normal	Did not converge	12.8	12.61	25.4	6.0956	-	-0.993 (-1.018, -0.917)
					REA	---	---	Did not run	-	-	-	-	-	-
	Clinical response	Naïve	No	FE	FE	Independent		Converged	36.29	24.03	60.32	1.0007	-	
					RE	Independent	Uniform	Converged	33.57	27.67	61.24	1.0020	0.188	-
					FEA	**Independent**		**Converged (sig)**	**37.77**	**25.93**	**63.7**	**1.0014**	**-**	-0.851 (-1.50, -0.178)
					REA	Independent	Uniform	Converged	34.99	28.97	63.96	1.0102	0.139	-0.868 (-1.633, -0.09)
		Exposed	No	FE	FE	Independent		Converged	18.12	13.11	31.23	1.0003	-	-
					RE	**Independent**	**Half-normal**	**Converged**	**16.83**	**14.28**	**31.11**	**1.0020**	**0.215**	**-**
					FEA	Independent		Did not converge	15.47	14.24	29.71	1.1283	-	-1.400 (-3.067, 0.286)
					REA	---	---	Did not run	-	-	-	-	-	-
	Serious infections	Overall	No	FE	FE	Exchangeable	Half-normal	Converged	31.89	10.26	42.14	1.0004	-	-
					RE	**Exchangeable**	**Half-normal**	**Converged**	**29.85**	**11.06**	**40.92**	**1.0022**	**0.293**	**-**
					FEA	Exchangeable	Half-normal	Did not converge	26.75	12.12	38.88	1.3034	-	-3.904 (-115.845, 80.394)
					REA	---	---	Did not run	-	-	-	-	-	-

Phase	Outcome	Biologic exposure	PBO risk sig*	Baseline model distribution[1,3]	Model	Baseline assumption[2]	Prior distribution for SD[3]	Result	Dbar	pD	DIC	Max. Gelman-Rubic	SD	B
Maintenance	Clinical remission	Naïve	Yes	RE Posterior	FE	Independent		Converged	30.63	22.14	52.77	1.0006	-	-
					RE	**Independent**	**Half-normal**	**Converged**	**26.88**	**23.08**	**49.96**	**1.0240**	**0.363**	**-**
					FEA	Independent		Did not converge	25.12	23.6	48.72	1.2809	-	-1.306 (-3.243, -0.572)
					REA	Independent	Half-normal	Converged (not sig)	24.65	23.86	48.51	1.0439	0.216	-1.267 (-2.773, 0.202)
		Exposed	No	FE	FE	Independent		Converged	15.72	15.34	31.05	1.0017	-	-
					RE	**Independent**	**Half-normal**	**Converged**	**15.74**	**15.43**	**31.17**	**1.0090**	**0.206**	**-**
					FEA	Independent		Did not converge	17.1	16.29	33.4	1.4826	-	-0.56 (-12.25, 7.555)
					REA	---	---	Did not run	-	-	-	-	-	-
	Clinical response	Naïve	Yes	RE Posterior	FE	Independent		Converged	24.63	22.14	46.77	1.0007	-	-
					RE	**Independent**	**Half-normal**	**Converged**	**24.17**	**22.7**	**46.86**	**1.0166**	**0.207**	**-**
					FEA	Independent		Did not converge	23.31	22.88	46.19	1.1026	-	-1.183 (-4.275, 3.122)
					REA	---	---	Did not run	-	-	-	-	-	-
		Exposed	Yes	RE Posterior	FE	Independent		Converged	15.31	15.19	30.51	1.0013	-	-
					RE	**Independent**	**Half-normal**	**Converged**	**15.38**	**15.29**	**30.66**	**1.0035**	**0.201**	**-**
					FEA	Independent		Did not converge	16.64	16.09	32.73	2.1830	-	-0.123 (-8.427, 13.707)
					REA	---	---	Did not run	-	-	-	-	-	-

Abbreviations: CrI, credible interval; FE, fixed effects; FEA, fixed effects with baseline-risk adjustment; PBO, placebo; RE, random effects; REA, random effects with baseline-risk adjustment; SD, standard deviation.

Notes:

* FE RD models tested to replicate the treat-through ITT rates in sensitivity analysis.

1. The posterior distribution of the baseline model was used if the 95% CrI of the PBO absolute rate from the model's predictive distribution differed from the median rate by greater than 2 factors.
2. Instead of the default uniform (0, 5) prior, a half-normal (0, 0.32^2) prior for between-study heterogeneity SD was used if most (≥50%) of treatments in the network were informed by a single study.
3. An exchangeable baseline assumption with a half-normal (0, 0.32^2) prior for heterogeneity was used if ≥1 reference/PBO arms(s) in the network has a zero value (i.e., no events).

A7. Priority question. CS, Document B, section B.2.9.6.1. Please explain why the rate of clinical remission for the bio-exposed population exceeds that of the bio-naïve population in the maintenance NMAs.

Company response:

As observed in the upadacitinib maintenance data, there is a higher placebo response rate in the bio-naive/non-Bio-IR population (17.6%) compared with bio-experienced/Bio-IR population (7.5%) while the upadacitinib response is consistent between the two subgroups (Table 14).

This placebo response pattern has previously been reported in other studies and reflects the fact that bio-naive patients may have less refractory disease compared with bio-exposed patients, and therefore that disease has an improved response to placebo. (6-12).

A summary of trials' data for bio-naïve and bio-exposed populations included in the NMA is presented in Table 15. Except for in the OCATVE Sustain study, the placebo rate was lower for bio-exposed compared with bio-naïve populations in each trial including the upadacitinib trials.

Following adjustment for placebo, higher clinical remission rates are observed for upadacitinib in the bio-experienced/Bio-IR compared with bio-naïve/non-Bio-IR population (Table 14). The placebo-adjusted rates are 33% for 15 mg QD and 42% for 30 mg QD for the bio-exposed population compared with the bio-naïve population (26% for 15 mg QD and 36% for 30 mg QD).

In the NMA, a lower placebo remission rate for the bio-exposed population would lead to better results when the active treatment has a similar performance for the bio-naïve and bio-exposed populations. The NMA results are therefore indicative of the strength of upadacitinib clinical trial results.

Table 14: Clinical remission per Adapted Mayo score at Week 52 in U-ACHIEVE maintenance study – overall population and by prior treatment failure (NRI-C†) (Cohort 1; ITT_A population)

Endpoint, n (%)	U-ACHIEVE maintenance study						
	UPA 15 mg QD	UPA 30 mg QD	PBO	Adjusted treatment diff vs PBO, % (95% CI)§		p-value‡	
				UPA 15 mg QD	UPA 30 mg QD	UPA 15 mg QD	UPA 30 mg QD
Clinical remission per Adapted Mayo score at Week 52, n (%)							
Overall population							
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior biologic failure status							
Bio-exposed (Bio-IR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bio-naïve (non-Bio-IR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†NRI-C is non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
‡For the overall population, response rate difference based on the CMH test adjusted for baseline stratification factors. For bio subgroups, response rate difference is calculated based on normal approximation to the binomial distribution. §Achieved statistical significance based on the pre-specified multiple testing procedure controlling the overall type I error rate at the 0.05 level.
Abbreviations: Bio-IR, biologic therapy-intolerant or inadequate responder; CI, confidence interval; CMH, Cochran Mantel-Haenszel; diff, difference; Non-Bio-IR, inadequate response, loss of response, or intolerance to conventional therapy but not failed biologic therapy; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; QD, once daily dosing; PBO, placebo; UPA, upadacitinib.

Table 15: Absolute rates of clinical remission in UC clinical trials in bio-exposed and bio-naïve maintenance in placebo and active treatment arms

Study (active treatment)	Patient population	Treatment arm	Clinical remission N	Clinical remission n	Absolute rate
GEMINI 1 (vedolizumab)	Bio-naïve	VED300Q4W	73	35	47.9%
	Bio-naïve	VED300Q8W	72	33	45.8%
	Bio-naïve	Placebo	79	15	19.0%
	Bio-exposed	VED300Q4W	40	14	35.0%
	Bio-exposed	VED300Q8W	43	16	37.2%
	Bio-exposed	Placebo	38	2	5.3%
NCT02039505 (vedolizumab)	Bio-naïve	VED300Q8W	24	13	54.2%
	Bio-naïve	Placebo	28	10	35.7%
	Bio-exposed	VED300Q8W	17	10	58.8%
	Bio-exposed	Placebo	14	3	21.4%
OCTAVE Sustain (tofacitinib)	Bio-naïve	TOF10	104	46	44.2%
	Bio-naïve	TOF5	115	48	41.7%
	Bio-naïve	Placebo	109	12	11.0%
	Bio-exposed	TOF10	93	34	36.6%
	Bio-exposed	TOF5	83	20	24.1%
	Bio-exposed	Placebo	89	10	11.2%
U-ACHIEVE Study 3 (upadacitinib)	Bio-naïve	UPA15	[redacted]	[redacted]	[redacted]
	Bio-naïve	UPA30	[redacted]	[redacted]	[redacted]
	Bio-naïve	Placebo	[redacted]	[redacted]	[redacted]
	Bio-exposed	UPA15	[redacted]	[redacted]	[redacted]
	Bio-exposed	UPA30	[redacted]	[redacted]	[redacted]
	Bio-exposed	Placebo	[redacted]	[redacted]	[redacted]
ULTRA-2 (adalimumab)	Bio-naïve	ADA40Q2W	89	28	31.5%
	Bio-naïve	Placebo	56	16	28.6%
	Bio-exposed	ADA40Q2W	36	8	22.2%
	Bio-exposed	Placebo	29	3	10.3%
UNIFI (ustekinumab)	Bio-naïve	UST90Q12W	95	45	47.4%
	Bio-naïve	UST90Q8W	79	40	50.6%
	Bio-naïve	Placebo	84	27	32.1%
	Bio-exposed	UST90Q12W	77	21	27.3%
	Bio-exposed	UST90Q8W	97	37	38.1%
	Bio-exposed	Placebo	91	15	16.5%

Abbreviations: ADA, adalimumab; Q2W, every other week; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; TOF, tofacitinib; UC, ulcerative colitis; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

A8. CS, Appendices, section D.1.2.2, Table 5. Table 5 shows that 3 trials (Probert et al [2003], Sandborn et al [2012] and Sandborn et al [2020]) were excluded from the NMAs as they 'cannot be used in the NMA'. Please provide further detail to explain why these studies could not be used in the NMAs.

Company response:

Reasons as to why the following three references could not be used in the NMA are:

- Probert et al (2003) (Gut. 2003;52(7):998-1002) (13); outcomes were measured with the Baron score, whereas all other studies included in the NMA reported outcomes measured with the Mayo score.

- Sandborn et al (2012) (The New England journal of medicine. 2012;367(7):616-24) (14); this reference reports on results of a Phase 2 study of tofacitinib where Phase 3 data is available, this was an exclusion criterium in the additional PICOS table (original Company submission appendices; Appendix D1.2, Table 3).

- Sandborn et al (2020) (Gastroenterology. 2020;158(3):562-72.e12) (12); this reference reports on the results of the VISIBLE 1 trial (vedolizumab IV vs vedolizumab SC). It was excluded as the induction period was open label (IV only) and therefore not suitable for the induction NMA. Additionally, for the maintenance phase it only reports clinical remission (and not clinical response), all other treatments report both clinical response and remission (and this is a requirement for inclusion in the cost-effectiveness model) and therefore vedolizumab SC (VISIBLE 1 trial) was excluded from the maintenance NMA.

Section B: Clarification on cost-effectiveness data

The EAG has identified some structural issues with the company's model which should first be resolved. The EAG may subsequently have additional questions related to the cost-effectiveness data.

B1. Priority question. CS, Document B, section B.3.2.2 and Company Excel model. The company model allows patients to transition between the 'response without remission' health state and the 'remission' health state. This transition does not match the model schematic and/or text description provided in the company submission. Clinical advice to the EAG suggests that the transition matrices used in the company model generate clinically implausible results. For example, in the bio-exposed population, the percentage of patients in remission after the induction phase (8 weeks) is [redacted] and, in the following cycle (the first maintenance cycle), the percentage of patients in remission is [redacted] of patients.

Please clarify which of the following is accurate:

• the model schematic and text description of the pathway provided in the company submission, or

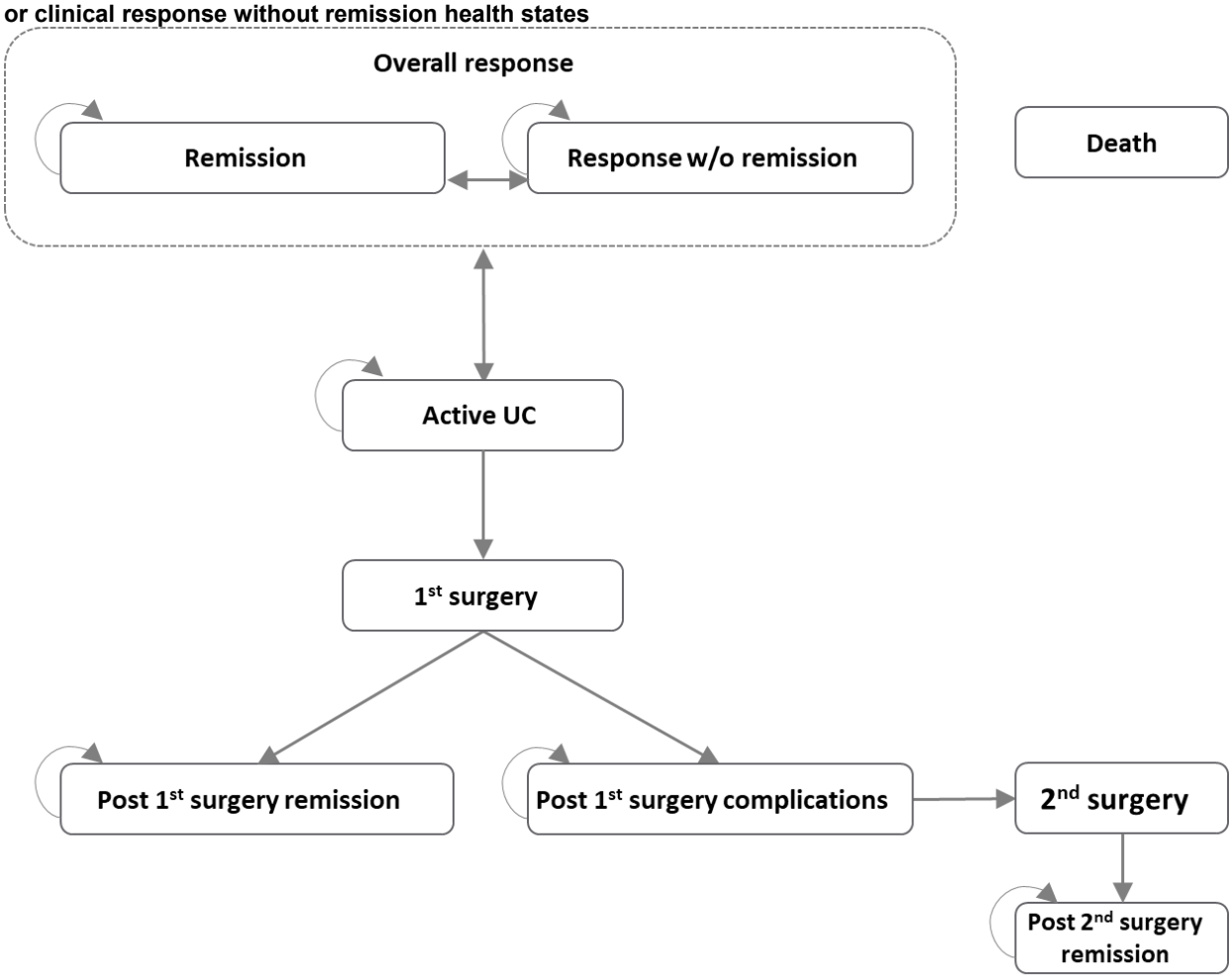
• the pathway modelled in the submitted company Excel model.

Please provide justification for the transition matrices used in the company model that generate the cost-effectiveness results or provide an alternative model that uses alternative transition matrices or algorithms.

Company response:

The EAG is correct that the model allows patients to transition between the 'response without remission' health state and the 'remission' health state. Please find an amended Markov model schematic below, with an arrow added to reflect the movement between the clinical response (clinical remission or clinical response without remission) health states:

Figure 1: Revised Markov model diagram with arrow representing movement between clinical remission or clinical response without remission health states



Abbreviations: UC, ulcerative colitis

These transitions between health states are necessary to estimate clinical results between initial induction response and maintenance NMA results. While no method is optimal, an approach that has been previously employed in TA547 was adopted (15, 16). The method generates an initial jump due to the one step adjustment employed for all treatments.

We accept that a “smoother” approach could be interpreted as more clinically plausible. However, it would add additional complexity to the model. Nevertheless, a smoother approach was tested for the upadacitinib arm to assess whether a more extensive update is likely to meaningfully change costs or QALYs over a lifetime horizon.

As previously discussed, there are currently no data available to inform health state transitions during the period between the end of induction (Week 8) and the end of

maintenance (Week 60). Consequently, there are no midpoint efficacy outputs that can be used to estimate the trend of remission/response proportions.

In lieu of intermediate efficacy data, there needs to be an estimation in the model to connect the efficacy at the end of induction to the end of maintenance. To do so, we based our approach on a previously submitted method - see TA547, Tofacitinib for UC, Section B.3.3.1.2 (15, 16).

In response to the example cited by the EAG (UPA bio-exposed), we tested an alternative “smoothed” method of transitioning patients from the end of induction to the end of Year 1 of maintenance treatment. The “smoothed” method uses the same constant probability of loss of response as does the current method. To allocate the overall response patients between remission and response without remission, the percent of patients in remission is slowly increased each cycle such that the target percent of patients in remission is reached at the end of 1 year of maintenance treatment. Note that this is done via a manual splitting of patients between remission and response rather than assigning transition probabilities between states. After 1 year of maintenance treatment, the proportion of patients in remission relative to response without remission is held constant (consistent with the current method). The difference in the percent of patients in remission in Year 1 of maintenance treatment between the two approaches is presented in Figure 2.

Figure 2: ‘Smoothed’ and current approach methods of transitioning patients from the end of induction to the end of Year 1 of maintenance treatment

Figure redacted [CiC]

The “smoothed” approach moves patients more gradually towards the 1-year maintenance treatment efficacy targets.

To isolate the impact of this alternative approach, we implemented the “smoothed” approach to the upadacitinib arm of the model to enable comparison with the costs and QALYs generated for upadacitinib using the base case approach. The difference in overall costs and QALYs between the two approaches over a lifetime for upadacitinib bio-exposed patients is presented in Table 16. The alternative method does not produce meaningfully different results over the lifetime of the model, which is approximately 60 years. We note that the revised version of the model provided

does not support comparative analyses, or analyses of extended induction or sequencing as it was developed to assess the need for further modifications.

For upadacitinib bio-exposed patients, keeping all else equal to the base-case in the model, implementing the 'smoothed' first year of maintenance approach produces a [redacted]% change in lifetime costs and a [redacted]% change in lifetime QALYs compared with the approach presented in the submission. We view this difference as insignificant over the 60-year lifetime of the model and consider the base case approach appropriate.

Table 16: Cost-effectiveness results for the 'smoothed' and current approach for transitioning patients from the end of induction to the end of Year 1 of maintenance treatment in the bio-exposed population

Parameter	'Smoothed' approach	Current approach	
	UPA 45 mg QD	UPA 45 mg QD	Difference between approaches
Total costs, £	[redacted]	[redacted]	[redacted]
Total LYG	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]

Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; QD, once-daily dosing; UPA, upadacitinib

B2. Priority question. CS, Document B, section B.3.11.3. Please provide a model and corresponding cost-effectiveness estimates which include up to 4 lines of treatment sequencing for biologic-naïve patients and include up to 3 lines of treatment for biologic-exposed patients.

Company response:

Currently the model has the flexibility to allow for one further line of subsequent treatment, for both bio-naïve and bio-exposed patients, and scenario analyses were run in the submission to consider the impact of assuming a subsequent line of treatment before conventional therapy. The structure is adopted to address the cost-effectiveness of upadacitinib compared to currently available treatments.

Sequential use of other treatments is common but variable, with cost-effectiveness being potentially sensitive to the choice of subsequent treatment. This uncertainty is equivalent across all previous UC TAs, as acknowledged in the final technical report for TA633 (17). Clinical input sought for the submission confirmed the variability in treatment practices across England and in the clinical presentation of each patient.

UC is a heterogeneous disease, with treatment choices being influenced by several patient-specific factors. For instance, treatment is considered based on treatment history and response to previous treatment, antibody tests, or anticipated speed of action and safety profile. Clinicians often start with a biosimilar TNF-alpha inhibitor, escalate the dose, or switch to another TNF-alpha inhibitor, before moving to more recently approved and more effective therapies.

Considering the increase in the number of UC treatment options in recent years, clinicians are still learning which therapies work best for specific patients and clinical situations. As a result, there is considerable uncertainty associated with defining sequences of treatments routinely used in clinical practice; this was acknowledged by the ERG in the ongoing filgotinib UC appraisal [ID3736] (18) as well as by the ERG in TA633 (17).
Furthermore, due to the large number of possible sequences, it is not practical to model all of them.

Data availability also poses a challenge for modelling treatment sequences, with data unavailable to accurately estimate the probability of response or remission in third- or fourth-line. TA633 did not model a subsequent line of treatment for the bio-exposed population for this reason (17). Further, strong efficacy assumptions are required, generalizing the treatment effect from the bio-exposed population to all possible combinations of treatment sequences. It becomes more difficult to interpret the true direct cost-effectiveness of different comparators when subsequent treatment efficacy is included making the value of such analyses marginal. The model developed for this appraisal is consistent with the previously published technology appraisal for ustekinumab (TA633) (17) and adopts a model structure that has remained largely consistent over recent submissions to NICE for UC treatments (16, 19, 20). The modelling approach was further considered reasonable by UK clinical experts consulted for model development. Please see Table 57 in the company submission document comparing the features of the economic model with models used in these appraisals.

The final scope for this appraisal is focused on assessing the cost-effectiveness of UPA versus approved comparators as single treatments rather than comparing treatment sequences. As such, treatment sequencing is not appropriate in the base-case analysis and modelling one line of subsequent treatment in a scenario analysis is appropriate. Upadacitinib 15 mg QD and upadacitinib 30 mg QD remained cost-effective versus all comparators in both the bio-naïve and bio-exposed populations when considering treatment sequencing.

To further support decision making and in acknowledgement of the relevance of treatment sequencing to clinical practice, additional scenarios have been run considering the following subsequent treatments options listed in Table . In all scenarios, upadacitinib 15 mg QD and upadacitinib 30 mg QD remained cost-effective versus all comparators in both the bio-naïve and bio exposed populations (see Table 17 to Table 20).

Table 17: Subsequent treatments tested in scenario analyses

Bio-naïve patients	Bio-exposed patients
Ustekinumab	Ustekinumab
Tofacitinib	Tofacitinib
Vedolizumab IV	Vedolizumab IV
Adalimumab biosimilar	

Abbreviations: IV, intravenous

Table 17: Scenario analyses: Incremental results UPA 15 mg maintenance dose vs comparator (ICER as cost per QALY, £), bio-naive

Scenario	Description	ADA biosimilar	ADA	GOL	IFX biosimilar	IFX	TOF	UST	VED SC	VED IV
Base case		Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Sequencing - ustekinumab	Upon loss of response, patients receive treatment with ustekinumab	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	N/A	Dominated by UPA	Dominated by UPA
Sequencing - tofacitinib	Upon loss of response, patients receive treatment with tofacitinib	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	N/A	Dominated by UPA	Dominated by UPA	Dominated by UPA
Sequencing – vedolizumab IV	Upon loss of response, patients receive treatment with vedolizumab IV	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	N/A	N/A
Sequencing – adalimumab biosimilar	Upon loss of response, patients receive treatment with adalimumab biosimilar	N/A	N/A	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA

Abbreviations: ADA, adalimumab; GOL, golimumab: ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A not applicable; SC, subcutaneous; TOF, tofacitinib, UC, ulcerative colitis; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 18: Scenario analyses: Incremental results UPA 30 mg maintenance dose vs comparator (ICER as cost per QALY, £), bio-naive

Scenario	Description	ADA biosimilar	ADA	GOL	IFX biosimilar	IFX	TOF	UST	VED SC	VED IV
Base case		14,927	14,254	15,019	10,320	8,844	11,033	8,440	6,798	241
Sequencing - ustekinumab	Upon loss of response, patients receive treatment with ustekinumab	14,178	13,493	14,252	9,481	7,978	10,154	N/A	5,887	Dominated by UPA
Sequencing - tofacitinib	Upon loss of response, patients receive treatment with tofacitinib	14,354	13,653	14,435	9,552	8,014	N/A	7,591	5,871	Dominated by UPA
Sequencing – vedolizumab IV	Upon loss of response, patients receive treatment with vedolizumab IV	13,933	13,247	14,002	9,231	7,725	9,887	7,310	N/A	N/A
Sequencing – adalimumab biosimilar	Upon loss of response, patients receive treatment with adalimumab biosimilar	N/A	N/A	14,726	9,975	8,481	10,675	8,071	6,407	Dominated by UPA

Abbreviations: ADA, adalimumab; GOL, golimumab: ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A not applicable; SC, subcutaneous; TOF, tofacitinib, UC, ulcerative colitis; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 19: Scenario analyses: Incremental results UPA 15 mg maintenance dose vs comparator (ICER as cost per QALY, £), bio-exposed

Scenario	Description	ADA biosimilar	ADA	UST	VED SC	VED IV	TOF
Base case		761	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Sequencing - ustekinumab	Upon loss of response, patients receive treatment with ustekinumab	Dominated by UPA	Dominated by UPA	N/A	Dominated by UPA	Dominated by UPA	Dominated by UPA
Sequencing - tofacitinib	Upon loss of response, patients receive treatment with tofacitinib	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Sequencing – vedolizumab IV	Upon loss of response, patients receive treatment with vedolizumab IV	N/A	N/A	Dominated by UPA	N/A	N/A	Dominated by UPA

Abbreviations: ADA, adalimumab; GOL, golimumab: ICER, incremental cost effectiveness ratio; IFX, infliximab; IV, intravenous; N/A not applicable; SC, subcutaneous; TOF, tofacitinib, UC, ulcerative colitis; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 20: Scenario analyses: Incremental results UPA 30 mg maintenance dose vs comparator (ICER as cost per QALY, £), bio-exposed

Scenario	Description	ADA biosimilar	ADA	UST	VED SC	VED IV	TOF
Base case		13,360	12,758	8,306	8,216	5,638	8,711
Sequencing - ustekinumab	Upon loss of response, patients receive treatment with ustekinumab	12,674	12,061	N/A	7,433	4,810	7,976
Sequencing - tofacitinib	Upon loss of response, patients receive treatment with tofacitinib	12,793	12,168	7,545	7,443	4,765	N/A
Sequencing – vedolizumab IV	Upon loss of response, patients receive treatment with vedolizumab IV	12,449	11,386	7,297	N/A	N/A	7,757

Abbreviations: ADA, adalimumab; GOL, golimumab: ICER, incremental cost effectiveness ratio; IFX, infliximab; IV, intravenous; N/A not applicable; SC, subcutaneous; TOF, tofacitinib, UC, ulcerative colitis; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

B3. Priority question. CS, Document B, section B.3.4. For patients in the U-ACHIEVE and U-ACCOMPLISH induction studies and in the U-ACHIEVE maintenance study, please provide mean EQ-5D utility values for remission, response without remission and active UC (non-responders from the induction studies and/or patients who lost response in the maintenance study), for bio-naïve and bio-exposed patients separately.

Company response:

The upadacitinib U-ACHIEVE and U-ACCOMPLISH clinical trials collected quality of life data using the EQ-5D-5L instrument. Individual patient data from the U-ACHIEVE and U-ACCOMPLISH trials were used to estimate the mean EQ-5D health utility for each of the health states. EQ-5D-5L responses, age, and sex were used to calculate the EQ-5D-3L index using the mapping function developed by the Decision Support Unit (Hernandez Alava et al. 2017) (21), as per NICE reference case.

The mean, associated SD, median, and quartiles were described by Full Mayo score, consistent with previous economic evaluations in UC. Repeated measures were included with all observations considered independent. In line with the request from NICE, analyses were also stratified by previous biologic use.

The utility value for the active UC health state was calculated based on observations at baseline in the induction trials. Patients who lost response and moved to active UC within the trial were not included since they had recently received an active treatment and therefore may not be representative of the active UC health state for long-term assessment.

Utility values for remission and response without remission were calculated excluding baseline values, including observations at Week 8 of the induction study and Week 52 of the maintenance study.

Table 21: Trial utility values – full population

Health state	Observations	EQ-5D mean value (SD)
Remission (excluding baseline values; induction and maintenance studies)	[redacted]	[redacted]
Response without remission (excluding baseline values; induction and maintenance studies)	[redacted]	[redacted]
Active UC (baseline values; induction studies)	[redacted]	[redacted]

Abbreviations: EQ-5D, EuroQol 5-dimension; SD, standard deviation; UC, ulcerative colitis

Table 22: Trial utility values – bio-naïve population

Health state	Observations	EQ-5D mean value (SD)
Remission (excluding baseline values; induction and maintenance studies)	[redacted]	[redacted]
Response without remission (excluding baseline values; induction and maintenance studies)	[redacted]	[redacted]
Active UC (baseline values; induction studies)	[redacted]	[redacted]

Abbreviations: EQ-5D, EuroQol 5-dimension; SD, standard deviation; UC, ulcerative colitis

Table 23: Trial utility values – bio-exposed population

Health state	Observations	EQ-5D mean value (SD)
Remission (excluding baseline values; induction and maintenance studies)	[redacted]	[redacted]
Response without remission (excluding baseline values; induction and maintenance studies)	[redacted]	[redacted]
Active UC (baseline values; induction studies)	[redacted]	[redacted]

Abbreviations: EQ-5D, EuroQol 5-dimension; SD, standard deviation; UC, ulcerative colitis

The base-case model incorporates utility values taken from literature to keep consistency between previous submissions to NICE (TA633 [ustekinumab], TA329 [adalimumab, golimumab, infliximab] and TA547 [tofacitinib]) (16, 17, 20). The utility values for remission, response without remission and active UC were obtained from Woehl et al. 2008 (22), a UK (n=180) study, and are reflective of patients from real-world clinical practice. As discussed in the company submission, collecting utility values from real-world clinical practice can provide values that are more appropriate compared to those collected in clinical trials.

B4. Priority question. CS, Document B, section B.3.10. Please justify and provide evidence that demonstrates why total QALYs are [redacted] for bio-exposed patients receiving upadacitinib compared to bio-naïve patients receiving upadacitinib.

Company response:

As discussed in the response to question A7, in the U-ACHIEVE maintenance study, higher rates of remission were observed for upadacitinib 15 mg QD and upadacitinib 30 mg QD in the bio-exposed population than in the bio-naïve population (Table ***24***).

Table 24: Results for clinical remission

Treatment	Odds ratio vs. PBO Median (95% CrI)	Predicted absolute outcome rate, median (95% CrI)
Bio-naïve maintenance NMA (RE model)		
UPA15	[redacted]	[redacted]
UPA30	[redacted]	[redacted]
Bio-exposed maintenance NMA (RE model)		
UPA15	[redacted]	[redacted]
UPA30	[redacted]	[redacted]

Abbreviations: CrI, credible interval; NMA, network meta-analysis; PBO, placebo; RE, random effects; UPA15 or UPA30, upadacitinib 15 mg/30mg.

Considering clinical response (clinical remission or response without remission), the rates were higher in the bio-naive population for upadacitinib 15 mg QD and upadacitinib 30 mg QD; however, the differences between the two populations were small (Table ***25***), especially for upadacitinib 15 mg QD.

Table 25: Results for clinical response

Treatment	Odds ratio vs. PBO Median (95% CrI)	Predicted absolute outcome rate, median (95% CrI)
Bio-naïve maintenance NMA (RE model)		
UPA15	[redacted]	[redacted]
UPA30	[redacted]	[redacted]
Bio-exposed maintenance NMA (RE model)		
UPA15	[redacted]	[redacted]
UPA30	[redacted]	[redacted]

Abbreviations: CrI, credible interval; NMA, network meta-analysis; PBO, placebo; RE, random effects; UPA15 or UPA30, upadacitinib 15 mg/30mg.

The maintenance NMA results drive health state occupancy from the end of induction to Week 52, and for the remainder of the model's lifetime time horizon. The remission health state is associated with a higher utility value of 0.87 compared with the value of 0.76 applied to patients in the response without remission health state. Both these values are higher than the utility value applied to patients in active UC (0.41). This translates to higher total QALYs for upadacitinib 15 mg QD in the

bio-exposed population compared with the bio-naïve population ([redacted] in the base-case probabilistic analysis). For upadacitinib 30 mg QD, slightly higher QALYs are observed in the bio-naïve population compared with the bio-exposed population ([redacted]). This is explained by the larger difference in overall response between the two populations for upadacitinib 30 mg QD (83.6% in the bio-naïve population versus 77.4% in the bio-exposed population) leading to a larger per-cycle probability of loss of response in the bio-exposed population.

We also note that the mean age at baseline in the bio-exposed population is slightly higher than the mean age in the bio-naïve population (42.69 years versus 42.99 years). This reflects the patients recruited to the U-ACHIEVE and U-ACCOMPLISH induction studies. All else being equal, a lower baseline age results in higher QALYs since mortality is based on population life tables and a lifetime time horizon (interpreted as until patients reach 100 years of age) is considered. In clinical practice, one might expect the mean age of the bio-exposed population to be higher than the bio-naïve population.

Section C: Textual clarification and additional points

C1. Priority question. Please provide the Statistical Analysis Plans for the U-ACHIEVE and U-ACCOMPLISH induction studies, and for the U-ACHIEVE maintenance study.

Company response:

The Statistical Analysis Plans for U-ACHIEVE (induction and maintenance) and U-ACCOMPLISH (induction) studies have been uploaded separately.

- U-ACHIEVE: m14234-legacy-csr.pdf, page 18036 [CiC]
- U-ACCOMPLISH: m14675-legacy-csr.pdf, page 8584 [CiC]

C2. CS, Document B, sections B.2. and B.3. Regarding the clinical and economic systematic literature reviews, please clarify the number of independent reviewers involved in data extraction and in the quality assessment.

Company response:

In the original Company submission appendices, Appendix D1.2 describes data extraction as applicable to all conducted SLRs:

‘The title/abstract screening was conducted by two blinded, independent researchers in parallel using the pre-defined Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) criteria presented in Table 2. Discrepancies between researchers were resolved by a third independent researcher. The same process was followed at full text screening. Data from included studies were extracted into a pre-defined Excel-based template by a single analyst and all results were 100% quality checked by a research associate.’

Quality assessment was conducted in the same manor by the same number of independent reviewers (2).

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21. Hernández-Alava M, Pudney S. Econometric modelling of multiple self-reports of health states: the switch from EQ-5D-3L to EQ-5D-5L in evaluating drug therapies for rheumatoid arthritis. Journal of Health Economics. 2017;55:139-52.
22. Woehl A, Hawthorne A, McEwan P, editors. The relation between disease activity, quality of life and health utility in patients with ulcerative colitis. Gut; 2008: British Med Assoc House, Tavistock Square, London WC1H 9JR, England: BMJ Publishing Group.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

[ID3953] - Upadacitinib for treating moderately to severely active Ulcerative Colitis

Patient Organisation Submission

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 over 47,000 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. 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 Crohn's & Colitis UK's annual reports and accounts (crohnsandColitis.org.uk)
4b. Has the organisation received any funding from the manufacturer(s) of the	No

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.	
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.

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.[1] [2] *"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."* **Quote from a person living with Ulcerative Colitis.** 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 with moderate to severe Ulcerative Colitis that this guidance is targeting. 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.[3] 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).[4]

[1] Crohn's and Colitis UK (2018) Quality of Life Survey https://ibduk.org/ibd-standards
[2] IBD UK (2019) IBD Standards
[3] NICE (2019) NICE Guideline on Ulcerative Colitis: Management (NG130) https://www.nice.org.uk/guidance/ng130/chapter/Recommendations
[4] 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

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 huge amount of weight over 2 and a half stone in just 2 weeks wasn't expected out the blue in my life."
Quote from a person living with Ulcerative Colitis.

Mortality

There are risks and mortality associated with untreated and uncontrolled disease.

NICE Guideline on Ulcerative Colitis 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'.[5]

This is echoed by BSG Guidelines that state that 'acute severe Colitis is a potentially life-threatening condition'.[6]

Acute severe Colitis has a 1% mortality risk and a 29% chance of requiring emergency surgery to remove the inflamed bowel (colectomy).[7] 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.[8]

[5] NICE (2019) Guideline on Ulcerative Colitis: Management: Overview | Ulcerative Colitis: management | Guidance | NICE
[6] The British Society of Gastroenterology (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] Ibid
[8] Ibid

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[9]
- Perforation of the bowel[10]

Additional complications of chronic, uncontrolled, active Ulcerative Colitis also include:

- Osteoporosis and vitamin D deficiency. The major risk factors for osteoporosis complicating IBD are age, steroid use and disease activity[11]
- Anaemia[12].
- Increased risk of cancer[13]

Impact on emotional and mental health

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.[14] 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 and its medical treatment (e.g., corticosteroid therapy), surgery, including specifically

[9] Parray, F. Q. et al. (2012). Ulcerative Colitis: a challenge to surgeons. Int. J. Prev. Med. 3, 749–63.
[10] IBDUK (2019) IBD Standards 2019: Homepage | IBD UK
[11] Mowat C, Cole A, Windsor A et al. (2011) Guidelines for the management of inflammatory bowel disease in adults. Gut, 60, 571-607.
[12] Crohn's and Colitis Foundation.(2020) Anaemia. https://www.crohnscolitisfoundation.org/sites/default/files/2020-03/anemia.pdf
[13] The British Society of Gastroenterology (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
[14] Cosnes J, et al., (2011). Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology, 140 (6), 1785-94.

	colectomy and stoma formation.[15] 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."* **Quote from a person living with Ulcerative Colitis.** "*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."* **Quote from a person living with Ulcerative Colitis.** *"When I am unwell the constant anaemia make everyday life feel like wading through treacle, the pain can be crippling. The very real concern of faecal incontinence gives me physical symptoms of stress as well as affecting me emotionally and mentally."* **Quote from a person living with Ulcerative Colitis.** The experience of caring for someone with IBD can be especially difficult given that it is to some degree an invisible condition and due to the unpredictable nature of the symptoms, which many also find extremely uncomfortable to talk about, and the effects of treatment. For parents of young people, there are challenges around providing support, while enabling independence and seeing lives and aspiration affected by the son or daughter's condition. "*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*." **Quote from the parent of a person living with Ulcerative Colitis.** **Social functioning**

[15] Graff L. A. et al., (2009). Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. Inflamm Bowel Dis, 15 (7), 1105-18.

	Social functioning can be impaired - leading to an inability to work, attend school, participate in leisure activities, or have intimate relationships. *"During the majority of my time living with UC and the ever-changing drugs, I had no quality of life. I was off sick from work for 8 months. I was unable to drive my children to or from school or make them their breakfast as this was the time, usually until about midday, that I could not leave the toilet. There was no fun time with my 3 wonderful children or my husband, I was always in bed, in pain or on the toilet. We did not cuddle or play, because if any of them touched my tummy, it would be so sore. This period of illness really affected my confidence. My friends gave up coming around as I was so poorly. My quality of work really dropped. I continuously made mistakes because of the side effects from all the drugs."* **Quote from a person living with Ulcerative Colitis.** 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.[16]
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, are 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*

[16] Gay M et al. (2011) Crohn's, Colitis and Employment – from Career Aspirations to Reality. Crohn's and Colitis UK.

	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*." **Quote from a person living with Ulcerative Colitis.** "*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."* **Quote from a person living with Ulcerative Colitis.** *"My 'moon face' from the constant use of prednisolone was depressing and because of my ill health my hair became really thin. Prednisolone also affected my mood. I was so angry and unhappy. This also kept me awake at night, so I took sleeping pills."* **Quote from a person living with Ulcerative Colitis.** **Steroids** "Corticosteroids have no proven efficacy in maintaining remission in IBD and should not be used for this purpose."[17] 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.[18] **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.

	"Surgery would have been a massive emotional and psychological barrier for our son at this stage in his life." **Quote from a person living with Ulcerative Colitis.** *"Personally I'm not prepared for the drastic surgery of having my colon removed*." **Quote from a person living with Ulcerative Colitis.** 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 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."* **Quote from a person living with Ulcerative Colitis.**

[17] 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

[18] 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

	Surgery has significant associated long- and short-term risks which include: - general anaesthetic complications - infections - adhesions - pouchitis - pouch leakage - abscesses - fistulae - small bowel obstruction - post-operative bleeding - sexual dysfunction - delayed wound healing - nerve damage.[19,20] 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).[21] 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 %; $p < 0.001$).[22] We would also urge the Committee to consider the persistent quality of life issues that impact multiple domains, including psychological and sexual functioning. 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.[23]

[19] Ibid
[20] Brown, C. et al., (2015). Long-term outcomes of colectomy surgery among patients with Ulcerative Colitis. *Springerplus,* 4, 573.
[21] Waljee A, et al., (2006). Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in Ulcerative Colitis. Gut, 55 (11), 1575–1580.
[22] Johnson P, Richard C, Ravid A, Spencer L, Pinto E, Hanna M, Cohen Z, McLeod R. Female infertility after ileal pouch-anal anastomosis for Ulcerative Colitis. Dis Colon Rectum. 2004 Jul;47(7):1119-26. doi: 10.1007/s10350-004-0570-7.
[23] Brown, C. et al., (2015). Long-term outcomes of colectomy surgery among patients with Ulcerative Colitis. *Springerplus,* 4, 573.

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. *"I was steroid dependent and all conventional UC therapies failed – including anti TNF (Infliximab). Long term steroid use resulted in osteoporosis at age 28. I was housebound for many years due to UC and was unable to work. Quality of life was zero."* **Quote from a person living with Ulcerative Colitis.** 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 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.[24] 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.

[24] Roda, G. (2016). Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. *Clin Transl Gastroenterol*, 7 (1), e135.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	One of the key advantages is that Upadacitinib is an oral therapy and would give patients a treatment option to be taken at home, which will allow people to be treated at home. Furthermore 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 would result in an associated reduction in NHS costs due to reduced infusions. 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.**
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Prescription costs faced people living with long-term and chronic conditions, including Ulcerative Colitis, in England, are shown to contribute to economic disadvantage, which can impact adherence and lead to

	complications and increased cancer risks and cost to the NHS.[25] However, the disadvantage is not specific to Upadacitinib, and the value of an additional treatment option may will remain beneficial as it will reduce the risk of loss of response.
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 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. Although not specific to Upadacitinib, prescription costs may also be a factor associated with lower income.

Other issues	
13. Are there any other issues that you would like the committee to consider?	None

Key messages

14. 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.
- 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.
- Upadacitinib offers a novel and effective treatment option and increases choice for both clinicians and patients (in the context of shared decision making).
- Upadacitinib may delay or prevent surgery in UC patients. This is particularly important for patients who have exhausted all over treatment options and wish to avoid or delay surgery (e.g. to complete studies.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

[ID3953] - Upadacitinib for treating moderately to severely active ulcerative colitis

Professional organisation submission

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	**British Society of Gastroenterology**

3. Job title or position	[redacted]
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 British Society of Gastroenterology was established in 1937 and is focused on the promotion of gastroenterology and hepatology. It has over three and a half thousand members drawn from the ranks of physicians, surgeons, pathologists, radiologists, scientists, nurses, dietitians, and others interested in the field. It is funded by members and has charity status (Charity no 1149074) Its main activities include: 1. Education and Training (annual scientific meeting, postgraduate training, clinical update meetings) 2. Supporting research into gut and liver disease (supporting academic development, promoting Gut) 3. Enhancing service standards (clinical service development, guidelines, sharing of best practice) 4. Supporting the gastrointestinal community

	5. Promoting awareness of gastroenterology
4b. Has the organisation received any funding from the 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.	**No**
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	There is no medical cure for Ulcerative Colitis so currently the main aim of treatment is to keep disease in remission, prevent flares, reduce hospitalisation and avoid surgery. Maintaining disease in remission helps reduce the disability associated with disease and improve the quality of life for patients. Patients with poorly controlled disease are at higher risk of surgery ie

progression, to improve mobility, to cure the condition, or prevent progression or disability.)	colectomy which may require a stoma (which is permanent in many cases) and also at risk of complications such as steroid dependency, hospital admission and development of colorectal cancer. Effective control of patient symptoms, and improvement of mucosal inflammation has been shown to improve the quality of life, reduce loss of working days and decrease the overall cost of care.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Clinically significant responses to treatment in Ulcerative colitis is most commonly assessed by the Mayo score or a variation thereof (1) The original description of the Mayo Score included an assessment of 2 patient-reported outcomes [PROs; stool frequency (SF) and rectal bleeding (RB)], the endoscopic appearance of the mucosa (endoscopic score, ES), and a Physician's Global Assessment (PGA), each of which were scored on a scale from 0 to 3, giving a maximum total score of 12. There is some concern about using PGA in studies so the adapted Mayo score is commonly used now The Adapted Mayo Score is a composite score of UC disease activity based on the following 3 subscores: a. Stool frequency subscore (SFS), scored from 0 (normal number of stools) to 3 (5 or more stools more than normal). b. Rectal bleeding subscore (RBS), scored from 0 (no blood seen) to 3 (blood alone passed). c. Endoscopic subscore, scored from 0 (normal or inactive disease) to 3 (severe disease, spontaneous bleeding, ulceration). The overall Adapted Mayo score ranges from 0 to 9 where higher scores represent more severe disease. Clinical remission is defined as an Adapted Mayo score ≤ 2, with SFS ≤ 1 and not higher than Baseline, RBS of 0, and endoscopic subscore ≤ 1. Clinical response per Partial Adapted Mayo Score is defined as a decrease in Partial Adapted Mayo score ≥ 1 point and ≥ 30% from Baseline, plus a decrease in RBS by ≥ 1 point or an absolute RBS ≤ 1. There are other scoring systems for Ulcerative colitis, such as the Simple Colitis Activity Index (SCAI) and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS), which compare well to the Adapted Mayo Score and the Mayo Endoscopic Score (MES)

	Scoring systems for quality of life indicators in Ulcerative colitis which involve patient reported outcomes include the IBDQ and SF-36 (1) April N Naegeli, DrPH, MPH, Theresa Hunter, PhD, Yan Dong, PhD, Ben Hoskin, BSc, Chloe Middleton-Dalby, MRes, James Hetherington, BSc, Diana Stefani-Hunyady, MD, PhD, James B Canavan, MD, PhD, Full, Partial, and Modified Permutations of the Mayo Score: Characterizing Clinical and Patient-Reported Outcomes in Ulcerative Colitis Patients, *Crohn's & Colitis 360*, Volume 3, Issue 1, January 2021 (2) Yarlas A, Maher S, Bayliss M, et al. The Inflammatory Bowel Disease Questionnaire in Randomized Controlled Trials of Treatment for Ulcerative Colitis: Systematic Review and Meta-Analysis. *J Patient Cent Res Rev*. 2020;7(2):189-205. Published 2020 Apr 27. doi:10.17294/2330-0698.1722
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Despite well-defined pathways and updated guidelines, existing therapies have significant drawbacks, highlighting a major unmet therapeutic need for people living with moderate to severe ulcerative colitis. Specifically, primary failure of anti-TNF induction therapy occurs in 19–58% of patients in clinical trials (3-5). Among patients responsive to anti-TNF therapies, discontinuation due to secondary loss of response occurs in 17 to 22% of patients and approximately 40% required dose escalation to maintain treatment efficiency(3-5)(6). Treatment failure is even higher among patients undergoing second line TNF inhibitor therapy. In a meta-analysis the proportion of patients have discontinued treatment due to loss of response was 68-77% at 12 months and 82 -90% by the end of year 2(6). Diminishing efficacy stems in part from immunogenicity and the formation of antibodies against biologics (7). Evolution in our knowledge of disease pathophysiology and immune mechanisms led to development of other biologics such as Vedolizumab, which blocks the integrin α4β7 on leukocyte cells, thereby blocking lymphocyte trafficking to intestinal mucosa, and IL12/23 inhibition with ustekinumab and more recently the development of oral small molecules (non-biological) like the Janus kinase inhibitor, Tofacitinib. While all of these agents have been shown to be effective in the management of moderate-to-severe ulcerative colitis, the overall long term response rates continue to be in the 50-60% range beyond the first year of treatment and up to 50% of patients either do not respond or will have loss of response over time(8-10). In clinical practice, the high rate of non-response or incomplete response to ulcerative colitis medication indicates a need for newer therapeutic strategies. 3. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353(23):2462-76.

	4. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146(1):85-95; quiz e14-5. 5. Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142(2):257-65 e1-3. 6. Gordon JP, McEwan PC, Maguire A, Sugrue DM, Puelles J. Characterizing unmet medical need and the potential role of new biologic treatment options in patients with ulcerative colitis and Crohn's disease: a systematic review and clinician surveys. Eur J Gastroenterol Hepatol. 2015;27(7):804-12. 7. Kennedy NA, Heap GA, Green HD, Hamilton B, Bewshea C, Walker GJ, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol. 2019;4(5):341-53. 8. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):699-710. 9. Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, et al. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2019;381(13):1201-14. 10. Sandborn WJ, Su C, Panes J. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2017;377(5):496-7
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Moderate-to-severe ulcerative colitis that does not respond to conventional treatments including steroids and immunomodulators (azathioprine/mercaptopurine) currently qualifies for advanced treatments with biologics as per NICE Guidelines and Technology Appraisals (TA 329, 342, 547 and 633), and the BSG Guidelines (2019). The MHRA Licence for biologics in the treatment of Ulcerative colitis currently extends to Infliximab, Adalimumab, Golilumab, Vedolizumab, Ustekinumab and Tofacitinib.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, there are national and international guidelines available. In the UK, we follow: 1. The British Society of Gastroenterology IBD guidelines mainly- citation as below: Lamb CA et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019 Dec;68(Suppl 3):s1-s106. doi: 10.1136/gutjnl-2019-318484. 2. NICE guidance for the management of ulcerative colitis(2019) https://www.nice.org.uk/guidance/ng130 accessed 24 December 2021

	3. European Crohns and Colitis Organisation: most recent guidelines citation as below: Raine T et al. ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment. J Crohns Colitis. 2021 Oct 12
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The BSG guidelines recommend that "ulcerative colitis patients on maintenance therapy with high-dose mesalazine, who required two or more courses of corticosteroids in the past year, or who become corticosteroid-dependent or refractory, require treatment escalation with thiopurine, anti-TNF therapy, vedolizumab or tofacitinib. The choice of drug should be determined by clinical factors, patient choice, cost, likely adherence and local infusion capacity."(1) Since publication of the BSG guidance, Ustekinumab (a biological therapy targeting the p40 subunit, common to cytokines IL12 &IL-23 has been licensed and also approved by NICE (2): "as an option for treating moderately to severely active ulcerative colitis in adults when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment, only if a tumour necrosis factor-alpha inhibitor has failed (that is the disease has responded inadequately or has lost response to treatment) or a tumour necrosis factor-alpha inhibitor cannot be tolerated or is not suitable, and the company provides ustekinumab at the same price or lower than that agreed with the Commercials Medicines Unit". 1. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019. 2. NICE. Ustekinumab for treating moderately to severely active ulcerative colitis. Technical appraisal guidance 633. wwwniceorguk/guidance/ta633. June 202
• What impact would the technology have on the current pathway of care?	Upadacitinib will be an additional therapeutic option for moderate-to-severe UC patients. There are no head to head studies comparing upadacitinib to current available treatments. In the U-Accomplish/U-Achieve studies of upadacitinib in Ulcerative colitis, patients who had an inadequate response, loss of response, or intolerance to aminosalicylates, immunosuppressants (azathioprine/mercaptopurine or methotrexate), corticosteroids and/or biologics. 50.7% and 51.1% were biologic inadequate responders in upadacitinib and placebo groups, respectively. The rapidity of response to treatment is impressive with Upadacitinib which is attractive to patients as there symptoms will improve decreasing disease burden (63 percent of patients

	treated with upadacitinib achieved clinical response (per partial Adapted Mayo Score) at week 2 versus 26 percent of those receiving placebo (p<0.001).) In addition the high remission rates at 8 weeks are impressive (33 percent of patients achieved the primary endpoint of clinical remission (per Adapted Mayo Score) compared to 4 percent of patients treated with placebo at week 8 (p<0.001). Remission is a hard endpoint when compared to clinical response Upadacitinib like tofacitinib is an oral agent. The once /day dosing of upadacitinib is more convenient to patients and likely to help with compliance. Preserving upadacitinib for post failure of anti-TNF / vedo/ustekinumab is not felt to appropriate given the high response rate to upadacitinib and the other advantages listed above. A systematic review and network meta-analysis of all biologics and small molecules in the treatment of moderate-to-severe ulcerative colitis (Burr NE et al, Gut 2021;**0**:1–12. doi:10.1136/gutjnl-2021-326390) indicates that in terms of clinical remission and clinical response, upadacitinib 45 mg once daily ranked first in all patients, in patients previously exposed to antitumour necrosis factor (TNF)-□ therapies, and in patients naïve to these drugs. Ref: U-Achieve - Sandborn WJ, Ghosh S, Panes J, Schreiber S, D'Haens G, Tanida S, Siffledeen J, Enejosa J, Zhou W, Othman AA, Huang B, Higgins PDR. Efficacy of Upadacitinib in a Randomized Trial of Patients With Active Ulcerative Colitis. Gastroenterology. 2020 Jun;158(8):2139-2149.e14. doi: 10.1053/j.gastro.2020.02.030. Epub 2020 Feb 22. Erratum in: Gastroenterology. 2020 Sep;159(3):1192. PMID: 32092309. U-accomplish - Vermeire S, Danese S, Zhou W, et al. OP23 Efficacy and safety of upadacitinib as induction therapy in patients with Moderately to Severely Active Ulcerative Colitis: Results from phase 3 U-ACCOMPLISH study. *J Crohns Colitis*. 2021;15(Suppl 1):S021-S022. Published 2021 May 27. doi:10.1093/ecco-jcc/jjab075.022
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Upadacitinib will be an additional therapeutic option for UC patients who fail aminosalicylates, steroids or require repeated steroid doses, and in those who have failed or are intolerant of thiopurines . As above consideration should be given to allowing it to be used before failure of biologic medications eg anti TNF, ustekinumab and vedolizumab or as an alternative to

	tofacitinib. Individual Healthcare Organisations will need to make their own decisions related to the positioning of Upadicitinibin relation to other biologics based on the published evidence, and emerging information.
• How does healthcare resource use differ between the technology and current care?	In UC upadacitinib is used at 45 mg OD for 8 weeks for induction therapy, and then at 15mg or 30mg for maintenance treatment.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Upadacitinib would be used exclusively in secondary and tertiary care by IBD gastroenterologists experienced in the care of people living with ulcerative colitis after and in line with NICE TA approval
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None- all already in place
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes The key studies U-Accomplish and U-achieve included patient who has inadequate response, loss of response, or intolerance to aminosalicylates, immunosuppressants, corticosteroids and/or biologics. So these studies included patients who have not responded to therapies that we have currently available in the NHS, showing that this drug will provide clinical meaningful benefits. U-ACCOMPLISH was a multicentre, randomized, double-blind, placebo-controlled trial (NCT03653026) that enrolled patients with moderate-to-severe UC (defined as adapted Mayo score 5–9 with centrally read endoscopic score 2–3) who had inadequate response, loss of response, or intolerance to aminosalicylates, immunosuppressants, corticosteroids and/or biologics. Patients were randomized 2:1 to UPA 45 mg QD or placebo (PBO) for 8 weeks. At week 8, responders entered the

	maintenance phase and non-responders entered the extended treatment period to receive open-label UPA 45 mg once/day for additional 8 weeks. The primary endpoint (clinical remission per adapted Mayo Score) and ranked secondary endpoints including symptomatic, endoscopic– histologic evaluations from the 8-week PBO-controlled period are reported here. Non-responder imputation incorporating multiple imputation for missing data due to COVID-19 are reported. Results: 522 patients were randomized (UPA, n=345; PBO, n=177); the intent-to-treat population included 341 patients in UPA and 174 patients in PBO group. Baseline demographics and disease characteristics were similar between groups; 50.7% and 51.1% were biologic inadequate responders in UPA and PBO groups, respectively. A significantly higher proportion of patients receiving UPA 45 mg QD (33.5%) versus PBO (4.1%) achieved the primary endpoint (adjusted treatment difference: 29.0% [23.2, 34.7]; P <0.0001 In U-Achieve adults with moderate to severe ulcerative colitis who achieved a clinical response (per Adapted Mayo Score) following an 8-week study period of once-daily upadacitinib (45 mg) induction treatment were re-randomized to receive upadacitinib 15 mg, upadacitinib 30 mg or placebo for an additional 52 weeks.[1] All secondary endpoints were met, including the achievement of endoscopic improvement, histologic-endoscopic mucosal improvement (HEMI) and corticosteroid-free clinical remission at week 52.[1] 49 percent of patients treated with upadacitinib 15 mg and 62 percent of patients treated with upadacitinib 30 mg achieved endoscopic improvement at 52 weeks versus 14 percent of patients in the placebo group (p<0.001).[1] In addition, 35 percent of patients on upadacitinib 15 mg and 49 percent of patients on upadacitinib 30 mg achieved HEMI compared to 12 percent of patients in the placebo group (p<0.001). Of patients who were in remission at the completion of the 8-week induction studies, corticosteroid-free remission was achieved in 57 percent of patients in the upadacitinib 15 mg group and 68 percent of patients in the upadacitinib 30 mg group compared to 22 percent of patients in the placebo group (p<0.001). A total of 746 patients who completed the 8-week upadacitinib induction treatment with clinical response and received at least one dose of the study drug in the maintenance period were included in the safety analysis.[1] The safety results of upadacitinib (15 mg or 30 mg) were consistent with the safety profile observed in the Phase 3 induction studies in ulcerative colitis, as well as in previous studies across indications.[1-6] No new safety risks were identified.[1-6] The most common adverse events observed in the upadacitinib groups during the 52-week study period were nasopharyngitis, exacerbation of ulcerative colitis and blood

	creatine phosphokinase increase.[1] The exposure-adjusted event rates of serious adverse events per 100 patient years were 12.6 events in the upadacitinib 15 mg group, 10.6 events in the upadacitinib 30 mg group and 21.9 events in the placebo group.[1] The rates of serious infections were 4.9, 3.0 and 6.2 events per 100 patient years in the upadacitinib 15 mg, upadacitinib 30 mg and placebo groups, respectively.[1] The rates of adverse events leading to treatment discontinuation per 100 patient years were 6.0 events and 6.0 events in patients receiving upadacitinib 15 mg and upadacitinib 30 mg, respectively, compared with 20.3 events in the placebo group.[1] Malignancies (excluding non-melanoma skin cancer) reported in the study included one event in the upadacitinib 15 mg group, two events in the upadacitinib 30 mg group and one event in the placebo group.[1] Adjudicated thrombotic events were reported in the upadacitinib 15 mg group (two events of pulmonary embolism), 30 mg group (two events of deep vein thrombosis) and the placebo group (one event of ovarian vein thrombosis).[1] One adjudicated major adverse cardiovascular event (MACE) was reported in the upadacitinib 30 mg group and one was reported in the placebo group.[1] One patient in the placebo group experienced events of adjudicated gastrointestinal perforation.[1] No deaths were reported.[1] U-Achieve - Sandborn WJ, Ghosh S, Panes J, Schreiber S, D'Haens G, Tanida S, Siffledeen J, Enejosa J, Zhou W, Othman AA, Huang B, Higgins PDR. Efficacy of Upadacitinib in a Randomized Trial of Patients With Active Ulcerative Colitis. Gastroenterology. 2020 Jun;158(8):2139-2149.e14. doi: 10.1053/j.gastro.2020.02.030. Epub 2020 Feb 22. Erratum in: Gastroenterology. 2020 Sep;159(3):1192. PMID: 32092309. U-accomplish - Vermeire S, Danese S, Zhou W, et al. OP23 Efficacy and safety of upadacitinib as induction therapy in patients with Moderately to Severely Active Ulcerative Colitis: Results from phase 3 U-ACCOMPLISH study. *J Crohns Colitis*. 2021;15(Suppl 1):S021-S022. Published 2021 May 27. doi:10.1093/ecco-jcc/jjab075.022 References 1-6 as per above link OP23 Efficacy and safety of upadacitinib as induction therapy in patients with Moderately to Severely Active Ulcerative Colitis: Results from phase 3 U-ACCOMPLISH study (nih.gov)

	References 1-6 as per above link
• Do you expect the technology to increase length of life more than current care?	This techonology is not directly aimed at increasing length of life, but its effectiveness in reducing hospitalisation and need for surgery is indirectly expected to increase life by reducing disease burden and allow for better disease control and less disability.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, having a further treatment option should mean more patients will get into remission and thus reduce disease burden and allow for better disease control and less disability. This could potentially reduce hospitalisations, colorectal cancer rates and colectomy rates although current evidence for this is lacking. Upadicitinib Studies show a decrease and normalisation of FACIT-F (Functional Assessment of Chronic Illness Therapy – fatigue) scores.(ECCO 2022 abstract presentation)
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not licensed for <18 years Use with caution in patients >65 years Contraindicated in patients with Absolute lymphocyte count less than 500 cells/mm^3; absolute neutrophil count less than 1000 cells/mm^3; active serious infection including localised infection; active tuberculosis; haemoglobin less than 8 g/dL Use caution in patients with risk factors for VenoThromboEmbolism (VTE). Patients should be informed of the signs and symptoms of VTE before starting treatment and advised to seek urgent medical attention if these develop. Upadacitinib should be discontinued if clinical features of VTE occur.
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,	Easier to use than the currently available Pan-Jak inhibitor (tofacitinib) as once a day dosing. Dose adjustment is required (similar to tofacitinib) The recommended induction dosage is 45 mg once daily for 8 weeks. The recommended maintenance dosage is 15 mg once daily. A maintenance dosage of 30 mg once daily may be considered for patients with refractory, severe, or extensive disease.

any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Discontinue if adequate therapeutic response is not achieved with the 30 mg dosage. Use the lowest effective dosage needed to maintain response
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Prior to treatment update immunizations and consider evaluating for active and latent tuberculosis, viral hepatitis, hepatic function, and pregnancy status – this is similar to currently used biologics and tofacitinib Avoid initiation or interrupt Upadacitinib if absolute lymphocyte count is less than 500 cells/mm3 , absolute neutrophil count is less than 1000 cells/mm3 , or hemoglobin level is less than 8 g/dL Discontinue if no response after induction dose 45 mg for 8 weeks If partial response can be continued on 35 mg once/day
15. Do you consider that the use of the technology will result in any substantial health-related benefits	Ustekinumab, vedolizumab and infliximab are all started in hospital as an IV induction dosing regime, followed by a sub-cutaneous or intravenous manintenance dosing option.

that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Upadacitinib does not require any in-hospital infusion which is helpful for patient as well as for reducing the burden on NHS Infusion Suites . If patients are switched to sub cut vedo/infliximab they require training to do this which takes some time and nursing resources All subcut drugs need correct storage etc which can be difficult for some patients and has an impact on their life choices (eg some patients don't want to live in university halls as they would have to store their drug in a fridge) and also has an impact on travel arrangements eg needing to keep drug cool when flying or abroad. Rapid onset of action with reduction in rectal bleeding within days has a big impact on patient quality of life
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Upadacitinib is a selective Jak1 inhibitor (tofacitinib is non selective) so it has a novel mechanism of action. This selectivity may result in fewer side effects but longer term data required to confirm this. The efficacy data is impressive and therefore has the potential to make a significant and substantial impact on patients suffering from ulcerative colitis. Our current treatments are limited by high proportion of non-responders as well as patients losing response and therefore there is an unmet need to have newer treatments that may be more effective.

• Is the technology a 'step-change' in the management of the condition?	Yes I think so. There are no head to head trials that include upadacitinib in comparison to existing biologics or small moelcules in UC. However a network meta-analysis showed upadacitinib to be the best performing agent for the induction of clinical remission in moderate to severe ulcerative colitis Lasa JS, Olivera PA, Danese S, Peyrin-Biroulet L. Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2022 Feb;7(2):161-170.
• Does the use of the technology address any particular unmet need of the patient population?	Yes As detailed above many patients fail to respond, lose response or cannot tolerate current available treatments so the availability of upadacitinib would be a life line for those patients
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?	Common side effects include Acne; cough; fever; increased risk of infection; nausea; neutropenia; oropharyngeal pain; weight increased which all can have an adverse impact on a patients quality of life. There are also common side effects with other available treatments ie steroids, vedolizumab, Anti-TNF, Tofacitinib and ustekinumab, The Jak inhibitors are known to increase lipids but has not been shown to increase cardiovascular risks. Reactivation of herpes infection eg herpes simplex and herpes zoster is a well documented risk for patients on Jak inbibitors (2-3.5% of patients_

	Rare side effects: deep vein thrombosis,Venous thromboembolism- patient would need to stop medication and take anticoagulants for at least three month Malignancy including non melanoma skin cancer. Patients will be advised to use sunscreen. This risk is also there for other advanced treatments used in UC Reactivation of infections eg TB- screening required as per other advance treatments used in UC Serious infections – eg meningitis - This risk is also there for other advanced treatments used in UC
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes treatments used in U-ACCOMPLISH and U-ACHIEVE reflect UK clinical practice
• If not, how could the results be extrapolated to the UK setting?	N/a
• What, in your view, are the most important outcomes, and were they measured in the trials?	As detailed above Mayo score has been shown to be a validated outcome measure with meaningful benefits to patients . I think U U-ACCOMPLISH and U-ACHIEVE primary outcome measures were appropriate and important. Rapid improvement in rectal bleeding scores translate to real difference to patients quality of life
• If surrogate outcome measures were used, do they	N/a

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. Are you aware of any new evidence for the comparator treatment(s) since the publication of the most recent NICE technology appraisal guidance?	Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy Technology appraisal guidance [TA329- Vedolizumab for treating moderately to severely active ulcerative colitis Technology appraisal guidance [TA342]Published: 05 June 2015 Ustekinumab for treating moderately to severely active ulcerative colitis Technology appraisal guidance [TA633]

	Tofacitinib for moderately to severely active ulcerative colitis Technology appraisal guidance [TA547]Published: 28 November 2018 These TA are all still relevant. Long term real world data now available which confirm efficacy and safety of these medications.
21. How do data on real-world experience compare with the trial data?	No real world published data on upadacitinib in UC to my knowledge
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None within a defined pathway of care for all individuals with moderate-severely active ulcerative colitis meeting criteria for prescription for Upadacitinib Upadacitinib is not licensed for <16 year old and there is limited data for those 75 years and older

22b. Consider whether these issues are different from issues with current care and why.	Anti-TNFs are used widely in the paediatric cohort Ustekinumab/vedolizumab or tofacitinib not used in paediatric patients at present. Similar concerns re the safety of thiopurines and anti-TNFs in the elderly particularly regarding infection. Long term safety data of ustekinumab and vedolizumab would suggest these drugs may have a better safety profile in the elderly. Similar concerns re tofacitinib in >65 years

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Efficacy data for upadacitinib is impressive
- Safety data similiar to currently available treatments
- Oral medications preferred by patients
- Rapid onset of action allows patients to get back to college/university/work qucikly
- Given limitations of current treatments having an additional option makes this very attractive

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

[ID3953] - Upadacitinib for treating moderately to severely active ulcerative colitis

Professional organisation submission

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	**(1)** [redacted] (2) [redacted]
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).	**UKCPA is a not-for-profit organisation, which invest all surplus back into the association in order to provide better services and benefits for members, and to support initiatives which improve patient care.**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

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 and maintain clinical, steroid free and endoscopic remission in patients with moderately to severely active ulcerative colitis.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Clinical remission (per Adapted Mayo Score) is defined as stool frequency sub score (SFS) ≤1 and not greater than baseline, rectal bleeding sub score (RBS) of 0 and endoscopic sub score ≤1. Endoscopic improvement (mucosal healing) Histologic-endoscopic mucosal improvement (HEMI) Corticosteroid-free clinical remission Improve quality of life

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, currently (limited) treatment options - not effective in more than one third of patients and can be associated with adverse effects that limit use Currently no curative treatments lifelong disease associated with significant morbidity and potential for social and psychological complications if poorly controlled or tolerated Will offer additional JAK treatment option
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Medical treatments include aminosalicylates, corticosteroids, thiopurines (azathioprine & mercaptopurine), methotrexate, ciclosporin, biologic medicines (adalimumab, infliximab, golimumab, vedolizumab & ustekinumab) and small molecule inhibitor tofacitinib. Treatments due NICE this year: ozanimod and filgotinib (small molecule inhibitor) Surgery
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	British Society of Gastroenterology ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment NICE: Ulcerative colitis management
• Is the pathway of care well defined? Does it vary or are there differences of opinion	Yes, to a point. Start with non-biologic agents (topical and/or oral) then once qualify can use any biologic medicines which will be chosen based on individual patient factors such as route of administration preference, frequency of administration and any contraindicating factors (e.g., patients with moderate-

between professionals across the NHS? (Please state if your experience is from outside England.)	severe heart failure cannot have anti TNF therapy). Price/cost-effectiveness of the treatment will also be taken into consideration.
• What impact would the technology have on the current pathway of care?	Additional medical options before surgery is required
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?	No difference
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care.
• What investment is needed to introduce the technology? (For	None

example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Unable to tell at this stage
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Contraindicated in the following patients: Absolute lymphocyte count less than 500 cells/mm3 Absolute neutrophil count less than 1000 cells/mm3 Active serious infection including localised infection Active tuberculosis Active viral infections Haemoglobin less than 8 g/dL Patients with history of DVT/PE Upadacitinib induced-liver injury (to be withheld while investigated)

	Caution in the following: 65 years and over Known malignancy Avoid in pregnancy and breastfeeding Avoid in severe hepatic impairment (limited information available) Caution in severe renal impairment (limited information available) Lipid profile to be monitored
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 or ease of use or additional tests or monitoring needed.)	This may be easier than other treatment options as this is an oral agent. This will be easier for patients and may be preferable in comparison to self-injection or attending the infusion unit for an infusion. As it is an oral agent it will help the capacity of an already stretched infusion unit and will avoid hospital visits for the patient which is significant due to the potential risk of infection when attending a hospital site. As this is an oral agent it does not have any special temperature storage conditions in comparison to other options such as adalimumab which needs to be stored in a fridge. This reduces the potential for wastage as medicines that have temperature requirements such as refrigeration could lead to temperature excursions that means the medicine can no longer be used and must be wasted. As an oral agent you remove the risk of injection site reactions. This is also of benefit in needle phobic/exhausted patients.

	Additional monitoring is required for this medicine but is similar to the monitoring already required for current treatments and so sustainable within services: Monitor neutrophils, lymphocytes and haemoglobin before starting treatment, and as clinically indicated thereafter; interrupt treatment if absolute neutrophil count less than 1000 cells/mm^3, absolute lymphocyte count less than 500 cells/mm^3, or haemoglobin less than 8 g/dL—treatment may be restarted when levels return above these values. Monitor hepatic transaminases before starting treatment, and as clinically indicated thereafter—interrupt treatment if drug-induced liver injury suspected Monitor lipids 12 weeks after starting treatment, and then as clinically indicated. Monitor for signs of VTE
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients will be escalated to a biologic agent or Janus kinase inhibitors if they have responded inadequately to conventional therapy including aminosalicylates, corticosteroids and mercaptopurine or azathioprine. Patients will be switched from one biologic to another if they are unable to tolerate it or they are not responding to it. This will be assessed by: • checking symptoms and symptom history

	• conducting tests such as faecal calprotectin, CRP, drug trough and antibodies level (if available) • ruling out other causes of symptoms such as infection • primary or secondary loss of response Treatment will be stopped if patient is in deep remission clinically and endoscopically, or if patients develop serious side effects or adverse reactions secondary to treatment; or patients acquire new co-morbidities which place them into contra-indication category.
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?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	Yes – limited options to treat ulcerative colitis and being an oral agent makes this a significant change in ulcerative colitis management. Once daily dosing vs tofacitinib bd

benefits and how might it improve the way that current need is met?	Upadacitinib was significantly more effective than placebo at treating patients with ulcerative colitis.
• Is the technology a 'step-change' in the management of the condition?	Yes. As an oral agent this could be used 2nd or 3rd line following conventional therapy.
• Does the use of the technology address any particular unmet need of the patient population?	Additional oral option for the management and treatment of ulcerative colitis.
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?	Side effect profile mostly similar to other treatment options with the exception of the following: Acne – which may affect patients' quality of life if this is significant and visible. Weight gain – this may be of benefit for a large portion of patients with ulcerative colitis as generally they are undernourished and of low weight. However, if weight gain becomes significant this may affect quality of life and lead to other health problems. Lipid profile is monitored and will be referred to GP for management if becomes out of range.

	Dyslipidaemia – could create other health conditions and may lead to the need of medication, all of which would impact on the patient's quality of life. DVT/PE – will significantly affect that patient as would lead to necessity of anticoagulant therapy and may cause other conditions such as stroke which could significantly affect the patient's quality of life Upadacitinib requires the patient to have more frequent blood tests compared with other treatment options. This may impact on the patient's life and quality of life Additional pressure on phlebotomy /costs
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?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Induction and maintenance of clinical remission, endoscopic healing, corticosteroid free remission and medication safety are the most important outcome measures, and these were reported in the trial data.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Too early to say at this point. Consider if recent issues with VTE events with tofacitinib (another JAK inhibitor) is a class effect.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of the most recent NICE technology appraisal guidance?	No

21. How do data on real-world experience compare with the trial data?	As not licenced for this indication unable to comment
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Some CCG's will only pay for four treatments per patient, therefore would need to make this available to all so patients are not disadvantaged. Given the number of agents already available (and in development), this is unlikely to have a significant cost impact if competitively priced (PAS is available for its rheumatoid arthritis indication), vs alternative JAK inhibitors . Pathway placement will be important vs. biosimilars and alternative JAK inhibitors
22b. Consider whether these issues are different from issues with current care and why.	No
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- oral option
- alternative JAK inhibitor
- competitive price required
- once daily dosing
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Upadacitinib for treating moderately to severely active ulcerative colitis [ID3953]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135585

Completed 29 June 2022

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Upadacitinib for treating moderately to severely active ulcerative colitis [ID3953]

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Date completed: 29 June 2022

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135585.

Acknowledgements: The authors would like to thank Chris Probert, Professor of Gastroenterology, University of Liverpool who provided feedback on a draft version of 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.

Declared competing interests of the authors: Within the last 3 years, Dr Burkitt has received fees for speaking from Takeda and Janssen, and reimbursement for attending a symposium from Janssen. Professor Probert has received consultancy fees and speaker fees from Celltrion, Dr Falk Pharma and Sandoz.

This report should be referenced as follows: Greenhalgh J, Mahon J, Houten R, Edwards K, Donegan S, Boland A, Beale S, Dundar Y, McEntee J and Burkitt M. Upadacitinib for treating moderately to severely active ulcerative colitis [ID3953]: A Single Technology Appraisal. LR*i*G, University of Liverpool, 2022.

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Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
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Yenal Dundar	Critical appraisal of the company search strategies
Joanne McEntee	Critical appraisal of the company submission
Michael Burkitt	Clinical advice and critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

5-ASA	aminosalicylates
ADA	adalimumab
AE	adverse event
AESI	adverse event of special interest
AMS	adapted Mayo score
Bio-IR	biologic therapy-intolerant or inadequate responder
CI	confidence interval
CPK	creatinine phosphokinase
CS	company submission
CSR	clinical study report
CT	conventional therapy/treatment
EAER	exposure adjusted event rates
EAG	External Assessment Group
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5-dimension-5-level questionnaire
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
FE	fixed effects
FEA	fixed effects with baseline risk adjustment
FMS	Full Mayo Score
GI	gastrointestinal
GOL	golimumab
IBD	inflammatory bowel disease
IBDQ	inflammatory bowel disease questionnaire
IFX	infliximab
ITT	intention-to-treat
JAK	Janus kinase
LS	least squares
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
Non-Bio-IR	inadequate response, loss of response, or intolerance to conventional therapy but not failed biologic therapy
ONS	Office for National Statistics
PAS	Patient Access Scheme
PGA	physician global assessment
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PY	patient-years
QALY	quality adjusted life year
RE	random effects

REA	random effects with baseline risk adjustment
RBS	rectal bleeding subscore
RCP	Royal College of Physicians
RCT	randomised controlled trial
RR	re-randomised
SAE	serious adverse event
SD	standard deviation
SmPC	Summary of Product Characteristics
SCCAI	Simple Clinical Colitis Activity Index
SLR	systematic literature review
SUCRA	surface under the cumulative ranking curve
TEAE	treatment-emergent adverse event
TNF	tumour necrosis factor
TNF-α	tumour necrosis factor-alpha
TOF	tofacitinib
TSAP	trial statistical analysis plan
TT	treat through
U-ACHIEVE	the induction and maintenance trial discussed in the company submission
U-ACCOMPLISH	the induction trial discussed in the company submission
UC	ulcerative colitis
UST	ustekinumab
VED	vedolizumab

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained.

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the company base case ICERs per QALY gained. Sections 1.3 explain the key issues clinical effectiveness identified by the EAG in more detail. Section 1.4 outlines the key cost effectiveness issues identified by the EAG. A summary of EAG probabilistic and deterministic cost effectiveness results is presented in Section 1.5.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 *Overview of the EAG's key issues*

Table A Summary of key issues

Issue	Summary of issue	Report sections
Issue 1	Lack of direct evidence for the comparison of upadacitinib versus relevant comparators	Section 2.5.4
Issue 2	Network meta-analysis statistical issues	Section 3.6.2
Issue 3	Company modelled treatment pathway is not a good reflection of NHS clinical practice	Section 5.4.1
Issue 4	Company choice of utility values	Section 5.4.2
Issue 5	High and low doses of upadacitinib maintenance treatments	Section 5.4.3

1.2 *Overview of key model outcomes*

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a QALY. An ICER is the ratio of the extra cost for every QALY gained.

Clinical advice to the EAG is that the company model treatment pathway does not reflect NHS clinical practice. The EAG has modelled an alternative pathway that more closely represents NHS clinical practice than the company model treatment pathway.

1.3 *The clinical effectiveness evidence: summary of the EAG's key issues*

Issue 1 Lack of direct evidence for the comparison of upadacitinib versus the relevant comparators

Report section	**Section 2.5.4**
Description of issue and why the EAG has identified it as important	The company has provided clinical effectiveness evidence from three RCTs, namely two 8-week induction trials (U-ACHIEVE and U-ACCOMPLISH) and one 52-week maintenance trial (U-ACHIEVE). Trial results demonstrate the clinical effectiveness of upadacitinib versus placebo. There is no direct effectiveness evidence for the comparison of upadacitinib versus any relevant comparators listed in the final scope issued by NICE, i.e., adalimumab, infliximab, golimumab, tofacitinib, ustekinumab and vedolizumab.
What alternative approach has the EAG suggested?	The company has carried out NMAs to generate indirect clinical effectiveness evidence for the comparison of upadacitinib versus relevant comparators
What is the expected effect on the cost effectiveness estimates?	The effect of this issue is influenced by confidence in company NMA results (see Issue 2)
What additional evidence or analyses might help to resolve this key issue?	None

EAG=External Assessment Group; RCT=randomised controlled trial

Issue 2 Company NMA methodological issues

Report section	**Section 3.6.2**
Description of issue and why the EAG has identified it as important	The EAG has identified three NMA methodological issues which cast doubt on the robustness of NMA results: • for all networks (induction and maintenance), the consistency assumption could not be tested formally • trial design and descriptions of the intervention and placebo treatments of the trials included in the company maintenance NMAs raise issues that cannot be resolved • the company and the EAG preferred approaches to generating NMA results differ; however, outputs are generally similar
What alternative approach has the EAG suggested?	The EAG is unable to suggest an alternative approach
What is the expected effect on the cost effectiveness estimates?	The effect of these issues on cost effectiveness is not known
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion regarding the plausibility and robustness of NMA results

EAG=External Assessment Group; NMA=network meta-analysis

1.4 *The cost effectiveness evidence: summary of the EAG's key issues*

Issue 3 Company model structure is not a good reflection of NHS clinical practice

Report section	**Section 5.4.1**
Description of issue and why the EAG has identified it as important	The company model treatment pathway does not reflect NHS clinical practice and results in most patients, regardless of treatment, ending up in the Active UC health state for many decades with no active treatment
What alternative approach has the EAG suggested?	The EAG has modelled an alternative pathway that more closely represents NHS clinical practice than the company model treatment pathway.
What is the expected effect on the cost effectiveness estimates?	See EAG cost effectiveness results
What additional evidence or analyses might help to resolve this key issue?	None - this issue has been resolved

EAG=External Assessment Group; UC=ulcerative colitis

Issue 4 Company choice of utility values

Report section	**Section 5.4.2**
Description of issue and why the EAG has identified it as important	The company has used published utility estimates in the model. The NHS Reference Case favours the use of utility values estimated from trial data
What alternative approach has the EAG suggested?	The EAG has carried out a scenario that uses utility values generated from EQ-5D data that were collected during the three upadacitinib trials
What is the expected effect on the cost effectiveness estimates?	See EAG cost effectiveness results
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion to determine the most realistic utility values for use in the company model

EAG=External Assessment Group; EQ-5D=EuroQol 5-dimension

Issue 5 High and low doses of maintenance treatments

Report section	**Section 5.4.3**
Description of issue and why the EAG has identified it as important	In the company model, separate analyses are carried out for low (15mg) and high (30mg) maintenance doses of upadacitinib versus comparators (30% high dose:70% standard dose). The EAG considers that this is an unfair comparison
What alternative approach has the EAG suggested?	The EAG considers that results from company scenario analysis 7 (ratio of 30% high: 70% standard maintenance doses of for all treatments) are informative
What is the expected effect on the cost effectiveness estimates?	See EAG cost effectiveness results
What additional evidence or analyses might help to resolve this key issue?	None - this issue has been resolved

EAG=External Assessment Group

1.5 *Summary of EAG's preferred assumptions and resulting ICER*

The EAG has presented results for the bio-naïve and bio-experienced populations for two maintenance doses of upadacitinib (15mg and 30mg). The EAG has presented results for the comparison of upadacitinib (Patient Access Scheme [PAS] price) versus adalimumab (biosimilar price). Cost effectiveness results for upadacitinib versus all other comparators are presented in Section 5.

Table A Summary of EAG's preferred assumptions and resulting cost effectiveness results for the **bio-naïve population**: upadacitinib (PAS price) versus adalimumab (biosimilar list price)

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Upadacitinib (15mg)			
Company's base case (probabilistic)	[redacted]	[redacted]	**Upadacitinib dominates**
R1: Trial-based utility values (deterministic)	[redacted]	[redacted]	**Upadacitinib dominates**
R2: EAG revised treatment pathway (deterministic)	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Maintenance phase drug dose spit 30% high dose: 70% standard dose (deterministic)	[redacted]	[redacted]	£4,483
EAG's preferred scenario (R1-R3) (deterministic)	[redacted]	[redacted]	**Upadacitinib dominates**
EAG's preferred scenario (R1-R3) (probabilistic)	[redacted]	[redacted]	**Upadacitinib dominates**
Upadacitinib (30mg)			
Company's base case (probabilistic)	[redacted]	[redacted]	£15,264
R1: Trial-based utility values (deterministic)	[redacted]	[redacted]	£31,042
R2: EAG revised treatment pathway (deterministic)	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Maintenance phase drug dose spit 30% high dose: 70% standard dose (deterministic)	[redacted]	[redacted]	£4,483
EAG's preferred scenario (R1-R3) (deterministic)	[redacted]	[redacted]	**Upadacitinib dominates**
EAG's preferred scenario (R1-R3) (probabilistic)	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table B Summary of EAG's preferred assumptions and resulting cost effectiveness results for the **bio-exposed** population: upadacitinib (PAS price) versus adalimumab (biosimilar list price)

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Upadacitinib (15mg)			
Company's base case (probabilistic)	[redacted]	[redacted]	£1,186
R1: Trial-based utility values (deterministic)	[redacted]	[redacted]	£1,448
R2: EAG revised treatment pathway (deterministic)	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Maintenance phase drug dose spit 30% high dose: 70% standard dose (deterministic)	[redacted]	[redacted]	£4,656
EAG's preferred scenario (R1-R3) (deterministic)	[redacted]	[redacted]	**Upadacitinib dominates**
EAG's preferred scenario (R1-R3) (probabilistic)	[redacted]	[redacted]	**Upadacitinib dominates**
Upadacitinib (30mg)			
Company's base case (probabilistic)	[redacted]	[redacted]	£14,146
R1: Trial-based utility values (deterministic)	[redacted]	[redacted]	£25,274
R2: EAG revised treatment pathway (deterministic)	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Maintenance phase drug dose spit 30% high dose: 70% standard dose (deterministic)	[redacted]	[redacted]	£4,656
EAG's preferred scenario (R1-R3) (deterministic)	[redacted]	[redacted]	**Upadacitinib dominates**
EAG's preferred scenario (R1-R3) (probabilistic)	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group: ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year

For further details of the exploratory and sensitivity analyses carried out by the EAG, are provided in Section 5.

2 INTRODUCTION AND BACKGROUND

2.1 *Introduction*

This appraisal focuses on the use of upadacitinib (RINVOQ™) to treat patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy (CT) or a biologic agent, including tumour necrosis factor (TNF)-alpha inhibitors (adalimumab, golimumab, and infliximab), tofacitinib, ustekinumab, and vedolizumab. In this External Assessment Group (EAG) report, the term 'company submission' (CS) refers to the company's document B, which is the company's full evidence submission.

The company has focused on two patient populations, (i) non-biologic inadequate responders (Non-Bio-IR)/bio-naïve, i.e., patients with an inadequate response, loss of response, or intolerance to CT but have not failed biologic therapy, and (ii) biologic inadequate responders (Bio-IR)/bio-exposed, i.e., patients with an inadequate response, loss of response, or intolerance to biologic therapy. The company has presented evidence for both patient populations for both the induction phase and the maintenance phase of treatment.

2.2 *Ulcerative colitis*

Ulcerative colitis is a chronic relapsing and remitting systemic inflammatory bowel disease (IBD) that involves inflammation of the mucosal surface of the inner lining of the large intestine.[1,2] Inflammation starts distally in the rectum and progresses proximally through the colon.[2] UC is classified (via colonoscopy) according to the extent of disease:[1,2]

- proctitis: inflammation is limited to the rectum
- left-sided colitis: inflammation occurs proximal to the rectum but does not extend beyond the splenic flexure (or 50cm from the anus)
- extensive colitis (or pancolitis): inflammation extends beyond the splenic flexure (or <15 to 20cm from the anus)

UC has a worldwide geographic spread.[3] The UK has one of the highest incidence rates of UC, although exact UC incidence and prevalence rates are unknown due to differences in detection rates and diagnostic criteria between studies.[4] In England, approximately 146,000 people are estimated to have UC, of whom approximately 52% have moderate to severe disease.[5] UC affects any age group and affects males and females equally.[2,3,6] The cause of UC is unknown, however, there are known environmental and genetic risk factors.[2] The peak onset of the disease is between the ages of 15 years and 30 years, with a smaller onset peak between 50 years and 70 years of age.[2]

Diagnosis of UC is based on patients' clinical symptoms and evidence from histological and endoscopic tests, which is also used to rule out other causes (i.e., Crohn's disease).[7] Several classification systems exist to assess UC disease severity, including the Mayo Clinic score, which is often used in clinical trials.[8] Clinical advice to the EAG is that the Simple Clinical Colitis Activity Index (SCCAI),[9] is used in the NHS to assess disease severity (alongside inflammatory biomarkers) but that clinical practice varies across England and Wales.

Symptoms of UC often begin gradually, and patients experience unpredictable periods of spontaneous remission and relapse.[2,10] The most common symptom is bloody diarrhoea with or without mucus. Other symptoms include rectal bleeding, urgency, tenesmus, weight loss, and fatigue.[2,10,11]

Patients with UC have an increased risk of death in the first year following diagnosis, but after the first year the risk is comparable to the general population.[10] However, UC is a lifelong condition that can be a significant burden for patients and their families.[6] The symptoms of UC can negatively impact patients' functioning, well-being, and quality of life across different areas, including physical, psychological, sexual, and social domains.[10] The symptoms can affect patients' daily activities such as the ability to attend school or work, or to carry out parenting tasks.[12] Patients can also experience social stigmatisation leading to the avoidance of group interactions.[13]

2.3 *Upadacitinib*

Upadacitinib is a selective and reversible oral small-molecule Janus kinase (JAK) inhibitor that has a greater affinity for JAK1 than JAK2, JAK3, or tyrosine kinase 2.[14] JAK 1 inhibition modulates the signalling of pro-inflammatory cytokines involved in UC pathogenesis, thereby reducing the underlying inflammatory symptoms of the disease (CS, p15).

2.4 *Company's overview of current service provision*

2.4.1 Treatments in the pathway

The NICE clinical care pathway for patients with UC and the proposed positioning of upadacitinib are shown in Figure 1. The company's proposed positioning of upadacitinib is as an advanced treatment option for [redacted].

Clinical advice to the EAG is that Figure 1 is a reasonable reflection of NHS clinical practice for patients with UC. In brief, it is common for patients to receive CT prior to treatment with biologic therapy. Clinical advice to the EAG is that patients receive successive biologic

treatments depending on response. In rare cases, patients who are hospitalised due to severe acute symptoms may be treated with a biologic agent in the first instance; some of these patients may later be switched to treatment with CT if they have a complete response, however, this is unlikely.

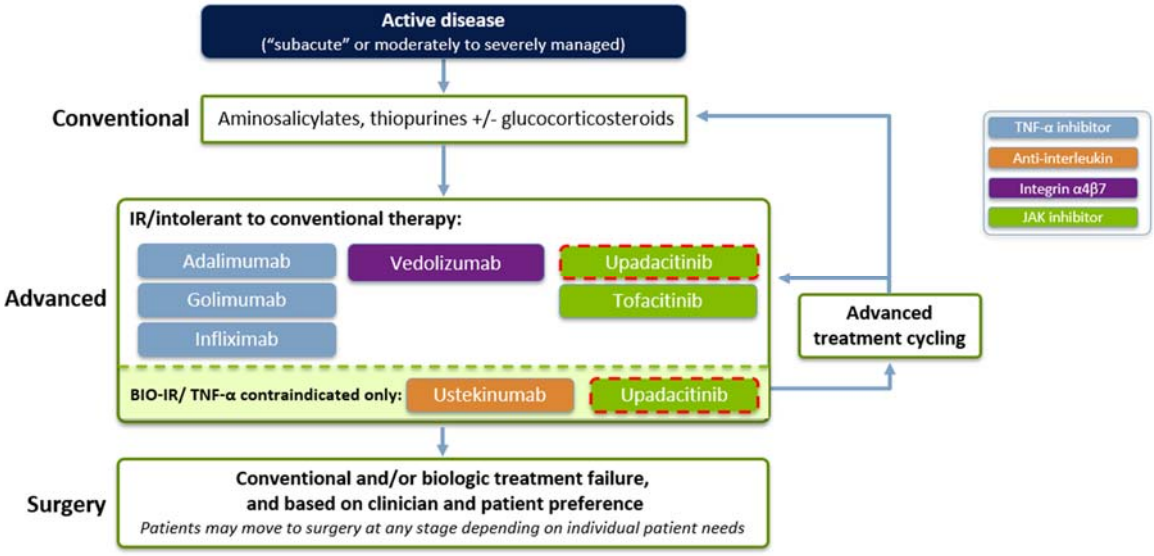

Figure 1 Treatment pathway for patients with ulcerative colitis

Bio-IR=patients with inadequate response to biologic therapy; IR=inadequate response; JAK=Janus kinase; TNF=tumour necrosis factor
Source: CS, Figure 1

Current management options for patients with moderately to severely active UC include pharmacological or surgical interventions. All patients are initially prescribed pharmacological treatment (CT and, if required, a biologic agent). Surgery is recommended for patients who do not respond to medical treatments or who are at risk of life-threatening complications.[2,7] Patients may also elect to have surgery to alleviate symptoms and improve their quality of life.[2] Surgical intervention is eventually required by 20% to 30% of patients with UC.[2]

Clinical advice to the EAG is that patients with moderately to severely active UC are typically managed using a sequential treatment approach, with the choice of treatment depending on factors including patient preference, patient contraindications, safety, drug speed of onset, patient antibody responses to prior biologics, any side effects resulting from previous biologics, and cost. Treatment goals extend beyond the alleviation of symptoms to include outcomes such as maintaining a steroid-free remission, preventing surgery and hospitalisation, and improving patient quality of life.[2,10]

Conventional therapy

First-line pharmacologic treatment for inducing remission in patients with moderately to severely active UC is usually CT (aminosalicylates [5-ASA], thiopurines, glucocorticosteroids). Clinical advice to the EAG is that 5-ASAs are most often used in the first instance and may be combined with corticosteroids. In NHS clinical practice, there has been a move away from the use of thiopurines due to their side effect profiles. Thiopurines are unsuitable as treatments for patients in some subgroups, such as older patients, or younger patients with additional risk factors (i.e., increased risk of infection). Clinical advice to the EAG is that a substantial number of patients with moderate to severe disease are not successfully treated with CT and will move on to treatment with a biologic therapy, usually within 6 months.

Biologic therapy

According to NICE guidance, biologic therapies such as TNF-alpha inhibitors (adalimumab, infliximab, or golimumab[15]) and tofacitinib[16] can be used to treat patients with moderately to severely active UC who have had an inadequate response, lost response, or who are contraindicated to CT. Vedolizumab[17] and ustekinumab[18] are also options for patients who are not suited to, or who have contraindications to treatment with TNF-alpha inhibitors.[18]

Clinical advice to the EAG is that most patients who are eligible for treatment with a biologic agent usually receive a TNF-alpha inhibitor, such as adalimumab or infliximab, in the first instance. Both adalimumab and infliximab are available as biosimilars. Clinical advice to the EAG is that in NHS clinical practice there is access to adalimumab and infliximab drug levels and antidrug antibody assays, which enable an objective assessment to be made of treatment response through therapeutic drug monitoring. Golimumab is more expensive than adalimumab and infliximab and is therefore used infrequently in NHS clinical practice as a first-line TNF-alpha inhibitor. Drug levels and antidrug antibody assays are not available for golimumab in the NHS. Clinical advice to the EAG is that vedolizumab may be selected as a first-line biologic agent for patients where there is concern about using TNF-alpha inhibitors (i.e., for patients with prior heart failure or increased risk of infections). In line with NICE guidance,[18] ustekinumab can be used as a first-line biologic for patients who have contraindications to TNF-alpha inhibitors. Clinical advice to the EAG is that factors such as

the slow onset of vedolizumab and the known safety issues associated with any treatment are considered when making treatment decisions.

See Figure 1 for details of current NHS treatment pathway.

Upadacitinib

Clinical advice to the EAG is that if the use of upadacitinib was recommended by NICE, the management of patients with moderately to severely active UC would not change greatly but the additional treatment option, particularly for patients who have contraindications to treatment with TNF-alpha inhibitors. for whom the only alternative treatment option is ustekinumab, would be welcomed.

2.4.2 Number of patients eligible for treatment with upadacitinib

The company provided estimates of the number of patients who would be eligible for treatment with upadacitinib (Budget Impact Analysis,[19] Table 4 and Table 5). The company estimates that the total number of patients eligible for treatment with upadacitinib in Year 1 is 12,989 (including a prevalent population of 12,469 patients and an incident population of 520 patients). The EAG estimates (Table 1 and Table 2) and the company's estimates are similar. However, clinical advice to the EAG is that the proportion of patients with moderate or severe disease in Table 1 and Table 2 are higher than the proportions seen in NHS clinical practice.

Table 1 EAG estimate of the number of patients potentially eligible for treatment with upadacitinib in year 1 – prevalent population

Population	Proportion	Year 1 (2023)	Source
Adult population aged ≥18 years, England	-	45,209,976	ONS 2022[20]
Prevalence of UC in adults	0.24%	108,504	NICE resource impact template for ustekinumab[21]
Proportion of patients with moderate or severe disease	52%	56,422	NICE resource impact template for ustekinumab[21]
Total eligible for treatment with non-CT	22%	**12,412**	NICE resource impact template for ustekinumab[21]

CT=conventional therapy; ONS=Office for National Statistics; UC=ulcerative colitis
Source: adapted from the company BIA report (Table 4)[19]

Table 2 EAG estimate of the number of patients potentially eligible for treatment with upadacitinib in year 1 – incident population

Population	Proportion	Year 1 (2023)	Source
Adult population aged ≥18 years, England	-	45,209,976	ONS 2022[20]
Incidence of UC in adults	0.01%	4,521	Incidence of UC assumed to be 10 per 100,000 patient-years, derived from NICE NG130[22]
Proportion of patients with moderate or severe disease	52%	2,351	NICE resource impact template for ustekinumab[21]
Total eligible for treatment with non-CT	22%	**517**	NICE resource impact template for ustekinumab[21]

CT=conventional therapy; ONS=Office for National Statistics; UC=ulcerative colitis
Source: adapted from the company BIA report (Table 5)[19]

2.5 *Critique of the company's definition of the decision problem*

A summary of the final scope[23] issued by NICE, the decision problem addressed by the company, and EAG comments are presented in Table 3. Each parameter is discussed in more detail in the text following Table 3 (Section 2.5.1 to Section 2.5.7)

Table 3 Summary of the decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Population	People with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or who were intolerant to either conventional therapy or a biologic agent	As per scope	As per scope
Intervention	Upadacitinib	As per scope	As per scope
Comparator(s)	• TNF-alpha inhibitors (adalimumab, golimumab and infliximab) • Tofacitinib • Ustekinumab • Vedolizumab • Filgotinib (subject to ongoing NICE appraisal) • Ozanimod (subject to ongoing NICE appraisal) • Conventional therapies (including aminosalicylates, oral corticosteroids, and/or immunomodulators without biological treatments	• TNF-a inhibitors (adalimumab, golimumab, and infliximab) • Tofacitinib • Ustekinumab • Vedolizumab • The company does not consider filgotinib or ozanimod to be relevant comparators to upadacitinib as, at the time of writing, they were both subject to ongoing NICE appraisal and do not represent the standard of care for the patient population described in the final scope.[23] The EAG considers the company rationale for excluding filgotinib and ozanimod as comparators is reasonable. • The company does not consider CT as a relevant comparator, as it is usually given earlier in the treatment pathway i.e., before biologic therapy or the proposed positioning of upadacitinib.	Clinical advice to the EAG is that the exclusion of CT as a comparator to upadacitinib is reasonable. The EAG, therefore, considers that all relevant comparators have been addressed by the company. **Direct evidence** The company has presented clinical effectiveness evidence for upadacitinib from three trials; the U-ACHIEVE and U-ACCOMPLISH 8-Week induction trials, and the U-ACHIEVE 52-Week maintenance trial. All three trials compare the efficacy and safety of upadacitinib to placebo (not a comparator of interest). **Indirect evidence** In the absence of any direct evidence, the company conducted NMAs to compare the clinical efficacy of upadacitinib with TNF-alpha inhibitors (adalimumab, golimumab, infliximab), tofacitinib, ustekinumab, and vedolizumab. The EAG considers that the company NMA results can be used to inform treatment decision making if the identified methodological issues are of no major concern.

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
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 (including readmission) • Rates of surgical intervention • Endoscopic healing • Endoscopic remission combined with histological improvement • Corticosteroid-free remission • Achieving mucosal healing • Adverse effects of treatment • Health-related quality of life	As per scope Please also note that 'Endoscopic healing combined with histological improvement corticosteroid free remission' is addressed as two separate outcomes in the submission: • Endoscopic healing combined with histological improvement • Corticosteroid-free remission	**Direct evidence** The company has presented clinical effectiveness evidence from the three upadacitinib (versus placebo) trials for most of the outcomes listed in the final scope[23] issued by NICE. Rate of relapse is not presented as a clinical outcome but is estimated from the NMA results to provide a loss of response estimate for use within the company's economic model. In the upadacitinib induction trials, the primary outcome is assessed at 8 weeks. Some patients in the company's induction trials received upadacitinib for a further 8 weeks. This longer time period is more in line with the experience of patients treated in NHS clinical practice who may typically receive induction treatments for 3 to 6 months before treatments are changed due to lack of response. The company's evidence demonstrates that there is a potential benefit of extended induction period (CS, p67). **Indirect evidence** The company has provided NMA results for upadacitinib versus the relevant comparators for three of the outcomes listed in the final scope[23] issued by NICE. The outcomes addressed are clinical remission, clinical response, and safety. The company states that NMAs are conducted for three safety outcomes (including discontinuation due to AEs, SAEs and serious infections), in both the induction phase and maintenance phase (CS, Appendix D, Table 8); however, NMA results are only presented for serious infections in the induction phase.

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
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 a similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator, and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.	As per scope	The company has provided cost effectiveness results in terms of the incremental cost per quality adjusted life year gained. Outcomes were assessed over a lifetime time horizon and costs were considered from an NHS and PSS perspective.

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Other considerations	If the evidence allows the following subgroups will be considered: • people who have been previously treated with 1 or more biologics • and people who have not received a prior biologic The availability and cost of biosimilar products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic induction does not include specific treatment combinations guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	As per scope	**Direct evidence** The company has presented data from the three upadacitinib (versus placebo) trials for two patient subpopulations: (i) non-biologic inadequate responders (bio-naïve), and (ii) biologic inadequate responders (bio-exposed). Efficacy data are presented for these subpopulations for 4/12 outcomes for the induction trials, and 9/13 outcomes for the maintenance trial (see Section 7.1 and Section 7.2). Safety results are not presented separately for the two subpopulations; clinical advice to the EAG is that safety outcomes would not differ between the subpopulations. **Indirect evidence** The company has provided NMA results for upadacitinib versus relevant comparators for two subpopulations: (i) bio-naïve patients and (ii) bio-exposed patients. Data are presented for these subpopulations for three of the outcomes listed in the final scope[23] issued by NICE (Section 3.5). The EAG highlights that results for risk of serious infection are presented for the overall population only and not by prior biologic status.

AE=adverse event; CT=conventional therapy; EAG=External Assessment Group; NMA=network meta-analysis; PSS=Personal Social Services; SAE=serious adverse event; TNF=tumour necrosis factor inhibitor
Source: Final scope[23] issued by NICE and CS, Table 1

2.5.1 Source of clinical effectiveness data

Intervention

The company identified three phase 3, multi-centre, double-blind, placebo-controlled trials that provided data for the efficacy and safety of upadacitinib for patients with moderately to severely active UC. Two of the trials were 8-week induction trials (U-ACHIEVE [M14-234] sub-study 2[24] and U-ACCOMPLISH [M14-675])[25] that compared a 45mg once-daily dose of upadacitinib to placebo. The third trial (U-ACHIEVE [M14-234] sub-study 3),[26] was a 52-week maintenance trial that compared either a 15mg or a 30mg once-daily dose of upadacitinib to placebo.

Comparators

The company did not identify any relevant direct evidence comparing upadacitinib to any of the comparators listed in the final scope[23] issued by NICE, i.e., TNF-alpha inhibitors (adalimumab, golimumab, and infliximab), tofacitinib, ustekinumab, and vedolizumab. Therefore, the company generated indirect effectiveness evidence for upadacitinib versus these comparators by carrying out network meta-analyses (NMAs) using data from 18 additional trials.[27-41]

2.5.2 Population

The population described in the final scope[23] issued by NICE is people with moderately to severely active UC who have had an inadequate response, lost response, or are intolerant to either CT or a biologic agent. While no age restrictions are specified in the NICE scope,[23] the EAG highlights that the marketing authorisation of the drug is limited to adults aged 16 to 75 years old. Furthermore, the efficacy and safety of upadacitinib has not yet been established in patients ≥75 years.[42]

In the three upadacitinib trials, the company recruited patients with moderately to severely active UC defined using the Adapted Mayo score; however, in the patients recruited to the trials included in the company's NMAs, moderately to severely active UC is defined using the Full Mayo score. In response to clarification Question A3, the company stated that there is no validated scoring system to assess disease activity for patients with UC but that the Full Mayo score has historically been used in clinical trials in this disease area. The company referred to draft guidance from the Food and Drug Administration (FDA), in which the FDA questioned the value of the physician's global assessment (PGA) component of the Full Mayo score and advised that the PGA should not be used to support a marketing application.[43] The company performed an a priori analysis and found that the concordance rate between the Full Mayo

score and Adapted Mayo score, as used in the upadacitinib trials, was 94%. Clinical advice to the EAG is that the company rationale for using of the Adapted Mayo score is reasonable.

Clinical advice to the EAG is that in the NHS, disease severity is usually assessed using the SCCAI rather than the Mayo score. The Mayo score is typically used in trials but is reliant on the assessment of endoscopic appearance which is not always available in clinical practice; conversely, the SCCAI factors in the symptoms of UC that are important to patients (i.e., stool frequency, bleeding, urgency), but is not a very specific marker for active colitis. In NHS clinical practice, the SCCAI assessment is supplemented with biomarker measures and/or endoscopy. Clinical advice to the EAG is that the SSCAI and Mayo score are comparable when used to identify different severities of UC.

Patients with proctitis were excluded from the upadacitinib trials. Clinical advice to the EAG is that the exclusion of patients with proctitis is common practice in clinical trials in this disease area as the clinical symptoms of proctitis are often different to symptoms of left-sided or pan-colitis. Clinical advice to the EAG is that patients with proctitis who are treated with biologics respond in a similar way to treatment as patients with left-sided or pan-colitis.

Clinical advice to the EAG is that the baseline characteristics of patients recruited to the three upadacitinib trials are broadly representative of patients with moderately to severely active UC treated in the NHS.

2.5.3 Intervention

Upadacitinib (Rinvoq®) is a small molecule selective and reversible JAK inhibitor. The company has provided the following information about upadacitinib in the draft summary of product characteristics (SmPC):[42]

- upadacitinib is administered orally and is available as 15mg, 30mg, or 45mg prolonged-release tablets
- for the induction phase, the recommended dose of upadacitinib is 45mg once daily for 8 weeks. For patients who do not achieve adequate therapeutic benefit by Week 8, this regimen may be continued for a further 8 weeks
- for the maintenance phase, the recommended dose of upadacitinib is 15mg or 30mg once daily. For patients aged ≥65 years, the recommended dose is 15mg once daily

Upadacitinib currently has marketing authorisations for treating rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and atopic dermatitis. A marketing authorisation application was filed to the European Medicines Agency (EMA) in [redacted] for the use of upadacitinib to treat [redacted] On 19th May 2022, the EMA Committee for Medicinal Products for Human

Use adopted a positive opinion for the use of upadacitinib in UC.[44] The company expects a UK marketing authorisation to be granted in [redacted].

The Medicines and Healthcare products Regulatory Agency (MHRA) has issued a safety update[45] (October 2021) for tofacitinib, a JAK inhibitor used to treat UC. Tofacitinib should not be used in patients older than 65 years of age, people who are current or past smokers, or individuals with other cardiovascular (such as diabetes or coronary artery disease) or malignancy risk factors unless there are no suitable treatment alternatives. The increased risks associated with tofacitinib were reported in a post-marketing study conducted in patients with rheumatoid arthritis. It is not known whether the safety concerns associated with the JAK inhibitor tofacitinib will arise with the use of the JAK inhibitor upadacitinib. The results of the ongoing U-ACTIVATE[46] extension study in patients treated with upadacitinib for up to 288 weeks will provide evidence of the long term safety and efficacy of upadacitinib. The company expects that interim results from the U-ACTIVATE trial will be available in October 2022 and the final results will be available in the third quarter of 2024 (CS, p114).

The EMA safety committee is carrying out a review[47] to determine whether the risks associated with tofacitinib are also associated with all JAK inhibitors authorised in the EU for the treatment of inflammatory disorders, and whether the marketing authorisations for these medicines should be amended.

2.5.4 Comparators

The company considered that filgotinib, ozanimod, or CT were not relevant comparators to upadacitinib. The company highlights (CS, p13) that when the CS was submitted to NICE (April 2022), filgotinib and ozanimod were both subject to ongoing NICE appraisals and were therefore not recommended for use in the NHS. The EAG considers that the exclusion of filgotinib and ozanimod as comparators is appropriate. The NICE guidance for filgotinib (TA792[48]) was published in June 2022. Filgotinib is now recommended as an option for treating moderately to severely active UC in adults when conventional or biological treatment cannot be tolerated, or the disease has responded inadequately or lost response to treatment.[48] The NICE guidance for ozanimod is expected to be published in September 2022.[49] The company did not consider that CT was a relevant comparator as CT is used before biologic treatment. Clinical advice to the EAG is that the company's exclusion of CT as a comparator to upadacitinib is appropriate.

In the absence of any direct evidence, the company conducted NMAs to compare the clinical effectiveness of upadacitinib with TNF-alpha inhibitors (adalimumab, golimumab, and infliximab), tofacitinib, ustekinumab, and vedolizumab. However, the EAG has some concerns

about the NMA methods. First, for all networks, the reliability of the NMA results is unclear because the consistency assumption could not be tested formally. Second, trial design and descriptions of the intervention and placebo treatments of the included maintenance phase trials raised issues that cannot be solved. Third, the company and the EAG preferred approaches to generating NMA results are different. If these three methodological issues are of no major concern, the EAG considers that company NMA results should be used to inform decision making (Section 3.5).

2.5.5 Outcomes

The company has presented clinical effectiveness evidence from each of the three upadacitinib trials (versus placebo) for all of the outcomes listed in the final scope[23] issued by NICE, except for rate of relapse, which is not reported as a clinical outcome, but is estimated using NMAs (to provide a loss of response estimate for use in the company's economic model). Definitions of the disease-specific outcomes assessed by the company are provided in the CS (Table 8). The company addressed "endoscopic healing combined with histological improvement corticosteroid free remission" as two separate outcomes. Results for UC-related hospitalisations and UC-related surgeries are presented in the Clinical Study Reports (CSRs) for each trial.[24,25] Outcomes are presented for the induction phase up until Week 8, and for the maintenance phase up until Week 52. The length of the induction trials (8 weeks) is consistent with the trials used in previous appraisals,[5,16] however clinical advice to the EAG is that, in NHS clinical practice, the treatment induction phase typically lasts between 3 and 6 months.

The company has only carried out NMAs for a subset of the outcomes specified in the final scope[23] issued by NICE, namely clinical remission, (FMS ≤2 with no subscore >1), clinical response (decrease from baseline in FMS ≥3 points and ≥30%, accompanied by a decrease in rectal bleeding subscore [RBS] of ≥1 or an absolute RBS ≤1), and safety. The company states (CS, p80) that NMAs were conducted for three safety outcomes, namely discontinuation due to adverse events [AEs], serious adverse events [SAEs], and serious infections; however, only results of an NMA for the outcome of serious infections (in the induction phase) were presented in the CS. Except for the NMA for serious infections, all outcomes in the NMAs were assessed after an induction phase of 6 to 10 weeks, and a maintenance phase of 44 to 54 weeks.

2.5.6 Economic analysis

As specified in the final scope[23] issued by NICE, the cost effectiveness of treatment was expressed in terms of incremental cost per QALY. Outcomes were assessed over a lifetime

horizon and costs were considered from an NHS and Personal Social Services (PSS) perspective.

2.5.7 Other considerations

Subgroups

In the final scope[23] issued by NICE, it is stated that, if the evidence allows, the following subgroups should be considered:

- people who have been previously treated with one or more biologics
- and people who have not received a prior biologic

The company presented results from three trials of upadacitinib (versus placebo) for two subgroups: namely (i) Non-Bio-IR patients and, (ii) Bio-IR patients. Non-Bio-IR patients are defined as patients who had an inadequate response or intolerance to CT and included patients who had previously had a biologic therapy but had stopped for reasons other than inadequate response or intolerance. Bio-IR patients are defined as patients who have documented intolerance or inadequate response to one or more approved biologics used to treat UC. The company presented efficacy data for these two subpopulations for a subgroup of the outcomes listed in the final scope[23] issued by NICE, including four of twelve reported outcomes for the induction phase, and nine of thirteen reported outcomes for the maintenance phase (Section 7.1 and Section 7.2).

Due to the absence of direct evidence for upadacitinib versus relevant comparators, the company conducted NMAs. The results from the NMAs were presented for two subpopulations, namely (i) bio-naïve patients and, (ii) bio-exposed patients. The company presented efficacy data for each subpopulation for a subgroup of the outcomes listed in the final scope[23] issued by NICE, namely clinical remission and clinical response. The EAG highlights that results for the outcome of risk of serious infection were only presented for the overall population and not by subpopulation.

In the upadacitinib induction trials, some patients were classified as biologic-naïve who had previously received a biologic therapy ([redacted]). To ensure the comparability of the trial subpopulations, the company used upadacitinib trial patient-level data to separate patients into the biologic-naïve and biologic-exposed cohorts.

Other issues

The company does not anticipate that a NICE recommendation for the use of upadacitinib as a treatment option for eligible patients with moderately to severely active UC will raise any equality or equity issues.

Upadacitinib is available to the NHS at a discounted PAS price. Golimumab, tofacitinib, ustekinumab and vedolizumab are all available to the NHS at discounted PAS prices. Adalimumab and infliximab are available as biosimilars. The company has presented cost effectiveness estimates using the PAS price for upadacitinib and list prices (lowest available) for the comparators.

3 CLINICAL EFFECTIVENESS

3.1 *Critique of the methods of review(s)*

Full details of the methods used by the company to identify and select clinically relevant evidence to demonstrate the effectiveness of upadacitinib are presented in the CS (Appendix D). An assessment of the extent to which the review was conducted in accordance with the LR*i*G in-house systematic review checklist is presented in Table 4. The EAG conducted its own searches and did not identify any additional trials that provided information on the clinical effectiveness of upadacitinib. The EAG considers that the company's review was conducted to a good standard.

Table 4 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes, and study designs?	Yes	CS, Appendix D.1.2, Table 2
Were appropriate sources searched?	Yes	CS, Appendix D.1.1
Was the timespan of the searches appropriate?	Yes	CS, Appendix D.1.1
Were appropriate search terms used?	Yes	CS, Appendix D.1.1, Table 1
Were the eligibility criteria appropriate to the decision problem?	Yes	CS, Appendix D.1.2, Table 1, and Table 2
Was study selection applied by two or more reviewers independently?	Yes	CS, Appendix D.1.2
Was data extracted by two or more reviewers independently?	Yes	Company clarification response (Question C2)
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	CS, Appendix D.3, Table 27, and Table 28
Was the quality assessment conducted by two or more reviewers independently?	Yes	Company clarification response (Question C2)
Were attempts to synthesise evidence appropriate?	Yes	NMAs were conducted to allow a comparison of upadacitinib with appropriate comparators. The EAG summary and critique of the company's approach are presented in Section 3.5 and Section 3.6

CS=company submission; EAG=External Assessment Group; NMA=network meta-analysis
Source: LR*i*G in-house checklist

3.2 *EAG summary and critique of clinical effectiveness evidence*

3.2.1 Included trials

Three randomised controlled trials (RCTs) that provide clinical effectiveness evidence for upadacitinib versus placebo were identified: the U-ACHIEVE induction trial, the U-ACCOMPLISH induction trial and the U-ACHIEVE maintenance trial.

To compare the clinical effectiveness of treatment with upadacitinib versus the biological treatments listed in the final scope[23] issued by NICE, the company conducted NMAs. The NMAs were conducted for patients with moderately to severely active UC who had not received previous treatment with biologic drugs (Non-Bio-IR) or had received previous treatment with biologic drugs (Bio-IR). The EAG critique and discussion of the company's NMAs are presented in Section 3.5 to Section 3.6 of this EAG report. Details of the comparator trials included in the company NMAs are available in the CS (Appendix D, Section D.1.3.1.4).

3.2.2 Trials of upadacitinib: trial characteristics

U-ACHIEVE and U-ACCOMPLISH induction trials

The design of the U-ACHIEVE and U-ACCOMPLISH induction trials is identical (CS, p29). Both trials were two-part, phase 3, international, double-blind, placebo controlled RCTs. Patients recruited to the trials had moderately to severely active UC (defined as an Adapted Mayo score of 5 to 9 points and an endoscopy score of 2 to 3) and had an inadequate response, loss of response or intolerance to CT.

Permitted concomitant treatments were corticosteroids, antibiotics, 5-ASA and methotrexate. Treatment with azathioprine and 6-mercaptopurine was not permitted. The company acknowledges (CS, p118) that in the NHS, the immunomodulators azathioprine and 6-mercaptopurine are used as part of CT for patients with moderate to severe UC. Clinical advice to the EAG and to the company is that the low levels of immunomodulator use (limited to methotrexate) in the U-ACHIEVE and U-ACCOMPLISH induction trials is unlikely to affect the applicability of the trial results to UK clinical practice.

Patients were recruited to the U-ACHIEVE trial (N=474) from 199 sites in 40 countries and patients were recruited to the U-ACCOMPLISH trial (N=522) from 204 sites in 43 countries. Overall, 14 patients were recruited from the UK.

In Part 1 of the induction trials, patients were randomised in a 2:1 ratio to receive upadacitinib (45mg daily), or placebo for 8 weeks. The primary outcome was the proportion of patients who achieved clinical remission according to the Adapted Mayo score at Week 8. Randomisation factors were previous use of biologics, corticosteroid use (yes or no) and baseline Adapted Mayo score (≤7 or >7).

Patients in the induction trials were categorised into two subgroups (CS, p31):

- **Non-Bio-IR population.** Patients who had an inadequate response or intolerance to CT but who had not failed biologic therapy.
- **Bio-IR population.** Patients with documented inadequate response, loss of response, or intolerance to biologic therapy

The company provided further information about prior biologic use in the Non-Bio-IR population in response to clarification Question A1. The main reasons that patients in the Non-Bio-IR population had discontinued prior biologic treatment were related to lack of financing (e.g., no insurance cover) or the ending of a clinical study programme (Company clarification response, Table 1).

Part 2 of the induction trials was an open-label, extended induction phase. Patients in the placebo arm who had not achieved a clinical response received treatment with upadacitinib for 8 weeks and patients who had not achieved a clinical response to upadacitinib in Part 1 were able to continue with treatment for a further 8 weeks.

The company has reported results from the U-ACHIEVE and U-ACCOMPLISH trial intention-to-treat (ITT1) populations, i.e., all randomised patients who received ≥1 dose of study drug during Part 1 (CS, Table 12).

U-ACHIEVE maintenance trial

Patients who achieved a clinical response to upadacitinib at Week 8 or Week 16 of the U-ACHIEVE and U-ACCOMPLISH induction trials were recruited to the U-ACHIEVE maintenance trial. Patients were randomised in a 1:1:1 ratio to receive upadacitinib 15mg daily, upadacitinib 30mg daily, or placebo for 52 weeks. Randomisation was stratified by previous biologic use (yes or no) at Week 0, clinical remission status (yes or no) at Week 0 and corticosteroid use (yes or no) at Week 0. The primary endpoint was the proportion of patients who achieved clinical remission (measured by the Adapted Mayo score) at Week 52.

Four patient cohorts from the U-ACHIEVE maintenance trial are identified in the CS. The company highlights (CS, p33) that only Cohort 1 is of relevance to this appraisal. This cohort included the 847 patients who were randomised to the placebo arm or the lower and higher maintenance doses of upadacitinib (15mg and 30mg daily).

The company reports results from the U-ACHIEVE maintenance trial ITT_A population. The ITT_A population (n=451) is a subset of the 847 patients in Cohort 1. The 451 patients were the first randomised patients who responded to treatment with 45mg upadacitinib at 8 weeks (CS, Table 13). The ITT_A population includes 271 patients from the U-ACHIEVE induction

trial, 158 patients from the U-ACCOMPLISH induction trial and 21 patients from a dose-ranging phase 2b substudy of the U-ACHIEVE trial.

3.2.3 Patient characteristics

The baseline characteristics of patients recruited to the U-ACHIEVE and U-ACCOMPLISH induction trials (ITT1 population), and to the U-ACHIEVE maintenance trial (ITT_A population) are presented in the CS (Table 10). The EAG agrees with the company that the patient baseline characteristics are well-balanced between arms. Clinical advice to the EAG is that the patients recruited to the trials are generally representative of patients treated in NHS clinical practice who have moderately to severely active UC.

The number of prior medications (related to UC) that patients in the U-ACHIEVE and U-ACCOMPLISH induction trials (ITT1 population) and the U-ACHIEVE maintenance trial (ITT_A population) had received are presented in the CS (Table 11). Clinical advice to the EAG is that these treatments are in line with treatments used in NHS clinical practice.

3.2.4 Quality assessment

The company conducted a quality assessment of the U-ACHIEVE and U-ACCOMPLISH induction trials and the U-ACCOMPLISH maintenance trials using the minimum criteria recommended by NICE.[50] The results are presented in the CS (Table 21). The company also conducted a risk of bias assessment using the Cochrane Risk of Bias tool.[51] The results of this assessment are presented in the CS (Appendix D2).

The EAG considers that the three trials are of good methodological quality. The company reports that there were unexpected imbalances in dropouts between trial arms in all three trials. In the U-ACHIEVE induction trial, 4.1% of patients in the upadacitinib arm discontinued the trial, compared with 13.0% of the patients in the placebo arm. In the U-ACCOMPLISH induction trial, 3.2% of patients in the upadacitinib arm discontinued the trial compared with 7.5% of the patients in the placebo arm. The proportion of patients discontinuing the U-ACHIEVE maintenance trial was 33.1% (upadacitinib 15mg) versus 21.4% (upadacitinib 30mg) versus 65.8% in the placebo arm. The main reason for discontinuation in the placebo arm and the upadacitinib 15mg arm of the U-ACHIEVE maintenance trial was lack of efficacy.

3.2.5 Statistical approaches used to analyse data

In addition to the information provided in the CS, information relevant to the statistical approaches taken by the company to analyse trial data has been extracted from the CSRs,[24-26] the trial statistical analysis plans[52-54] (TSAP) and the trial protocols.[55,56] The EAG considers that the approaches adopted by the company were appropriate.

3.3 *Upadacitinib induction trials: efficacy results*

The primary endpoint of the induction trials was the proportion of patients who achieved clinical remission per Adapted Mayo score at Week 8. The population of interest in the CS is the ITT1 population, i.e., patients randomised to receive upadacitinib or placebo in Part 1 of the induction trials. The results for the primary endpoint for the ITT population and the Non-Bio-IR and Bio-IR populations are provided in the CS (Table 22). Results for the key secondary endpoints for the ITT population are provided in the CS (Table 23) and results for the Non-Bio-IR and Bio-IR populations for three key secondary endpoints (endoscopic improvement, endoscopic remission, clinical response per adapted Mayo score) are provided in the CS (Table 24). A summary of the outcomes is presented in Table 48 (Appendix 7.1).

For all outcomes (primary and secondary) and all patients (ITT, Non-Bio-IR and Bio-IR), the adjusted results favoured upadacitinib versus placebo. The results of the health-related quality of life (HRQoL) outcomes (measured using the Functional Assessment of Chronic Illness Therapy [FACIT-F] questionnaire and the Inflammatory Bowel Disease Questionnaire [IBDQ]) also favoured treatment with upadacitinib versus placebo.

Hospitalisations and surgery

In the U-ACHIEVE trial, [redacted] patients experienced UC-related hospitalisations, [redacted] patients from the upadacitinib arm and [redacted] patients from the placebo arm. In the U-ACCOMPLISH trial, [redacted] patients experienced UC-related hospitalisations, [redacted] patients from the upadacitinib arm and [redacted] patients from the placebo arm.

In the U-ACCOMPLISH trial, [redacted] patients experienced UC-related surgeries, [redacted] patients from the upadacitinib arm and [redacted] patient from the placebo group. [redacted] of the patients in the U-ACHIEVE trial experienced UC-related surgery.

3.3.1 U-ACHIEVE maintenance trial: efficacy results

The results for the primary endpoint for the ITT_A, Non-Bio-IR and Bio-IR populations are provided in the CS (Table 25). Key secondary endpoint results for the ITT_A population are provided in the CS (Table 26) and key secondary endpoint results for the Non-Bio-IR and Bio-IR subpopulations are provided in the CS (Table 27). A summary of the results is presented in Table 49 (Appendix 7.2) of this EAG report.

In the ITT_A population, all the adjusted results favoured upadacitinib versus placebo. In the Non-Bio-IR and Bio-IR populations, the adjusted results for the primary outcome favoured upadacitinib versus placebo, as did most of the adjusted results for the secondary outcomes. The exceptions were in the 15mg upadacitinib arm of the Non-Bio-IR group (CS, p72), namely:

- clinical remission per Adapted Mayo score at Week 52 among patients who achieved clinical remission per Adapted Mayo score in the U-ACHIEVE induction or U-ACCOMPLISH induction trials
- clinical remission per Adapted Mayo score and corticosteroid free for ≥90 days at Week 52 among patients in clinical remission at the end of the U-ACHIEVE or U-ACCOMPLISH induction trials
- mucosal healing at Week 52.

The results of the HRQoL outcomes also favoured treatment with upadacitinib versus placebo.

Hospitalisations and surgery

[redacted] patients experienced UC-related hospitalisations, [redacted] patient from the upadacitinib 15mg arm,[redacted] patients from the upadacitinib 30mg arm and [redacted] patients from the placebo arm. Overall,[redacted] patients experienced UC-related surgeries, [redacted] patient from the upadacitinib 30mg arm and [redacted] patient from the placebo arm.

3.4 *Safety results*

Direct evidence

The EAG highlights that induction trial safety data were collected from the patients who responded to treatment after 8-weeks, and not patients who continued treatment with upadacitinib for up to 16-weeks (as part of the extended treatment phase).

The company has presented safety data from the three upadacitinib trials (versus placebo) in the CS (Section B.2.10 and Appendix F). An overview was provided of all AEs, AEs in ≥2% of patients, SAEs, adverse events of special interest (AESIs), and AEs leading to discontinuation of the study drug for the 8-week induction trials and the 52-week maintenance trial (CS, Table 42 to Table 51). All reported AEs were treatment-emergent AEs (TEAEs), unless otherwise specified.

In brief, upadacitinib 45mg was generally well-tolerated in the 8-week induction trials. AEs were lower for upadacitinib 45mg compared to placebo in the U-ACHIEVE trial ([redacted] versus [redacted] respectively), but not in the U-ACCOMPLISH trial ([redacted] and [redacted] respectively) (CS, Table 42). In both induction trials, upadacitinib 45mg had numerically lower rates than placebo for SAEs, severe AEs, and AEs leading to discontinuation of the study drug (CS, Table 42). No deaths were reported in patients who received upadacitinib 45mg or placebo for either of the induction trials during the initial 8-week period. A summary of the rates and types of AEs reported in the induction trials is presented in the Appendix (Section 7.3.1) to this EAG report.

Upadacitinib (15mg and 30mg) also seemed well tolerated in the 52-week maintenance trial, where the rates of any AEs were similar for patients receiving upadacitinib 15mg or 30mg or

placebo ([redacted] and [redacted] versus [redacted] respectively). Treatment with upadacitinib (15mg and 30mg) had lower rates than placebo of SAEs ([redacted] and [redacted] versus [redacted] respectively), severe AEs ([redacted] and [redacted] versus [redacted] respectively), and AEs leading to discontinuation of the study drug ([redacted] and [redacted] versus [redacted] respectively). There were no deaths reported in patients who received upadacitinib (15mg or 30mg) or placebo during the 52-week maintenance trial. A summary of the rates and types of AEs reported in the induction trials is presented in the Appendix (Section 7.3.2) to this EAG report.

The EAG highlights that the conclusions that can be drawn from induction trial safety data are limited due to the short duration (up to 8 weeks) over which events were recorded.

Overall, clinical advice to the EAG is that there appear to be no concerns with the safety profile of upadacitinib compared to other targeted therapies for inflammatory bowel disease, and no concerns that would prompt additional monitoring during treatment with upadacitinib.

Indirect evidence

The company conducted an NMA comparing the risk of serious infection for upadacitinib versus other relevant comparators, including TNF-alpha inhibitors (adalimumab, golimumab, and infliximab), tofacitinib, ustekinumab and vedolizumab (CS, Section B.2.9.6.1, Table 37). The EAG highlights that the NMA results are not provided separately for the bio-naïve or bio-exposed populations. An EAG summary and critique of the company's NMAs are provided in Section 3.5 to Section 3.6 of this EAG report.

3.5 *EAG summary and critique of the indirect evidence*

The primary objective of the company NMAs was to compare the relative efficacy of upadacitinib versus TNF-alpha inhibitors (adalimumab, golimumab, and infliximab), tofacitinib, ustekinumab, and vedolizumab in adults with moderately to severely active UC who have had an inadequate response, loss of response or were intolerant to either CT or a biological agent.

To ensure comparability with other relevant NMAs, the company performed separate NMAs for three populations i.e., bio-naïve, bio-exposed and overall populations. The company conducted NMAs for a subset of the outcomes specified in the final scope[23] issued by NICE (Table 5). All the outcomes assessed were binary. The EAG highlights that three different AE NMAs (for the induction phase and maintenance phase) are listed in the CS (Appendix D, Table 8), namely discontinuations due to AEs, serious AEs, and serious infections; however, the company has only provided a single set of NMA results for induction phase serious infections.

Table 5 Main network meta-analyses carried out by the company*

Population	Induction phase data (Duration: 6-10 weeks)	Maintenance phase data (Duration: 44-54 weeks)
Bio-naive	Clinical remission Clinical response	Clinical remission Clinical response
Bio-exposed	Clinical remission Clinical response	Clinical remission Clinical response
Overall population	Serious infections	-

*The company planned to carry out treatment discontinuation due to AEs and SAE NMAs (CS, Appendix D), no results were reported in the CS or in the CS appendices
AEs=adverse event; CS=company submission; NMA=network meta-analysis; SAE=serious adverse event
Source: CS, Appendix D, Table 6

3.5.1 Trials included in the company NMAs

The company carried out a global systematic literature review (SLR) to identify relevant RCTs reporting on the efficacy and safety of upadacitinib and other relevant trials for patients with moderately to severely active UC. Full details of the global SLR are presented in the CS (Appendix D). After application of extensive inclusion/exclusion criteria and a feasibility assessment, 20 original studies (46 records) were eligible for inclusion in the company NMAs; a summary of the key characteristics of these 20 studies was included in the CS (Appendix D, Table 6). The EAG considers that reasons for excluding records during the review process were not always clearly documented; however, the EAG is satisfied that the SLR methods used by the company were mostly appropriate.

A full reference list of the 20 included trials is presented in the CS (Appendix D, Table 4). These studies provide efficacy and safety data for the following treatments:

- infliximab (5 trials)[27-30]
- adalimumab (4 trials)[31-34]
- golimumab (3 trials)[35,37,38]
- vedolizumab (2 trials)[36,39]
- ustekinumab (1 trial)[40]
- tofacitinib (3 trials)[41]
- upadacitinib (2 trials; U-ACHIEVE induction and maintenance, and U-ACCOMPLISH induction)[24-26]

The information presented in Table 6 shows the numbers of RCTs included in the company NMAs, as described in the main body of the CS. The company SLR identified more bio-naïve population RCT data than bio-exposed population RCT data, and more induction phase RCT data than maintenance phase RCT data. The company excluded the VARSITY[57] trial (adalimumab versus vedolizumab) from the NMAs on the grounds that is designed as a treat-through trial (CS Appendix D, Table 5); however, other treat-through trials were included in

the NMAs. The EAG considers that the 52 week maintenance data from the VARSITY[57] trial could have been included in the NMAs.

Table 6 Number of trials included in the company network meta-analyses

Population	Induction phase data (Duration: 6-10 weeks)		Maintenance phase data (Duration: 44-54 weeks)	
Bio-naive	Clinical remission (n=16)	Adalimumab (n=3)[31-33] Golimumab (n=1)[37] Infliximab (n=5)[27-30] Tofacitinib (n=2)[41] Upadacitinib (n=2)[24,25] Ustekinumab (n=1)[40] Vedolizumab (n=2)[36,39]	Clinical remission (n=8)	Adalimumab (n=1)[32] Golimumab (n=2)[35,37] Infliximab (n=1)[27] Upadacitinib (n=1)[26] Ustekinumab (n=1)[40] Vedolizumab (n=2)[36,39]
	Clinical response (n=16)	Adalimumab (n=3)[31-33] Golimumab (n=1)[37] Infliximab (n=5)[27-30] Tofacitinib (n=2)[41] Upadacitinib (n=2)[24,25] Ustekinumab (n=1)[40] Vedolizumab (n=2)[36,39]	Clinical response (n=8)	Adalimumab (n=1)[32] Golimumab (n=2)[35,37] Infliximab (n=1)[27] Upadacitinib (n=1)[26] Ustekinumab (n=1)[40] Vedolizumab (n=2)[36,39]
Bio-exposed	Clinical remission (n=7)	Adalimumab (n=1)[32] Tofacitinib (n=2)[41] Upadacitinib (n=2)[24,25] Ustekinumab (n=1)[40] Vedolizumab (n=1)[39]	Clinical remission (n=4)	Adalimumab (n=1)[32] Upadacitinib (n=1)[26] Ustekinumab (n=1)[40] Vedolizumab (n=1)[39]
	Clinical response (n=6)	Adalimumab (n=1)[32] Tofacitinib (n=2)[41] Upadacitinib (n=2)[24,25] Vedolizumab (n=1)[39]	Clinical response (n=3)	Adalimumab (n=1)[32] Upadacitinib (n=1)[26] Vedolizumab (n=1)[39]
Overall	Serious infections (n=12)	Adalimumab (n=3)[31-33] Golimumab (n=1)[38] Infliximab (n=1)[28] Tofacitinib (n=2)[41] Upadacitinib (n=2)[24,25] Ustekinumab (n=1)[40] Vedolizumab (n=2)[36,39]	-	-

Source: CS, Table 30 to Table 32

3.5.2 Quality assessment of the trials included in the NMAs

The company quality assessed the trials included in the NMAs using the minimum criteria recommended by NICE[50] and the Cochrane Risk of Bias[51] tool. The company quality assessments and EAG comments are presented in Appendix 7.4. The company and the EAG agree that the two main areas of concern were the lack of blinding of providers, patients or outcome assessors, and the handling of missing data. In addition, the EAG notes that, in trials where mixed populations were enrolled, patient characteristics were often only reported for

the overall population; the EAG therefore considers the assessment of baseline patient comparability is challenging.

Overall, the EAG agrees with the company and considers that the quality of the trials included in the NMAs was acceptable.

3.6 *Methodological approach to the NMAs*

The company explains (CS, p82) that for each feasible network, NMAs were conducted in a Generalised Linear Model framework using Bayesian Markov Chain Monte Carlo simulations and three chains with 100,000 runs each, with a burn-in that was half of the convergence sequence (set size of 10,000). The company assessed convergence using the Brooks-Gelman-Rubin method (Potential Scale Reduction Factor). All binary response outcomes were modelled with a binomial likelihood and logit link function.

3.6.1 Summary of company NMA model choices

Four models were fitted to each network: fixed-effect (FE), random effects (RE), fixed effects with baseline-risk adjustment (FEA) and random effects with baseline risk adjustment (REA). Models were selected based on model fit statistics (i.e., residual deviance, pD and deviance information criterion), leverage plots and density plots of posterior standard deviation; full details of the company model selection process are available from the clarification response (Table 13). When model fit statistics were similar for FE and RE models (CS, Appendix D, D.1.3.2.4, p57), the company chose the RE model. Models adjusted for baseline risk were selected when a baseline risk statistically significantly modified treatment effects; however, in many cases, models that adjusted for baseline risk could not be fitted to the data because of data limitations (company clarification response, Table 13).

3.6.2 Potential sources of heterogeneity across the trials included in the NMAs

The EAG has identified general sources of potential heterogeneity across the RCTs included in the NMAs, namely (i) study population and trial characteristics (ii) outcomes and (iii) maintenance study design.

(i) Study population and trial characteristics

Biologic experience

The company carried out NMAs for bio-naïve and biologic-exposed populations. However, some trials included in the NMAs reported outcomes for bio-naive versus bio-exposed populations and by prior experience with TNF-alpha inhibitors (mainly older RCTs) or treatment with vedolizumab rather than more generally by patient experience with biologics.

The CS does not provide the number of studies that used different definitions or results of sensitivity or subgroup analyses to assess the impact on these different population definitions on results.

Disease severity and ethnicity

Disease severity (i.e., how RCTs defined 'moderately to severely active UC' in the eligibility criteria) and ethnicity (i.e., several studies included predominantly Asian populations) could also be considered as potential important sources of heterogeneity. Clinical advice to the EAG is that these two sources are not of concern. The EAG agrees with this advice as, during TA633,[18] the ERG concluded that excluding Asian trials from the NMAs had a minor impact on results.

Specific patient and trial characteristics

Key characteristics of the designs of the trials used in the NMAs are provided in the CS (Appendix D, Table 6). The company additionally provided the baseline patient and disease characteristics of patients recruited to each of the included trials used in the NMAs (company clarification response, Table 3 and Table 4); data were presented separately for the bio-naïve and bio-exposed patients where available.

The induction phase trials ranged in duration from 6 weeks to 10 weeks. Half[27-31,33,37] of the trials enrolled bio-naïve patients only, while the remaining trials[24,25,32,36,39,40,58] enrolled a mixed patient cohort of biologic-naïve and biologic-exposed patients. A comparison of the baseline patient and disease characteristics across each of the arms of the trials included in the induction phase NMAs, showed that patients were of a comparable age (range from 34.3[29] to 44.4[24] years); however, disease duration (mean 3.7[30] to 9.1[24] years), C-reactive protein levels (mean 2.2[33] to 35.8[29]), the proportion of patients with extensive colitis or pan-colitis (37.5%[27] to 80.8%[28]), and the levels of use of concurrent medication (immunomodulators: 0.3%[25] to 54.5%,[27] steroids: 30.5%[39] to 80.0%[30]) varied.

The maintenance trials ranged in duration from 44 weeks to 54 weeks. Four[27,33,35,38] of the trials enrolled bio-naïve patients only, while the remaining trials[26,32,36,39-41] enrolled both biologic-naïve and biologic-exposed patients. Only three[27,32,33] of the trials used a treat-through (TT) study design, with the remaining trials[26,35,36,38-41] re-randomising patients who entered the maintenance phase. A comparison of the baseline patient and disease characteristics across each of the arms of the trials included in the maintenance phase NMAs, showed that the mean ages of patients were comparable (range from 38.3[36] to 45.2[41] years); however, there was variation between trials in disease duration (mean 5.4[35] to 9.9[41] years), C-reactive protein levels (mean 0.7[41] to 17.0[27]), the proportion of patients with extensive colitis or pan-colitis

(33.3%[36] to 68.3%[39]), and levels of concurrent medication (immunomodulators: 0.0%[24] to 54.5%,[27] steroids: 28.1%[35] to 65.3%[27]).

To explore whether (measured and unmeasured) study population and trial characteristics that could collectively influence a patient's response to treatment could impact on the relative effects of treatments, the company fitted FE and RE NMA models that adjusted for baseline risk/differences in mean placebo effects across studies (FEA and REA respectively). However, most of the adjusted models could not be fitted because of limited data; only 2/8 FEA models converged and only 3/8 of the REA models converged (company clarification response, Table 13).

The company demonstrated that the relative effects of treatments were significantly modified by baseline risk for the patients in the induction/bio-naïve/clinical response NMA i.e., baseline risk is a treatment-effect modifying characteristic and could therefore violate the consistency assumption for this NMA. The company appropriately reported FEA NMA results for these patients. However, as most of the adjusted models could not be fitted due to limited data, the consistency assumption could also be violated for the other NMAs. Formal statistical methods to assess the presence of inconsistency in the NMAs cannot be applied because of the star shaped nature of the networks (i.e., there is a lack of head-to-head trials). The EAG disagrees with the comment made by the company that there is very little evidence of inconsistency. Therefore, the EAG considers that, from a statistical perspective, the validity of the consistency assumption and the reliability of the NMA results are unknown. However, clinical advice to the EAG is that despite the differences in study population and trial characteristics, the RCTs included in the NMAs are appropriate sources of clinical data for decision making.

(ii) Outcomes

FMS/AMS definitions

The company highlights (CS, Appendix D, p33) that, to assess clinical remission and clinical response, some of the included trials used the Full Mayo Score (FMS) and other trials used Adapted Mayo Score (AMS). Clinical advice to the EAG is that including trials in the NMAs reporting either FMS or AMS is not of concern.

Duration of trial follow up periods

Trials were eligible for inclusion in the induction NMAs when outcomes were reported over durations of 6 to 10 weeks (upadacitinib trials: 8 weeks) and maintenance phase outcomes were reported over durations of 44 to 54 weeks (upadacitinib trial: 52 weeks). In submissions for previous NICE appraisals (TA547[16] and TA633[18]), it has been assumed that, over these durations, outcomes are broadly comparable. As highlighted during these NICE

appraisals,[16,18] even within these ranges, there is the possibility of bias against outcome data reported over a shorter induction phase and bias in favour of outcomes reported over a shorter maintenance phase. It is not possible to adjust for this source of heterogeneity. Clinical advice to the EAG is that the identified differences in study duration would not have a large effect on the NMA results.

Handling of missing outcome data

The company used non-response imputation to handle missing outcome data. This is a commonly employed approach for binary outcomes and involves assuming that subjects with missing data at scheduled assessment visits are considered as 'not achieved'. The EAG considers that the company approach is reasonable.

When analysing data from the three upadacitinib trials, the company also incorporated multiple imputation to handle missing data due to COVID-19. The company did not provide full details of the multiple imputation methods used. The EAG is therefore unable to comment on the validity of the company approach.

The company did not report the results of any sensitivity analyses that may have been carried out to assess the robustness of NMA results to assumptions made about missing data (e.g., excluding trials for which data were imputed).

(iii) Maintenance study design

Treat-through versus re-randomised responder design

The trials included in the company maintenance NMAs were of two different designs (treat through (TT) [n=3][27,32,33] and re-randomised (RR) [n=17]). Patients enrolled in the TT trials were randomised at baseline to treatment or placebo and had outcomes measured at the end of the induction phase and measured again at the end of the maintenance phase. Patients enrolled in the RR trials were randomised to treatment or placebo at baseline, with outcomes measured at the end of the induction phase; induction responders were then randomised to maintenance treatment or placebo, with outcomes measured at the end of the maintenance phase. Thus, not all the patients enrolled in the TT trials had responded to the treatment assigned during the induction phase whilst all patients in the RR maintenance trials had responded to induction treatment. This means that adopting a standard NMA approach for maintenance outcomes is inappropriate.

To make baseline outcome data from studies with different designs more comparable, the company adjusted data from the three TT trials to mimic data from the RR trials by using the number of induction responders as the number of patients entering the maintenance phase. A criticism of this approach is that it ignores any non-responders at the end of the induction

phase who might become responders by the end of the maintenance phase. When induction responder data were not reported in the TT trials, the values included in the company NMAs were estimated using the same approach adopted by the ERG during TA633;[18] the full details of this approach are not presented in the CS.

The EAG agrees that adjusting data from the three TT trials[27,32,33] is preferable to adjusting the data from the 17 RR trials based on the number of studies requiring the adjustment. However, the EAG considers the reliability of the method used by the company to re-calculate the RCT data (from TT to RR) is unknown.

The EAG notes that the company did not carry out any sensitivity analyses designed to exclude the TT trials[27,32,33] to assess the impact of this approach on the NMA results.

Heterogeneity in maintenance placebo arms of trials included in the NMAs

The EAG notes that the validity of the maintenance NMA results has been discussed by several NICE Appraisal Committees.[48] Most importantly, the company highlighted that the placebo arms of trials included in the company maintenance NMAs are fundamentally different. Over and above the difference due to differential trial designs (including outcome definitions), the company identified the following issues:

- patients in the placebo arms had received and responded to different induction treatments with potentially different persistence effects after treatment has ended
- some of the placebo arm patients had received and responded to placebo induction (TT studies and OCTAVE SUSTAIN [tofacitinib]), i.e., patients had effectively 'skipped' the induction phase

The company considers that these placebo group differences are of concern if placebo responders are less able to sustain their response or if they are potentially more susceptible to active treatment.

As per discussions at the recent NICE appraisal[48] of filgotinib to treat UC, the company recognised that heterogeneity in the maintenance placebo arms of the trials included in the NMAs was important to consider as it meant that judging the relative effectiveness of treatments beyond the period of induction was problematic. However, neither the company (nor the EAG) could identify a solution which would remove the uncertainty associated with the maintenance NMA results.

3.6.3 EAG comment on company choice of model fit for specific comparisons

The company identified the FEA model as being the most appropriate model for the induction/bio-naïve/clinical response NMA because baseline risk significantly modified the treatment effects. The EAG considers that this approach was appropriate.

For all other NMAs, the company identified the RE model as being the most appropriate model. The company did not always fit the same RE model. For example, for the induction/bio-exposed/clinical remission comparison, the company used an exchangeable baseline assumption with a half-normal (0, 0.32^2) prior distribution for the variance parameter as the network had one or more placebo arm(s) with no events. The EAG (and NICE guidance)[59] considers that independent baseline assumptions are preferred to exchangeable baseline assumptions when conducting NMAs. In addition, without evidence to support use of the company's informative prior distribution for the variance parameters, the EAG cannot comment on the reliability of this approach.

For all other RE NMAs, the company used an independent baseline assumption with a half-normal (0, 0.32^2) prior distribution as most (≥50% of interventions) in the network were informed by a single study. As the company provided limited evidence to support the use of an informative prior distribution for the between trial variance, the EAG cannot comment on the reliability of this approach.

The EAG therefore compared the model fit statistics for RE and FE models and concluded that the models were similar. As there were very few studies within each of the company NMA networks that made the same treatment comparison, the EAG preferred the FE NMA over the RE NMA model; when there are limited data upon which to estimate the between trial variance parameter, RE NMA results are often uncertain. However, the EAG recognises that, due to the many differences between the trials included in the NMAs, the FE model might underestimate heterogeneity.

As the company provided all the NMA data inputs as part of the clarification response, the EAG was able to replicate all the company's RE NMA results. The EAG then generated both (EAG) RE and (company/EAG) FE NMA results for all efficacy comparisons performed by the company (comparator versus upadacitinib), see Table 8 to Table 12 for EAG NMA results.

For all except the induction/bio-exposed/clinical remission NMA, the EAG (RE and FE) and the company (RE) results were similar in terms of point estimates; however, for some comparisons, EAG (RE or FE) NMA results statistically significantly favoured upadacitinib over a comparator when the company results did not demonstrate this same statistical advantage.

The EAG and company results from the induction/bio-exposed/clinical remission NMA, are very different; the company RE NMA results (exchangeable baseline assumption half-normal [0, 0.32^2] prior for the variance parameters) produce less favourable results for upadacitinib versus all comparators compared to the EAG RE NMA results (independent baseline assumption with uniform [0, 0.5] prior for the between trial variance), as per NICE guidance,[59] and compared to EAG FE NMA results. However, clinical advice to the EAG is that the company RE NMA results better reflect NHS clinical experience with these treatments. When results from models that make different assumptions generate substantially different results, then the limitations of the data should be explicitly considered if these data are to be used to inform decision

In summary, where the company and EAG NMA results are similar, the EAG considers that both sets of results can be used to inform decision making. Where, the company and the EAG results differ, the EAG is minded to be led by clinical advice (and focus on the company RE NMA results); data inputs into this specific NMA include zero values for placebo arms which, using the approach recommended by NICE guidance,[59] may have contributed to the generation of optimistic EAG FE and RE NMA results for upadacitinib versus comparators.

The company carried out quality assessments of all studies included in the company NMAs using two different tools (user guide for company evidence submission template[50] and Cochrane Risk of Bias[51] tool). However, the company did not report the results of any sensitivity analyses that were used to test whether removing studies with some risk of bias concerns from the NMAs influenced the NMA results.

3.7 *Results from the company NMAs*

In the CS, the company provided NMA results for combinations of different populations (bio-naïve and bio-exposed), different treatment phases (induction and maintenance) and different outcomes (clinical remission, clinical response and serious infection). For nine combinations of population, treatment phase and outcomes, results were presented as relative effect estimates of all relevant interventions versus placebo (odds ratios), surface under the cumulative ranking curve (SUCRA) values for each treatment and predicted absolute mean outcome rates for each treatment. The locations in the CS of these NMA results are shown in Table 7.

Table 7 Location of company NMA results (upadacitinib versus placebo)

Treatment phase	Population	Outcome	Location in CS	Model
Induction	Bio-naive	Clinical remission	Table 33	RE
		Clinical response	Table 35	FEA
	Bio-exposed	Clinical remission	Table 34	RE
		Clinical response	Table 36	RE
	Overall	Serious infections	Table 37	RE
Maintenance	Bio-naive	Clinical remission	Table 38	RE
		Clinical response	Table 40	RE
	Bio-exposed	Clinical remission	Table 39	RE
		Clinical response	Table 41	RE

CS=company submission; FEA=fixed-effect model with baseline–risk adjustment; RE=random effects

In summary, results from the company induction NMAs showed that upadacitinib was the best performing intervention versus placebo for clinical remission and clinical response. The results from the company's maintenance NMAs showed that upadacitinib 30mg ranked within the top three for all outcomes whereas upadacitinib 15mg ranked within the top four for all outcomes apart from maintenance/bio-naïve/clinical remission where it ranked 6th with a non-statistically significant OR vs. placebo.

As part of the clarification response (Question A5), the company provided median odds ratio and credible intervals for each comparator versus upadacitinib; these efficacy NMA results are presented in Table 8 to Table 12. The company used RE models for all NMAs except for the induction/bio-naive/response comparison where the company used a FEA NMA model. The EAG considers this FEA model choice was appropriate but prefers the use of an independent, rather than an exchangeable baseline; the EAG's results are not presented.

For the induction/bio-naïve/remission comparison, the EAG considers the company's choice of RE model is appropriate. The EAG and the company RE NMA results are the same; the EAG's results are not presented.

For all other comparisons, the company preferred RE NMA results, the EAG preferred FE NMA results. The company did not present FE NMA results; however, as the company and EAG FE results use the same methods, the company and EAG FE NMA results are expected to match and are presented in Table 8 to Table 12. For completeness and comparison, EAG RE NMA results for these comparisons are also included in these tables.

Table 8 Pairwise comparisons for company induction NMAs: comparator versus UPA (45mg), median odds ratio and 95% credible interval

Drug/ Outcome	IFX 10mg§	IFX 5mg§	VED 300mg	ADA 160/80mg	TOF 10mg	GOL 200/100mg	UST 6mg§	PBO
Bio-naïve population								
Clinical remission (company and EAG RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (company FEA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic-exposed population								
Clinical remission (company RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission (EAG FE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission (EAG RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (company RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (company/EAG FE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (EAG RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NB Odds ratio<1, result favours UPA
§ dose reflects mg per kg of body weight
ADA=adalimumab; EAG=External Assessment Group; FE=fixed-effect model; FEA=fixed-effect adjusted model; GOL=golimumab; IFX=infliximab; kg=kilograms; mg=milligrams; NMA=network meta-analysis; PBO=placebo; RE=random effect model; TOF=tofacitinib; UPA=upadacitinib; UST=ustekinumab; VED=vedolizumab
Source: Company clarification response, Table 5 to Table 8

Table 9 Pairwise comparisons for company maintenance NMAs: UPA (15mg) versus comparators, median odds ratio and 95% credible interval

Drug/ Outcome	IFX 10mg§	IFX 5mg§	VED 300mg Q4W	VED 300mg Q8W	TOF 10mg	TOF 5mg	GOL 100mg	GOL 50mg	UPA 30mg	ADA 40mg Q2W	UST 90mg Q12W	UST 90mg Q8W	PBO
Biologic-naïve population													
Clinical remission (company RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission (company/ EAG FE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission (EAG RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (company RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (company/ EAG FE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (EAG RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NB Odds ratio<1, result favours UPA
§ dose reflects mg per kg of body weight
ADA=adalimumab; GOL=golimumab; IFX=infliximab; kg=kilogram; mg=milligrams; NMA=network meta-analysis; PBO=placebo; Q2W=every other week; Q8W=every 8 weeks; Q12W=every 12 weeks; TOF=tofacitinib; UPA=upadacitinib; UST=ustekinumab; VED=vedolizumab
Source: Company clarification response, Table 9 to Table 12

Table 10 Pairwise comparisons for company maintenance NMAs: comparator versus UPA (15mg), median odds ratio and 95% credible interval

Drug/ Outcome	VED 300mg Q4W	VED 300mg Q8W	TOF 10mg	TOF 5mg[§]	UPA 30mg	ADA 40mg Q2W	UST 90mg Q12W	UST 90mg Q8W	PBO
Bio-exposed population									
Clinical remission (company RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission (company/ EAG FE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission (EAG RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (company RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (company/ EAG FE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (EAG RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NB Odds ratio<1, result favours UPA
[§] dose reflects mg per kg of body weight
ADA=adalimumab; EAG=External Assessment Group; FE=fixed-effects model; kg=kilogram; mg=milligrams;NMA=network meta-analysis; PBO=placebo; Q2W=every other week; Q4W=every four weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; RE=random effect model; TOF=tofacitinib; UPA=upadacitinib; UST=ustekinumab; VED=vedolizumab
Source: Company clarification response, Table 9 to Table 12

Table 11 Pairwise comparisons for company maintenance NMAs: comparator versus UPA (30mg), median odds ratio and 95% credible interval

Drug/ Outcome	IFX 10mg§	IFX 5mg§	VED 300mg Q4W	VED 300mg Q8W	TOF 10mg§	TOF 5mg§	GOL 100mg	GOL 50mg	UPA 15mg	ADA 40mg Q2W	UST 90mg Q12W	UST 90mg Q8W	PBO
Bio-naïve population													
Clinical remission (company RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission (company/ EAG FE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission (EAG RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (company RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (company/ EAG FE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (EAG RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NB Odds ratio<1, result favours UPA
§ dose reflects mg per kg of body weight
ADA=adalimumab; EAG=External Assessment Group; FE=fixed-effects model; GOL=golimumab; IFX=infliximab; kg=kilograms; mg=milligrams; NE=not estimated; NMA=network meta-analysis; PBO=placebo; Q2W=every other week; Q4W=every four weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; RE=random effect model; TOF=tofacitinib; UPA=upadacitinib; UST=ustekinumab; VED=vedolizumab
Source: Company clarification response to Table 9 to Table 12

Table 12 Pairwise comparisons for company maintenance NMAs: comparator versus UPA (30mg), median odds ratio and 95% credible interval

Drug/ Outcome	VED 300mg Q4W	VED 300mg Q8W	TOF 10mg§	TOF 5mg§	UPA 15mg	ADA 40mg Q2W	UST 90mg Q12W	UST 90mg Q8W	PBO
Bio-exposed population									
Clinical remission (company RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission (company/ EAG FE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical remission (EAG RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (company RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (company/ EAG FE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (EAG RE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NB Odds ratio<1, result favours UPA
§ dose reflects mg per kg of body weight
ADA=adalimumab; EAG=External Assessment Group; FE=fixed-effects model; kg=kilograms; mg=milligrams; NMA=network meta-analysis; PBO=placebo; Q2W=every other week; Q4W=every four weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; RE=random effect model; TOF=tofacitinib; UPA=upadacitinib; UST=ustekinumab; VED=vedolizumab
Source: Company clarification response to Table 9 to Table 12

3.7.1 Summary and interpretation of company and EAG efficacy NMA results

EAG NMA FE results are only described when they differ from company RE NMA results. EAG RE NMA results are presented for completeness only and are not described in the text.

Induction phase/bio-naïve population: comparator versus UPA (45mg) (Table 8)

For clinical remission, company RE and EAG FE point estimates were similar (and favoured UPA). UPA was statistically significantly more effective than infliximab (IFX 10mg), adalimumab (ADA), tofacitinib (TOF), ustekinumab (UST) and placebo; no statistically significant differences were found for UPA versus IFX (5mg), vedolizumab (VED), or golimumab (GOL). For clinical response, all the point estimates were similar (and favoured UPA). UPA was statistically significantly more effective than all comparators.

Induction phase/bio-exposed population: comparator versus UPA (45mg) (Table 8)

For clinical remission, company RE and the EAG FE point estimates were different (and favoured UPA); the company results were more conservative than the EAG results. However, for all comparisons, both approaches led to the same conclusions regarding statistically significant differences; UPA was statistically significantly more effective than VED, ADA and placebo; no statistically significant differences were found for UPA versus TOF or UST. For clinical response, all the point estimates were similar (and favoured UPA). UPA was statistically significantly more effective than VED, ADA, TOF, UST and placebo. No data were available for the comparison of UPA versus IFX (10mg or 5mg) or versus GOL (100mg or 50mg).

Maintenance phase/bio-naïve population: comparator versus UPA (15mg) (Table 9)

For clinical remission and clinical response, company RE and EAG FE point estimates were similar. No statistically significant differences were found for UPA (15mg) versus any of the active comparators with two exceptions. For clinical remission, EAG FE results showed UPA to be statistically significantly more effective than placebo, whereas the company RE results did not show this same statistical advantage (i.e., the company results were more conservative than the EAG results). For clinical response, EAG FE results showed UPA to be statistically significantly more effective than ADA, whereas the company RE results did not show this same statistical advantage (i.e., the company results were more conservative than the EAG results).

For clinical remission, company results showed that 8/13 point estimates favoured treatment the upadacitinib, whilst 5/13 point estimates favoured treatment with a comparator. For clinical response, company results showed that 10/13 point estimates favoured treatment with upadacitinib, whilst 3/13 point estimates favoured treatment with a comparator.

Maintenance phase/bio-exposed population: comparator versus UPA (15mg) (Table 10)

For clinical remission, company RE and EAG FE point estimates were similar (and favoured UPA), except when compared with UPA [30mg]). UPA (15mg) was statistically significantly more effective than TOF (5mg), UST (Q8W and Q12W) and placebo. No statistically significant differences were found for UPA (15mg) versus VED (Q4W or Q8W), TOF (10mg), UPA (30mg) or ADA.

For clinical response, company RE and EAG FE point estimates were similar (and favoured UPA, except when compared with TOF [10mg] and UPA [30mg]). UPA (15mg) was statistically significantly more effective than UST (Q12W) and placebo. No statistically significant differences were found for UPA (15mg) versus VED (Q4W or Q8W), TOF (10mg and 5mg), UPA (30mg), ADA or UST (Q8W). No data were available for the comparison of UPA (15mg) versus IFX (10mg or 5mg) or versus GOL (100mg or 50mg).

Maintenance phase/bio-naïve population: comparator versus UPA (30mg) (Table 11)

For clinical remission, company RE and EAG FE point estimates were similar (and favoured UPA except when compared to TOF [10mg or 5mg]). No statistically significant differences were found for UPA (30mg) versus IFX (10mg or 5mg), VED (Q4W or Q8W), GOL (100mg or 50mg), UPA (15mg), ADA (Q2W), TOF (10mg or 5mg), UST (Q12W or Q8W). However, UPA (30mg) was statistically significantly more effective than placebo.

For clinical response, company RE and EAG FE point estimates were similar (and all favoured UPA (30mg). No statistically significant differences were found for UPA (30mg) versus VED (Q8W) or TOF (10m or 5mg). The EAG FE results showed UPA (30mg) to be statistically significantly better than VED (Q4W), UST (Q8W and Q12W) and UPA (15mg), whereas the company RE results did not show the same statistical advantages. Both the company and the EAG found UPA (30mg) was statistically significantly more effective than IFX (10mg or 5mg), GOL (100mg or 50mg), ADA and placebo.

Maintenance phase/bio-exposed population: comparator versus UPA (30mg) (Table 12)

For clinical remission, company RE and EAG FE point estimates were similar (and favoured UPA). No statistically significant differences were found for UPA (30mg) versus VED (Q4W or Q8W) and UPA (15mg). The EAG FE results showed UPA (30mg) to be statistically significantly better than TOF (10mg) and ADA, whereas the company RE results did not show the same statistical advantages. Both the company and the EAG found UPA (30mg) was statistically significantly more effective than TOF (5mg), UST (Q8W and Q12W) and placebo. No data were available for the comparison of UPA (30mg) versus IFX (10mg or 5mg) or versus GOL (100mg or 50mg).

For clinical response, company RE and EAG FE point estimates were similar (and favoured UPA). No statistically significant differences were found for UPA (30mg) versus VED (Q4W or Q8W), TOF (10mg or 5mg) or UPA (15mg). The EAG FE results showed UPA (30mg) to be statistically significantly better than ADA whereas the company RE results did not show the same statistical advantage. Both the company and the EAG found that UPA (30mg) was statistically significantly more effective than UST (Q8W and Q12W) and placebo. No data were available for the comparison of UPA (30mg) versus IFX (10mg or 5mg) or versus GOL (100mg or 50mg).

Company NMA sensitivity analyses

The company stated (CS, p94) that the NMA data were re-analysed using risk difference rather than odds ratios and that the results from these analyses did not change the conclusions that could be drawn from the base case NMAs. The company NMA sensitivity analyses were not reported in the CS or in the CS appendices.

3.7.2 Company and EAG NMA efficacy conclusions

The company and the EAG concluded that, overall, the NMA results indicated that upadacitinib induction and maintenance treatments compared favourably with all comparators in the bio-naïve and bio-exposed populations for the outcomes of clinical remission and clinical response. For most comparisons, point estimates were similar, and all results that were statistically significantly different favoured treatment with upadacitinib. However, for many of the comparisons, no statistically significant differences were identified between treatments.

Statistical issues must be considered when interpreting results. First, for all networks, the reliability of the NMA results is unclear because the consistency assumption could not be tested formally. The company demonstrated that, for at least one comparison, there was some evidence that baseline risk modified the treatment effect. As baseline risk models could not

be fitted for most of the comparisons, this creates doubt about the validity of the consistency assumption across all the networks. Second, compared to the reliability of the induction phase NMA results, the reliability of the maintenance phase NMA results is more questionable as trial design and descriptions of the intervention and placebo treatments of the included trials raise issues that cannot be resolved. Third, the company and the EAG preferred approaches to generating NMA results are different. In summary, if these three methodological issues are of no major concern, the EAG considers that company NMA results should be used to inform decision making

3.7.3 Indirect evidence for safety and tolerability

The company states (CS, p80) that NMAs are conducted for three safety outcomes, including discontinuation due to AEs, SAEs, and serious infections; however, only results of an NMA for the outcome of serious infections (in the induction phase) are presented in the CS.

There were 12 trials[24,25,28,31-33,36,38-41] included in the NMA for serious infections in the induction phase. The results from the company RE NMA were presented for the overall population and not separately for the bio-naïve and bio-exposed subpopulations (Table 13). Company NMA results show that treatment with upadacitinib is associated with a low risk of serious infections and the risk is comparable with all other treatments.

Table 13 Results for overall population company induction serious infections RE NMA

Treatment	Odds ratio vs. PBO Median (95%CrI)	SUCRA score	Predicted absolute outcome rate to median (95% CrI)
GOL200/100	[redacted]	[redacted]	[redacted]
UST6	[redacted]	[redacted]	[redacted]
VED300	[redacted]	[redacted]	[redacted]
IFX5	[redacted]	[redacted]	[redacted]
TOF10	[redacted]	[redacted]	[redacted]
UPA45	[redacted]	[redacted]	[redacted]
ADA160/80	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]

ADA160/80=adalimumab 160/80mg induction; CrI=credible interval; GOL200/100=golimumab 200/100mg induction; IFX5=infliximab 5mg/kg body weight; PBO=placebo; RE=random effects; SUCRA=surface under the cumulative ranking curve; TOF10=tofacitinib 10mg; UPA45=upadacitinib 45mg; UST6=ustekinumab 6mg/kg body weight; VED300=vedolizumab 300mg.
Source: CS, Table 37

3.8 *Summary and conclusions of the clinical effectiveness evidence*

Direct evidence

Direct clinical effectiveness evidence to support the use of upadacitinib to treat moderately to severely active UC was derived from three RCTs, the U-ACCOMPLISH and U-ACHIEVE induction trials (8 weeks) and the U-ACHIEVE maintenance trial (52 weeks). The two induction trials are complete and the company expects the interim results of the U-ACTIVATE[46] trial to be available in October 2022 and the final results to be available in Q3 2024.

The three trials compared treatment with upadacitinib versus placebo; there was no direct evidence to compare treatment with upadacitinib with any of the comparators listed in the final scope[23] issued by NICE. All three trials of upadacitinib were of good methodological quality. The patients in the trials are representative of patients with moderately to severely active UC who are treated in the NHS.

Induction and maintenance phase trial outcomes were considered for the overall population, bio-naïve and bio-exposed populations. Company results showed that, except for a few minor exceptions, for all outcomes, and all populations, treatment with upadacitinib was statistically significantly more effective versus placebo. Improvement in HRQoL was statistically significantly greater for patients treated with upadacitinib versus patients treated with placebo. No unexpected trial safety outcomes were reported. However, results versus placebo are not relevant to NHS patients as several other treatments are available to treat active UC.

The EAG highlights that in the upadacitinib induction trials, the primary outcome is assessed at 8 weeks. This duration of follow-up is consistent with the duration of follow up for induction trials that informed previous NICE appraisals of drugs to treat active UC.[16,18] Some patients in the company's induction trials received upadacitinib for a further 8 weeks. This longer time period is more in line with the experience of patients treated in NHS clinical practice who may typically receive induction treatments for 3 to 6 months before treatments are changed due to lack of response. The company's evidence demonstrates that there is a potential benefit of extended induction period (CS, p 67).

Indirect evidence

The NMA results indicate that upadacitinib induction and maintenance treatments compared favourably with all comparators in the bio-naïve and bio-exposed populations for the outcomes of clinical remission and clinical response. Company NMA risk of serious infections (induction phase) results showed that patients treated with upadacitinib had a low risk of serious infections.

The EAG and the company noted several sources of heterogeneity in the trials included in the NMAs. Compared to the reliability of the induction NMA results, the maintenance phase NMAs have additional problems associated with trial design and the company and the EAG preferred approaches to generating NMA results are different. In summary, if these methodological issues are of no major concern, the EAG considers that company RE NMA results should be used to inform decision making.

Safety warning

Overall, clinical advice to the EAG is that there appear to be no concerns with the safety profile of upadacitinib compared to other targeted therapies for inflammatory bowel disease, and no concerns that would prompt additional monitoring during treatment with upadacitinib. The EMA safety committee is carrying out a review[47] to determine whether the risks associated with tofacitinib are also associated with all JAK inhibitors authorised in the EU (including upadacitinib) for the treatment of inflammatory disorders, and whether the marketing authorisations for these medicines should be amended.

4 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company to support of the use of upadacitinib as an option for treating moderately to severely active UC. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model (developed in Microsoft Excel).

4.1 *Published cost effectiveness evidence*

4.1.1 Objective of the company's literature searches

The company undertook a systematic review to identify economic evaluations as well as information about costs and resource use in a population with moderately to severely active UC. The company searched for studies published between 2000 and January 2022 (i.e., from 2000 to the date of the search). Details of the company search strategies are presented in the CS (Appendix G).

The search did not identify any previous cost effectiveness studies of upadacitinib in patients with moderately to severely UC; however, 10 studies[60-69] evaluating the cost effectiveness of different treatments for patients with moderately to severely UC from a UK health care system perspective were identified.

4.2 *EAG critique of the company's literature review*

A summary of the EAG critique of the company's literature review methods (CS, Appendix G) is presented in Table 14.

Table 14 EAG appraisal of systematic review methods (cost effectiveness)

Review process	EAG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Was data extracted by two or more reviewers independently?	Data were extracted by a single analyst and checked by a research associate
Were appropriate criteria used to assess the quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Not reported
Were any relevant studies identified?	10 relevant studies were identified[60-69]

EAG=External Assessment Group

4.3 *EAG conclusions*

The EAG has no concerns about the methods used by the company to identify the evidence that was catalogued in databases. However, the EAG considers that the company searches should have identified previous NICE appraisals of technologies[16-18] that are used to treat moderately or severely active UC.

The database searches carried out by the EAG did not identify any additional relevant studies and the EAG is satisfied that there are no relevant economic studies of upadacitinib available.

4.4 *Summary of the company's submitted economic evaluation*

4.4.1 NICE Reference Case checklist

Table 15 NICE Reference Case checklist completed by EAG

Attribute	Reference case	Does the de novo economic evaluation match the Reference Case?
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	The EAG considers the company choice of comparators was appropriate
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	EAG considers that the company modelled treatment pathway does not reflect NHS clinical practice and that incremental QALYs may be [redacted]
Perspective on costs	NHS and PSS	Partly. Focus is on NHS costs
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	The company model is populated with company NMA results
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes. However, the company has used published utility values rather than estimating utility values from upadacitinib trial EQ-5D data
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

EAG=External Assessment Group; EQ-5D=EuroQol-5 dimension; HRQoL=health-related quality of life; NMA=network meta-analysis; PSS=Personal Social Services; QALY=quality adjusted life year
Source: NICE Reference Case[50]

Table 16 Critical appraisal checklist for the economic analysis completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partly	The EAG identified some methodological issues associated with the company NMAs. These issues may cast doubt on the robustness of effectiveness estimates used to populate the company model
Were all the important and relevant costs and consequences for each alternative identified?	Partly	As the modelled treatment pathway does not reflect NHS practice it is not clear whether all important and relevant costs and consequences have been identified
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Partly	The company carried out a wide range of deterministic sensitivity and scenario analyses. However, as the company modelled treatment pathway does not reflect NHS clinical practice these results may not be informative

EAG=External Assessment Group; NMA=network meta-analysis
Source: Drummond and Jefferson 1996[70] and EAG comment

4.4.2 Model outputs

The company model estimates total lifetime costs and total lifetime QALY gains for each treatment arm. Incremental costs and incremental QALYs are used to generate ICERs. This approach is in line with the NICE Reference Case.[50]

4.4.3 Population

The company analysis considers [redacted]. This is in line with the anticipated marketing authorisation for upadacitinib.

Two subpopulations are considered:

- **Bio-naïve**: Patients that have had no previous exposure to biologic therapies
- **Bio-exposed**: Patients who had an inadequate response or intolerance to CT or a biologic treatment, and those who have received biologic therapy in the past but stopped therapy based on reasons other than inadequate response or intolerance

As shown in (Table 17), the baseline characteristics of the modelled populations reflect the characteristics of the patients recruited to the two UPA induction trials.

Table 17 Baseline characteristics of the modelled populations

Characteristic	Bio-naïve population	Bio-exposed population
Mean age, years (SE)	42.99 (0.79)	42.69 (0.79)
Number of male patients, n (%)	209 (66.8)	203 (58.5)
Mean weight, kg (SE)	73.09 (1.06)	72.3 (0.94)
Number of patients <55kg, n (%)	53 (16.9)	56 (16.1)
Proportion of patients 55 to 85kg, n (%)	194 (62.0)	221 (63.7)
Proportion of patients >85kg, n (%)	66 (21.1)	70 (20.2)

SE=standard error
Source: CS, Table 64

4.4.4 Interventions and comparators

The intervention is upadacitinib. The company considered all the comparators listed in the final scope[23] issued by NICE except:

- filgotinib – at the time of writing the CS, filgotinib had not yet been recommended by NICE (filgotinib was subsequently recommended by NICE in June 2022 [TA792[48]])
- ozanimod – not yet recommended by NICE (subject to an ongoing NICE appraisal)
- CT – not considered an appropriate comparator as would typically be given to patients prior to treatment with a biologic agent. However, CT is used as a concomitant therapy. The cost of CT concomitant therapy is negligible compared with other costs.

Details about the intervention and comparator treatments are provided in Table 18.

Table 18 Intervention and comparator treatments

	Bio-naïve	Bio-exp	Duration of induction phase	Dosage	
				Induction phase	Maintenance phase (standard and high dosages)
Intervention					
UPA (oral)*	✓	✓	8 weeks	45mg QD	15mg QD 30mg QD
Comparators					
ADA (and biosimilar) (SC)	✓	✓	8 weeks	160mg at Week 0, 80mg at Week 2, then 40mg every other week	40mg Q2W 40mg Q1W
GOL (SC)*	✓	X	6 weeks	Initial dose of 200mg, followed by 100mg at week 2	50mg Q4W 100mg Q4W
IFX (and biosimilar) (IV)	✓	X	8 weeks	5mg/kg at Weeks 0, 2, 6	5mg/kg Q8W 10mg/kg Q8W
TOF (oral)*	✓	✓	8 weeks	10mg BID for 8 weeks	5mg BID 10mg BID
UST (IV)*	✓	✓	8 weeks	Single dose based on body weight at Week 0 ~6 mg/kg: ≤55 kg=260mg >55kg to ≤85kg=390mg >85kg=520mg	90mg Q12W 90mg Q8W
VED (IV)*	✓	✓	8 weeks	300mg at Weeks 0, 2, 6	300mg Q8W 300mg Q4W
VED (SC)	✓	✓	8 weeks	300 mg at Weeks 0, 2, 6	108mg Q2W 108mg Q2W

* Extended induction phase permitted (duration=8 weeks, except for VED where duration=4weeks)
ADA=adalimumab; BID=twice daily; GOL=golimumab; IFX=infliximab; IV=intravenous; QD=once daily; QW1=every week; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; SC=subcutaneous; TOF=tofacitinib; UST=ustekinumab; VED=vedolizumab
Source: CS, Table 58, Table 59, Table 60 and Table 61

Several treatment-related assumptions were used in the company model. These are presented in Table 19.

Table 19 Treatment-related assumptions used in the company model

Parameter	Assumption
Extended induction for delayed response	Extended induction is not considered in the company base case analysis, only in a scenario analysis
Dose escalation during the maintenance phase	Individual analyses are provided for the standard (15mg QD) and high (30mg QD) maintenance doses. For the comparators with two levels of dose, it is assumed that 30% of patients would receive the high dose
Constant loss of response	The probabilities of loss of response from the remission and response without remission health states are assumed to be constant over time
Treatment continuation	No treatment stopping rule for responders and remitters
Treatment sequencing	Patients discontinuing treatment are assumed to receive CT in the base case. One line of subsequent treatment (ustekinumab) is considered in a scenario analysis

CT=conventional therapy; QD=once daily
Source: CS, Table 92

4.4.5 Perspective, time horizon and discounting

The model perspective appears to be that of the NHS. The time horizon is lifetime (up to age 100 years) and the cycle length is 4 weeks (a half-cycle correction was not applied). Costs and outcomes are discounted at a rate of 3.5% per annum.

4.4.6 Model structure

The structure of the company model is in line with models used to inform the NICE appraisals of ustekinumab (TA633[18]), adalimumab, golimumab and infliximab (TA329[15]) and vedolizumab (TA342[17]). The model has a hybrid structure: a decision tree to model the induction phase and a Markov model to model the maintenance phase, subsequent treatments and surgery (see Figure 2 and Figure 3 respectively). A description of the Markov model health states is provided in Table 20.

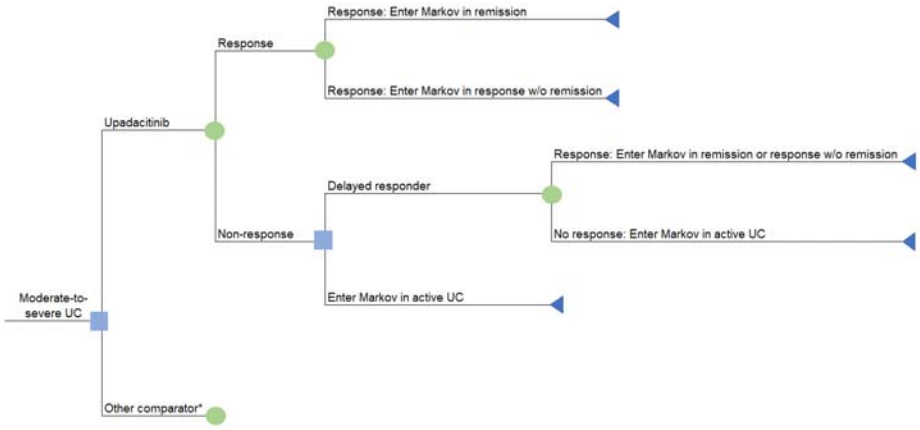

Figure 2 Company decision tree (induction phase)

Source: CS, Figure 9

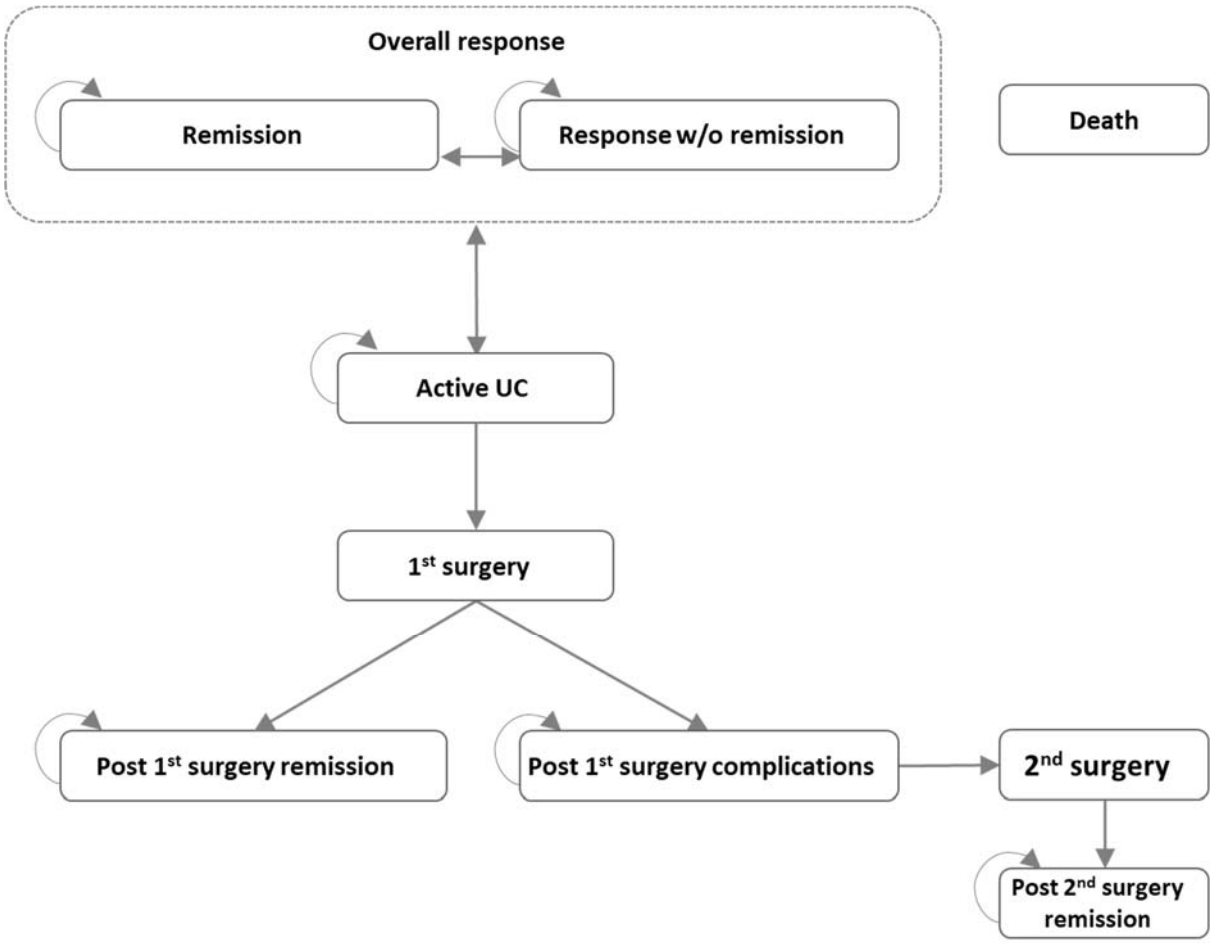

Figure 3 Company Markov model (maintenance phase, subsequent treatment and surgery)

Source: CS, Figure 10

Table 20 Description of company Markov model health states and the data sources used to move patients between health states

Health state	Definition
Remission	Full Mayo score of 0 to 2 with no individual subscore >1 Data source: company NMAs
Response without remission	A decrease from baseline in the Full Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1, but not meeting remission definition Data source: company NMAs
Active UC	Full Mayo score of 6 to 12 ('remission' or 'response without remission' not achieved)
First surgery	First surgical intervention to resolve UC (assumed duration of 6 months); could include acute complications Excess mortality due to surgery is assumed to be 30% and was applied during the 6-month surgery health states Data source: annual probability of 1st and 2nd surgery (0.47%) was derived from Misra 2016[71] and applied to the Active UC health state
Post-first surgery remission	No chronic complications from first surgery.
Post-first surgery complications	Chronic complications from first surgery such as wound infection, bowel obstruction, intra-abdominal abscess, or anastomotic leak Data source: chronic complications of first surgery (33.5%) were derived from a national report 2014). The annual probability of late chronic complications (5.64%) is based on a weighted average of values derived by Segal 2018,[72] Gonzalez 2014, Ferrante 2008 and Suzuki 2012). Loftus 2008 was excluded as an outlier
Second surgery	Second surgical intervention due to pouch failure (assumed duration of 6 months); could include acute complications Excess mortality due to surgery is assumed to be 30% and was applied during the 6-month surgery health states Data source: annual probability of 1st and 2nd surgery (0.47%) was derived from Misra 2016[71]
Post-second surgery remission	No chronic complications from second surgery. All patients remain in this health state until death
Death	Absorbing state. The model is populated with general population all-cause mortality data adjusted for age and gender (ONS National Life Tables for 2018-20)[73] weighted by baseline male: female ratio

NB Publications cited in the CS were not always referenced
CS=company submission; NMA=network meta-analyses; ONS=Office of National Statistics; UC=ulcerative colitis
Source: CS, Table 56 and Table 92

4.4.7 Health state remission and response transition probabilities

The company model was populated with remission and response probabilities generated by the company NMAs. The length of the induction phase of treatment varied by treatment; most treatments were associated with a standard induction phase of 6 to 8 weeks. An extended induction phase (length of standard phase plus a follow-on phase of between 4 and 8 weeks) was considered in scenario analysis. The length of time that maintenance phase data were available ranged from 44 to 54 weeks. The lengths of the standard induction, extended induction and maintenance phases for all treatments are provided in the CS (Table 73).

The company base case clinical remission and response probabilities at the end of the induction phase and end of the maintenance phase are presented in Table 21 and Table 22 respectively.

Table 21 Company base case clinical remission and response probabilities at the end of the induction phase

Treatment	Bio-naïve population				Bio-exposed population			
	Remission		Response without remission		Remission		Response without remission	
Drug	Standard	Ext.	Standard	Ext.	Standard	Ext.	Standard	Ext.
UPA 45mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160mg/ 80mg	[redacted]		[redacted]		[redacted]		[redacted]	
ADA 160mg/ 80mg biosimilar	[redacted]		[redacted]		[redacted]		[redacted]	
GOL 200mg/ 100mg	[redacted]	15.50%	[redacted]	12.60%				
IFX 5mg	[redacted]	15.50%	[redacted]	12.60%				
IFX 5mg biosimilar	[redacted]	15.50%	[redacted]	12.60%				
TOF 10mg	[redacted]	12.50%	[redacted]	27.90%	[redacted]	5.90%	[redacted]	31.80%
UST 6mg	[redacted]	13.50%	[redacted]	51.90%	[redacted]	1.40%	[redacted]	45.10%
VED 300mg	[redacted]	16.00%	[redacted]	20.00%	[redacted]	6.70%	[redacted]	19.70%
VED 108mg	[redacted]	16.00%	[redacted]	20.00%	[redacted]	6.70%	[redacted]	19.70%
Notes	Random effects	TA633[18]	Fixed effects adjusted	TA633[18]	Random effects	TA633[18]	Random effects	TA633[18]

Source: CS, Table 65, Table 66, Table 67 and Table 68

Table 22 Company base case clinical remission and response probabilities at the end of the maintenance phase

Treat-ment	Bio-naïve population				Bio-experienced population			
	Remission		Response without remission		Remission		Response without remission	
Dose	Standard	High	Standard	High	Standard	High	Standard	High
UPA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA BIO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL	[redacted]	[redacted]	[redacted]	[redacted]				
IFX	[redacted]	[redacted]	[redacted]	[redacted]				
IFX BIO	[redacted]	[redacted]	[redacted]	[redacted]				
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VED	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model	Random effects	Random effects	Random effects	Random effects	Random effects	Random effects	Random effects	Random effects

Source: CS, Table 69, Table 70, Table 71 and Table 72

4.4.8 Health-related quality of life

EQ-5D-5L data were collected during the U-ACCOMPLISH and U-ACHIEVE trials. However, the company chose to use the published utility values (Woehl 2008[74] and Arseneau 2006)[75] that had been used in previous NICE appraisals (TA329,[15] TA342,[17] TA547[16] and TA633[18]). The company considered that these values were a better representation of HRQoL in clinical practice than trial data. Published post-surgery (1st and 2nd) remission, post-surgery complications and serious AEs were adjusted to account for the general decline in HRQoL with age by applying the method described by Ara 2010.[76] Utility values used in the company base case analysis are presented in Table 23.

Table 23 Company (age-adjusted) base case utility values

Health state	Base case value	References
Active ulcerative colitis	0.410	Woehl 2008[74]
Remission	0.870	
Response (no remission)	0.760	
Surgery (1st and 2nd)	0.610	Arseneau 2006[75]
Post-surgery remission (1st and 2nd)	0.720	Woehl 2008[74]
Post-surgery complications	0.340	Arseneau 2006[75]
Serious infection	-0.156	Stevenson 2016[77]

Source: CS, Table 78 and Table 79

4.4.9 Adverse events

The company model only includes serious infection AEs. This approach is in line with the approach taken in the models that informed previous NICE appraisals (TA547[16] and TA633[18]). Discontinuations due to AEs were not explicitly modelled and serious infections were treated as one-off events that occurred during the induction phase. Company serious infection NMA results were used to populate the model. In all treatment arms, the probability of serious infection was <1%.

4.4.10 Drug costs

Drug acquisition costs

The company analyses use the PAS price for upadacitinib and list prices (British National Formulary [BNF])[78] for all comparator drugs. Where multiple drug prices were available, the lowest price was used. Drug dosing regimens were obtained from the upadacitinib draft SmPC[79] and published comparator treatment SmPCs.[80-85]

Infliximab dose varies by patient weight. The average weights of the bio-naïve and bio-exposed populations enrolled in the U-ACHIEVE induction and U-ACCOMPLISH induction trials were 73.09kg and 72.30kg respectively. These weights were used to estimate drug acquisition costs for patients treated with infliximab.

Ustekinumab intravenous dose is based on weight category (≤55kg, 55 to 85kg and >85kg). The company used the proportions of patients in the upadacitinib trials who were in each of these three weight categories to estimate drug acquisition costs for patients receiving ustekinumab.

Drug administration costs

Drug administration costs are presented in Table 24.

Table 24 Model drug administration costs

Administration route	Notes	Source	Cost
Intravenous drugs	Non-admitted face-to-face follow-up outpatient visit (Healthcare Resource Group [HRG] code: WF01A)	NHS Reference Costs 2019/20	£125.44
Subcutaneous injections	Patients are assumed to self-administer – consistent with TA633[18] assumption	-	£0

Source: CS, p156

4.4.11 Health state resource use and unit costs

The company has assumed that the same levels of resource use and costs apply to bio-naïve and bio-exposed patients.

The company modelled the resource use and costs associated with outpatient (consultant visit, blood test, and elective endoscopy) and inpatient (emergency endoscopy, care without colectomy and stoma care) events. Resource use estimates for all events except surgery were extracted from Tsai 2008[65] (these non-surgery estimates were provided by a panel of UK gastroenterologists) and reported costs were updated using NHS Reference Costs 2019-20.[86] As Tsai 2008[65] did not report resource use or costs associated with surgery, these costs were estimated using data reported by Buchanan 2011[87] (the approach used in TA633[18]). The following assumptions were employed:

- first surgery: 40% of patients received restorative ileal pouch-anal anastomosis (IPAA) surgery and 60% received ileostomy, and one acute complication was included in the total cost
- second surgery: all patients received an ileostomy.

Surgery costs were inflated to 2020/21 prices using the NHS Cost Inflation Index (NHSCII) (PSSRU 2021).[88]

The annual health state costs used in the company model are shown in Table 25 (see TA633[18] for details of cost sources).

Table 25 Company model annual health state costs

Health state	Cost per health state, per year
Remission	£371.05
Response (without remission)	£998.29
Active ulcerative colitis	£2,378.44
Surgery	£2,827.64
Post-surgery remission	£952.93
Post-surgery complications	£6,352.79
First phase surgery	£15,782.58
Second surgery for pouch failure	£11,336.74

Source: CS, Table 85

4.4.12 Adverse reaction resource use and costs

The only AE cost included in the company model was the cost associated with serious infections. This cost was estimated by using the average cost (NHS Reference Costs 2019/20[86]) of five different types of serious infections, namely sepsis, pneumonia, urinary tract infection, respiratory tract infection and bronchitis. The average cost used in the company model was £2,685; see CS, Table 86 for more details.

4.5 *Severity*

The company assumed that the mortality rate for a patient with UC was the same as the mortality rate for the general population as the only treatment received by patients with UC that is associated with a risk of death is surgery. However, the company considered that UC has a significant burden for patients in terms of the effect of UC on HRQoL. The company used the QALY shortfall calculator developed by Schneider 2022[89] to estimate QALY shortfall results. The company estimated that the absolute QALY shortfall ranges for the bio-naïve and bio-exposed populations were between [redacted] and [redacted], and [redacted] and [redacted], respectively. This accounted for a proportional QALY shortfall for bio-naïve and bio-exposed population of ranges between [redacted] and [redacted], and [redacted] and [redacted], respectively.

4.6 *Company cost effectiveness results*

The company generated base case cost effectiveness results for the bio-naïve (upadacitinib 15mg and 30mg maintenance doses) and bio-exposed (upadacitinib 15mg and 30mg maintenance doses) populations. In all analyses, 30% of patients in the comparator arms were assumed to have received the high maintenance dose of treatment (where applicable), and the remaining 70% were assumed to have received the standard maintenance dose. Results were generated using the confidential discounted PAS price for upadacitinib and list prices for the comparator drugs.

4.6.1 Bio-naïve population

Upadacitinib 15mg maintenance dose

The company analyses showed that treatment with upadacitinib (15mg) dominated all comparator drugs.

Table 26 Base case results: bio-naive population (15mg)

Technologies	Total		Incremental versus baseline		ICER (£/QALY)	
	Costs (£)	QALYs	Costs (£)	QALYs	Versus baseline	Incremental
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
GOL	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
IFX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
TOF	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

NB PAS price for upadacitinib and list prices for all comparator drugs
ADA=adalimumab; GOL=golimumab; IFX=infliximab; ICER=incremental cost effectiveness ratio; IV=intravenous; PAS=Patient Access Scheme; QALY=quality adjusted life year; SC=subcutaneous; TOF=tofacitinib; UPA=upadacitinib; UST=ustekinumab; VED=vedolizumab
Source: CS, Table 93

Upadacitinib 30mg maintenance dose

The company analyses showed that upadacitinib (30mg) was associated with the highest QALYs and the highest costs. In a fully incremental analysis, the cost effectiveness frontier comprised adalimumab biosimilar, golimumab and upadacitinib. Upadacitinib was associated with an ICER per QALY gained of £15,333 versus golimumab.

Table 27 Base case results: bio-naive population (30mg)

Technologies	Total		Incremental versus baseline		ICER (£/QALY)	
	Costs (£)	QALYs	Costs (£)	QALYs	Versus baseline	Incremental
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
GOL	[redacted]	[redacted]	[redacted]	[redacted]	£14,969	14,969
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£50,119	Dominated
IFX	[redacted]	[redacted]	[redacted]	[redacted]	£63,419	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£45,063	Dominated
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£22,497	Extendedly dominated
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	£48,122	Dominated
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	£70,055	Dominated
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	£15,264	£15,333

NB PAS price for upadacitinib and list prices for all comparator drugs
ADA=adalimumab; GOL=golimumab; IFX=infliximab; ICER=incremental cost effectiveness ratio; IV=intravenous; PAS=Patient Access Scheme; QALY=quality adjusted life year; SC=subcutaneous; TOF=tofacitinib; UPA=upadacitinib; UST=ustekinumab; VED=vedolizumab
Source: CS, Table 94

4.6.2 Bio-exposed population

Table 28 Base case results: bio-exposed population (15mg)

Technologies	Total		Incremental versus baseline		ICER (£/QALY)	
	Costs (£)	QALYs	Costs (£)	QALYs	Versus baseline	Incremental
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	114,500	Extendedly dominated
UPA 15mg	[redacted]	[redacted]	[redacted]	[redacted]	1,186	1,186
UST	[redacted]	[redacted]	[redacted]	[redacted]	116,854	Dominated
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	66,556	Dominated
TOF	[redacted]	[redacted]	[redacted]	[redacted]	26,583	Dominated
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	112,615	Dominated

NB PAS price for upadacitinib and list prices for all comparator drugs
ADA=adalimumab; ICER=incremental cost effectiveness ratio; IV=intravenous; PAS=Patient Access Scheme; QALY=quality adjusted life year; SC=subcutaneous; TOF=tofacitinib; UPA=upadacitinib; UST=ustekinumab; VED=vedolizumab
Source: CS, Table 97

Table 29 Base case results: bio-exposed population (30mg)

Technologies	Total		Incremental versus baseline		ICER (£/QALY)	
	Costs (£)	QALYs	Costs (£)	QALYs	Versus baseline	Incremental
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Reference	Reference
ADA	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	£118,563	Extendedly dominated
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	£76,532	Extendedly dominated
TOF	[redacted]	[redacted]	[redacted]	[redacted]	£26,828	Extendedly dominated
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	£105,952	Dominated
UPA 30mg	[redacted]	[redacted]	[redacted]	[redacted]	£14,146	14,146

NB PAS price for upadacitinib and list prices for all comparator drugs
ADA=adalimumab; ICER=incremental cost effectiveness ratio; IV=intravenous; PAS=Patient Access Scheme; QALY=quality adjusted life year; SC=subcutaneous; TOF=tofacitinib; UPA=upadacitinib; UST=ustekinumab; VED=vedolizumab
Source: CS, Table 98

4.6.3 Probabilistic sensitivity analyses

The company carried out probabilistic sensitivity analyses (PSAs). The following parameters were varied: baseline patient characteristics, health state utilities, surgery inputs, efficacy inputs (probability of remission and response without remission) and costs (direct medical costs, AE costs and indirect costs). A total of 5,000 simulations were run.

Table 30 Probabilities of upadacitinib being the most cost effective treatment option

Technology	Willingness to pay threshold	
	£20,000	£30,000
Bio-naïve population		
Upadacitinib (15mg, maintenance dose)	[redacted]	[redacted]
Upadacitinib (30mg, maintenance dose)	[redacted]	[redacted]
Bio-exposed population		
Upadacitinib (15mg, maintenance dose)	[redacted]	[redacted]
Upadacitinib (30mg, maintenance dose)	[redacted]	[redacted]

NB PAS price for upadacitinib and list prices for all comparator drugs
PAS=Patient Access Scheme
Source: CS, Figure 11 to Figure 14

4.6.4 Deterministic sensitivity analyses

The company carried out a range of deterministic sensitivity analyses as shown in Table 31.

Table 31 Company deterministic sensitivity analyses

Parameter	Variation
Time horizon	5 years to lifetime
Discount rates	0% and 6%
Baseline characteristics (age, proportion male and weight)	±1.96 standard error
Health state utilities	±10%
Efficacy response at Week 8 and maintenance response	NMA 95% CrIs
Proportion of patients on 'high dose' maintenance regimens	±20%
Adverse event rates	±10%
All cost items, except drug costs, which were not varied	±20%

CrIs=credible intervals; NMA=network meta-analysis
Source: CS, pp193-4

Bio-naïve population

Results from the company adalimumab biosimilar DSA have been presented as adalimumab biosimilar was the comparator with the lowest cost. The 10 comparators that had the greatest effect on net monetary benefit (NMB) results are presented in Table 32.

Table 32 Univariate deterministic sensitivity analysis results: bio-naïve population, upadacitinib (15mg) versus adalimumab biosimilar

Parameter	Net monetary benefit	
	Lower bound	Upper bound
Probability of remission by end of maintenance	£8,682	£149,048
Probability of response without remission by end of maintenance	£11,053	£41,233
End of induction, % remission	£14,799	£25,855
End of induction, % response without remission	£21,693	£25,342
Health state utility – active ulcerative colitis	£22,052	£18,612
Health state utility – remission	£17,679	£21,019
Time horizon (in years)	£17,388	£20,332
Discount rates	£22,153	£19,313
Health state utility – response without remission	£19,180	£21,485
Apply age-specific health utility weight?	£18,285	£20,332

NB PAS price for upadacitinib and list prices for all comparator drugs
PAS=Patient Access Scheme
Source: CS, Table 101

Table 33 Univariate deterministic sensitivity analysis results: bio-naïve population, upadacitinib (30mg) versus adalimumab biosimilar and versus golimumab

Parameter	Adalimumab biosimilar		Golimumab	
	Net monetary benefit			
	Lower bound	Upper bound	Lower bound	Upper bound
Probability of remission by end of maintenance	£5,316	£84,758	£1,522	£80,965
Probability of response without remission by end of maintenance	£9,752	£38,135	£5,958	£34,341
End of induction, % remission - UPA 45	£14,146	£25,354	£10,352	£21,561
Probability of remission by end of maintenance (low dose) -GOL 200/100	n/a	n/a	£17,823	£10,754
Health utility – active ulcerative colitis	£23,339	£16,172	£18,916	£13,008
Time horizon (in years)	£12,726	£19,756	£9,164	£15,962
Health utility - remission	£14,443	£21,130	£11,919	£17,008
Discount rates	£23,502	£17,872	£19,442	£14,218
Health utility - response without remission	£17,186	£22,326	£13,554	£18,370
Apply age-specific health utility weight?	£15,529	£19,756	n/a	n/a
End of induction, % response without remission - UPA 45	£21,139	£24,847	£17,345	£21,054

NB PAS price for upadacitinib and list prices for all comparator drugs
n/a=not applicable; PAS=Patient Access Scheme
Source: CS, Table 102 and Table 103

Bio-exposed population

Table 34 Univariate deterministic sensitivity analysis results: bio-exposed population, upadacitinib (15mg) versus adalimumab biosimilar

Parameter	Net monetary benefit	
	Lower bound	Upper bound
Probability of remission by end of maintenance	£8,407	£71,060
Probability of response without remission by end of maintenance	£19,528	£48,968
End of induction, % remission - UPA 45	£17,864	£26,451
End of induction, % response without remission - UPA 45	£17,681	£23,370
Health state utility – remission	£16,846	£22,040
Health state utility - active ulcerative colitis	£22,824	£19,255
Discount rates	£22,793	£20,054
Time horizon (in years)	£18,399	£21,040
Probability of remission by end of maintenance (low dose) - ADA 160/80 biosimilar	£21,470	£19,004
Apply age-specific health utility weight?	£18,681	£21,040

NB PAS price for upadacitinib and list prices for all comparator drugs
PAS=Patient Access Scheme
Source: CS, Table 104

Table 35 Univariate deterministic sensitivity analysis results: bio-exposed population, upadacitinib (30mg) versus adalimumab biosimilar and versus tofacitinib

Parameter	Adalimumab biosimilar		Tofacitinib	
	Net monetary benefit			
	Lower bound	Upper bound	Lower bound	Upper bound
Probability of remission by end of maintenance	£11,041	£14,978	£5,345	£82,746
Health utility – remission	£16,345	£12,802	£12,030	£18,495
Probability of response without remission by end of maintenance (high dose) - UPA 45	£12,383	£15,196	£13,331	£38,904
End of induction, % remission – UPA 45	n/a	n/a	£14,493	£21,947
Percent of patients on high dose maintenance - UPA 30 mg	£10,922	£13,360	n/a	n/a
Time horizon (years)	n/a	n/a	£13,021	£17,250
Health utility - active ulcerative colitis	£12,321	£14,591	£19,194	£15,306
Annual direct medical costs based on health state – active ulcerative colitis	£14,346	£12,375	n/a	n/a
Apply age-specific health utility weight?	£14,999	£13,360	£14,594	£17,250
Probability of response without remission by end of maintenance (low dose) - ADA 160/80 biosimilar	£13,699	£12,067	n/a	n/a
Probability of remission by end of maintenance (low dose) - ADA 160/80 biosimilar/TOF 10	£13,534	£12,106	£18,094	£14,507
Discount rates	n/a	n/a	£19,497	£16,048
End of induction, % response without remission - ADA 160/80 biosimilar (ADA)/UPA 45 (TOF)	£13,808	£12,647	£14,336	£19,272

NB PAS price for upadacitinib and list prices for all comparator drugs
n/a=not applicable; PAS=Patient Access Scheme
Source: CS, Table 105 and Table 106

4.6.5 Scenario analyses

The company ran nine scenario analyses as shown in Table 36.

Table 36 Company scenario sensitivity analyses

No	Scenario	Details
1	Time horizon (10 years)	Based on TA342[17]
2	Time horizon (50 years)	Based on TA633[18]
3	Extended induction	Delayed responders are included in the analysis
4	Treatment sequencing	Upon loss of response, a second treatment is initiated for each comparator (ustekinumab)
5	Swinburn et al utility data	Utilities for active UC, remission, response and post-surgery remission
6	Vaizey et al utility data	Utilities for active UC, remission and response
7	Maintenance dose of UPA 70% 15mg: 30% 30mg split	UPA maintenance dosing is 70% 15mg and 30% 30mg
8	Spontaneous remission from Active UC	Spontaneous remission probability of 1% per cycle applied
9	Loss of response	Probability of loss of response reduced by 25% after Year 1

TA=technology appraisal; UC=ulcerative colitis; UPA=upadacitinib
Source: CS, Table 111

Table 37 Summary of company scenario analyses results

No	Scenario	Summary of results
1	Time horizon (10 years)	Conclusions of the analysis did not change for the 15mg and 30mg doses for the bio-naïve and bio-exposed populations
2	Time horizon (50 years)	Conclusions of the analysis did not change for the 15mg and 30mg doses for the bio-naïve and bio-exposed populations
3	Extended induction	Adalimumab and adalimumab biosimilar were excluded from this scenario since extended induction is not an option for these treatments Upadacitinib remained cost effective at both upadacitinib 15mg and 30mg maintenance doses for both bio-naïve and bio-exposed populations
4	Treatment sequencing	Upadacitinib remained cost effective at both standard and high maintenance doses for both the bio-naïve and bio-exposed populations
5	Swinburn et al[90] utility data	This scenario resulted in higher QALYs for all treatments compared with the base case. Upadacitinib remained cost effective at both upadacitinib 15mg and 30mg maintenance doses for both the bio-naïve and bio-exposed populations
6	Vaizey et al utility data	This scenario resulted in higher QALYs for all treatments compared with the base case and Scenario 5. Upadacitinib remained cost effective at both upadacitinib 15mg and 30mg maintenance doses for the bio-exposed populations and the standard dose for the bio-naïve population
7	Maintenance dose of UPA 70% 15mg: 30% 30mg split	Upadacitinib remained cost effective for both the bio-naïve and bio-exposed populations. This analysis was run probabilistically
8	Spontaneous remission from Active UC	Upadacitinib remained cost effective at both upadacitinib 15mg and 30mg maintenance doses for both the bio-naïve and bio-exposed populations
9	Loss of response	Upadacitinib remained cost effective at both upadacitinib 15mg and 30mg maintenance doses for both the bio-naïve and bio-exposed populations

NB PAS price for upadacitinib and list prices for all comparator drugs
QALY=quality adjusted life year; PAS=Patient Access Scheme; UC=ulcerative colitis; UPA=upadacitinib
Source: CS, pp209-227

4.7 *Validation of the cost effectiveness analyses*

The company undertook technical and internal validation of the cost effectiveness analysis by preparing the model in line with best practice and NICE guidance.[50] Two independent modellers reviewed the company model structures and parameters, and another independent modeller reviewed the model for coding errors, inconsistencies, and the plausibility of inputs. The company also compared the company model outcomes versus the outcomes reported in a recent publication (Lohan 2019)[63] that was based on a previously submitted model to NICE. The company concluded that, based on external validation, there was a reasonable range of consistency within the constraints of comparison; summary results of the comparison are presented in the CS (Table 146).

5 EAG CRITIQUE OF COMPANY ECONOMIC MODEL

5.1 *Introduction*

The EAG has undertaken a comprehensive check of the company model. The EAG is satisfied that the elements of the model presented in Table 38 do not raise any concerns for the EAG.

Table 38 Elements of the company model that do not raise concerns for the EAG

Population	The company has appropriately generated separate sets of results for the bio-naïve and bio-exposed populations
Patient weight	The company model uses estimates of patient weight based on the patients in the upadacitinib induction trials. The EAG considers that as patient weight in the upadacitinib trials is similar to patient weight in trials of treatments for the same indication, these are appropriate values to use in the economic model
Comparators	The company has generated cost effectiveness results for the relevant comparators listed in the final scope[23] issued by NICE
Parameter values	Model parameter values match those presented in the CS
Costs	The EAG is satisfied that the company has used appropriate approaches to estimate drug and resource use costs
Discounting	The company has carried out discounting correctly
PSA	The EAG has checked that PSA parameter values are reasonable and has re-run the PSA. The EAG considers that the company PSAs have been carried out appropriately
Stress testing - extreme values	The company model generates appropriate results when extreme parameter values are used

CS=company submission; EAG=External Assessment Group; PSA=probabilistic sensitivity analysis

However, the EAG model checking exercise identified several areas of concern and these are discussed in Section 5.2 .

5.2 *Modelling issues with unknown impact on company cost effectiveness results*

5.2.1 Company model structure

The company model structure and assumptions are broadly in line with cost effectiveness models that have been used to inform previous NICE appraisals of drugs used to treat active UC (TA633[18] and TA342[17]). However, clinical advice to the EAG is that the company model does not capture the current experience of NHS patients and describes a treatment pathway that may be considered unethical by patients and health care professionals. In the company model, patients only receive one line of active treatment, most patients have a response to treatment for only a short period of time, and the proportion of patients who receive surgery is very low. This results in most patients, irrespective of treatment, spending decades in the active UC health state where they only receive CT. The company model is therefore of limited value to decision makers.

5.2.2 Modelling error

The company bio-exposed population NMA results suggest that, for all treatments, the percentage of patients in clinical remission increases between Week 8 (the end of the induction period) and Week 52 (the end of the maintenance period). The algorithms in the company model result in the majority of this increase occurring between Week 8 and Week 12. For example, the upadacitinib algorithms result in clinical remission rates increasing from [redacted] in Week 8 to [redacted] in Week 12. Clinical advice to the EAG is that whilst it is possible that the number of patients in clinical remission may increase over time and may be higher at 12 months than at Week 8, it is unlikely that a [redacted] increase in remission rates would ever occur within a 4-week period. In response to clarification Question B1, the company amended the model and resolved this issue for patients treated with upadacitinib; however, the company did not resolve the issue for patients treated with any of the comparators. As the company demonstrated that fixing this error did not have a significant impact on cost effectiveness results, the EAG used the original model submitted by the company as adopting this approach means the impact of this error affects both the intervention and comparator arms.

5.2.3 Induction phase clinical effectiveness estimates

The company model is populated with results from the company induction RE NMAs, except for induction/bio-exposed/clinical remission comparison and in this case the model is populated with FEA NMA results. In Section 3.6.3 of this report, the EAG discussed the robustness of the induction phase NMA results generated using RE and FEA models. The EAG considers that, all issues considered, the company parameter value choices are appropriate.

5.2.4 Maintenance phase clinical effectiveness estimates

In Section 3.6.3 of this report, the EAG discussed the robustness of the company maintenance phase RE NMA results. The EAG considers that there are specific issues relating to the construction of the NMAs which mean that the results generated by the company and EAG maintenance NMAs are questionable. It has not been possible to identify more certain effectiveness estimates. The EAG highlights that the effect of using questionable maintenance phase effectiveness estimates to populate the company model is unknown.

5.2.5 Extended induction

The company conducted a scenario analysis which included an extended induction period for non-responders. Clinical advice to the EAG is that the induction period in the NHS is longer than 8 weeks. However, the extended induction clinical evidence provided by the company is limited to a simple analysis of evidence from TA633[18] and pooled upadacitinib trials. Therefore, the EAG considers this analysis is not robust.

5.3 *Modelling issues with impact on company cost effectiveness -EAG exploration*

Summary details of company model issues with a known impact on cost effectiveness results are provided in Table 39.

Table 39 Summary of EAG key company model issues

Aspect considered	EAG comment	Section of EAG report
Treatment pathway	The company model treatment pathway does not reflect NHS clinical practice and results in most patients, regardless of treatment, ending up in the Active UC health state for many decades with no active treatment. The EAG has modelled an alternative pathway that more closely represents NHS clinical practice than the company model treatment pathway	5.4.1
Utility values	The company has used published utility estimates in the model. The NHS Reference Case[50] favours the use of utility values estimated from trial data. Therefore, the EAG has carried out a scenario that uses utility values generated from the EQ-5D data that were collected during the three upadacitinib trials	5.4.2
High and low doses of maintenance treatments	In the company model, separate analyses are carried out for low (15mg) and high (30mg) maintenance doses of upadacitinib versus comparators (30% high dose:70% standard dose). The EAG considers that this is an unfair comparison and that results from company scenario analysis 7 (ratio of high:standard maintenance doses of 30%:70% for all treatments) are informative	5.4.3
Surgery probability	In the company model, a small proportion (0.47%) of patients in the Active UC health state receive surgery each year. Clinical advice to the EAG is that this rate is lower than the rate for NHS patients with active UC. The EAG has assessed the impact of using higher surgery rates for patients in the Active UC state in a scenario analysis	5.4.4
Remission after Week 52	Loss of remission over the lifetime of the model for any treatment is assumed to be constant after Week 8. This was tested in a scenario analysis in the company submission where the probability of loss of remission/response was reduced by 25% after Year 1. The EAG has run a scenario to explore the impact of varying this assumption	5.4.4
Resource use	Clinical advice to the EAG is that the number of consultant contacts that patients in the Clinical Remission and Response without Remission health states are likely to be overestimates. Reducing the number of consultant contacts for patients in these two health states had a negligible effect on cost effectiveness results	NA

AEs	The only AE included in the company model is serious infections and these are assumed to only occur during the induction phase. Clinical advice to the EAG is that biologic treatments are immunosuppressants, which means the risk of serious infection is present for the duration of a patient's treatment. The EAG tested the impact of patients in the maintenance phase experiencing serious infections. The effect of this modification to company model on cost effectiveness results was negligible	NA
Conventional therapy	Clinical advice to the EAG is that, in the model, the treatments that make up CT do not reflect NHS clinical practice. The EAG explored the effect of changing CT costs on cost effectiveness results. As the total cost of CT is low compared to the costs of other treatments, the impact of changing CT costs on cost effectiveness results was negligible	NA
Spontaneous remission	Consistent with previous appraisals, the company has carried out a scenario analysis that includes modelling spontaneous remission (1% per cycle). Clinical advice to the EAG is that spontaneous remission is unlikely to occur in clinical practice. The EAG highlights that results from this analysis are in line with company base case results	NA

AE=adverse event; CT=conventional therapy; EAG=External Assessment Group; NA=not applicable; UC=ulcerative colitis
Source: LR*i*G in-house checklist

5.4 *EAG revisions to company model*

5.4.1 Modelled treatment pathway

In the company base case model, only one line of treatment is considered and so patients who have not had an adequate response to treatment in the induction phase or who stop responding to treatment in the maintenance phase enter the Active UC health state. This means that, by the end of 2 years, most patients (bio-naïve or bio-exposed) who received any treatment end up in the Active UC health state. For example, by the end of Week 8 and Year 2 respectively, [redacted] and [redacted] of bio-exposed patients who initially received adalimumab are in the Active UC health state (receiving CT). Even for bio-exposed patients treated with upadacitinib, the most effective treatment in the model, most patients end up in the Active UC health state by the end of Year 2.

The only way for a patient to leave the Active UC state is by having surgery or dying. In the model, as only 1 in 217 patients in the Active UC health state have surgery each year, this means that most people in the Active UC health state remain there until they die (the mean time that a patient remains in the Active UC state is 14 years, but patients can stay in this health state for over 50 years). Patients in the Active UC health state experience a low HRQoL (0.41) and are likely to be admitted to hospital. Clinical advice to the EAG is that patients with active UC treated in NHS clinical practice are either offered surgery within 12 months or are prescribed the treatment which previously gave them the best symptom alleviation, even if the patient was not considered to have responded to this treatment.

The model structure allows the company to run a scenario whereby patients can receive two lines of treatment; however, this does little to resolve the issue and only slightly delays the point at which patients enter the Active UC health state. The EAG asked the company to increase the number of lines of treatment that patients are able to receive in the model (clarification Question B2); the company did not make this change. Even if the company had made this change, it is unlikely that the change would have stopped almost all patients spending most of the model time horizon in the Active UC health state.

The EAG highlights that the company maintenance phase treatment pathway has been used in models that have been used to inform previous NICE appraisals of drugs to treat active UC (TA342[17] and TA633[18]). However, the EAG considers that whilst the treatment pathway may have been appropriate in the past, NHS practice has evolved, and the maintenance phase treatment pathway modelled by the company is no longer a reasonable reflection of the experience of patients with active UC treated in NHS clinical practice.

To generate clinical effectiveness results that more closely reflect NHS clinical practice, the EAG has replaced the company Active UC health state with an 'On Subsequent Treatment' health state. The EAG has not included the option of surgery in this health state. This health state includes patients who have:

- achieved remission on a treatment after having failed to achieve remission on earlier treatment(s)
- failed to achieve long-term remission on any drug and are unwilling or unsuitable for surgery and therefore are indefinitely prescribed the treatment which gave them the most symptom alleviation (without achieving remission).

Patients in the On Subsequent Treatment health state are modelled to receive a basket of biologic treatments based on the market share data provided by the company.[19] The EAG considered that using market share data for the fifth line of treatment would most likely represent the types of treatments NHS patients receive over the long-term. The treatment costs were weighted according to the market share data. The basket of treatment effectiveness estimate (remission or response without remission) was taken from the company maintenance bio-naïve NMAs and was used to model effectiveness for both bio-naïve and bio-exposed populations as effectiveness estimates were unavailable for some of the options used to treat patients in the bio-exposed population.

The EAG approach creates a more realistic patient pathway that includes long-term treatment use and moves away from the company base case Active UC health state, with its low utility value and high number of patients. The EAG approach also negates the need for the second-

line therapy option within the company model or the introduction of a model with multiple lines of biologic treatments.

5.4.2 Choice of utility parameter values

The company model is populated with published utility values.[74] In line with the NICE Reference Case,[50] the EAG has used utility values estimated from EQ-5D data collected during the three upadacitinib trials. The company adjusted the published utility values by adding a disutility to account for the effect of serious infections on HRQoL. The EAG considers that the effect of serious infection on HRQoL is already incorporated within the upadacitinib trial utility estimates and to include a serious infection disutility would be double-counting. The EAG preferred utility values are shown in Table 40.

Table 40 Utility values generated from EQ-5D data collected during the upadacitinib trials

Health state	Sub-group	Values used in the company base case	Upadacitinib trial-based values
Remission	Bio-naïve	0.87	[redacted]
Response without remission		0.76	[redacted]
Active ulcerative colitis		0.41	[redacted]
Remission	Bio-exposed	0.87	[redacted]
Response without remission		0.76	[redacted]
Active ulcerative colitis		0.41	[redacted]

EQ-5D=EuroQol 5-dimension
Source: Woehl et al[74]

5.4.3 High and low doses of maintenance treatments

In the company model, 30% of patients treated with each of the comparator drugs are assumed to be on the high dose maintenance treatment and the remaining 70% are assumed to be on the standard dose. Clinical advice to the EAG is that the proportion of patients on high dose maintenance treatments varies between treatments and for some treatments (e.g., golimumab and tofacitinib) a high dose maintenance treatment is rarely prescribed. However, clinical advice to the EAG is that, assuming 30% of patients are treated with the high dose across all treatments is reasonable.

The company has presented cost effectiveness results for both the standard (15mg) and high (30mg) dose of upadacitinib versus comparators in the CS; all comparator drugs are assumed to have been prescribed in 30:70 ratio of high to standard maintenance doses. The EAG considers that this is an inconsistent comparison between upadacitinib and comparator treatments. Clinical advice to the EAG is that whilst the proportion of patients who will be prescribed high dose upadacitinib maintenance therapy in clinical practice is currently unknown, an assumption of 30:70 ratio of high to standard maintenance doses is not

unreasonable. The EAG therefore considers that results from company scenario 7 (CS, Table 107), i.e., maintenance treatments prescribed at a ratio of 30% standard dose: 70% high dose for all treatments are relevant to decision makers.

5.4.4 Scenario analyses

Loss of remission

In the company model, loss of remission is calculated by estimating the reduction in response with and without remission between Week 8 and Week 52. The company has assumed that this rate can be applied for the duration of the model time horizon. This assumption results in most patients being off treatment within 2 years (or more rapidly). Clinical advice to the EAG is that this does not capture the experience of patients treated in NHS clinical practice. To test the importance of the company assumption, the EAG ran a scenario in which all patients in the Remission health state at week 52 remained in that health state unless they died (general population mortality rate applied).[73]

Surgery rates

The company base case rate of surgery for patients with active UC used (Misra 2016)[71] was estimated by analysing Health Episode Statistics data for colectomy procedures carried out on patients with a diagnosis of UC that was refractory to medical treatment and who were hospitalised. Misra 2016[71] reported that, over 15 years, 6.9% of patients had a colectomy (this is equivalent to an annual rate of 0.46%). To allow this estimate to be used in the model, the company converted this rate to a probability per cycle of first surgery for patients in the Active UC health state; the same rate was also used for the probability of a patient undergoing a second revision surgery after being left with complications following the first surgery.

Clinical advice to the EAG is that approximately 50% of patients who do not respond to active treatments will undergo surgical procedures. The other 50% of patients are offered surgery but choose not to have surgery; these patients are likely to continue to receive the treatment that had given them their best symptom alleviation to date, even if this best symptom alleviation did not constitute response. The EAG considers that, in the treatment pathway modelled by the company, the rate of surgical procedures used for patients in the Active UC health state is too low. The EAG has run a scenario using a 50% annual rate of first surgery and a 100% annual rate of second revision surgery.

5.5 *Impact on the ICER per QALY gained of additional clinical and economic analyses presented by the EAG*

The EAG made three revisions to the company model to generate an EAG preferred base case ICER per QALY gained:

- R1: EAG revised treatment pathway
- R2: use of upadacitinib trial utility values in place of published values
- R3: use of upadacitinib high and standard dose maintenance treatments in the same ratio as comparator treatments (30:70) (company scenario 7).

The EAG also carried out two scenario analyses:

- S1: patients in remission at Week 52 remain in remission until death
- S2: annual rate of first surgery from the active health state is 50% and all patients with post-surgery complications have a second surgery.

The EAG revisions have been applied to two different populations (the bio-naive population and the bio-exposed population) for two different maintenance doses of upadacitinib (15mg and 30mg). Details of how the EAG revised the company model are presented in Appendix 7.5. of this EAG report.

The results in Table 41 to Table 44 have been generated for the comparison of upadacitinib (PAS price) versus adalimumab (biosimilar price); bio-naïve/bio-exposed populations, 15mg and 30mg maintenance doses. Results for upadacitinib versus all other comparator treatments are presented in Appendix 7.5. Fully incremental results for the bio-naïve and bio-exposed populations are presented in Table 45 and Table 46 respectively.

All comparators are available to the NHS at confidential discounted prices. As results in this report have been generated using some drug prices that are not relevant to the NHS, the EAG has only provided a limited discussion of results. Results generated using the confidential discounted prices for all comparator treatments are presented in a confidential appendix.

EAG discussion of revision results

Results from the EAG probabilistic and deterministic results are similar for the comparison of upadacitinib versus adalimumab. Results from the EAG preferred scenario (R1-R3), for each population and each maintenance dose, show that treatment with upadacitinib generates more QALYs at a lower cost than each of the comparators, and therefore is dominant.

EAG discussion of scenario analysis results

Results from the two EAG scenario analyses demonstrate the [redacted] on base case cost effectiveness results of varying the loss of response to treatment and the surgery rate. These results support the EAG conclusion that company model results should not be used to inform decision making.

Table 41 EAG revisions to company model, **bio-naïve** population, UPA (15mg) maintenance dose: upadacitinib vs adalimumab biosimilar (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Adalimumab (biosimilar)		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,483
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,925
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 42 EAG revisions to company model, **bio-naïve** population, UPA (30mg) maintenance dose: upadacitinib vs adalimumab biosimilar (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Adalimumab (biosimilar)		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,264
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,927
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,042
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,483
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,745
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,370
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 43 EAG revisions to company model, **bio-exposed** population, UPA (15mg) maintenance dose: upadacitinib vs adalimumab biosimilar (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Adalimumab (biosimilar)		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,186
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£761
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,448
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,656
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,619
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 44 EAG revisions to company model, **bio-exposed** population, UPA (30mg) maintenance dose: upadacitinib vs adalimumab biosimilar (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Adalimumab (biosimilar)		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,146
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,360
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,274
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,656
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,772
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,992
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 45 EAG base case, **bio-naïve** population: fully incremental analyses (PAS price for upadacitinib)

EAG base case			Incremental		ICER £/QALY
	Cost	QALYs	Cost	QALYs	
UPA 45mg	[redacted]	[redacted]	[redacted]	[redacted]	-
GOL 200/100mg	[redacted]	[redacted]	[redacted]	[redacted]	**UPA dominates**
TOF 10mg	[redacted]	[redacted]	[redacted]	[redacted]	**UPA dominates**
ADA 160/80mg biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	**UPA dominates**
ADA 160/80mg	[redacted]	[redacted]	[redacted]	[redacted]	**UPA dominates**
IFX 5mg biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	**UPA dominates**
UST 6mg	[redacted]	[redacted]	[redacted]	[redacted]	**UPA dominates**
IFX 5mg	[redacted]	[redacted]	[redacted]	[redacted]	**UPA dominates**
VED 108mg	[redacted]	[redacted]	[redacted]	[redacted]	**UPA dominates**
VED 300mg	[redacted]	[redacted]	[redacted]	[redacted]	**UPA dominates**

ADA=adalimumab; EAG=External Assessment Group; GOL=golimumab; ICER=incremental cost effectiveness ratio; IFX=infliximab; PAS=Patient Access Scheme; QALY=quality adjusted life year; TOF=tofacitinib; UPA=upadacitinib; UST=ustekinumab; VED=vedolizumab

Table 46 EAG base case, **bio-exposed** population: fully incremental analyses (PAS price for upadacitinib, list prices other drugs)

EAG base case			Incremental		ICER £/QALY
	Cost	QALYs	Cost	QALYs	
UPA 45mg	[redacted]	[redacted]	[redacted]	[redacted]	-
ADA 160/80mg biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	**UPA dominates**
TOF 10mg	[redacted]	[redacted]	[redacted]	[redacted]	**UPA dominates**
ADA 160/80mg	[redacted]	[redacted]	[redacted]	[redacted]	**UPA dominates**
UST 6mg	[redacted]	[redacted]	[redacted]	[redacted]	**UPA dominates**
VED 108mg	[redacted]	[redacted]	[redacted]	[redacted]	**UPA dominates**
VED 300mg	[redacted]	[redacted]	[redacted]	[redacted]	**UPA dominates**

ADA=adalimumab; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; TOF=tofacitinib; UPA=upadacitinib; UST=ustekinumab; VED=vedolizumab

5.6 *Treatment severity modifiers*

The company has used the Hernandez Alava EQ-5D data, information published in HSE 2017-2018 and the QALY shortfall calculator developed by Schneider 2022[89] to estimate QALYs for the general population, and used the company model base case results to estimate QALYs for people living with active UC.

The EAG considers that all QALY estimates should be calculated using the same data source, namely the company model. The EAG has estimated the expected total QALYs for the general population using company model age and sex-specific background utility and mortality rates. The EAG total QALY estimates for patients with active UC have been generated using the EAG preferred base case assumptions.

The EAG considers that as the [redacted] (Table 47), an additional QALY weighting for severity is not necessary.

Table 47 Summary of decision modifiers - severity

Treatment	Expected total QALYs for the general population	Total QALYs that people living with active UC would be expected to have with current treatment (EAG base case)	Absolute QALY shortfall	Proportional QALY shortfall
Bio-naïve population				
UPA (15mg) maintenance dose	[redacted]	[redacted]	[redacted]	[redacted]
UPA (30mg) maintenance dose	[redacted]	[redacted]	[redacted]	[redacted]
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]
IFX biosimilar	[redacted]	[redacted]	[redacted]	[redacted]
GOL	[redacted]	[redacted]	[redacted]	[redacted]
VED	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]
TOF	[redacted]	[redacted]	[redacted]	[redacted]
Bio-exposed population				
UPA (15mg) maintenance dose	[redacted]	[redacted]	[redacted]	[redacted]
UPA (30mg) maintenance dose	[redacted]	[redacted]	[redacted]	[redacted]
ADA biosimilar	[redacted]	[redacted]	[redacted]	[redacted]
VED	[redacted]	[redacted]	[redacted]	[redacted]
UST	[redacted]	[redacted]	[redacted]	[redacted]
TOF	[redacted]	[redacted]	[redacted]	[redacted]

ADA=adalimumab; EAG=External Assessment Group; GOL=golimumab; IFX=infliximab; QALY=quality adjusted life year; TOF=tofacitinib; UPA=upadacitinib; UC=ulcerative colitis; UST=ustekinumab; VED=vedolizumab
Source: EAG calculations using company model

5.7 *Conclusions*

The EAG considers that, even if the company NMA results are considered sufficiently reliable to inform decision making, the company approach to modelling generates cost effectiveness results that are unreliable and should not be used to inform decision making. The costs and QALYs generated by the EAG preferred scenario (R1: upadacitinib trial utility values, R2: more realistic treatment pathway, R3: 30% low dose: 70% high dose for all maintenance treatments) are [redacted] than the costs and QALYs generate by the company base case.

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7 APPENDICES

7.1 *Appendix 1: EAG summary of results from the U-ACHIEVE and U-ACCOMPLISH induction trials*

Table 48 Primary and key secondary endpoints reported in the CS for the U-ACCOMPLISH and U-ACHIEVE induction trials

	Adjusted treatment difference versus placebo % (95% CI); p-value		
	Population	**U-ACHIEVE**	**U-ACCOMPLISH**
Primary endpoint: Proportion of patients who achieved clinical remission per Adapted Mayo score at Week 8	Overall ITT1	[redacted]	[redacted]
	Bio-IR	[redacted]	[redacted]
	Non-Bio-IR	[redacted]	[redacted]
Endoscopic improvement at Week 8	Overall ITT1	[redacted]	[redacted]
	Bio-IR	[redacted]	[redacted]
	Non-Bio-IR	[redacted]	[redacted]
Endoscopic remission at Week 8	Overall ITT1	[redacted]	[redacted]
	Bio-IR	[redacted]	[redacted]
	Non-Bio-IR	[redacted]	[redacted]
Clinical response per Adapted Mayo score at Week 8	Overall ITT1	[redacted]	[redacted]
	Bio-IR	[redacted]	[redacted]
	Non-Bio-IR	[redacted]	[redacted]
Clinical response per Partial Adapted Mayo score at Week 2	Overall ITT1	[redacted]	[redacted]
Histologic-endoscopic mucosal improvement at Week 8	Overall ITT1	[redacted]	[redacted]
No reported bowel urgency at Week 8	Overall ITT1	[redacted]	[redacted]
No reported abdominal pain at Week 8	Overall ITT1	[redacted]	[redacted]
Histologic improvement at Week 8	Overall ITT1	[redacted]	[redacted]
Change from Baseline in IBDQ Total score at Week 8, LS mean	Overall ITT1	[redacted]	[redacted]
Mucosal healing at Week 8	Overall ITT1	[redacted]	[redacted]
Change from Baseline in FACIT-F score at Week 8, LS mean	Overall ITT1	[redacted]	[redacted]

CS=company submission; Bio-IR=biologic therapy-intolerant or inadequate responder; CI=confidence interval; FACIT-F=Functional Assessment of Chronic Illness Therapy; IBDQ=Inflammatory Bowel Disease Questionnaire; ITT=intention to treat; LS=least squares; Non-Bio-IR=inadequate response, loss of response, or intolerance to conventional therapy but not failed biologic therapy;
Source: Extracted from CS, Table 22 and Table 23

7.2 *Appendix 2: EAG summary of results from the U-ACHIEVE maintenance study*

Table 49 Primary and secondary endpoints reported in the CS for the U-ACHIEVE maintenance trial

	Adjusted treatment difference vs placebo % (95% CI); p-value		
	U-ACHIEVE Maintenance		
	Population	UPA 15mg daily	UPA 30mg daily
Primary endpoint: Proportion of patients who achieved clinical remission per Adapted Mayo score at Week 52	ITT_A	[redacted]	[redacted]
	Bio-IR	[redacted]	[redacted]
	Non-Bio-IR	[redacted]	[redacted]
Endoscopic improvement at Week 52	ITT_A	[redacted]	[redacted]
	Bio-IR	[redacted]	[redacted]
	Non-Bio-IR	[redacted]	[redacted]
Clinical remission per Adapted Mayo score at Week 52 among patients who achieved clinical remission per Adapted Mayo score in U-ACHIEVE induction or U-ACCOMPLISH induction studies	ITT_A	[redacted]	[redacted]
	Bio-IR	[redacted]	[redacted]
	Non-Bio-IR	[redacted]	[redacted]
Clinical remission per Adapted Mayo score and corticosteroid free for ≥90 days at Week 52 among patients who achieved clinical remission per Adapted Mayo score in U-ACHIEVE induction or U-ACCOMPLISH induction studies	ITT1	[redacted]	[redacted]
	Bio-IR	[redacted]	[redacted]
	Non-Bio-IR	[redacted]	[redacted]
Endoscopic improvement at Week 52 among patients with endoscopic improvement in U-ACHIEVE induction or U ACCOMPLISH induction studies	ITT_A	[redacted]	[redacted]
	Bio-IR	[redacted]	[redacted]
	Non-Bio-IR	[redacted]	[redacted]
Endoscopic remission at Week 52	ITT_A	[redacted]	[redacted]
	Bio-IR	[redacted]	[redacted]
	Non-Bio-IR	[redacted]	[redacted]
Clinical response per Adapted Mayo score at	ITT_A	[redacted]	[redacted]

	Adjusted treatment difference vs placebo % (95% CI); p-value		
	U-ACHIEVE Maintenance		
	Population	UPA 15mg daily	UPA 30mg daily
Week 52	Bio-IR	[redacted]	[redacted]
	Non-Bio-IR	[redacted]	[redacted]
Histologic-endoscopic mucosal improvement at Week 52	ITT_A	[redacted]	[redacted]
	Bio-IR	[redacted]	[redacted]
	Non-Bio-IR	[redacted]	[redacted]
Change from Baseline in IBDQ Total score at Week 52, LS mean	ITT_A	[redacted]	[redacted]
Mucosal healing at Week 52	ITT_A	[redacted]	[redacted]
	Bio-IR	[redacted]	[redacted]
	Non-Bio-IR	[redacted]	[redacted]
No reported bowel urgency at Week 52	ITT_A	[redacted]	[redacted]
No reported abdominal pain at Week 52	ITT_A	[redacted]	[redacted]
Change from Baseline in FACIT-F score at Week 52, LS mean	ITT_A	[redacted]	[redacted]

CS=company submission; Bio-IR=biologic therapy-intolerant or inadequate responder; CI=confidence interval; FACIT-F=Functional Assessment of Chronic Illness Therapy; IBDQ=Inflammatory Bowel Disease Questionnaire; ITT=intention to treat; LS=least squares; Non-Bio-IR=inadequate response, loss of response, or intolerance to conventional therapy but not failed biologic therapy
Source: Extracted from CS, Table 25, Table 26 and Table 27

7.3 *Appendix 3: Safety results for upadacitinib versus placebo*

U-ACHIEVE and U-ACCOMPLISH 8-week Induction trial safety data is reported in the CS (Section B.2.10 and Appendix F) (upadacitinib 45mg versus placebo). Adverse events in both induction trials were coded using the Medical Dictionary for Regulatory Activities (MedDRA),[91] version 23.0. The safety populations (SA1) of both induction trials included patients who had received ≥1 dose of upadacitinib 45mg once daily (QD) in Part 1 (up to Week 8). The company provided any AE, AEs in ≥2% of patients, SAEs, AESIs, and AEs leading to discontinuation data.

The mean (standard deviation [SD]) duration of study drug exposure was similar between upadacitinib and placebo in both the U-ACHIEVE (upadacitinib: [redacted] and placebo: [redacted] and U-ACCOMPLISH (upadacitinib: [redacted] and placebo: [redacted] induction trials (part 1). The mean duration of study drug exposure was also similar between the upadacitinib and placebo arms in the U-ACHIEVE maintenance trial (upadacitinib 15mg: [redacted] upadacitinib 30mg: [redacted], and placebo: [redacted]

7.3.1 Induction trials

Overview of adverse events

An overview of the AEs that occurred in the U-ACHIEVE and U-ACCOMPLISH induction trials up to Week 8 is presented in the CS (Table 42). In summary, the rates of any AEs were higher for upadacitinib 45mg in the U-ACCOMPLISH trial only ([redacted] versus [redacted] for placebo). In both trials lower incidence rates were found for upadacitinib 45mg compared to placebo for SAEs, severe AEs and AEs leading to drug discontinuation, but not for AEs possibly related to the study drug (U-ACHIEVE[redacted] for placebo, U-ACCOMPLISH: [redacted] versus [redacted] for placebo). There [redacted] deaths [redacted] AEs that had led to death reported in the upadacitinib 45mg or placebo arms of either induction trial.

Adverse events leading to drug discontinuation

The most common AEs leading to discontinuation in any treatment arm in either induction trial were those related to gastrointestinal (GI) disorders; these rates were numerically higher in patients treated with placebo [redacted] and [redacted] compared to upadacitinib 45mg ([redacted] in both trials) (see CS, Section B.2.10.1.1, Table 46).

Adverse events reported in ≥2% of patients

The most common AEs (reported in ≥2% of patients by week 8) across both induction trials are reported in the CS (Section B.2.10.1.1, Table 43). The most common AEs reported by either induction trial in patients treated with upadacitinib 45mg were blood creatine

phosphokinase (CPK) increase, acne and nasopharyngitis. For placebo, the most common AEs reported by either induction trial included worsening of UC, anaemia and headache.

Serious adverse events

The most common SAEs reported by week 8 for patients treated with upadacitinib 45mg or placebo in either of the induction trials were related to GI disorders, infections and infestations. The frequency of GI disorders was lower in upadacitinib 45mg treated patients than in placebo for both the U-ACHIEVE ([redacted] vs [redacted] respectively) trial and the U-ACCOMPLISH ([redacted] vs [redacted] respectively) trial. Rates of infection and infestation were similar between the upadacitinib 45mg and placebo arms of both induction trials (see CS, Section B.2.10.1.1, Table 44).

Adverse events of special interest

Adverse events of special interest that occurred in the U-ACHIEVE and the U-ACCOMPLISH induction trials are presented in the CS (Section B.2.10.1.1, Table 45). The most commonly reported AESIs for upadacitinib 45mg in the induction trials included neutropenia, CPK elevation, anaemia and lymphopenia. For placebo, the most commonly reported AESIs in the induction trials included anaemia, CPK elevation and hepatic disorder.

7.3.2 Maintenance trial

Overview of adverse events

An overview of adverse events reported in the U-ACHIEVE maintenance trial up to week 52 is presented in Table 47 of the CS. During the 52-week maintenance trial, the overall incidence of adverse events was similar for patients receiving 15mg or 30mg of upadacitinib or placebo ([redacted], [redacted] and [redacted] respectively). For both the upadacitinib 15mg and 30mg arms, incidence rates were lower than placebo for SAEs ([redacted] respectively), severe AEs ([redacted] respectively), and AEs leading to drug discontinuation [redacted] respectively). There were [redacted] deaths [redacted] AEs that led to death reported in either the upadacitinib or placebo arms.

Adverse events leading to drug discontinuation

The most common AEs leading to discontinuation in any treatment arm of the U-ACHIEVE maintenance trial were related to GI disorders, infections and infestations, with rates being higher in the placebo groups than for upadacitinib 15mg and 30mg (GI disorders: [redacted] respectively; infections: [redacted] respectively) (see CS, Section B.2.10.1.1, Table 51).

Adverse events reported in ≥2% of patients

The most common AEs (reported in ≥2% of patients) in the U-ACHIEVE 52-week maintenance trial are reported in the CS (Section B.2.10.1.2, Table 48). The most common AEs reported in patients treated with upadacitinib 15mg or 30mg were nasopharyngitis, worsening of UC, and blood CPK increase. In the placebo arm, the most common AEs were nasopharyngitis, worsening of UC and arthralgia.

Serious adverse events

The most common SAEs reported in ≥2% of patients in the U-ACHIEVE 52-week maintenance trial for patients treated with upadacitinib (15mg or 30mg) or placebo were related to GI disorders, and infections and infestations. For both upadacitinib 15mg and 30mg, the frequency of GI disorders was lower compared to placebo ([redacted] respectively). Similarly, the rates of infections and infestations were lower for patients receiving upadacitinib 15mg and 30mg compared to placebo ([redacted] respectively) (see CS, Section B.2.10.1.2, Table 49).

Adverse events of special interest

Adverse events of special interest that occurred in the U-ACHIEVE maintenance trial are presented in the CS (Section B.2.10.1.2, Table 50). The most commonly reported AESIs for upadacitinib 15mg or 30mg included neutropenia, CPK elevation, anaemia, lymphopenia and hepatic disorder. For placebo, the most commonly reported AESIs in the maintenance trial included CPK elevation, anaemia and hepatic disorder.

7.3.3 Induction trials: pooled safety analysis

The company provided a pooled analysis of 8-week safety data from the U-ACHIEVE and U-ACCOMPLISH induction trials (CS, Section B.2.10 and Appendix F). For the 8-week induction period, the company provide data on the incidence of AEs, AEs reported in ≥2% of patients and AESIs.

Overview of adverse events

For the pooled analysis, the AE events for upadacitinib and placebo that occurred in the 8-week induction trials are presented in Table 52 of the CS. Upadacitinib 45mg had higher rates than placebo for rates of any AE ([redacted] respectively), and any AE possibly related to the study drug by investigator assessment ([redacted] respectively). Lower incidence rates were found for upadacitinib 45mg compared to placebo for SAEs ([redacted] respectively), severe AEs ([redacted] respectively), and AEs leading to discontinuation ([redacted] respectively). [redacted] deaths were reported in the upadacitinib or placebo arms.

Adverse events reported in ≥2% of patients

The most common AEs (reported in ≥2% of patients by week 8) for upadacitinib and placebo in the pooled analysis are reported in the CS (Table 53). In the pooled analysis, the most common AEs reported for upadacitinib 45mg until week 8 were acne, nasopharyngitis and blood CPK increase. In the placebo group, the most common AEs up to week 8 were worsening of UC, headache and anaemia.

Adverse events of special interest

The rates of AESIs for upadacitinib and placebo in the pooled analysis are presented in the CS (Table 54). The most frequently occurring AESIs for upadacitinib 45mg were neutropenia and anaemia, and for the placebo arm was anaemia.

7.3.4 Maintenance trial: pooled safety analysis

The company provided pooled safety data for maintenance treatment with upadacitinib 15mg and 30mg (CS, Appendix F). For the maintenance phase, the company presented data on the incidence of exposure-adjusted AEs per 100 patient-years (PY) and AEs reported in ≥5 events per 100PY.

Overview of adverse events

In the pooled analysis (15mg and 30mg upadacitinib) of the maintenance trial, exposure-adjusted event rates (EAERs) for AE categories, including AEs, SAEs, severe AEs, AEs leading to drug discontinuation and AEs with a possibility of being related to the study drug were presented in the CS (Appendix F, Table 29). In all of these AE categories, rates were lower for upadacitinib (15mg or 30mg) than placebo:

- Any AEs (upadacitinib 15mg: [redacted], upadacitinib 30mg: [redacted], and placebo: [redacted])
- SAEs (upadacitinib 15mg: [redacted], upadacitinib 30mg: [redacted], and placebo: [redacted])
- Severe AEs (upadacitinib 15mg[redacted] upadacitinib 30mg[redacted], and placebo: [redacted]
- AEs leading to drug discontinuation (upadacitinib 15mg: [redacted], upadacitinib 30mg: [redacted] and placebo: [redacted]
- AEs that may be drug-related by investigator assessment (upadacitinib 15mg: [redacted], upadacitinib 30mg: [redacted] and placebo: [redacted])

The EAERs of these categories were similar between the upadacitinib 15mg and 30mg doses, except that the upadacitinib 30mg dose showed a higher rate of any AE leading to discontinuation of the drug, and any AE with reasonable possibility of being related to the drug.

Adverse events reported in ≥10 events[E]/100 patient-years

The most frequently reported (≥10 events[E]/100 patient-years) AEs are presented in the CS (Appendix F, Table 30). In summary:

- For upadacitinib 15mg, the most frequently reported AEs were worsening of UC (versus for placebo), and nasopharyngitis (for placebo)
- For upadacitinib 30mg, the most commonly reported AEs were nasopharyngitis (for placebo), and increased blood CPK (for placebo)
- For placebo, the most frequently occurring AEs were worsening of UC (for upadacitinib 15mg and 30mg respectively), and nasopharyngitis (for upadacitinib 15mg and 30mg respectively)

7.4 *Appendix 4: Quality assessment of trials included in the NMA analysis*

Table 50 Company and EAG quality assessment of trials included in the company NMAs

Study	Was randomisation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Was allocation adequately concealed?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Did the analysis included an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
ACT-1[27] (NCT00036439)	Yes	Yes	Yes	No	No	No	Yes
EAG assessment (if different from the company):				Unclear (no mention of who was blinded to treatment)			Partial (ITT but no mention of methods for missing data handling)
ACT-2[27] (NCT00096655)	Yes	Yes	Yes	No	No	No	Yes
EAG assessment (if different from the company):				Unclear (no mention of who was blinded to treatment)			Partial (ITT but no mention of methods for handling missing data)
Japic CTI-060298[28]	Yes	Yes	Yes	No	No	No	Yes
EAG assessment (if different from the company):				Unclear (no mention of who was blinded to treatment)			Partial (ITT but no mention of methods for missing data handling)
Jiang 2015[29]	Yes	Yes	Yes	No	No	No	Yes
EAG assessment (if different from the company):				Unclear (no mention of who was blinded to treatment)			Partial (ITT but no mention of methods for missing data handling)
NCT01551290[30]	Yes	Not clear	Yes	No	Not clear	No	Yes
EAG assessment (if different from the company):	Unclear (randomisation method not given)		Unclear (randomisation method not given)	Unclear (no mention of who was blinded to treatment)			Partial (ITT but no mention of methods for missing data handling)

Study	Was randomisation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Was allocation adequately concealed?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Did the analysis included an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
ULTRA-1[31] (NCT00385736)	Yes	Yes	Yes	Yes	No	No	Yes
EAG assessment (if different from the company):							
ULTRA-2[32,92-96] (NCT02065622)	Yes	Yes	Yes	Yes	No	No	Yes
EAG assessment (if different from the company):				Unclear (no mention of who was blinded to treatment)			
M10-447[33] (NCT00853099)	Yes	Yes	Yes	No	No	No	Yes
EAG assessment (if different from the company):				Unclear (no mention of who was blinded to treatment)			
SERENE-UC[34,97] (NCT02065622)	Yes	Yes	Yes	Yes	Not clear	No	Yes
EAG assessment (if different from the company):					No (rates of discontinuation were low and comparable between groups. Provide numbers and reasons for discontinuation)		
PURSUIT-J[35] (NCT01863771)	Yes	Yes	Yes	No	Yes	No	Yes
EAG assessment (if different from the company):				Unclear (no mention of who was blinded to treatment)			

Study	Was randomisation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Was allocation adequately concealed?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Did the analysis included an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
PURSUIT-M[38] (NCT00488631)	Yes	Yes	Yes	No	No	No	Yes
EAG assessment (if different from the company):				Unclear (no mention of who was blinded to treatment)			
PURSUIT-SC[37] (NCT00487539)	Yes	Yes	Yes	No	No	No	Yes
EAG assessment (if different from the company):				Unclear (no mention of who was blinded to treatment)			
GEMINI-1[36,98,99] (NCT00783718)	Yes	Yes	Yes	No	No	No	Yes
EAG assessment (if different from the company):				Unclear (no mention of who was blinded to treatment)			Partial (ITT but no mention of methods for missing data handling)
NCT02039505[39,100]	Yes	Yes	Yes	Yes	No	No	Yes
EAG assessment (if different from the company):				Yes (except for study site pharmacists)			Partial (ITT but no mention of methods for missing data handling)
UNIFI[40,101-105] (NCT02407236)	Yes	Yes	Yes	No	No	No	Yes
EAG assessment (if different from the company):				Unclear (no mention of who was blinded to treatment)			

Study	Was randomisation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Was allocation adequately concealed?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there unexpected imbalances in dropouts between groups?	Were any outcomes measured but not reported?	Did the analysis included an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
OCTAVE-1[41,58,106-118] (NCT01465763)	Yes	Yes	Yes	Yes	No	No	Yes
EAG assessment (if different from the company):				Unclear (no mention of who was blinded to treatment)			
OCTAVE-2[41,58,106-118] (NCT01458951)	Yes	No	Yes	Yes	No	No	Yes
EAG assessment (if different from the company):		Yes (except for gender)		Unclear (no mention of who was blinded to treatment)			
OCTAVE Sustain[41,58,106-118] (NCT01458574)	Yes	No	Yes	No	Yes	No	Yes
EAG assessment (if different from the company):		Yes (except for smoking status)		Unclear (no mention of who was blinded to treatment)			

EAG=External Assessment Group; ITT=intention to treat; NMA=network meta-analysis
Source: CS, Appendix D, Table 27

7.5 *Appendix 5: Microsoft Excel revisions made by the EAG to the company model*

This appendix contains details of the changes that the EAG made to the company model. The EAG has added an additional sheet named 'EAG basket of subs txts' to the company model. The values in this sheet are needed to run the EAG scenarios.

To change between the 15mg and 30mg maintenance doses of upadacitinib, values in cells G144 and G228 in the sheet named 'Inputs – Tx related' need to be amended.

Table 51 EAG revisions to the company model

EAG revisions	Implementation instructions
R1: Use trial based utility values that are separate for bio-naïve and bio-exposed subgroups	In Sheet 'Inputs General' Change cell G55 to =IF(EAG_Mod_A=1, IF(subgroup_id=1,[redacted]),0.87) Change cell G56 to =IF(EAG_Mod_A=1, IF(subgroup_id=1,[redacted]),0.76) Change cell G57 to =IF(EAG_Mod_A=1, IF(subgroup_id=1,[redacted]),0.41) Change cell H55 to =IF(EAG_Mod_A=1,IF(subgroup_id=1,$G55-NORM.INV(0.975,0,1)*([redacted] /(SQRT([redacted])),$G55-NORM.INV(0.975,0,1)*([redacted] /(SQRT([redacted])))),MAX(0,$G55*(1-HU_var_per))) Change cell I55 to =IF(EAG_Mod_A=1,IF(subgroup_id=1,$G55+NORM.INV(0.975,0,1)*([redacted] /(SQRT([redacted]))),$G55+NORM.INV(0.975,0,1)*([redacted] /(SQRT(136)))),MIN(1,$G55*(1+HU_var_per))) Change cell H56 to =IF(EAG_Mod_A=1,IF(subgroup_id=1,$G56-NORM.INV(0.975,0,1)*([redacted] SQRT([redacted]))),$G56-NORM.INV(0.975,0,1)[redacted] /(SQRT([redacted])))),MAX(0,$G56*(1-HU_var_per)))

EAG revisions	Implementation instructions
	Change cell I56 to =IF(EAG_Mod_A=1,IF(subgroup_id=1,$G56+NORM.INV(0.975,0,1)*([redacted])),$G56+NORM.INV(0.975,0,1)*([redacted])),MIN(1,$G56*(1+HU_var_per))) Change cell H57 to =IF(EAG_Mod_A=1,IF(subgroup_id=1,$G57-NORM.INV(0.975,0,1)*([redacted])),$G57-NORM.INV(0.975,0,1)*([redacted])),MAX(0,$G57*(1-HU_var_per))) Change cell I57 =IF(EAG_Mod_A=1,IF(subgroup_id=1,$G57+NORM.INV(0.975,0,1)*([redacted])),$G57+NORM.INV(0.975,0,1)*([redacted])),MIN(1,$G57*(1+HU_var_per))) **Remove AE disutility** Change cell G61 =IF(EAG_Mod_A=1,0,-0.156) In sheet M_Int: Change cell BN9 to: =IF(EAG_Mod_A=1,0,BN10/BN2/13) In sheet M_Comp: Change cell BN9 to: =IF(EAG_Mod_A=1,0,BN10/BN2/13) **For PSA runs** In Sheet 'Inputs - PSA' Change G59 to 0 Change G130 to 0

EAG revisions	Implementation instructions
R2: Basket of treatments in the 'Active UC' health state	In Sheet 'Inputs General' **Change utility values** Change cell G57 to =IF(EAG_Mod_B=1,'EAG basket of subs txs'!AD15,IF(EAG_Mod_A=1, IF(subgroup_id=1,0[redacted]),0.41)) **Turn off surgery** Change cell G132 to =IF(EAG_Mod_B=1,0,IF(EAG_Mod_E=1,50%,0.47%)) In Sheet 'Inputs Regimen costs' Change cell G52 =IF(EAG_Mod_B=1,'EAG basket of subs txs'!AF15+'EAG basket of subs txs'!AH15,VLOOKUP($E52,lib_maint_cost_naive,5,FALSE)) Change cell G66 =IF(EAG_Mod_B=1,'EAG basket of subs txs'!AF15+'EAG basket of subs txs'!AH15,VLOOKUP($E66,lib_maint_esc_cost_naive,5,FALSE)) Change cell G109 =IF(EAG_Mod_B=1,'EAG basket of subs txs'!AF15+'EAG basket of subs txs'!AH15,VLOOKUP($E109,lib_maint_cost_exp,5,FALSE)) Change cell G123 =IF(EAG_Mod_B=1,'EAG basket of subs txs'!AF15+'EAG basket of subs txs'!AH15,VLOOKUP($E123,lib_maint_esc_cost_exp,5,FALSE)) In Sheet 'M_Int' Change cell DW5 =IF(EAG_Mod_B=1,0,VLOOKUP(DW$4,direct_cost_HS,2,FALSE)/13) Change cell EH5 =IF(EAG_Mod_B=1,0,VLOOKUP(EH$4,direct_cost_HS,2,FALSE)/13)

EAG revisions	Implementation instructions
	In Sheet 'M_Comp' Change cell DW5 =IF(EAG_Mod_B=1,0,VLOOKUP(DW$4,direct_cost_HS,2,FALSE)/13) Change cell EH5 =IF(EAG_Mod_B=1,0,VLOOKUP(EH$4,direct_cost_HS,2,FALSE)/13)
R3: 30:70 maintenance split in line with comparator treatments	In sheet 'Inputs – Tx related' Change cell G144 to: =IF(EAG_Mod_C=1,30%,100%) Change cell G228 to: =IF(EAG_Mod_C=1,30%,100%) Change cell F228 to: =IF('Inputs - General'!$G$2,'Inputs - PSA'!$F$377,$G$228)
S1: Everyone stays in remission at 12 months	In Sheet 'Calc - Model States and TP' Change cell H47 to =IF(EAG_Mod_D=1,1,1-J47-K47) Change cell J47 to =IF(EAG_Mod_D=1,0,$E$19) Change cell K47 to =IF(EAG_Mod_D=1,0,$E$20) Change cell H253 to

EAG revisions	Implementation instructions
	=IF(EAG_Mod_D=1,1,1-J253-K253) Change cell J253 to =IF(EAG_Mod_D=1,0,$F$19) Change cell K253 to =IF(EAG_Mod_D=1,0,$F$20)
S2: Change the annual rate of 1st surgery to 50%	In Sheet 'Inputs General' Change cell G132 to =IF(EAG_Mod_E=1,50%,0.47%)
S2: Change the annual rate of 2nd surgery post complications to 50%	In Sheet 'Inputs General' Change cell G135 to =IF(EAG_Mod_F=1,100%,0.47%) **Set the higher bound to 100%** Change cell I135 =IF(EAG_Mod_F=1,1,$G135*1.05)

7.6 *Appendix 6: EAG cost effectiveness results: UPA versus comparator*

Table 51 EAG revisions to company model, **bio-naïve** population, UPA (15mg) maintenance dose: upadacitinib vs adalimumab (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Adalimumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,343
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 52 EAG revisions to company model, **bio-naïve** population, UPA (30mg) maintenance dose: upadacitinib vs adalimumab (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Adalimumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,594
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,254
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,643
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,343
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,952
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,274
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 53 EAG revisions to company model**, bio-exposed** population, UPA (15mg) maintenance dose: upadacitinib vs adalimumab (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Adalimumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£472
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,842
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,218
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 54 EAG revisions to company model, **bio-exposed** population, UPA (30mg) maintenance dose: upadacitinib vs adalimumab (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Adalimumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,398
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,758
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,135
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,842
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,424
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,362
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 55 EAG revisions to company model, **bio-naïve** population, UPA (15mg) maintenance dose: upadacitinib vs infliximab (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Infliximab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 56 EAG revisions to company model, **bio-naïve** population, UPA (30mg) maintenance dose: upadacitinib vs infliximab (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Infliximab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,060
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,844
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,481
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,962
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 57 EAG revisions to company model, **bio-naïve** population, UPA (15mg) maintenance dose: upadacitinib vs infliximab biosimilar (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Infliximab (biosimilar)		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 58 EAG revisions to company model, **bio-naïve** population, UPA (30mg) maintenance dose: upadacitinib vs infliximab biosimilar (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Infliximab (biosimilar)		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,642
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,320
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,567
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,509
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 59 EAG revisions to company model, **bio-naïve** population, UPA (15mg) maintenance dose: upadacitinib vs tofacitinib (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Tofacitinib		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£397,399
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,976,895
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,913,277*

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib
*South-West quadrant

Table 60 EAG revisions to company model, **bio-naïve** population, UPA (30mg) maintenance dose: upadacitinib vs tofacitinib (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Tofacitinib		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,173
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,033
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,031
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£341,856
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,421,146
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,652
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,913,277*

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib
*South-West quadrant

Table 61 EAG revisions to company model, **bio-exposed** population, UPA (15mg) maintenance dose: upadacitinib vs tofacitinib (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Tofacitinib		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 62 EAG revisions to company model, **bio-exposed** population, UPA (30mg) maintenance dose: upadacitinib vs tofacitinib (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Tofacitinib		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,592
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,711
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,797
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,685
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,783
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 63 EAG revisions to company model, **bio-naïve** population, UPA (15mg) maintenance dose: upadacitinib vs ustekinumab (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Ustekinumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 64 EAG revisions to company model, **bio-naïve** population, UPA (30mg) maintenance dose: upadacitinib vs ustekinumab (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Ustekinumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,932
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,440
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,640
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,712
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 65 EAG revisions to company model, **bio-exposed** population, UPA (15mg) maintenance dose: upadacitinib vs ustekinumab (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Ustekinumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 66 EAG revisions to company model, **bio-exposed** population, UPA (30mg) maintenance dose: upadacitinib vs ustekinumab (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Ustekinumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,221
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,306
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,753
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,074
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,934
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 67 EAG revisions to company model, **bio-naïve** population, UPA (15mg) maintenance dose: upadacitinib vs vedolizumab IV (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Vedolizumab (IV)		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,459,203*
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£170,986,021*
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£197,912,032*

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IV=intravenous; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib
*South-West quadrant

Table 68 EAG revisions to company model, **bio-naïve** population, UPA (30mg) maintenance dose: upadacitinib vs vedolizumab IV (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Vedolizumab (IV)		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£321
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£241
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£498
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£64,455,050*
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£768,576,731*
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,725
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£197,912,032*

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IV=intravenous; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib
*South-West quadrant

Table 69 EAG revisions to company model, **bio-exposed** population, UPA (15mg) maintenance dose: upadacitinib vs vedolizumab IV (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Vedolizumab (IV)		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IV=intravenous; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 70 EAG revisions to company model, **bio-exposed** population, UPA (30mg) maintenance dose: upadacitinib vs vedolizumab IV (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Vedolizumab (IV)		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,326
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,638
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,622
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,559
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; IV=intravenous; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 71 EAG revisions to company model, **bio-naïve** population, UPA (15mg) maintenance dose: upadacitinib vs vedolizumab SC (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Vedolizumab (SC)		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,585,139
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£130,740,406*
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£150,757,357*

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; SC=subcutaneous; UPA=upadacitinib
*South-West quadrant

Table 72 EAG revisions to company model, **bio-naïve** population, UPA (30mg) maintenance dose: upadacitinib vs vedolizumab SC (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Vedolizumab (SC)		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,110
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,798
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,056
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,737,148*
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£569,228,647*
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,515
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£150,757,357*

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; SC=subcutaneous; UPA=upadacitinib
*South-West quadrant

Table 73 EAG revisions to company model, **bio-exposed** population, UPA (15mg) maintenance dose: upadacitinib vs vedolizumab SC (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Vedolizumab (SC)		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadactinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; SC=subcutaneous; UPA=upadacitinib

Table 74 EAG revisions to company model, **bio-exposed** population, UPA (30mg) maintenance dose: upadacitinib vs vedolizumab SC (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Vedolizumab (SC)		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,382
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,216
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,479
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R3: Upadacitinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,414
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,689
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; SC=subcutaneous; UPA=upadacitinib

Table 75 EAG revisions to company model, **bio-naïve** population, UPA (15mg) maintenance dose: upadacitinib vs golimumab (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Golimumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,027,915*
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,540,924*
R3: Upadacitinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,780,929*

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib
*South-West quadrant

Table 76 EAG revisions to company model, **bio-naïve population**, UPA (30mg) maintenance dose: upadacitinib vs golimumab (PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Golimumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,333
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,019
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,938
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,038,920*
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,716,915*
R3: Upadacitinib high and standard dose maintenance in the same ratio (30:70) as comparator treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,303
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,166
B1. EAG combined revisions (R1-R3) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R3) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,780,929*

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib
*South-West quadrant

Single Technology Appraisal

EAG report – factual accuracy check and confidential information check

Upadacitinib for treating moderately to severely active ulcerative colitis [ID3953]

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG 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 the end of **145 July 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Key issues

Issue 1 Incorrect cost-effectiveness results in the Executive Summary

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 14, Section 1.5 (Summary of EAG's preferred assumptions and resulting ICER). Table A.	The results in rows R1 and R2 have been mixed up in this table for both upadacitinib 15 mg and upadacitinib 30 mg. This is a labelling error.	Align results with the correct results in Table 41 and Table 42.	Thank you for your response. The EAG has relabelled R1 and R2 in Table A.
Page 15, Section 1.5 (Summary of EAG's preferred assumptions and resulting ICER). Table B.	The results in rows R1 and R2 have been mixed up in this table for both upadacitinib 15 mg and upadacitinib 30 mg. This is a labelling error.	Align results with the correct results in Table 43 and Table 44.	Thank you for your response. The EAG has relabelled R1 and R2 in Table B.

Issue 2 Incorrect description of base case analysis

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
First paragraph of Section 4.4.7 (Health state remission and response transition probabilities), page 70.	Current text: 'The length of the induction phase of treatment varied by treatment; most treatments were associated with a standard induction phase (ranging in length from 6 to 8 weeks) and an extended induction phase (length of standard phase	Suggest amending to the following: 'The length of the induction phase of treatment varied by treatment; most treatments	Text amended as suggested.

	plus a follow-on phase of between 4 and 8 weeks).' An extended induction phase (length of standard phase plus a follow-on phase of between 4 and 8 weeks) was only considered in a scenario analysis, not the base case so this text is misleading.	were associated with a standard induction phase **of** 6 to 8 weeks. An extended induction phase (length of standard phase plus a follow-on phase of between 4 and 8 weeks) **was considered in scenario analysis**.'	

Issue 3 Incorrect description of NMA results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG STA Report page 49 "In [redacted]. The results from the company's maintenance NMAs were mixed; upadacitinib (30mg) ranked within the top three for all outcomes [redacted]"	Company proposes an accurate description upadacitinib 15 mg results, such as: In summary [redacted] versus placebo for all outcomes. The results from the company's maintenance NMAs showed that upadacitinib 30mg ranked [redacted] all outcomes whereas upadacitinib 15mg ranked within [redacted] for all outcomes apart from maintenance/bio-naïve/clinical remission	The description is factually incorrect due to omission of information: NMAs for clinical response but also for clinical remission showed that upadacitinib was the best performing intervention vs. Placebo (see tables 33 and 35 in CS) Second statement regarding upadacitinib 15mg is factually incorrect due to : according to tables 38-41 in the CS, UPA15 ranked 2nd, 3rd or 4th for all outcomes with statistically	Thank you. Text amended in line with company proposal except "for all outcomes" in the company sentence about the induction NMAs has been replaced with "for clinical remission and clinical response" to be clear that upadacitinib was not the best performing intervention versus placebo for serious infections.

	where it ranked [redacted] with a non-statistically significant OR vs. Placebo.	significant OR vs. Placebo, apart from maintenance/bio-naïve/clinical remission where UPA15 ranked 6th with a non-statistically significant OR vs. placebo. As such, 'less well than' is not appropriate in this context.	

Issue 4 Error in endpoint description

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 3, page 24. Column (Final scope issued by NICE) - outcome measure reported as: 'Endoscopic remission combined with histological improvement corticosteroid-free remission' is incorrect	'Endoscopic remission combined with histological improvement corticosteroid-free remission' is incorrect' should be reported as two separate outcome measures: • Endoscopic healing combined with histological improvement • Corticosteroid-free remission	Missing bullet in the final scope leading to misunderstanding regarding endpoint.	NICE has confirmed the missing bullet. Bullet points in table 3 amended.
Page 30: The company addressed "endoscopic healing combined with histological improvement corticosteroid free remission" as two separate outcomes.	'Endoscopic remission combined with histological improvement corticosteroid-free remission' is incorrect' should be reported as two separate outcome measures:	Missing bullet in the final scope leading to misunderstanding regarding endpoint.	NICE has confirmed the missing bullet. Bullet points in table 3 amended.

	• Endoscopic healing combined with histological improvement • Corticosteroid-free remission		

Issue 5

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Give full details of inaccuracy found including page number in EAG report	Give details of any corrections that should be made	Justify why the error needs correcting and the impact it will have	N/A

(please cut and paste further tables as necessary)

Other issues

Issue 6 Inaccurate criteria reported for clinical response

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Clinical response is defined in the EAG report as a decrease from baseline in FMS ≥3 points and ≥30%. Page 30, Section 2.5.5 (Outcomes), paragraph 2.	Clinical response should instead be defined as a decrease from baseline in FMS ≥2 points and ≥30%.	To correctly report the clinical response criteria in the report.	The EAG refers the company to the description of clinical response within the CS, "FMS ≥3 points and ≥30%" which appears in the CS (as a footnote to Table 29 (p78), the first paragraph on p80 and in Appendix D). No change required.

Issue 7 Inaccurate proportions/percentages of discontinuations reported

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
U-ACHIEVE induction trial discontinuation is reported as 4% in the EAG report. Page 36, Section 3.2.4 (Quality assessment), paragraph 2.	Discontinuation should instead be reported as 4.1% as per the convention used (to one decimal place) for the other discontinuation data points in the section.	To correctly report the discontinuation rate in the report.	Thank you. The EAG has been updated as advised.
U-ACHIEVE induction trial discontinuation is reported as 33% in the EAG report. Page	Discontinuation should instead be reported as 33.1% as per the convention used (to	To correctly report the discontinuation rate in the report.	Thank you. The EAG has been updated as advised.

36, Section 3.2.4 (Quality assessment), paragraph 2.	one decimal place) for the other discontinuation data points in the section.		
U-ACHIEVE induction trial discontinuation is reported as 21% in the EAG report. Page 36, Section 3.2.4 (Quality assessment), paragraph 2.	Discontinuation should instead be reported as 21.4% as per the convention used (to one decimal place) for the other discontinuation data points in the section.	To correctly report the discontinuation rate in the report.	Thank you. The EAG has been updated as advised.
U-ACHIEVE induction trial discontinuation is reported as 66% in the EAG report. Page 36, Section 3.2.4 (Quality assessment), paragraph 2.	Discontinuation should instead be reported as 65.8% as per the convention used (to one decimal place) for the other discontinuation data points in the section.	To correctly report the discontinuation rate in the report.	Thank you. The EAG has been updated as advised.

Issue 8 Table source incorrectly reported

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The Table from which the source data is taken in the Company submission document is reported as Table 45. Page 115, Section 7.3.1 (Adverse events leading to drug discontinuation), paragraph 1.	The Table from which the source data was taken should be cited as Table 46.	To correctly report the source data Table.	Thank you. Table reference amended.

Issue 9 Incorrect comparator reported in description of results in the Executive Summary

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14, Section 1.5 (Summary of EAG's preferred assumptions and resulting ICER),	The text above Table A inaccurately reports that results have been presented for the comparison of upadacitinib versus upadacitinib (biosimilar price). Current text: 'The EAG has presented results for the comparison of upadacitinib (Patient Access Scheme [PAS] price) versus upadacitinib (biosimilar price).'	Suggest amending to the following: 'The EAG has presented results for the comparison of upadacitinib (Patient Access Scheme [PAS] price) versus **adalimumab** (biosimilar price).'	Thank you. Text amended.

Issue 10 Incorrect or incomplete reporting of modelling assumptions and descriptions of health states

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 19 (Treatment-related assumptions used in the company model), Page 68, Section 4.4.4 (Intervention and comparators).	The table suggests that treatment sequencing was not considered in the Company Submission. This is misleading since treatment sequencing was considered in a scenario analysis. Current text: 'None. Patients discontinuing treatment are assumed to receive CT.'	Suggest amending to the following: 'Patients discontinuing treatment are assumed to receive CT **in the base case**. **One line of subsequent treatment**	Thank you. Text amended to include reference to the sequencing scenario analysis.

		(ustekinumab) is considered in a scenario analysis.' This aligns with the CS.	
First surgery health state description, Table 20 (Description of company Markov model health states and the data sources used to move patients between health states), Page 70, Section 4.4.6 (Model structure).	Description of data source could be amended for accuracy. Current text: 'Data source: probability of 1st and 2nd surgery (0.47%) was derived from Misra 2016[71]'	Suggest amending to the following: 'Data source: **annual** probability of 1st and 2nd surgery (0.47%) was derived from Misra 2016[71] **and applied to the active UC health state**'	Thank you. Text amended.
Post-first surgery complications health state description, Table 20 (Description of company Markov model health states and the data sources used to move patients between health states), Page 70, Section 4.4.6 (Model structure).	Description of data source could be amended for accuracy. Current text: 'Data source: chronic complications of first surgery (33.5%) were derived from a national report 2014). The rate of late chronic complications (5.64%) is based on a weighted average of values derived by Segal 2018,[72] Gonzalez 2014, Ferrante 2008 and Suzuki 2012). Loftus 2008 was excluded as an outlier'	Suggest amending to the following: 'Data source: chronic complications of first surgery (33.5%) were derived from a national report 2014). The **annual probability** of late chronic complications (5.64%) is based on a weighted average of values derived by Segal 2018,[72] Gonzalez 2014, Ferrante 2008 and Suzuki 2012). Loftus 2008 was excluded as an outlier'	Thank you. Text amended.

Second surgery health state description, Table 20 (Description of company Markov model health states and the data sources used to move patients between health states), Page 70, Section 4.4.6 (Model structure).	Description of data source could be amended for accuracy. Current text: 'Data source: probability of 1st and 2nd surgery (0.47%) was derived from Misra 2016[71]'	Suggest amending to the following: 'Data source: **annual** probability of 1st and 2nd surgery (0.47%) was derived from Misra 2016[71]'	Thank you. Text amended.
Post-first surgery remission health state description, Table 20 (Description of company Markov model health states and the data sources used to move patients between health states), Page 70, Section 4.4.6 (Model structure).	Description of the post-first surgery remission health state reads 'No chronic complications from first surgery. Patients moving into this health state remain in this health state until death.' The second sentence is incorrect since patients can experience chronic complications from this health state and would then be at risk of needing a second surgery.	Remove the second sentence so that the description instead simply reads 'No chronic complications from first surgery.'	Thank you. Text removed.

Issue 11 Incomplete model figure

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Figure 2 (Company decision tree (induction phase)), Page 69, Section 4.4.6 (Model structure).	The diagram does not show an arrow between remission and response without remission health states as per the revised	Amend graph to include an arrow between remission and response without remission health states as per the revised	Thank you. Diagram changed.

	figure provided during clarification questions.	figure provided during clarification questions.	

Issue 12 Incorrect or incomplete references

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 23 (Company (age-adjusted) base case utility values), Page 73, section 4.4.8 (Health-related quality of life)	Incorrect reference used for post-surgery complications. The EAG report references Woehl 2008, however the correct reference is Arseneau et al. 2006.	Please replace the reference with Arseneau et al. 2006.	Thank you. Reference updated.
Table 23 (Company (age-adjusted) base case utility values), Page 73, section 4.4.8 (Health-related quality of life)	Incomplete reference reported for serious infection. The original source for the value in TA329 was Stevenson 2016, as reported in the Company Submission.	Please provide the original source (Stevenson 2016).	Thank you. Reference updated.

Issue 13 Incomplete description of scenario

Location of incorrect marking	Description of incorrect marking	Amended marking	
Section 4.6.4 (Scenario analyses), Table 36, Page 84.	Scenario 8 label could be clearer. Current text: 'Spontaneous remission from UC'	Suggest amending to the following: 'Spontaneous remission from **Active** UC'	Thank you. Scenario description amended.
Section 4.6.4 (Scenario analyses), Table 37, Page 85.	Scenario 8 label could be clearer. Current text: 'Spontaneous remission from UC'	Suggest amending to the following: 'Spontaneous remission from **Active** UC'	Thank you. Scenario description amended.

Issue 14 Inaccurate text in summary of EAG key company model issues

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Table 39 (Summary of EAG key company model issues), Section 5.3 (Modelling issues with impact on company cost effectiveness – EAG exploration), Page 88.	The current text regarding remission after week 52 does not acknowledge that the Company Submission included a scenario testing this assumption (scenario 9).	Propose amending to the following: 'Loss of remission over the lifetime of the model for any treatment is	Thank you. Text amended.

	Current text: 'Loss of remission over the lifetime of the model for any treatment is assumed to be constant after Week 8. The EAG has run a scenario to explore the impact of varying this assumption'	assumed to be constant after Week 8. **This was tested in a scenario analysis in the Company Submission where the probability of loss of remission/response was reduced by 25% after Year 1.** The EAG has run a scenario to explore the impact of varying this assumption.'	
Table 39 (Summary of EAG key company model issues), Section 5.3 (Modelling issues with impact on company cost effectiveness – EAG exploration), Page 89.	The EAG report states that the individual elements of CT are not specified in the company submission, however, Table 62 of the Company Submission provided this information. Current text: 'The individual elements of CT are not specified.'	We request the removal of this sentence.	Thank you. The EAG has removed this sentence.

Single Technology Appraisal

Upadacitinib for treating moderately to severely active ulcerative colitis [ID3953]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the 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 EAR that are likely to be discussed by the committee. The key issues in the EAR 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 EAR.

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 EAR 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 evaluation, 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.

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 redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is the end of **26 August 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.

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)	AbbVie UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Not applicable**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2: Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1: Lack of direct evidence for the comparison of upadacitinib versus relevant comparators	No	The Company wish to point out that the lack of direct evidence for comparison is a common challenge in economic evaluations for HTA. The manual for NICE health technology evaluations (PMG36) (1) details NICE's stance on indirect comparisons, namely that manufacturers should follow methods outlined in the technical support document (TSD) evidence synthesis series. The Company submission for upadacitinib adhered to these TSDs (TSD 1–5) (2-6). A placebo-controlled clinical trial design has been adopted in several comparator trials for therapies that have been assessed and recommended by NICE for use in patients with moderately to severely active ulcerative colitis (UC), as assessed in TA329 (adalimumab [ULTRA 1, ULTRA 2], golimumab [PURSUIT-SC/M], infliximab [ACT 1, ACT 2]) (7), TA342 (vedolizumab [GEMINI 1, GEMINI 2, GEMINI 3]) (8), TA547 (tofacitinib [OCTAVE 1, OCTAVE 2) (9), and TA633 (ustekinumab [UNIFI) (10). Furthermore, placebo-controlled trials, which utilised a common placebo treatment arm as the anchor for treatment comparisons, facilitated the inclusion of upadacitinib in the network meta-analysis (NMA) presented in the Company submission. The Company acknowledge the lack of direct evidence for the comparison of upadacitinib versus relevant comparators and that the use of indirect evidence is a source of uncertainty. The large number of relevant treatment options means that even if upadacitinib had a comparator in the control arm, this would not provide direct evidence against all other available relevant comparator treatments available for UC.

2: Network meta-analysis statistical issues	Yes	Upadacitinib was consistently shown to be the most efficacious advanced therapy for moderately-to-severely active UC at inducing and maintaining clinical response and remission in both biologic-exposed and biologic-naïve populations, considering four separate NMAs (Company NMA, EAG NMA, and NMAs published by Lasa et al (2022) (11) and Burr et al (2021) (12)). To reaffirm that the results from the Company NMA are reproducible, and arguably conservative, the Company have included Table 3 (induction) and Table 4 (maintenance) in Appendix A, which present high-level side-by-side comparisons of the NMA results from the four separate NMAs. The British Society of Gastroenterology (BSG) organisation submission refers to the Lasa 2022 and Burr 2021 NMAs, highlighting that upadacitinib 45mg ranked first in all patients (bio-naïve and bio-exposed), as well as stating that *'The rapidity of response to treatment is impressive with upadacitinib'* and *'In addition, the high remission rates at 8 weeks are impressive'* (13). Additionally, clinical advice received by both the Company and the EAG was that, despite the differences in study populations and trial characteristics, the randomised controlled trials (RCTs) included in the NMAs were appropriate sources of clinical data for decision-making. Clinician statements included: *'had 7 patients on upadacitinib in UC, all are still on drug, which is unique. Upadacitinib for the treatment of UC is as effective as most effective (infliximab) and more durable'* (14).
3: Company modelled treatment pathway is not a good reflection of NHS clinical practice	Yes	The Company believes that the submitted cost-effectiveness model (CEM) is suitable for addressing the NICE decision problem, namely, what is the cost effectiveness of upadacitinib versus relevant comparators in the bio-naïve and bio-exposed populations. The submitted CEM aims to address this by reflecting clinical practice as closely as possible whilst recognising that a model is a simplification of reality and is limited by data availability. The Company note that the scope of the appraisal is not to determine the most cost-effective treatment sequence among the approximately 800 to 900 possible permutations and believes its approach is aligned with previous appraisals in UC, including TA633 (See Table 5 in Appendix B.1 [Table 57 in CS], which compares the key features of the Company's approach with recent UC appraisals). In acknowledgement of the uncertainty associated with costs and outcomes following failure of biologic treatment in the CEM, this TE response includes new scenarios, including those considering shorter time horizons of 2 years and 5 years; time points at which a large proportion of the patient cohort has entered the active UC health state. Upadacitinib remained dominant or highly cost effective versus all comparators

		in these scenario analyses in both the bio-naïve (Table 17) and bio-exposed (Table 18) populations. These results are to be expected since clinical and quality-of-life benefits from upadacitinib treatment are accrued in the remission and response health states. The incremental benefit of upadacitinib is therefore not derived from 'Active UC' but from disease control through clinically important outcomes documented in the upadacitinib clinical trials; outcomes that AbbVie have understood from the BSG submission to represent a step change in management of moderately to severely active UC. In addition, the Company has concerns regarding the modelling approach proposed by the EAG, specifically regarding treatment sequencing, efficacy estimates, treatment duration and utility values, as outlined below. **Treatment sequencing/subsequent treatments** The choice of biologic, especially after a loss of response/failure of a first biologic, is a complex clinical decision. There are a wide range of factors (incl. patients characteristics, prognostic factors, response to prior treatment, reason for discontinuation) to take into consideration for each patient. Therefore, clinicians and patients need choice to select and agree on the most appropriate biologic in each instance. The BSG guidelines support this as well, stating *'The choice of drug should be determined by clinical factors, patient choice, cost, likely adherence and local infusion capacity'* (15). As such, it is important that patients receive treatment that works for their individual specific UC presentation and setting. This challenge has also been discussed in previous appraisals (TA633, TA547), in TA633 the ERG noted that *'sequential use of therapies is common in practice, but variable and cost effectiveness is potentially sensitive to the choice of subsequent treatment'* and that this creates uncertainty, which was considered equally relevant to previous appraisals (16). Additionally, new biologic treatments entering the market change the dynamics and change the potential order in which biologics are used. Due to the lack of data and the expert knowledge that clinical response rates decrease with each subsequent line of biologic treatment as their prognostic characteristics are likely to change, modelling sequences will not reduce decision uncertainty. In fact, as evidence with increasing and unknown uncertainty is introduced into the analysis with each additional line of treatment considered, the relevance

		for decision making becomes more uncertain. This is not aligned to face validity of trial results, the NMA results from Company, EAG or External Parties, nor statements from experts. The Company's submitted CEM, however, does allow for treatment sequencing to be explored and submitted a scenario analysis. For further details, see Appendix B.2. **Estimates of efficacy** The EAG modelled a 'basket of treatments' in their 'on subsequent treatment' health state, where patients would move to after failing the first biologic considered in the model. The Company would like to highlight several limitations with this proposed EAG approach that lack face validity: 1) Assumes same levels of clinical efficacy and utility as bio-naïve population 2) Assumes that patients who have failed all treatments available default back to 'the best one' and achieve same level of efficacy as the first time they received this treatment (prior to failing) 3) No consideration of surgery from this 'basket' health state, which is not aligned with clinical practice, and it is therefore assumed that patients will be on pharmacological treatments until death. Clinical experts have highlighted that with each additional line of treatment, they observe a reduction in efficacy. This can also be seen across all advanced treatment trial data, where a reduction in clinical response and remission rates are observed when comparing the bio-exposed populations with the bio-naïve population (see Table 6 and Table 7 in Appendix C). Therefore, the use of bio-naïve efficacy data is considered inaccurate and significantly overestimates the effectiveness of subsequent lines of biologic treatment. In fact, since this 'on subsequent treatment' health state includes all available treatments, this approach would benefit treatments with worse efficacy since it will be beneficial to fail the first treatment in the sequence, contrary to face validity, observed data, and clinical advice. It would also cancel out any benefit gained by more effective treatment, such as upadacitinib, when calculating ICERs, as upadacitinib is included in the 'basket of treatments'. Further supporting evidence can be found in Appendix B.3. Furthermore, the Company wish to highlight that the biologic-exposed population in the upadacitinib UC clinical trials included subjects who had ≥1 biologic previously (52.8% of total trial populations) and of this bio-exposed trial population, 37.5%, 37.9%, 19.5% and 5% had previously failed 1, 2, 3 or ≥4 biologics,

		respectively, as detailed in Table 8 (Appendix C) (17, 18). Therefore, the Company is of the opinion that the data used in the Company's submitted CEM for the bio-exposed population is representative of clinical efficacy across multiple lines of biologic treatments and represents a conservative interpretation of cost effectiveness. **Utility values** The utility value applied to the 'on subsequent treatment' health state is a weighted average of the values for remission and response without remission from the upadacitinib UC trials. As such, all patients in the EAG model have a utility value at least equal to the utility value associated with response to treatment until death, which lacks face validity. Patients who lose response to treatment (relapse) would have experienced a decrease in their quality of life due to disease symptoms, more aligned with the 'active UC' health state. Clinicians highlighted this reduction in quality of life: *'If untreated, a 40-50% reduction in quality of life would be expected for moderate-to-severe UC. Work will be severely impact with an increased impact on joblessness, social life, relationships.' (14)* While these are the Company's core concerns, there are additional issues with the EAG's proposed approach highlighted in Appendix B.3 and B.4.
4: Company choice of utility values	Yes	**Original utility values** UK quality-of-life data is important for deriving long-term decisions from the NHS and Personal Social Services) PSS perspective. As explained in the Company submission, Woehl et al (2008) was selected as the preferred source of quality-of-life data since utility values were derived from a large sample of patients (n=180) in the UK, to better reflect a UK population. Additional reasons for the selection of the Woehl et al (2008) data has been set out in the Company submission (Section B3.4.5). **Clinical opinion** Clinical expert input received by the Company supports the Company's view that utility data collected in a trial setting is likely to underestimate the true quality of life burden experienced by patients with UC, and

		this is likely to be especially true for the active UC health state considering the limited follow-up of clinical trial. Clinician statements included: '*being in a trial alters the QoL with a benefit. Self-selected patients that are likely to feel rewarded by the increase in number of interactions with a dedicated team associated with a trial*'. Clinical expert input received by the Company suggested that it is reasonable to use observational data where longer-term quality-of-life data is not available from a clinical trial (14). Clinician feedback included: '*would like to see multiple years of QoL data, might be reasonable to use observational study data where this is not available'*. In the ustekinumab UC appraisal (TA633), the NICE committee noted patient expert's reflections on utility values, stating that it is possible that some effects on quality of life (such as feeling out of control) may not be captured in clinical trials. This is also reflected in the statements on patient experience of UC in the Crohn's and Colitis organisation submission (TE papers) (1). To reaffirm the results from the Company submission, this response includes scenarios testing several utility data sources, namely, Woehl et al (2008) (19), Swinburn et al (2012) (20), Vaizey et al (2014) (21), as well as the utility data collected in the upadacitinib UC trials. Upadacitinib remained dominant or highly cost effective versus all comparators in these scenario analyses in both the bio-naïve (Table 17) and bio-exposed (Table 18) populations.
5: High and low doses of upadacitinib maintenance treatments	Yes	The company understands the EAG's concern and have provided updated probabilistic base-case analyses with a 70%:30% dose split between the 15 mg and 30 mg upadacitinib maintenance doses to align with comparators. The Company consulted additional clinical experts and heard that, considering clinical evidence, this assumption was plausible. Nevertheless, deterministic analysis of 15 mg and 30 mg were conducted for completeness and as recognition that the Committee may find these useful as supporting information for decision making. In conclusion, the EAG's concern notwithstanding, the Company submission, Clarification Letter, and this Technical Engagement response systematically appraised and modelled the best available evidence. The evidence is reflective of treatment for adult patients with moderately to severely active UC who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent in the NHS. In conclusion, upadacitinib within its marketing authorisation represents cost effective use of NHS resources in the base case and all revised scenario analysis.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3: Additional issues

Issue	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue: Surgery rates	Scenario analyses (Section 5.4.4, page 92)	Yes	The assumption that the EAG has made regarding surgery in their scenario analysis (50% of patients with active UC progress to surgery every year) conflicts with published literature. The lifetime risk of colectomy associated with UC is estimated to be around 25% (clinical expert opinion) (14). The EAG scenario assumption was based on clinical expert opinion not seen be the Company, whereas the Company's submission annual surgery rates (0.47%) were based on Hospital Episode Statistics (HES) data (22), further validated by clinical experts both before submission and again for this response. HES data is considered a robust, and UK-relevant, source of evidence by clinical experts, and the most reliable data source to inform the probability of surgery in the model (14). Additionally, data suggest that there has been a reduction in colectomy rates over time, likely due to more advanced treatments that have become available, indicating that the Company submission surgical rates could be considered higher than they would be in 2022. Worsley et al (2020) (23) showed that patients with UC, admitted for active disease during 2013-2016 had significantly lower cumulative probability of colectomy compared to patients admitted during 2003-2007 or 2008-2012 (based on HES data). They reported one-year and three-year incidence of colectomy after acute admission as 0.17 and 0.21. Another study looked at the reduction of surgery for UC, showing that between 2005 and 2018 yearly colectomy rates per 100 UC patients fell from 1.47 to 0.44 ($p<0.001$) (24). In summary, the Company concludes that the EAG scenario for surgery is not relevant for this decision problem.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
5: High and low doses of upadacitinib maintenance treatments	The original submission presented analyses separately for the two maintenance doses of upadacitinib (15 mg and 30 mg daily). For comparators, 30% of patients were assumed to be receiving the escalated maintenance dose with the remaining 70% on the standard dose (where applicable).	The revised base-case analysis applies a ratio of standard:escalated maintenance doses of 70%:30% applied for all treatments, including upadacitinib, in line with EAG preferences. Separate analyses are presented for the two upadacitinib maintenance doses for reference.	See Appendix D.1 for the revised base-case results
Company's base case following technical engagement (or revised base case)	Incremental QALYs: See Section B.3.10.1 of Company submission	See Appendix D.1 for the revised base-case results	See Appendix D.1 for the revised base-case results

Appendix A: NMA comparison results

Table 3: Overview induction NMAs – ranked treatments (most favoured on top)

	Biologic-naïve population					Biologic-exposed population			
	Company NMA	**EAG NMA**	**Lasa et al 2022 NMA †**	**Burr er at 2021 NMA**		**Company NMA**	**EAG NMA**	**Lasa et al 2022 NMA †**	**Burr er at 2021 NMA**
Clinical remission (RE model)	**UPA45** IFX5 VED300 GOL200/100 IFX10 TOF10 UST6 ADA160/80 PBO	**UPA45** IFX5 VED300 GOL200/100 IFX10 TOF10 UST6 ADA160/80 PBO	**UPA45** OZA1 IFX5 TOF10 UST6 GOL200 VED300 FIL200 ADA160/80 ETRO105 FIL100 PBO	**UPA45** IFX5 IFX10 VED300 OZA1‡ FIL200‡ GOL400/200 TOF10 UST130 GOL200/100 ADA160/80 ETRO105‡ UST6 FIL100‡ ADA80/40	**Clinical remission (RE model)**	**UPA45** UST6 TOF10 VED300 ADA160/80 PBO	**UPA45** TOF10 UST6 VED300 ADA160/80 PBO	**UPA45** OZA1‡ IFX5 TOF10 UST6 GOL200 VED300 FIL200‡ ADA160/80 ETRO105‡ FIL100‡ PBO	**UPA45** UST6 TOF10 UST130 ETRO105‡ VED300 FIL200‡ OZA1‡ FIL100‡ ADA160/80
Clinical response (RE model)	**UPA45** UST6 IFX10 TOF10 ADA160/80 VED300 GOL200/100 PBO	NR	N/A	**UPA45** UST6 IFX10 IFX5 VED300 FIL200‡ UST130 GOL400/200 TOF10 GOL200/100 ETRO105‡ FIL100‡ ADA160/80 ADA80/40	**Clinical response (FEA model)**	**UPA45** TOF10 UST6 VED300 ADA160/80 PBO	**UPA45** TOF10 UST6 VED300 ADA160/80 PBO	N/A	**UPA45** FIL200‡ UST6 TOF10 UST130 FIL100‡ ETRO105‡ VED300 ADA160/80 IFX10 UST6 IFX5

Abbreviations: ADA160/80, adalimumab 160/80 mg induction; EAG, external assessment group; ETRO105, etrolizumab 105 mg; FEA, fixed effects with baseline-risk adjustment; FIL200/100, filgotinib 200/100 mg; GOL400/200/100, golimumab 400/200/100 mg induction; IFX5/IFX10, infliximab 5 mg/kg body weight/10 mg/kg body weight; N/A, not applicable; NMA, network meta-analysis; NR, not reported; OZA1, ozanimod 1 mg; PBO, placebo; RE, random effects; TOF10, tofacitinib 10 mg; UPA45, upadacitinib 45 mg; UST130/6, ustekinumab 130 mg/kg body weight/6 mg/kg body weight; VED300, vedolizumab 300 mg.

Note: Treatments are listed in order of most favoured to least favoured. † Overall patient population results, as data for UPA by prior treatment exposure were not available. ‡ Treatment not considered a relevant comparator at the time of the upadacitinib Company submission. Sources: Lasa et al (2022) (11) and Burr et al (2021) (12).

Table 4: Overview maintenance NMAs – ranked treatments (most favoured on top)

	Biologic-naïve population					Biologic-exposed population			
	Company NMA	**EAG NMA**	**Lasa et al 2022 NMA†**	**Burr er at 2021 NMA**		**Company NMA**	**EAG NMA**	**Lasa et al 2022 NMA†**	**Burr er at 2021 NMA**
	Biologic-naïve population					**Biologic-exposed population**			
Clinical remission (RE model)	TOF10 TOF5 **UPA30** VED300Q4W VED300Q8W **UPA15** GOL100 GOL50 UST90Q8W UST90Q12W IFX10 IFX5 ADA40Q2W PBO	TOF10 TOF5 **UPA30** GOL100 VED300Q4W **UPA15** VED300Q8W GOL50 UST90Q8W UST90Q12W IFX10 IFX5 ADA40Q2W PBO	**UPA30** **UPA15** FIL200‡ VED108Q2W TOF5 VED300Q8W OZA1‡ UST90Q8W GOL100 ETRO105Q4W‡ FIL100‡ PBO	NA	**Clinical remission (RE model)**	**UPA30** **UPA15** VED300Q8W VED300Q4W TOF10 UST90Q8W ADA40Q2W TOF5 UST90Q12W PBO	**UPA30** **UPA15** VED300Q4W VED300Q8W TOF10 UST90Q8W TOF5 ADA40Q2W UST90Q12W PBO	**UPA30** **UPA15** FIL200‡ VED108Q2W TOF5 VED300Q8W OZA1‡ UST90Q8W GOL100 ETRO105Q4W‡ FIL100‡ PBO	NA
Clinical response (RE model)	**UPA30** TOF10 VED300Q8W **UPA15** TOF5 VED300Q4W UST90Q8W UST90Q12W GOL100 IFX10 GOL50 IFX5 ADA40Q2W PBO	**UPA30** TOF10 VED300Q8W **UPA15** TOF5 VED300Q4W UST90Q8W UST90Q12W GOL100 IFX10 GOL50 IFX5 ADA40Q2W PBO	NA	NA	**Clinical response (RE model)**	**UPA30** TOF10 **UPA15** TOF5 VED300Q8W VED300Q4W UST90Q8W ADA40Q2W UST90Q12W PBO	**UPA30** TOF10 **UPA15** TOF5 VED300Q8W VED300Q4W UST90Q8W ADA40Q2W UST90Q12W PBO	NA	NA

Abbreviations: ADA40Q2W, adalimumab 40 mg every other week; EAG, external assessment group; ETRO105Q4W, etrolizumab 105 mg every 4 weeks; FIL200/100, filgotinib 200/100 mg; GOL100/50, golimumab 100/50 mg induction; IFX5/IFX10, infliximab 5 mg/kg body weight/10 mg/kg body weight; NA, not applicable; NMA, network meta-analysis; OZA1, ozanimod 1 mg; PBO, placebo; RE, random effects; TOF5/10, tofacitinib 5 mg/10 mg; UPA15/30, upadacitinib 15 mg/30 mg; UST90Q8W/UST90Q12W, ustekinumab 90 mg every 8 weeks/every 12 weeks; VED300Q4W/VED300Q8W, vedolizumab 300 mg every 4 weeks/every 8 weeks.
Note: Treatments are listed in order of most favoured to least favoured. † Overall patient population results, as data for UPA by prior treatment exposure were not available. ‡ Treatment not considered a relevant comparator at the time of the upadacitinib Company submission.
Sources: Lasa et al (2022) (11) and Burr et al (2021) (12).

Appendix B: Supporting evidence

B.1 Economic analysis comparison with previous UC appraisals

Table 5: Features of the economic analysis compared with previous UC appraisals

Factor	Previous appraisals				Current appraisal	
	TA329 AG	TA342	TA547	TA633	Chosen values	Justification
Time horizon	Lifetime	10 years	Lifetime	Lifetime	Lifetime (100 years of age)	Adopted to capture all important differences in costs and outcomes between the technologies being compared per NICE reference case and aligned with previous TAs
Model structure	State-transition Markov cohort model – AG	Hybrid decision tree-Markov model	Markov model	Hybrid decision tree-Markov model	Hybrid decision tree- Markov model	Captures induction and maintenance phases. Consistent with previous appraisals
Cycle length	2 weeks	6 weeks (induction), 8 weeks (maintenance)	8 weeks	2 weeks	4 weeks	Short enough to capture changes in health state occupancy, and to address the concern in TA633 regarding the 2-week cycle length.
Treatment waning effect	No	No	No	No	No	Consistent with previous appraisals
Source of utilities	Woehl et al.	GEMINI 1, Punekar and Hawkins et al., utility decrements for AEs were taken from clinical trials.	Woehl et al.	Woehl et al. and Arseneau et al.	Woehl et al. and Arseneau et al.	Aligned with TA633 (UST)
Source of costs	Published literature	NHS list price and BNF, December 2013	2016/17 NHS reference cost, (eMIT, MIMs, PSSRU)	2017/18 NHS reference cost, BNF, MIMS, previous TAs, published literature	2019/20 NHS reference costs, BNF, published literature	Consistent with previous appraisals
Pharmacological treatment AEs	No AEs were considered	Serious infection, tuberculosis, lymphoma, hypersensitivity and injection site reaction	Serious infection	Serious infection	Serious infection	
Stopping rule	Yes	Yes	No	No	No	
Spontaneous remission	No	No	No	No	No	

Abbreviations: AE, adverse event; AG, assessment group; BNF, British National Formulary; eMIT, electronic Market Information Tool; MIMS, Monthly Index Medical Specialties; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit; TA, technology appraisal; UC, ulcerative colitis; UST, ustekinumab.

B.2 Treatment sequencing in Company's CEM

The Company's submitted model follows previous appraisals (TA633, TA547) that have not explored sequencing in the base case, but rather in a scenario analysis due to subsequent treatment uncertainty.

The Company's submitted CEM allows for treatment sequencing by allowing patients to move to a second biologic before entering the active UC health state where patients are assumed to receive conventional therapy. Efficacy data from the bio-exposed population were used in this scenario, representing patients who have received ≥1 biologic previously. To be able to model treatment sequencing accurately, efficacy data would be required from patients who were treated with each specific sequence of biologics. Clinical experts state that there are no such controlled studies available, and typically they see a reduced number of patients respond with each additional line of biologic treatment (e.g. they see only 30–40% of patients responding to 3L biologic (14)).

B.3 Efficacy data

The efficacy data used in the model (for all treatments) represent conditional probabilities of response and remission at Week 52 for patients who are responders at the end of induction. They do not reflect the probabilities of response and remission following lack of (or loss of) response to prior treatment. Based on current inputs, the EAG revision assumes that 61% of patients in the 'subsequent treatment' health state are in remission, with the remaining 39% having response without remission. This is held constant throughout the model time horizon. As mentioned above, the EAG model ignores the fact that, based on the NMA data and depending on choice of treatment, 30-70% of patients are neither in remission nor response without remission at Week 52.

In the EAG report it is stated that the subsequent treatment basket includes patients who 'failed to achieve long-term remission on any drug and are unwilling or unsuitable for surgery and therefore are indefinitely prescribed the treatment which gave them the most symptom alleviation (without achieving remission)' as well as describe that bio-naïve population data was used for this health state 'The basket of treatment effectiveness estimate (remission or response without remission) was taken from the company maintenance bio-naïve NMAs and was used to model effectiveness for both bio-naïve and bio-exposed populations' (13). These statements contradict each other, as it is not considered likely in clinical practice that patients who have failed a treatment subsequently regain the response they initially had, instead they would have dose escalated to recapture response, before stopping treatment altogether.

B.4 BIM data

In the EAG report, it is stated that patients in the subsequent treatment health state are modelled to receive a basket of biologic treatments based on the market share provided by the company, which was utilised to estimate data for the fifth line of treatment.

The year five bio-naïve market share data used in the budget impact model was misinterpreted as the distribution of comparators in the fifth line of treatment, which was subsequently used to weight the utility, cost and efficacy data for treatment sequencing. The year-five market share data is consequentially being used to inform the weighting of fifth line treatment sequencing, rather than its intended purpose of determining the share of the market that each of the comparators would hold in the fifth year of being on the market. This subsequentially impacts the weighting of the efficacy data in the basket of subsequent treatments.

Appendix C: Additional clinical data

Table 6: Efficacy outcomes across treatments from clinical trials – induction

		Bio-naïve population			Bio-exposed population		
Trial	**Treatment**	**N**	**Clinical response**	**Clinical remission**	**N**	**Clinical response**	**Clinical remission**
U-ACCOMPLISH	UPA45	166	78%	33%	175	71%	22%
U-ACCOMPLISH	PBO	81	35%	4%	93	16%	1%
U-ACHIEVE Study 2	UPA45	145	81%	28%	174	68%	18%
U-ACHIEVE Study 2	PBO	72	36%	6%	82	13%	0%
OCTAVE 1	TOF	222	66%	25%	254	54%	13%
OCTAVE 1	PBO	57	49%	16%	65	18%	2%
OCTAVE 2	TOF	195	62%	22%	234	50%	12%
OCTAVE 2	PBO	47	32%	9%	65	26%	0%
UNIFI	UST	147	67%	18%	175	57%	13%
UNIFI	PBO	151	36%	10%	168	27%	1%
GEMINI 1	VED IV	130	53%	23%	82	39%	10%
GEMINI 1	PBO	76	26%	7%	63	21%	3%
NCT02039505	VED IV	79	53%	28%	85	27%	9%
NCT02039505	PBO	41	37%	15%	41	29%	10%
ULTRA-1	ADA 160/80	130	55%	18%	N/A	N/A	N/A
ULTRA-1	PBO	130	45%	9%	N/A	N/A	N/A
ULTRA-2	ADA 160/80	150	59%	21%	98	37%	9%
ULTRA-2	PBO	145	39%	11%	101	29%	7%
M10-447	ADA 160/80	90	50%	10%	N/A	N/A	N/A
M10-447	PBO	96	35%	11%	N/A	N/A	N/A
ACT-1	IFX10	122	61%	32%	N/A	N/A	N/A
ACT-1	IFX5	121	69%	39%	N/A	N/A	N/A
ACT-1	PBO	121	37%	15%	N/A	N/A	N/A
ACT-2	IFX10	120	69%	28%	N/A	N/A	N/A
ACT-2	IFX5	121	64%	34%	N/A	N/A	N/A
ACT-2	PBO	123	29%	6%	N/A	N/A	N/A
Japic CTI-060298	IFX5	104	55%	20%	N/A	N/A	N/A
Japic CTI-060298	PBO	104	36%	11%	N/A	N/A	N/A
Jiang 2015	IFX5	41	78%	54%	N/A	N/A	N/A

Jiang 2015	PBO	41	37%	22%	N/A	N/A	N/A
NCT01551290	IFX5	50	64%	22%	N/A	N/A	N/A
NCT01551290	PBO	49	33%	10%	N/A	N/A	N/A
PURSUIT-SC	GOL	253	51%	18%	N/A	N/A	N/A
PURSUIT-SC	PBO	251	30%	6%	N/A	N/A	N/A

Abbreviations: ADA, adalimumab; IFX, infliximab; IV, intravenous; GOL, golimumab; N/A, not applicable; PBO, placebo; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 7: Efficacy outcomes across treatments from clinical trials – maintenance

		Bio-naïve population			Bio-exposed population		
Trial	**Treatment**	**N**	**Clinical response**	**Clinical remission**	**N**	**Clinical response**	**Clinical remission**
U-ACHIEVE Study 3	UPA15	75	65%	40%	73	59%	41%
U-ACHIEVE Study 3	UPA30	77	81%	48%	77	70%	47%
U-ACHIEVE Study 3	PBO	65	29%	18%	84	17%	5%
OCTAVE Sustain	TOF10	104	64%	44%	93	59%	37%
OCTAVE Sustain	TOF5	115	57%	42%	83	45%	24%
OCTAVE Sustain	PBO	109	25%	11%	89	15%	11%
UNIFI	UST Q12W	95	77%	47%	77	56%	27%
UNIFI	UST Q8W	79	77%	51%	97	65%	38%
UNIFI	PBO	84	52%	32%	91	39%	16%
GEMINI 1	VED IV Q4W	73	56%	48%	40	43%	35%
GEMINI 1	VED IV Q8W	72	65%	46%	43	47%	37%
GEMINI 1	PBO	79	27%	19%	38	16%	5%
NCT02039505	VED IV Q8W	24	67%	54%	17	65%	59%
NCT02039505	PBO	28	36%	36%	14	36%	21%
ULTRA-2	ADA Q2W	89	49%	31%	36	42%	22%
ULTRA-2	PBO	56	43%	29%	29	21%	10%
ACT-1	IFX10	75	60%	32%	N/A	N/A	N/A
ACT-1	IFX5	84	56%	31%	N/A	N/A	N/A
ACT-1	PBO	45	38%	24%	N/A	N/A	N/A
PURSUIT-J	GOL100	32	56%	50%	N/A	N/A	N/A
PURSUIT-J	PBO	31	19%	6%	N/A	N/A	N/A
PURSUIT-M	GOL100	151	50%	34%	N/A	N/A	N/A
PURSUIT-M	GOL50	151	47%	33%	N/A	N/A	N/A
PURSUIT-M	PBO	154	31%	22%	N/A	N/A	N/A

Abbreviations: ADA, adalimumab; IFX, infliximab; IV, intravenous; GOL, golimumab; N/A, not applicable; PBO, placebo; QxW, every x weeks; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

Table 8: Upadacitinib UC trials – Previous biologics received

Previous biologics	U-ACCOMPLISH (induction) (n=515)		U-ACHIEVE (induction) (n=473)		Total (n=988)	
	Full trial population, n (%)	Bio-exposed portion of trial, n (%)	Full trial population, n (%)	Bio-exposed portion of trial, n (%)	Full trial populations, n (%)	Bio-exposed portion of trials, n (%)
0 (bio-naïve)	249 (48.3)	N/A	217 (45.9)	N/A	466 (47.2)	N/A
≥1 (bio-exposed)	266 (51.7)	**266 (100)**	256 (54.1)	**256 (100)**	522 (52.8)	**522 (100)**
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: N/A, not applicable.
Source: CSR U-ACCOMPLISH (18) and CSR U-ACHIEVE (17).

Appendix D: Updated cost-effectiveness results

Please note that there has been [redacted] PAS price, as mentioned in the cover letter.

Upadacitinib PAS prices used in the updated base-case and scenario analyses as presented in Table 9.

Table 9: Upadacitinib prices used in model

Name	Form	Dose per unit	Pack size	PAS price	PAS unit cost
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

D.1 Revised base-case results

D.1.1 Bio-naïve population

The fully incremental analysis for bio-naïve population is presented in Table 10. The analysis reflects the updated PAS price and Company acceptance of key issue 5 regarding dose split. The cost-effectiveness frontier is comprised of adalimumab biosimilar and upadacitinib. Upadacitinib is associated with an ICER of £2,470 versus adalimumab biosimilar. Upadacitinib strictly dominates golimumab, infliximab, ustekinumab, tofacitinib and vedolizumab. Upadacitinib is associated with a [redacted] probability of being the most cost-effective treatment at a willingness-to-pay threshold of £20,000 per QALY (see Figure 1). At a willingness-to-pay threshold of £30,000, the probability that upadacitinib is the most cost-effective treatment is [redacted]

Disaggregated results (costs and QALYs) are provided at the end of this document.

Table 10: Revised base-case results for the bio-naïve population: fully incremental cost-effectiveness results (probabilistic results)

Technologies	Total discounted costs	Total discounted LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	-	-	-	Reference	Reference
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UPA 45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,470	£2,470
GOL 200/100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,700	Dominated
IFX 5 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,958	Dominated
IFX 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£71,725	Dominated
UST 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,429	Dominated
TOF 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,038	Dominated
VED 108	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,915	Dominated
VED 300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£71,629	Dominated

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; GOL, golimumab; IV, intravenous; LYG, life years gained; QALYs, quality-adjusted life years; SC, subcutaneous therapy; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.
Ratio of standard:escalated maintenance doses of 70%:30% applied for all treatments.

Figure 1: Cost-effectiveness acceptability curve, bio-naïve population (probabilistic results)

FIGURE REDACTED [CIC]

D.1.2 Bio-exposed population

The fully incremental analysis for the bio-exposed population is presented in Table 11. The analysis reflects the updated PAS price and Company acceptance of key issue 5 regarding dose split. The cost-effectiveness frontier is comprised of adalimumab biosimilar and upadacitinib. Upadacitinib is associated with an ICER of £3,346 versus adalimumab biosimilar. Upadacitinib strictly dominates ustekinumab, tofacitinib and vedolizumab. Adalimumab is extendedly dominated by a combination of adalimumab biosimilar and upadacitinib. Upadacitinib is

associated with a [redacted] probability of being the most cost-effective treatment at a willingness-to-pay threshold of £20,000 per QALY (see Figure 2). At a willingness-to-pay threshold of £30,000, the probability that upadacitinib is the most cost-effective treatment is [redacted].

Disaggregated results (costs and QALYs) are provided at the end of this document.

Table 11: Revised base-case results for the bio-exposed population: fully incremental cost-effectiveness results (probabilistic results)

Technologies	Total discounted costs	Total discounted LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	-	-	-	Reference	Reference
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£79,099	Extended dominance
UPA 45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,346	£3,346
UST 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£124,019	Dominated
VED 108	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£68,897	Dominated
TOF 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,351	Dominated
VED 300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,537	Dominated

Abbreviations: ADA, adalimumab; GOL, golimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; LYG, life years gained; QALYs, quality-adjusted life years; SC, subcutaneous therapy; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.
Ratio of standard:escalated maintenance doses of 70%:30% applied for all treatments.

Figure 2: Cost-effectiveness acceptability curve, bio-exposed population (probabilistic results)

FIGURE REDACTED [CIC]

D.2 Revised analyses for UPA 15 mg maintenance dose

The analysis in section D.2 reflects the PAS price update and upadacitinib 15 mg only as the maintenance dose as a scenario to the updated base case.

D.2.1 Bio-naïve population

The fully incremental analysis for the upadacitinib 15 mg maintenance dose in the bio-naïve population is presented in Table 12. Upadacitinib is associated with the lowest costs and highest QALYs and therefore dominates all comparators.

Table 12: UPA 15 mg maintenance dose in the bio-naïve population: fully incremental cost-effectiveness results (deterministic results)

Technologies	Total discounted costs	Total discounted LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
UPA 45	[redacted]	[redacted]	[redacted]	-	-	-	Reference	Reference
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
GOL 200/100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
IFX 5 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
IFX 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
TOF 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
UST 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
VED 108	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
VED 300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; GOL, golimumab; IV, intravenous; LYG, life years gained; QALYs, quality-adjusted life years; SC, subcutaneous therapy; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

D.2.2 Bio-exposed population

The fully incremental analysis for the upadacitinib 15 mg maintenance dose in the bio-exposed population is presented in Table 13. Upadacitinib is associated with the highest QALYs and dominates all comparators apart from adalimumab biosimilar. The ICER for upadacitinib versus adalimumab biosimilar is £377.

Table 13: UPA 15 mg maintenance dose in the bio-exposed population: fully incremental cost-effectiveness results (deterministic results)

Technologies	Total discounted costs	Total discounted LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	-	-	-	Reference	Reference
UPA 45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£377	£377
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	--	Dominated
UST 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£97,208	Dominated
VED 108	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£84,758	Dominated
TOF 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,690	Dominated
VED 300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£120,544	Dominated

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG, life years gained; QALYs, quality-adjusted life years; SC, subcutaneous therapy; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

D.3 Revised analyses for UPA 30 mg maintenance dose

The analysis in section D.3 reflects the PAS price update and upadacitinib 30 mg only as maintenance dose as a scenario to the updated base case.

D.3.1 Bio-naïve population

The fully incremental analysis for the upadacitinib 30 mg maintenance dose in the bio-naïve population is presented in Table 14. The cost-effectiveness frontier is comprised of adalimumab biosimilar and upadacitinib. Upadacitinib has an ICER of £9,628 versus adalimumab biosimilar. All other comparators are strictly dominated or extendedly dominated.

Table 14: UPA 30 mg maintenance dose in the bio-naïve population: fully incremental cost-effectiveness results (deterministic results)

Technologies	Total discounted costs	Total discounted LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	-	-	-	Reference	Reference
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	--	Dominated
GOL 200/100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,525	Extended dominance
IFX 5 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,660	Dominated
IFX 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£62,113	Dominated
TOF 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,715	Extended dominance
UST 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,779	Dominated
VED 108	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£44,896	Dominated
UPA 45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,628	£9,628
VED 300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£69,072	Dominated

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IFX, infliximab; GOL, golimumab; IV, intravenous; LYG, life years gained; QALYs, quality-adjusted life years; SC, subcutaneous therapy; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

D.3.2 Bio-exposed population

The fully incremental analysis for the upadacitinib 30 mg maintenance dose in the bio-exposed population is presented in Table 15. Upadacitinib is associated with the highest costs and QALYs in this population. The cost-effectiveness frontier is comprised of adalimumab biosimilar and upadacitinib. Upadacitinib has an ICER of £8,532 versus adalimumab biosimilar. All other comparators are strictly dominated or extendedly dominated.

Table 15: UPA 30 mg maintenance dose in the bio-exposed population: fully incremental cost-effectiveness results (deterministic results)

Technologies	Total discounted costs	Total discounted LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	-	-	-		
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	--	Dominated
UST	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£97,208	Extended dominance
VED SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£84,758	Extended dominance
TOF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,690	Extended dominance
VED IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£120,544	Dominated
UPA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,532	£8,532

Abbreviations: ADA, adalimumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; LYG, life years gained; QALYs, quality-adjusted life years; SC, subcutaneous therapy; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.

D.4 Sensitivity analyses around revised base case

Several scenario analyses were run to explore the impact of various assumptions on the results of the analyses. The scenarios considered are described in Table 16. Results for the bio-naïve and bio-exposed populations are presented in Table 17 and Table 18, respectively. In all scenarios and in both populations, upadacitinib remains dominant or highly cost-effective (ICER<£6,500) versus all comparators.

Table 16: Scenario analysis settings

Aspect	UPA model base case	Scenario analysis
Time horizon	Lifetime (100 years of age)	**Scenario 1†:** 2 years **Scenario 2†:** 5 years **Scenario 3**: 10 years (based on TA342) **Scenario 4**: 50 years (based on TA633)
Extended induction (delayed responder)	No	**Scenario 5**: Included
Treatment sequencing	No	**Scenario 6**: Consideration of ustekinumab as subsequent therapy
Source of utility data	Woehl et al. (2008) (19) and Arseneau et al. (2006) (25) Upadacitinib clinical trial	**Scenario 7**: Swinburn et al. (2012) (20) **Scenario 8**: Vaizey et al. (2013) (21) **Scenario 9†:** UPA clinical trial utility data

Abbreviations: TA, technology appraisal; UC, ulcerative colitis; UPA, upadacitinib.
† Newly presented scenario (not originally included in the Company submission)

Table 17. Scenario analyses: Incremental results UPA vs comparator (ICER as cost per QALY, £), bio-naïve population

Scenario	Description	ADA biosimilar	ADA	GOL	IFX IV biosimilar	IFX IV	TOF	UST	VED SC	VED IV
Base case		£2,471	£1,331	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 1†	Time horizon:2 years	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 2†	Time horizon: 5 years	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 3	Time horizon:10 years (based on TA342)	£2,534	£1,350	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 4	Time horizon is updated to 50 years (based on TA633)	£2,472	£1,332	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 5: Extended induction	Delayed responders are included in the analysis	N/A	N/A	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 6: Treatment sequencing	Upon loss of response, a second treatment is initiated for each comparator (UST)	£362	£1,523	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 7: Utility data from Swinburn et al.	Utilities for active UC, remission, response, post-surgery remission	£1,982	£471	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 8: Utility data from Vaizey et al.	Utilities for active UC, remission, and response	£3,262	£823	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 9† Utility data from the clinical trial	Utilities for remission (0.872), response without remission (0.861), active UC (0.684)	£3,176	£755	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA

Abbreviations: ADA, adalimumab; GOL, golimumab: ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; N/A not applicable; SC, subcutaneous; TOF, tofacitinib, UC, ulcerative colitis; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.
Ratio of standard:escalated maintenance doses of 70%:30% applied for all treatments. † Newly presented scenario (not originally included in the Company submission)

Table 18: Scenario analyses: Incremental results UPA vs comparator (ICER as cost per QALY, £), bio-exposed population

Scenario	Description	ADA biosimilar	ADA	UST	VED SC	VED IV	TOF
Base case							
Scenario 1† Time horizon (2 years)	Time horizon is updated to 2 years	£198	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 2† Time horizon (5 years)	Time horizon is updated to 5 years	£2,514	£1,545	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 3: Time horizon (10 years)	Time horizon is updated to 10 years (based on TA342)	£3,080	£2,250	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 4: Time horizon (50 years)	Time horizon is updated to 50 years (based on TA633)	£2,908	£2,095	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 5: Extended induction	Delayed responders are included in the analysis	N/A	N/A	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 6: Treatment sequencing	Upon loss of response, a second treatment is initiated for each comparator (UST)	£2,072	£1,245	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 7: Utility data from Swinburn et al.	Utilities for active UC, remission, response, post-surgery remission	£3,770	£2,715	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 8: Utility data from Vaizey et al.	Utilities for active UC, remission, and response	£6,172	£4,444	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA
Scenario 9† Utility data from trial	Utilities for remission (0.882), response without remission (0.844), active UC (0.657)	£5,094	£3,130	Dominated by UPA	Dominated by UPA	Dominated by UPA	Dominated by UPA

Abbreviations: ADA, adalimumab; GOL, golimumab: ICER, incremental cost effectiveness ratio; IFX, infliximab; IV, intravenous; N/A not applicable; SC, subcutaneous; TOF, tofacitinib, UC, ulcerative colitis; UPA, upadacitinib; UST, ustekinumab; VED, vedolizumab.
Ratio of standard:escalated maintenance doses of 70%:30% applied for all treatments. † Newly presented scenario (not originally included in the Company submission)

D.5 Disaggregated QALY gain by health state for the base-case analysis

D.5.1 Bio-naïve population

Table 19: Summary of QALY gain by health state: UPA vs ADA, bio-naïve population

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; QALY, quality-adjusted life year; UC, ulcerative colitis; UPA, upadacitinib.

Table 20: Summary of QALY gain by health state: UPA vs ADA biosimilar, bio-naïve population

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; QALY, quality-adjusted life year; UC, ulcerative colitis; UPA, upadacitinib.

Table 21: Summary of QALY gain by health state: UPA vs GOL, bio-naïve population

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GOL, golimumab; QALY, quality-adjusted life year; UC, ulcerative colitis; UPA, upadacitinib.

Table 22: Summary of QALY gain by health state: UPA vs IFX, bio-naïve population

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IFX, infliximab; QALY, quality-adjusted life year; UC, ulcerative colitis; UPA, upadacitinib.

Table 23: Summary of QALY gain by health state: UPA vs IFX biosimilar, bio-naïve population

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IFX, infliximab; QALY, quality-adjusted life year; UC, ulcerative colitis; UPA, upadacitinib.

Table 24: Summary of QALY gain by health state: UPA vs TOF, bio-naïve population

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; TOF, tofacitinib; UC, ulcerative colitis; UPA, upadacitinib.

Table 25: Summary of QALY gain by health state: UPA vs UST, bio-naïve population

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; UC, ulcerative colitis; UPA, upadacitinib; UST, ustekinumab.

Table 26: Summary of QALY gain by health state: UPA vs VED IV, bio-naïve population

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IV, intravenous; QALY, quality-adjusted life year; UC, ulcerative colitis; UPA, upadacitinib; VED, vedolizumab.

Table 27: Summary of QALY gain by health state: UPA vs VED SC, bio-naïve population

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; SC, subcutaneous; UC, ulcerative colitis; UPA, upadacitinib; VED, vedolizumab.

D.5.2 Bio-exposed population

Table 28: Summary of QALY gain by health state: UPA vs ADA, bio-exposed population

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; QALY, quality-adjusted life year; UC, ulcerative colitis; UPA, upadacitinib.

Table 29: Summary of QALY gain by health state: UPA vs ADA biosimilar, bio-exposed population

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; QALY, quality-adjusted life year; UC, ulcerative colitis; UPA, upadacitinib.

Table 30: Summary of QALY gain by health state: UPA vs TOF, bio-exposed population

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; TOF, tofacitinib; UC, ulcerative colitis; UPA, upadacitinib.

Table 31: Summary of QALY gain by health state: UPA vs UST, bio-exposed population

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; UC, ulcerative colitis; UPA, upadacitinib; UST, ustekinumab.

Table 32: Summary of QALY gain by health state: UPA vs VED IV, bio-exposed population

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IV, intravenous; QALY, quality-adjusted life year; UC, ulcerative colitis; UPA, upadacitinib; VED, vedolizumab.

Table 33: Summary of QALY gain by health state: UPA vs VED SC, bio-exposed population

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; SC, subcutaneous; UC, ulcerative colitis; UPA, upadacitinib; VED, vedolizumab.

D.6 Summary of costs by health state

D.6.1 Bio-naïve population

Table 34: Summary of costs by health state: UPA vs ADA, bio-naïve population

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; UC, ulcerative colitis; UPA, upadacitinib.

Table 35: Summary of costs by health state: UPA vs ADA biosimilar, bio-naïve population

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; UC, ulcerative colitis; UPA, upadacitinib.

Table 36: Summary of costs by health state: UPA vs GOL, bio-naïve population

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GOL, golimumab; UC, ulcerative colitis; UPA, upadacitinib.

Table 37: Summary of costs by health state: UPA vs IFX, bio-naïve population

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IFX, infliximab; UC, ulcerative colitis; UPA, upadacitinib.

Table 38: Summary of costs by health state: UPA vs IFX biosimilar, bio-naïve population

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IFX, infliximab; UC, ulcerative colitis; UPA, upadacitinib.

Table 39: Summary of costs by health state: UPA vs TOF, bio-naïve population

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TOF, tofacitinib; UC, ulcerative colitis; UPA, upadacitinib.

Table 40: Summary of costs by health state: UPA vs UST, bio-naïve population

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: UC, ulcerative colitis; UST, ustekinumab; UPA, upadacitinib.

Table 41: Summary of costs by health state: UPA vs VED IV, bio-naïve population

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IV, intravenous; UC, ulcerative colitis; UPA, upadacitinib; VED, vedolizumab.

Table 42: Summary of costs by health state: UPA vs VED SC, bio-naïve population

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SC, subcutaneous; UC, ulcerative colitis; UPA, upadacitinib; VED, vedolizumab.

D.6.2 Bio-exposed population

Table 43: Summary of costs by health state: UPA vs ADA, bio-exposed population

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; UC, ulcerative colitis; UPA, upadacitinib.

Table 44: Summary of costs by health state: UPA vs ADA biosimilar, bio-exposed population

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; UC, ulcerative colitis; UPA, upadacitinib.

Table 45: Summary of costs by health state: UPA vs TOF, bio-exposed population

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TOF, tofacitinib; UC, ulcerative colitis; UPA, upadacitinib.

Table 46: Summary of costs by health state: UPA vs UST, bio-exposed population

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: UC, ulcerative colitis; UST, ustekinumab; UPA, upadacitinib.

Table 47: Summary of costs by health state: UPA vs VED IV, bio-exposed population

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IV, intravenous; UC, ulcerative colitis; UPA, upadacitinib; VED, vedolizumab.

Table 48: Summary of costs by health state: UPA vs VED SC, bio-exposed population

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active UC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery remission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SC, subcutaneous; UC, ulcerative colitis; UPA, upadacitinib; VED, vedolizumab.

D.7 Summary of predicted resource use by category of cost

D.7.1 Bio-naïve population

Table 49: Summary of predicted resource use by category of cost: UPA vs ADA, bio-naïve population

Item	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction – direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance - direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – surgery costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; AE, adverse event; UPA, upadacitinib.

Table 50: Summary of predicted resource use by category of cost: UPA vs ADA biosimilar, bio-naïve population

Item	Cost intervention	Cost comparator	Increment	Absolute increment	% absolute increment
Induction – direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance - direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – surgery costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; AE, adverse event; UPA, upadacitinib.

Table 51: Summary of predicted resource use by category of cost: UPA vs GOL, bio-naïve population

Item	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction – direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance - direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – surgery costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; GOL, golimumab; UPA, upadacitinib.

Table 52: Summary of predicted resource use by category of cost: UPA vs IFX, bio-naïve population

Item	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction – direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance - direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – surgery costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; IFX, infliximab; UPA, upadacitinib.

Table 53: Summary of predicted resource use by category of cost: UPA vs IFX biosimilar, bio-naïve population

Item	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction – direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance - direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – surgery costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; IFX, infliximab biosimilar; UPA, upadacitinib.

Table 54: Summary of predicted resource use by category of cost: UPA vs TOF, bio-naïve population

Item	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction – direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance - direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – surgery costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; TOF, tofacitinib; UPA, upadacitinib.

Table 55: Summary of predicted resource use by category of cost: UPA vs UST, bio-naïve population

Item	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction – direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance - direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – surgery costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; UPA, upadacitinib; UST, ustekinumab.

Table 56: Summary of predicted resource use by category of cost: UPA vs VED IV, bio-naïve population

Item	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction – direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance - direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – surgery costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; IV, intravenous; UPA, upadacitinib; VED, vedolizumab.

Table 57: Summary of predicted resource use by category of cost: UPA vs VED SC, bio-naïve population

Item	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction – direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance - direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – surgery costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; SC, subcutaneous; UPA, upadacitinib; VED, vedolizumab.

D.7.2 Bio-exposed population

Table 58: Summary of predicted resource use by category of cost: UPA vs ADA, bio-exposed population

Item	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction – direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance - direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – surgery costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; AE, adverse event; UPA, upadacitinib.

Table 59: Summary of predicted resource use by category of cost: UPA vs ADA biosimilar, bio-exposed population

Item	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction – direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance - direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – surgery costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; AE, adverse event; UPA, upadacitinib.

Table 60: Summary of predicted resource use by category of cost: UPA vs TOF, bio-exposed population

Item	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction – direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance - direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – surgery costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; TOF, tofacitinib; UPA, upadacitinib.

Table 61: Summary of predicted resource use by category of cost: UPA vs UST, bio-exposed population

Item	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction – direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance - direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – surgery costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; UPA, upadacitinib; UST, ustekinumab.

Table 62: Summary of predicted resource use by category of cost: UPA vs VED IV, bio-exposed population

Item	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction – direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance - direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – surgery costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; IV, intravenous; UPA, upadacitinib; VED, vedolizumab.

Table 63: Summary of predicted resource use by category of cost: UPA vs VED SC, bio-exposed population

Item	Cost intervention	Cost comparator	Increment	Absolute increment	
Induction – direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction – AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance - direct medical costs & administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – health state costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance – surgery costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; SC, subcutaneous; UPA, upadacitinib; VED, vedolizumab.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Upadacitinib for treating moderately to severely active ulcerative colitis [ID3953]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**John Caisley**
2. Are you (please tick all that apply):	☑ a patient with the condition? ☐ a carer of a patient with the condition?

	☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Crohn's & Colitis UK
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't ☑ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☑ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☑ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	In 2016, I started to suffer from what was soon diagnosed as a flare of ulcerative colitis (UC). For the next 2 years before I achieved remission, I suffered daily abdominal pain, urgency, diarrhoea, uncontrollable straining, tenesmus and proctalgia - I was opening my bowels up to 20 times a day. Prednisolone ≥ 20mg/day provided the only relief prior to remission. I maintained remission for 2-3 years before flaring again in March 2021 - symptoms were as before, but worse - faecal incontinence became a daily occurence. I failed to respond to further adalimumab, vedolizumab and tofacitinib, and the inflammation began to become steroid resistant. I stopped the steroids in February 2022 in preparation for surgery, In July this year, I underwent panproctocolectomy with end ileostomy, which will hopefully be curative.

	Throughout my flares, I continued to work as a medical technician for a very understanding NHS employer, though some days were spent solely in the toilet. In the weeks prior to surgery, the symptoms left me unable to either get to work, or even to work from home. I am fortunate to have a very supportive wife and 2 great kids, but this disease has had a huge impact on us all - I have missed years of their lives. I wasn't able to play with my kids, go out anywhere, or even eat the same food. I was unable to socialise, exercise or continue with my hobbies.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	The current treatments are great when they work, and increasing azathioprine and adalimumab doses to the maximum put me into remission within a week. Sadly nothing worked the second time. A combination of the difficulty getting a timely appointment with a Gastroenterologist and the time it takes to progress through the NICE guideline [NG130], makes achieving remission (or not) a very long process. In my second flare, I was continually pushing my local IBD nurses for the next treatment when it became apparent that whatever I was on, wasn't working. After 9 months, I asked for a surgical referral and 7 months later underwent surgery. The surgeon told me my colon was "rotten", and the histology report suggests that one section was soon likely to rupture and another likely to obstruct.
10. Is there an unmet need for patients with this condition?	Yes. Increasing the number of biologic / JAK treatments and allowing their earlier introduction to the treatment plan, has the potential to reduce mortality and morbidity from UC, reduce hospital admissions and the need for surgery.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	It will increase the number of medical options for treating UC

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Cost; potential side effects.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No.

Other issues	
15. Are there any other issues that you would like the committee to consider?	Yes. Allowing the earlier introduction of biologic / JAK treatments to the treatment plan.
Topic-specific questions	
16. [To be added by technical team if required, after receiving the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as “Is comparator X [excluded from company submission] considered to be established clinical practice in	

the NHS for treating [condition Y]?"] **if not delete highlighted rows and renumber below**	

Key messages

17. In up to 5 bullet points, please summarise the key messages of your statement:

- UC is a horrible disease, with a huge impact on personal, professional and family life
- The cost to both industry and healthcare associated with UC flares is high
- Increasing the number of medical options to treat UC is likely to reduce the mortality and morbidity of UC, reduce hospital admissions and the need for surgery.
- Allowing the earlier introduction of biologic / JAK treatments to the treatment plan may increase quality of life for UC sufferers, reduce hospital admissions and the need for surgery.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Upadacitinib for treating moderately to severely active ulcerative colitis [ID3953]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the 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 EAR that are likely to be discussed by the committee. The key issues in the EAR 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 EAR.

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 EAR 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 evaluation, 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 redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is the end of **8 Septembe 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.

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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.

Technical engagement response form

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)	NPPG
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 EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1: Lack of direct evidence for the comparison of upadacitinib versus relevant comparators	Yes/No	No further comments on behalf of NPPG
2: Network meta-analysis statistical issues	Yes/No	No further comments on behalf of NPPG
3: Company modelled treatment pathway is not a good reflection of NHS clinical practice	Yes/No	No further comments on behalf of NPPG
4: Company choice of utility values	Yes/No	No further comments on behalf of NPPG
5: High and low doses of upadacitinib maintenance treatments	Yes/No	No further comments on behalf of NPPG

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues

Issue	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue: Insert additional issue			

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

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Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
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
PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Upadacitinib for treating moderately to severely active ulcerative colitis [ID3953]

Technical engagement response form

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Technical engagement response form

NICE National Institute for Health and Care Excellence

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)	UKCPA
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 EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1: Lack of direct evidence for the comparison of upadacitinib versus relevant comparators	No	Lack of direct evidence between majority of the comparators listed in the proposed TA. To date only VARSITY trial has investigated Vedolizumab vs Adalimumab as direct comparison (Vedolizumab >Adalimumab). Therefore, the issue highlighted is not unique to the proposed technology.
2: Network meta-analysis statistical issues	Yes	Consider the following two peer reviewed published NMA which have broadly reached the same conclusions for moderate-severe UC. Upadacitinib ranked highest in both NMA for clinical remission and response. Conversely, it ranked highest for rate of adverse events (non-serious). These NMA also include filgotinib in the analysis which has now been NICE TA approved. In clinical practice, in addition to generally sequencing the therapies, a key question is how to sequence the three JAK inhibitors licensed (tofacitinib, filgotinib and upadacitinib). Therefore, these two NMA could inform the appraisal. Burr NE, et al. Gut 2021;0:1–12. Efficacy of biological therapies and small molecules in moderate to severe ulcerative colitis: systematic review and meta-analysis.

		Lasa, J.S., et al. Lancet Gastroenterol Hepatol 2022; 7: 161–70. Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis
3: Company modelled treatment pathway is not a good reflection of NHS clinical practice	No	No response
4: Company choice of utility values	No	No response
5: High and low doses of upadacitinib maintenance treatments	No	No response

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues

Issue	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue: Insert additional issue			

NICE National Institute for Health and Care Excellence

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Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
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
PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Upadacitinib for treating moderately to severely active ulcerative colitis [ID3953]

Technical engagement response form

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Technical engagement response form

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)	**Janssen**
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 EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1: Lack of direct evidence for the comparison of upadacitinib versus relevant comparators	No	No comments
2: Network meta-analysis statistical issues	No	No comment
3: Company modelled treatment pathway is not a good reflection of NHS clinical practice	No	No comment
4: Company choice of utility values	No	No comment
5: High and low doses of upadacitinib maintenance treatments	No	No comment

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues

Issue	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue: Insert additional issue			

NICE National Institute for Health and Care Excellence

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Sensitivity analyses around revised base case
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Single Technology Appraisal
Upadacitinib for treating moderately to severely active ulcerative colitis [ID3953]
Technical engagement response form
EAG response to company response to technical engagement

Key issues for engagement

Please note EAG additional analyses provided at the end of the document.

All: Please use the table below to respond to the key issues raised in the EAR.

Table 1: Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1: Lack of direct evidence for the comparison of upadacitinib versus relevant comparators	No	The Company wish to point out that the lack of direct evidence for comparison is a common challenge in economic evaluations for HTA. The manual for NICE health technology evaluations (PMG36) (1) details NICE's stance on indirect comparisons, namely that manufacturers should follow methods outlined in the technical support document (TSD) evidence synthesis series. The Company submission for upadacitinib adhered to these TSDs (TSD 1–5) (2-6). A placebo-controlled clinical trial design has been adopted in several comparator trials for therapies that have been assessed and recommended by NICE for use in patients with moderately to severely active ulcerative colitis (UC), as assessed in TA329 (adalimumab [ULTRA 1, ULTRA 2], golimumab

		[PURSUIT-SC/M], infliximab [ACT 1, ACT 2]) (7), TA342 (vedolizumab [GEMINI 1, GEMINI 2, GEMINI 3]) (8), TA547 (tofacitinib [OCTAVE 1, OCTAVE 2) (9), and TA633 (ustekinumab [UNIFI) (10). Furthermore, placebo-controlled trials, which utilised a common placebo treatment arm as the anchor for treatment comparisons, facilitated the inclusion of upadacitinib in the network meta-analysis (NMA) presented in the Company submission. The Company acknowledge the lack of direct evidence for the comparison of upadacitinib versus relevant comparators and that the use of indirect evidence is a source of uncertainty. The large number of relevant treatment options means that even if upadacitinib had a comparator in the control arm, this would not provide direct evidence against all other available relevant comparator treatments available for UC.
EAG response:		No additional comment.
2: Network meta-analysis statistical issues	Yes	Upadacitinib was consistently shown to be the most efficacious advanced therapy for moderately-to-severely active UC at inducing and maintaining clinical response and remission in both biologic-exposed and biologic-naïve populations, considering four separate NMAs (Company NMA, EAG NMA, and NMAs published by Lasa et al (2022) (11) and Burr et al (2021) (12)). To reaffirm that the results from the Company NMA are reproducible, and arguably conservative, the Company have included Table 2 (induction) and Table 3 (maintenance) in Appendix A, which present high-level side-by-side comparisons of the NMA results from the four separate NMAs. The British Society of Gastroenterology (BSG) organisation submission refers to the Lasa 2022 and Burr 2021 NMAs, highlighting that upadacitinib 45mg ranked first in all patients (bio-naïve and bio-exposed), as well as stating that *'The rapidity of response to treatment is impressive with upadacitinib'* and *'In addition, the high remission rates at 8 weeks are impressive'* (13). Additionally, clinical advice received by both the Company and the EAG was that, despite the differences in study populations and trial characteristics, the randomised controlled trials (RCTs) included in the NMAs were appropriate sources of clinical data for decision-making. Clinician statements included: *'had 7 patients on upadacitinib in UC, all are still on drug, which is unique. Upadacitinib for the treatment of UC is as effective as most effective (infliximab) and more durable'* (14).

EAG response:		No additional comment.
3: Company modelled treatment pathway is not a good reflection of NHS clinical practice	Yes	The Company believes that the submitted cost-effectiveness model (CEM) is suitable for addressing the NICE decision problem, namely, what is the cost effectiveness of upadacitinib versus relevant comparators in the bio-naïve and bio-exposed populations. The submitted CEM aims to address this by reflecting clinical practice as closely as possible whilst recognising that a model is a simplification of reality and is limited by data availability. The Company note that the scope of the appraisal is not to determine the most cost-effective treatment sequence among the approximately 800 to 900 possible permutations and believes its approach is aligned with previous appraisals in UC, including TA633 (See Table 4 in Appendix B.1 [Table 57 in CS], which compares the key features of the Company's approach with recent UC appraisals). In acknowledgement of the uncertainty associated with costs and outcomes following failure of biologic treatment in the CEM, this TE response includes new scenarios, including those considering shorter time horizons of 2 years and 5 years; time points at which a large proportion of the patient cohort has entered the active UC health state. Upadacitinib remained dominant or highly cost effective versus all comparators in these scenario analyses in both the bio-naïve (**Error! Reference source not found.**) and bio-exposed (**Error! Reference source not found.**) populations. These results are to be expected since clinical and quality-of-life benefits from upadacitinib treatment are accrued in the remission and response health states. The incremental benefit of upadacitinib is therefore not derived from 'Active UC' but from disease control through clinically important outcomes documented in the upadacitinib clinical trials; outcomes that AbbVie have understood from the BSG submission to represent a step change in management of moderately to severely active UC. In addition, the Company has concerns regarding the modelling approach proposed by the EAG, specifically regarding treatment sequencing, efficacy estimates, treatment duration and utility values, as outlined below. **Treatment sequencing/subsequent treatments**

		The choice of biologic, especially after a loss of response/failure of a first biologic, is a complex clinical decision. There are a wide range of factors (incl. patients characteristics, prognostic factors, response to prior treatment, reason for discontinuation) to take into consideration for each patient. Therefore, clinicians and patients need choice to select and agree on the most appropriate biologic in each instance. The BSG guidelines support this as well, stating *'The choice of drug should be determined by clinical factors, patient choice, cost, likely adherence and local infusion capacity'* (15). As such, it is important that patients receive treatment that works for their individual specific UC presentation and setting. This challenge has also been discussed in previous appraisals (TA633, TA547), in TA633 the ERG noted that *'sequential use of therapies is common in practice, but variable and cost effectiveness is potentially sensitive to the choice of subsequent treatment'* and that this creates uncertainty, which was considered equally relevant to previous appraisals (16). Additionally, new biologic treatments entering the market change the dynamics and change the potential order in which biologics are used. Due to the lack of data and the expert knowledge that clinical response rates decrease with each subsequent line of biologic treatment as their prognostic characteristics are likely to change, modelling sequences will not reduce decision uncertainty. In fact, as evidence with increasing and unknown uncertainty is introduced into the analysis with each additional line of treatment considered, the relevance for decision making becomes more uncertain. This is not aligned to face validity of trial results, the NMA results from Company, EAG or External Parties, nor statements from experts. The Company's submitted CEM, however, does allow for treatment sequencing to be explored and submitted a scenario analysis. For further details, see Appendix B.2. **Estimates of efficacy** The EAG modelled a 'basket of treatments' in their 'on subsequent treatment' health state, where patients would move to after failing the first biologic considered in the model. The Company would like to highlight several limitations with this proposed EAG approach that lack face validity: 1) Assumes same levels of clinical efficacy and utility as bio-naïve population 2) Assumes that patients who have failed all treatments available default back to 'the best one' and achieve same level of efficacy as the first time they received this treatment (prior to failing)

		3) No consideration of surgery from this 'basket' health state, which is not aligned with clinical practice, and it is therefore assumed that patients will be on pharmacological treatments until death. Clinical experts have highlighted that with each additional line of treatment, they observe a reduction in efficacy. This can also be seen across all advanced treatment trial data, where a reduction in clinical response and remission rates are observed when comparing the bio-exposed populations with the bio-naïve population (see **Error! Reference source not found.** and **Error! Reference source not found.** in Appendix C). Therefore, the use of bio-naïve efficacy data is considered inaccurate and significantly overestimates the effectiveness of subsequent lines of biologic treatment. In fact, since this 'on subsequent treatment' health state includes all available treatments, this approach would benefit treatments with worse efficacy since it will be beneficial to fail the first treatment in the sequence, contrary to face validity, observed data, and clinical advice. It would also cancel out any benefit gained by more effective treatment, such as upadacitinib, when calculating ICERs, as upadacitinib is included in the 'basket of treatments'. Further supporting evidence can be found in Appendix B.3. Furthermore, the Company wish to highlight that the biologic-exposed population in the upadacitinib UC clinical trials included subjects who had ≥1 biologic previously (52.8% of total trial populations) and of this bio-exposed trial population, 37.5%, 37.9%, 19.5% and 5% had previously failed 1, 2, 3 or ≥4 biologics, respectively, as detailed in **Error! Reference source not found.** (Appendix C) (17, 18). Therefore, the Company is of the opinion that the data used in the Company's submitted CEM for the bio-exposed population is representative of clinical efficacy across multiple lines of biologic treatments and represents a conservative interpretation of cost effectiveness. **Utility values** The utility value applied to the 'on subsequent treatment' health state is a weighted average of the values for remission and response without remission from the upadacitinib UC trials. As such, all patients in the EAG model have a utility value at least equal to the utility value associated with response to treatment until death, which lacks face validity. Patients who lose response to treatment (relapse) would have experienced a decrease in their quality of life due to disease symptoms, more aligned with the 'active UC' health state. Clinicians highlighted this

		reduction in quality of life: *'If untreated, a 40-50% reduction in quality of life would be expected for moderate-to-severe UC. Work will be severely impact with an increased impact on joblessness, social life, relationships.' (14)* While these are the Company's core concerns, there are additional issues with the EAG's proposed approach highlighted in Appendix B.3 and B.4.
EAG response:		As stated in the EAG report (p.86) "clinical advice to the EAG is that the company model does not capture the current experience of NHS patients and describes a treatment pathway that may be considered unethical by patients and health care professionals. In the company model, patients only receive one line of active treatment, most patients have a response to treatment for only a short period of time, and the proportion of patients who receive surgery is very low. This results in most patients, irrespective of treatment, spending decades in the active UC health state where they only receive CT. The company model is therefore of limited value to decision makers." **Treatment sequencing/subsequent treatments** The EAG does not consider that representing longer-term treatment for UC using a 'basket of treatments' is a perfect solution; however, clinical advice to the EAG is that it is a more accurate representation of the experience of patients in NHS clinical practice than the model submitted by the company. The EAG considers that a lifetime model time horizon and the inclusion of subsequent treatments conform to the NICE Reference Case. The EAG considers that the 'basket of treatments' approach does not reflect treatment sequencing, for which data are not available. However, clinical advice to the EAG is that most patients do not spend prolonged periods in the active UC health state, instead they are managed with pharmacological treatments; the 'basket of treatments' approach allows the EAG to model this clinical advice. **Estimates of efficacy** The EAG has produced a scenario where treatment efficacy data for the bio-exposed population (where available) have been used to estimate the efficacy of the basket of treatments.

		Clinical advice to the EAG is that surgery is a rare event for people who start on biologic therapy. Its inclusion in the model is therefore unlikely to make a significant difference to the estimates of cost effectiveness. The EAG also highlights that the cost of surgery and the utility benefit from surgery mean that surgery is a highly cost effective treatment option. More patients treated with a comparator end up in the basket of treatment health state than patients treated with upadacitinib. This means that, if surgery was incorporated into the basket of treatments health state, the ICERs per QALY gained for the comparison of upadacitinib versus all treatments would increase. The EAG reiterates that modelling a basket of treatments is not without limitations; however, the EAG consider that this modelling approach more closely reflects NHS practice than the company modelling approach, and therefore provides more reliable ICERs per QALY gained. **Utility values** Clinical advice to the EAG is that, in contrast to company model outcomes, most NHS patients who are treated with pharmacological treatment do not have active UC (and, therefore, will not incur the QALYs [and costs] modelled by the company for patients with active UC); therefore, the EAG considers the use of remission and response utility values is appropriate.
4: Company choice of utility values	Yes	**Original utility values** UK quality-of-life data is important for deriving long-term decisions from the NHS and Personal Social Services) PSS perspective. As explained in the Company submission, Woehl et al (2008) was selected as the preferred source of quality-of-life data since utility values were derived from a large sample of patients (n=180) in the UK, to better reflect a UK population. Additional reasons for the selection of the Woehl et al (2008) data has been set out in the Company submission (Section B3.4.5). **Clinical opinion** Clinical expert input received by the Company supports the Company's view that utility data collected in a trial setting is likely to underestimate the true quality of life burden experienced by patients with UC, and this is likely to be especially true for the active UC health state considering the limited follow-up of clinical

		trial. Clinician statements included: '*being in a trial alters the QoL with a benefit. Self-selected patients that are likely to feel rewarded by the increase in number of interactions with a dedicated team associated with a trial*'. Clinical expert input received by the Company suggested that it is reasonable to use observational data where longer-term quality-of-life data is not available from a clinical trial (14). Clinician feedback included: '*would like to see multiple years of QoL data, might be reasonable to use observational study data where this is not available'*. In the ustekinumab UC appraisal (TA633), the NICE committee noted patient expert's reflections on utility values, stating that it is possible that some effects on quality of life (such as feeling out of control) may not be captured in clinical trials. This is also reflected in the statements on patient experience of UC in the Crohn's and Colitis organisation submission (TE papers) (1). To reaffirm the results from the Company submission, this response includes scenarios testing several utility data sources, namely, Woehl et al (2008) (19), Swinburn et al (2012) (20), Vaizey et al (2014) (21), as well as the utility data collected in the upadacitinib UC trials. Upadacitinib remained dominant or highly cost effective versus all comparators in these scenario analyses in both the bio-naïve (**Error! Reference source not found.**) and bio-exposed (**Error! Reference source not found.**) populations.
EAG response:		In line with the NICE Reference Case, the EAG has used utility values estimated from EQ-5D data collected during the three upadacitinib trials.
5: High and low doses of upadacitinib maintenance treatments	Yes	The company understands the EAG's concern and have provided updated probabilistic base-case analyses with a 70%:30% dose split between the 15 mg and 30 mg upadacitinib maintenance doses to align with comparators. The Company consulted additional clinical experts and heard that, considering clinical evidence, this assumption was plausible. Nevertheless, deterministic analysis of 15 mg and 30 mg were conducted for completeness and as recognition that the Committee may find these useful as supporting information for decision making. In conclusion, the EAG's concern notwithstanding, the Company submission, Clarification Letter, and this Technical Engagement response systematically appraised and modelled the best available evidence. The evidence is reflective of treatment for adult patients with moderately to severely active UC who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent in the NHS.

		In conclusion, upadacitinib within its marketing authorisation represents cost effective use of NHS resources in the base case and all revised scenario analysis.
EAG response:		No additional comment.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3: Additional issues

Issue	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue: Surgery rates	Scenario analyses (Section 5.4.4, page 92)	Yes	The assumption that the EAG has made regarding surgery in their scenario analysis (50% of patients with active UC progress to surgery every year) conflicts with published literature. The lifetime risk of colectomy associated with UC is estimated to be around 25% (clinical expert opinion) (14). The EAG scenario assumption was based on clinical expert opinion not seen be the Company, whereas the Company's submission annual surgery rates (0.47%) were based on Hospital Episode Statistics (HES) data (22), further validated by clinical experts both before submission and again for this response. HES data is considered a robust, and UK-relevant, source of evidence by clinical experts, and the most reliable data source to inform the probability of surgery in the model (14). Additionally, data suggest that there has been a reduction in colectomy rates over time, likely due to more advanced treatments that have become available, indicating that the Company submission surgical rates could be considered higher than they would be in 2022. Worsley et al (2020) (23) showed that patients with UC, admitted for active disease during 2013-2016 had significantly lower cumulative probability of colectomy compared to patients admitted during 2003-2007 or 2008-2012 (based

			on HES data). They reported one-year and three-year incidence of colectomy after acute admission as 0.17 and 0.21. Another study looked at the reduction of surgery for UC, showing that between 2005 and 2018 yearly colectomy rates per 100 UC patients fell from 1.47 to 0.44 (p<0.001) (24). In summary, the Company concludes that the EAG scenario for surgery is not relevant for this decision problem.
EAG response:			To estimate a colectomy rate, the company used HES data from patients who were admitted to hospital and had a UC diagnosis. The 'active UC' health state in the company model represents patients who are not responding to pharmacological therapy, have a low quality of life (0.4) and high resource use (£2,378). The EAG does not consider that the population in the Misra (2016) paper represents patients in the company model active UC health state. Clinical advice to the EAG is that all patients in the active UC health state (unless contraindicated) would be offered surgery in NHS clinical practice. Clinical advice to the EAG is that approximately half of the patients would be ineligible or choose not to have surgery and would be likely to receive the treatment that had afforded them the most symptom alleviation to date, even if this level of symptom alleviation was less than remission. The EAG thanks the company for identifying the Jenkinson (2021) study. This paper highlights how increasingly rare colectomy rates have become for patients with UC since the introduction of biological therapies in the NHS. The EAG considers this paper provides evidence to support the EAG's 'basket of treatments' modelling approach as it indicates that most patients with UC are managed with pharmacological therapy.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
5: High and low doses of upadacitinib maintenance treatments	The original submission presented analyses separately for the two maintenance doses of upadacitinib (15 mg and 30 mg daily). For comparators, 30% of patients were assumed to be receiving the escalated maintenance dose with the remaining 70% on the standard dose (where applicable).	The revised base-case analysis applies a ratio of standard:escalated maintenance doses of 70%:30% applied for all treatments, including upadacitinib, in line with EAG preferences. Separate analyses are presented for the two upadacitinib maintenance doses for reference.	See Appendix **Error! Reference source not found.** for the revised base-case results
Company's base case following technical engagement (or revised base case)	Incremental QALYs: See Section B.3.10.1 of Company submission	See Appendix **Error! Reference source not found.** for the revised base-case results	See Appendix **Error! Reference source not found.** for the revised base-case results

Appendix A: NMA comparison results

Table 2: Overview induction NMAs – ranked treatments (most favoured on top)

	Biologic-naïve population					Biologic-exposed population			
	Company NMA	**EAG NMA**	**Lasa et al 2022 NMA †**	**Burr er at 2021 NMA**		**Company NMA**	**EAG NMA**	**Lasa et al 2022 NMA †**	**Burr er at 2021 NMA**
Clinical remission (RE model)	**UPA45** IFX5 VED300 GOL200/100 IFX10 TOF10 UST6 ADA160/80 PBO	**UPA45** IFX5 VED300 GOL200/100 IFX10 TOF10 UST6 ADA160/80 PBO	**UPA45** OZA1 IFX5 TOF10 UST6 GOL200 VED300 FIL200 ADA160/80 ETRO105 FIL100 PBO	**UPA45** IFX5 IFX10 VED300 OZA1‡ FIL200‡ GOL400/200 TOF10 UST130 GOL200/100 ADA160/80 ETRO105‡ UST6 FIL100‡ ADA80/40	**Clinical remission (RE model)**	**UPA45** UST6 TOF10 VED300 ADA160/80 PBO	**UPA45** TOF10 UST6 VED300 ADA160/80 PBO	**UPA45** OZA1‡ IFX5 TOF10 UST6 GOL200 VED300 FIL200‡ ADA160/80 ETRO105‡ FIL100‡ PBO	**UPA45** UST6 TOF10 UST130 ETRO105‡ VED300 FIL200‡ OZA1‡ FIL100‡ ADA160/80
Clinical response (RE model)	**UPA45** UST6 IFX10 TOF10 ADA160/80 VED300 GOL200/100 PBO	NR	N/A	**UPA45** UST6 IFX10 IFX5 VED300 FIL200‡ UST130 GOL400/200 TOF10 GOL200/100 ETRO105‡ FIL100‡ ADA160/80 ADA80/40	**Clinical response (FEA model)**	**UPA45** TOF10 UST6 VED300 ADA160/80 PBO	**UPA45** TOF10 UST6 VED300 ADA160/80 PBO	N/A	**UPA45** FIL200‡ UST6 TOF10 UST130 FIL100‡ ETRO105‡ VED300 ADA160/80 IFX10 UST6 IFX5

Abbreviations: ADA160/80, adalimumab 160/80 mg induction; EAG, external assessment group; ETRO105, etrolizumab 105 mg; FEA, fixed effects with baseline-risk adjustment; FIL200/100, filgotinib 200/100 mg; GOL400/200/100, golimumab 400/200/100 mg induction; IFX5/IFX10, infliximab 5 mg/kg body weight/10 mg/kg body weight; N/A, not applicable; NMA, network meta-analysis; NR, not reported; OZA1, ozanimod 1 mg; PBO, placebo; RE, random effects; TOF10, tofacitinib 10 mg; UPA45, upadacitinib 45 mg; UST130/6, ustekinumab 130 mg/kg body weight/6 mg/kg body weight; VED300, vedolizumab 300 mg.
Note: Treatments are listed in order of most favoured to least favoured. † Overall patient population results, as data for UPA by prior treatment exposure were not available. ‡ Treatment not considered a relevant comparator at the time of the upadacitinib Company submission. Sources: Lasa et al (2022) (11) and Burr et al (2021) (12).

Table 3: Overview maintenance NMAs – ranked treatments (most favoured on top)

	Biologic-naïve population					Biologic-exposed population			
	Company NMA	**EAG NMA**	**Lasa et al 2022 NMA†**	**Burr er at 2021 NMA**		**Company NMA**	**EAG NMA**	**Lasa et al 2022 NMA†**	**Burr er at 2021 NMA**
	Biologic-naïve population					**Biologic-exposed population**			
Clinical remission (RE model)	TOF10 TOF5 **UPA30** VED300Q4W VED300Q8W **UPA15** GOL100 GOL50 UST90Q8W UST90Q12W IFX10 IFX5 ADA40Q2W PBO	TOF10 TOF5 **UPA30** GOL100 VED300Q4W **UPA15** VED300Q8W GOL50 UST90Q8W UST90Q12W IFX10 IFX5 ADA40Q2W PBO	**UPA30** **UPA15** FIL200‡ VED108Q2W TOF5 VED300Q8W OZA1‡ UST90Q8W GOL100 ETRO105Q4W‡ FIL100‡ PBO	NA	**Clinical remission (RE model)**	**UPA30** **UPA15** VED300Q8W VED300Q4W TOF10 UST90Q8W ADA40Q2W TOF5 UST90Q12W PBO	**UPA30** **UPA15** VED300Q4W VED300Q8W TOF10 UST90Q8W TOF5 ADA40Q2W UST90Q12W PBO	**UPA30** **UPA15** FIL200‡ VED108Q2W TOF5 VED300Q8W OZA1‡ UST90Q8W GOL100 ETRO105Q4W‡ FIL100‡ PBO	NA
Clinical response (RE model)	**UPA30** TOF10 VED300Q8W **UPA15** TOF5 VED300Q4W UST90Q8W UST90Q12W GOL100 IFX10 GOL50 IFX5 ADA40Q2W PBO	**UPA30** TOF10 VED300Q8W **UPA15** TOF5 VED300Q4W UST90Q8W UST90Q12W GOL100 IFX10 GOL50 IFX5 ADA40Q2W PBO	NA	NA	**Clinical response (RE model)**	**UPA30** TOF10 **UPA15** TOF5 VED300Q8W VED300Q4W UST90Q8W ADA40Q2W UST90Q12W PBO	**UPA30** TOF10 **UPA15** TOF5 VED300Q8W VED300Q4W UST90Q8W ADA40Q2W UST90Q12W PBO	NA	NA

Abbreviations: ADA40Q2W, adalimumab 40 mg every other week; EAG, external assessment group; ETRO105Q4W, etrolizumab 105 mg every 4 weeks; FIL200/100, filgotinib 200/100 mg; GOL100/50, golimumab 100/50 mg induction; IFX5/IFX10, infliximab 5 mg/kg body weight/10 mg/kg body weight; NA, not applicable; NMA, network meta-analysis; OZA1, ozanimod 1 mg; PBO, placebo; RE, random effects; TOF5/10, tofacitinib 5 mg/10 mg; UPA15/30, upadacitinib 15 mg/30 mg; UST90Q8W/UST90Q12W, ustekinumab 90 mg every 8 weeks/every 12 weeks; VED300Q4W/VED300Q8W, vedolizumab 300 mg every 4 weeks/every 8 weeks.
Note: Treatments are listed in order of most favoured to least favoured. † Overall patient population results, as data for UPA by prior treatment exposure were not available. ‡ Treatment not considered a relevant comparator at the time of the upadacitinib Company submission.
Sources: Lasa et al (2022) (11) and Burr et al (2021) (12).

Appendix B: Supporting evidence

B.1 Economic analysis comparison with previous UC appraisals

Table 4: Features of the economic analysis compared with previous UC appraisals

Factor	Previous appraisals				Current appraisal	
	TA329 AG	TA342	TA547	TA633	Chosen values	Justification
Time horizon	Lifetime	10 years	Lifetime	Lifetime	Lifetime (100 years of age)	Adopted to capture all important differences in costs and outcomes between the technologies being compared per NICE reference case and aligned with previous TAs
Model structure	State-transition Markov cohort model – AG	Hybrid decision tree-Markov model	Markov model	Hybrid decision tree-Markov model	Hybrid decision tree- Markov model	Captures induction and maintenance phases. Consistent with previous appraisals
Cycle length	2 weeks	6 weeks (induction), 8 weeks (maintenance)	8 weeks	2 weeks	4 weeks	Short enough to capture changes in health state occupancy, and to address the concern in TA633 regarding the 2-week cycle length.
Treatment waning effect	No	No	No	No	No	Consistent with previous appraisals
Source of utilities	Woehl et al.	GEMINI 1, Punekar and Hawkins et al., utility decrements for AEs were taken from clinical trials.	Woehl et al.	Woehl et al. and Arseneau et al.	Woehl et al. and Arseneau et al.	Aligned with TA633 (UST)
Source of costs	Published literature	NHS list price and BNF, December 2013	2016/17 NHS reference cost, (eMIT, MIMs, PSSRU)	2017/18 NHS reference cost, BNF, MIMS, previous TAs, published literature	2019/20 NHS reference costs, BNF, published literature	Consistent with previous appraisals
Pharmacological treatment AEs	No AEs were considered	Serious infection, tuberculosis, lymphoma, hypersensitivity and injection site reaction	Serious infection	Serious infection	Serious infection	
Stopping rule	Yes	Yes	No	No	No	
Spontaneous remission	No	No	No	No	No	

Abbreviations: AE, adverse event; AG, assessment group; BNF, British National Formulary; eMIT, electronic Market Information Tool; MIMS, Monthly Index Medical Specialties; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit; TA, technology appraisal; UC, ulcerative colitis; UST, ustekinumab.

B.2 Treatment sequencing in Company's CEM

The Company's submitted model follows previous appraisals (TA633, TA547) that have not explored sequencing in the base case, but rather in a scenario analysis due to subsequent treatment uncertainty.

The Company's submitted CEM allows for treatment sequencing by allowing patients to move to a second biologic before entering the active UC health state where patients are assumed to receive conventional therapy. Efficacy data from the bio-exposed population were used in this scenario, representing patients who have received ≥1 biologic previously. To be able to model treatment sequencing accurately, efficacy data would be required from patients who were treated with each specific sequence of biologics. Clinical experts state that there are no such controlled studies available, and typically they see a reduced number of patients respond with each additional line of biologic treatment (e.g. they see only 30–40% of patients responding to 3L biologic (14)).

B.3 Efficacy data

The efficacy data used in the model (for all treatments) represent conditional probabilities of response and remission at Week 52 for patients who are responders at the end of induction. They do not reflect the probabilities of response and remission following lack of (or loss of) response to prior treatment. Based on current inputs, the EAG revision assumes that 61% of patients in the 'subsequent treatment' health state are in remission, with the remaining 39% having response without remission. This is held constant throughout the model time horizon. As mentioned above, the EAG model ignores the fact that, based on the NMA data and depending on choice of treatment, 30-70% of patients are neither in remission nor response without remission at Week 52.

In the EAG report it is stated that the subsequent treatment basket includes patients who 'failed to achieve long-term remission on any drug and are unwilling or unsuitable for surgery and therefore are indefinitely prescribed the treatment which gave them the most symptom alleviation (without achieving remission)' as well as describe that bio-naïve population data was used for this health state 'The basket of treatment effectiveness estimate (remission or response without remission) was taken from the company maintenance bio-naïve NMAs and was used to model effectiveness for both bio-naïve and bio-exposed populations' (13). These statements contradict each other, as it is not considered likely in clinical practice that patients who have failed a treatment subsequently regain the response they initially had, instead they would have dose escalated to recapture response, before stopping treatment altogether.

B.4 BIM data

In the EAG report, it is stated that patients in the subsequent treatment health state are modelled to receive a basket of biologic treatments based on the market share provided by the company, which was utilised to estimate data for the fifth line of treatment.

The year five bio-naïve market share data used in the budget impact model was misinterpreted as the distribution of comparators in the fifth line of treatment, which was subsequently used to weight the utility, cost and efficacy data for treatment sequencing. The year-five market share data is consequentially being used to inform the weighting of fifth line treatment sequencing, rather than its intended purpose of determining the share of the market that each of the comparators would hold in the fifth year of being on the market. This subsequentially impacts the weighting of the efficacy data in the basket of subsequent treatments.

The EAG used the 5-year bio-naïve market share data to estimate the distribution of treatments for patients in the basket of treatments health state, not to represent treatment distribution in the fifth-line setting.

Additional EAG analyses

The EAG has updated the EAG scenarios/revisions and cost effectiveness results in light of the new company base case, which includes a revised PAS and acceptance of the 30%:70% split between the 30mg and 15mg upadacitinib maintenance doses.

In response to the company comments, the EAG has also generated results using effectiveness of subsequent treatment data generated by the bio-exposed NMAs. Where data for the bio-exposed population were not available (golimumab, infliximab and infliximab biosimilar), the EAG has used effectiveness data from the bio-naïve NMAs (see **New** scenario in Table 5 and Table 6).

Information about the market share of golimumab, infliximab and infliximab biosimilar are not available; therefore, the EAG has used the bio-naïve market share data for these treatments and re-weighted the remaining treatment estimates of market share.

The EAG basket of treatments has been updated to use the bio-exposed utility values for scenarios that include the trial-based utility values.

Pairwise analysis results for the comparison of upadacitinib versus adalimumab (biosimilar) have been generated to show the impact of individual EAG revisions on the ICERs per QALY gained (Table 5 and Table 6). Fully incremental analysis results for the comparison of upadacitinib versus all treatments are also shown in Table 7 and Table 8.

Table 5 EAG revisions to company model, **bio-naïve** population: upadacitinib vs adalimumab biosimilar (revised PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Adalimumab (biosimilar)		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,470
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,471
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,142
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
New: EAG preferred treatment pathway using bio-exposed NMA for effectiveness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,570
B1. EAG combined revisions (R1-R2a) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R2a) deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 6 EAG revisions to company model, **bio-exposed** population: upadacitinib vs adalimumab biosimilar (revised PAS price for upadacitinib)

Revision/EAG amendment	Upadacitinib		Adalimumab (biosimilar)		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (probabilistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,346
A2. Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,907
R1: Trial utility values and serious infection disutility removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,518
R2: EAG preferred treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
EAG revision: R1+R2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
New: EAG preferred treatment pathway using bio-exposed NMA for effectiveness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
S1: Remission at 12 months is permanent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£242
S2: Annual rate of 1st surgery of 50% and all patients with post-surgery complications have a 2nd surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,398
B1. EAG combined revisions (R1-R2a) - probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**
B2. EAG combined revisions (R1-R2a) - deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Upadacitinib dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; UPA=upadacitinib

Table 7 EAG base case, **bio-naïve** population: fully incremental analyses (revised PAS price for upadacitinib)

EAG base case			Incremental		ICER £/QALY
	Cost	QALYs	Cost	QALYs	
UPA 45	[redacted]	[redacted]	[redacted]	[redacted]	-
GOL 200/100	[redacted]	[redacted]	[redacted]	[redacted]	**Extendedly dominated by TOF**
TOF 10	[redacted]	[redacted]	[redacted]	[redacted]	**£3,976,384**
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	**Dominated by TOF**
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	**Dominated by TOF**
IFX 5 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	**Dominated by TOF**
UST 6	[redacted]	[redacted]	[redacted]	[redacted]	**Dominated by TOF**
IFX 5	[redacted]	[redacted]	[redacted]	[redacted]	**Dominated by TOF**
VED 108	[redacted]	[redacted]	[redacted]	[redacted]	**Dominated by TOF**
VED 300	[redacted]	[redacted]	[redacted]	[redacted]	**Dominated by TOF**

ADA=adalimumab; EAG=External Assessment Group; GOL=golimumab; ICER=incremental cost effectiveness ratio; IFX=infliximab; PAS=Patient Access Scheme; QALY=quality adjusted life year; TOF=tofacitinib; UPA=upadacitinib; UST=ustekinumab; VED=vedolizumab

Table 8 EAG base case, **bio-exposed** population: fully incremental analyses (revised PAS price for upadacitinib, list prices other drugs)

EAG base case			Incremental		ICER £/QALY
	Cost	QALYs	Cost	QALYs	
UPA 45	[redacted]	[redacted]	[redacted]	[redacted]	-
TOF 10	[redacted]	[redacted]	[redacted]	[redacted]	**Dominated by UPA**
ADA 160/80 biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	**Dominated by UPA**
ADA 160/80	[redacted]	[redacted]	[redacted]	[redacted]	**Dominated by UPA**
UST 6	[redacted]	[redacted]	[redacted]	[redacted]	**Dominated by UPA**
VED 108	[redacted]	[redacted]	[redacted]	[redacted]	**Dominated by UPA**
VED 300	[redacted]	[redacted]	[redacted]	[redacted]	**Dominated by UPA**

ADA=adalimumab; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; TOF=tofacitinib; UPA=upadacitinib; UST=ustekinumab; VED=vedolizumab

Upadacitinib for treating moderately to severely active ulcerative colitis [ID3953]

Redacted

Technology appraisal committee B [13 October 2022]

Chair: Charles Crawley

Lead team: Charles Crawley (Chair), Baljit Singh (Clinical), Henry Edwards (Cost)

Evidence assessment group: Liverpool Reviews and Implementation Group

Technical team: Catherine Spanswick, Carl Prescott, Henry Edwards

Company: AbbVie

NICE National Institute for Health and Care Excellence

Key issues

Issue	Resolved?	Tech team view	ICER impact
No direct evidence vs comparators – *influenced by confidence in NMA results*	No – cannot be resolved	Company approach acceptable	Unknown
NMA statistical issues – *plausibility and suitability of NMA results*	No – for discussion	NMAs results plausible but some uncertainty	Unknown
Modelled treatment pathway – *does not represent NHS practice*	No – for discussion	Choice does not have big impact	Small
Utility values – *trial utilities available, but not used in company base case*	No – for discussion	Choice does not have big impact	Small
High and low doses of upadacitinib maintenance treatments – *different doses with different costs available; what is used in NHS?*	Yes	No further discussion needed	Small

Abbreviations: ICER, incremental-cost effectiveness ratio; NMA, network meta-analysis

Additional issue after technical engagement

Issue	Resolved?	Tech team view	ICER impact
Surgery rates – *only relates to company base case (not EAGs)*	No – for discussion	Choice does not have big impact	Moderate

Abbreviations: ICER, incremental-cost effectiveness ratio; NMA, network meta-analysis

NICE technical team suggested recommendation

Upadacitinib should be recommended

Upadacitinib should be recommended in line with other JAK inhibitors tofacitinib and filgotinib

Suggested wording: *"Upadacitinib is recommended as an option for treating moderately to severely active ulcerative colitis in adults when conventional or biological treatment cannot be tolerated, or if the disease has not responded well enough or has stopped responding to these treatments"*

Rationale:

- Upadacitinib has broadly similar total costs and QALYs vs existing NICE recommended treatments for moderately to severely active ulcerative colitis, including other JAK inhibitors, tofacitinib and filgotinib, with indirect analyses suggesting upadacitinib may be more effective than some treatments
- Where company and EAG base cases differ, the impact on ICERs are generally small
- Low risk to the NHS – many other drugs available, this will be another option

Risks and uncertainties in suggested recommendation

Some uncertainty and risks with suggested recommendation

Uncertainty:

- EAG identified some unresolvable statistical issues in NMA results that add uncertainty

Risks:

- In a limited number of pairwise comparisons, tofacitinib was more effective than upadacitinib
- In some comparisons, upadacitinib was not the most cost-effective option but it was broadly a cost-effective use of NHS resources
- Recommendation may need to be updated following EMA's safety review of tofacitinib:

EMA's safety committee (PRAC) is carrying out a review to determine whether risks associated with tofacitinib are associated with all JAK inhibitors authorised in EU (including upadacitinib) for the treatment of inflammatory disorders, and whether marketing authorisations for these medicines should be amended

- For now there is nothing to be done so in the interim period it should be recommended alongside tofacitinib (TA547) with any NICE recommendations updated post EMA investigation

Abbreviations: PRAC, Pharmacovigilance Risk Assessment Committee

Background

Moderately to severely active UC is a severe, chronic and burdensome disease with many different treatment options

Upadacitinib is a potential additional treatment option for patients who have already had conventional therapy or a biologic agent

NICE National Institute for Health and Care Excellence

Disease background

Ulcerative colitis:

- Lifelong, progressive disease characterised by relapsing and remitting episodes of inflammation of the rectal and colonic mucosa
- Tiny ulcers develop on the surface of the lining of the colon (bleed and produce pus)

Epidemiology:

- Around 115,000 people in England have UC (52% moderate to severe disease - defined as Mayo clinic score - 6 to 12)
- Incidence peaks between 15 and 25 years. Smaller peak between 55 and 65 years

Risk factors:

- Unknown cause. Hereditary, infectious and immunological factors possible

Symptoms:

- Bloody diarrhoea, colicky abdominal pain, urgency and tenesmus; extra-intestinal manifestations (joints, eyes, skin and liver)

Complications:

- Haemorrhage, perforation, stricture formation, abscess formation and anorectal disease

Treatments:

- Pharmacological: conventional therapy (aminosalicylates, corticosteroids or thiopurines) and biologics (adalimumab, golimumab, infliximab, vedolizumab, tofacitinib or ustekinumab)
- Surgery: colectomy

Abbreviations: UC, ulcerative colitis

Mayo clinic score (MCS) for ulcerative colitis

Used for diagnosis and to assess disease activity

Component	Description	Points
Stool frequency subscore	Normal	0
	1–2 stools more than usual	1
	3–4 stools more than usual	2
	≥ 5 stools more than usual	3
Rectal bleeding subscore	No blood	0
	Streaks of blood < 50% of time with stool	1
	Obvious blood most of time with stool	2
	Blood alone passed	3
Endoscopic findings subscore	Normal/inactive disease	0
	Mild disease	1
	Moderate disease	2
	Erosions	3
Physician's global assessment	Normal	0
	Mild	1
	Moderate	2
	Severe	3

Adapted Mayo score:
- Total score of 0-9
- Primary and key secondary outcome measure in upadacitinib trials based on recommendation by regulatory agency

Full Mayo score:
- Total score of 0-12
- Moderate to severely active ulcerative colitis has total score of 6 to 12

Abbreviations: UC, ulcerative colitis

Upadacitinib (Rinvoq, AbbVie)

Marketing authorisation	• Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent • Granted in July 2022 • Contraindications – hypersensitivity to active substance or excipients, active tuberculosis, active serious infections, severe hepatic impairment, pregnancy
Mechanism of action	• Selective and reversible Janus kinase (JAK) inhibitor that preferentially inhibits JAK1 • Modulates the signalling of the JAK-dependent cytokines, which reduces inflammation in the gut and improves signs and symptoms of UC
Administration	Once-daily oral dosing: • Induction: 45 mg for 8 weeks, continued for a further 8 week if inadequate response • Maintenance: 15 mg or 30 mg based on patient presentation
Price	• List price (28 tablets per pack): £805.56 for 15 mg tablets; £1,281.54 for 30 mg tablets; £2087.10 for 45 mg tablets • Patient access scheme (PAS) discount in place (confidential)

Decision problem (1)

	Final scope	Company	EAG comments
Population	People with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent	*As per scope.* Subpopulations: • Non-Bio IR*, hereafter referred to as '**bio naïve population**' and defined as: *patients who had an inadequate response or intolerance to CT but had not failed biologic therapy* • Bio IR, hereafter referred to as '**bio exposed population**' and defined as: *patients who had an inadequate response or intolerance to CT or a biologic treatment*	*As per scope*

*Only 2% of non-Bio-IR population had previously been exposed to a biologic treatment and had stopped for reasons other than inadequate response, loss of response, or intolerance

Abbreviations: CT, conventional therapy; IR, inadequate response; UC, ulcerative colitis

Decision problem (2)

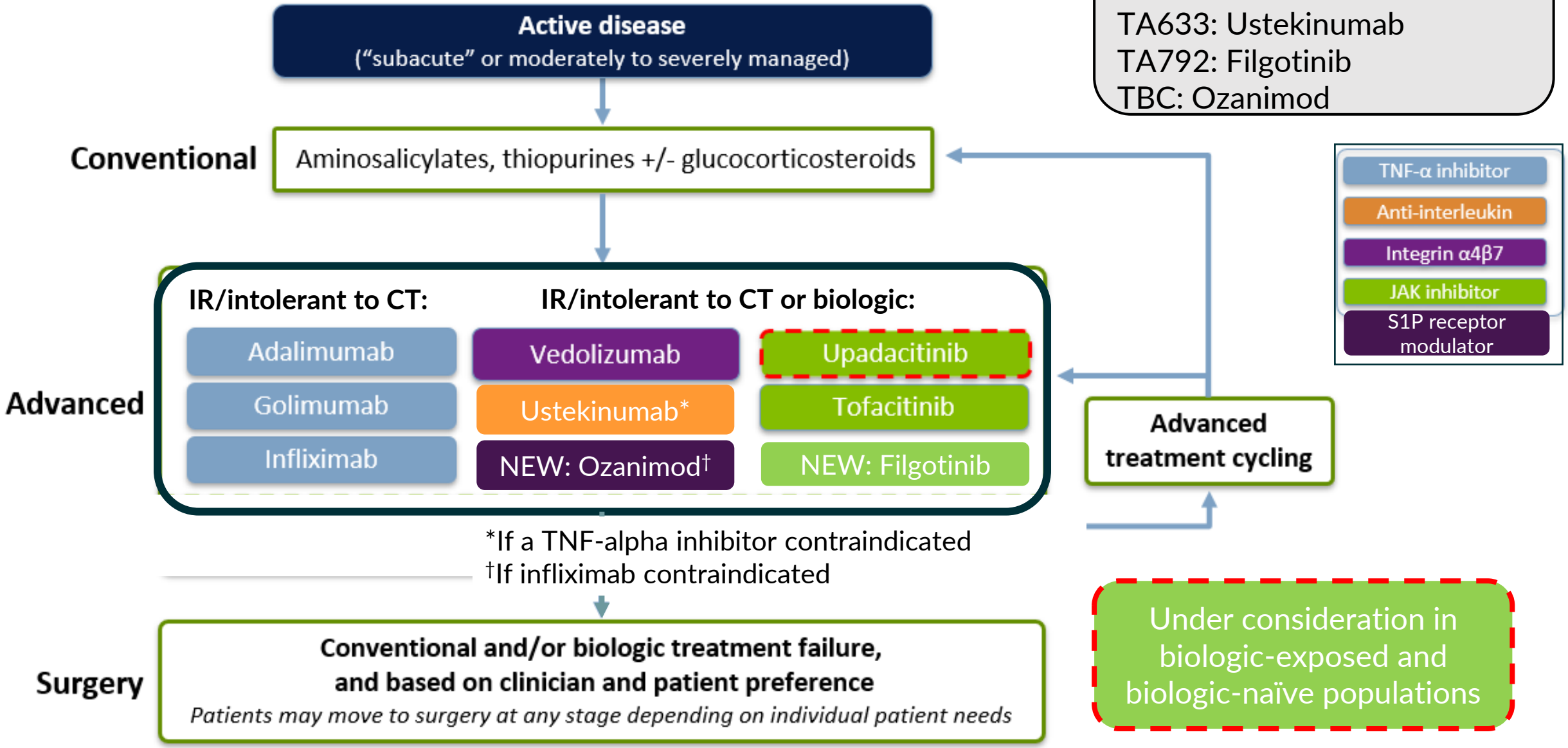
	Final scope	Company	EAG comments
Intervention	Upadacitinib	*As per scope*	*As per scope*
Comparators	• TNF-alpha inhibitors (adalimumab, golimumab, infliximab) • Tofacitinib • Ustekinumab • Vedolizumab • Filgotinib (ongoing NICE appraisal [TA792]) • Ozanimod (ongoing NICE appraisal [ID3841] expected publication 5 Oct) • Conventional therapies (including aminosalicylates, oral corticosteroids and/or immunomodulators), without biological treatments	• TNF-alpha inhibitors (adalimumab, golimumab, infliximab) • Tofacitinib • Ustekinumab • Vedolizumab Excludes: • Filgotinib and ozanimod – at time of submission, both subject to ongoing NICE appraisal and do not represent standard of care • Conventional therapies – given earlier in treatment pathway	Agrees with company approach

Decision problem (3)

	Final scope	Company	EAG comments
Outcomes	• 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 • Endoscopic remission combined with histological improvement • Corticosteroid-free remission • Achieving mucosal healing • Adverse effects of treatment • Health-related quality of life	*As per scope* Note: Endoscopic remission combined with histological improvement corticosteroid-free remission is addressed as 2 separate outcomes in submission • Endoscopic healing combined with histological improvement • Corticosteroid-free remission	*As per scope* Note: Rate of relapse not presented as a clinical outcome but is estimated from NMA results

Ulcerative colitis treatment pathway

TA329: TNF-alpha inhibitors
TA342: Vedolizumab
TA547: Tofacitinib
TA633: Ustekinumab
TA792: Filgotinib
TBC: Ozanimod



Abbreviations: IR, inadequate response; JAK, Janus kinase; S1P, sphingosine 1-phosphate; TNF-α, tumour necrosis factor-α

Recent NICE appraisals: tofacitinib

Technology appraisal	Class	Drug	Recommended as an option for treating moderately to severely active ulcerative colitis in adults …	Pathway positioning
TA547 (2018)	Janus kinase (JAK) inhibitor	Tofacitinib	…when conventional therapy or a biological agent cannot be tolerated or the disease has responded inadequately or lost response to treatment	Biologic naïve Biologic exposed

Position in pathway:

- Committee concluded tofacitinib used in the same place in pathway as biological therapies, instead of or after biologic therapy

Rationale for recommendation:

- Indirect comparison suggests that for people who have not had a TNF-alpha inhibitor, tofacitinib is more effective than adalimumab and golimumab as maintenance treatment. For people who have had a TNF-alpha inhibitor, tofacitinib is more effective than adalimumab as induction treatment.
- Compared with conventional therapy and biologicals, tofacitinib was considered cost effective

Recent NICE appraisals: ustekinumab

Technology appraisal	Class	Drug	Recommended as an option for treating moderately to severely active ulcerative colitis in adults ...	Pathway positioning
TA633 (2020)	Anti-interleukin	Ustekinumab	...when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment, only if: • a TNF-alpha inhibitor has failed (that is the disease has responded inadequately or has lost response to treatment) or • a TNF-alpha inhibitor cannot be tolerated or is not suitable	Biologic exposed

Position in pathway:

- TNF-alpha inhibitors most commonly used biological treatment
- People who cannot have TNF-alpha inhibitors usually offered vedolizumab, so this is the most relevant comparator for ustekinumab

Rationale for recommendation:

- When compared with vedolizumab, ustekinumab was considered cost effective
  - Ustekinumab not cost effective in people who have TNF-alpha inhibitors as a treatment option

Recent NICE appraisals: filgotinib

Technology appraisal	Class	Drug	Recommended as an option for treating moderately to severely active ulcerative colitis in adults …	Pathway positioning
TA792 (2022) *recommended after current submission*	JAK inhibitor	Filgotinib	…when conventional or biological treatment cannot be tolerated, or if the disease has not responded well enough or has stopped responding to these treatments	Biologic naïve Biologic exposed

Position in pathway:

- Filgotinib positioned 3 ways: biologic-naïve, biologic experienced after 1 line, biological experience after 2 lines

Rationale for recommendation:

- Indirect comparison suggests filgotinib likely to be as effective as most treatments offered after conventional therapy
- Filgotinib was likely to be cost effective compared with these other treatments

Upadacitinib: most similar to approach taken in filgotinib TA: biologic-naïve, biologic experienced (any line)

Recent NICE appraisals: ozanimod

Technology appraisal	Class	Drug	Recommended as an option for treating moderately to severely active ulcerative colitis in adults …	Pathway positioning
ID3841 (2022)	Sphingosine-1-phosphate inhibitor	Ozanimod	…only if: • conventional treatment cannot be tolerated or is not working well enough and infliximab is not suitable, or • biological treatment cannot be tolerated or is not working well enough	TNF-alpha inhibitor naïve TNF-alpha inhibitor experienced

Position in pathway:

- Company presented 2 positions: TNF-alpha inhibitor naïve and TNF-alpha inhibitor experienced because TNF-alpha inhibitors more commonly used after conventional therapy than other biological treatments, so
  - Ozanimod can be used after conventional treatment or after a TNF-alpha inhibitor

Rationale for recommendation:

- Standard treatments after conventional therapy are biological treatments or tofacitinib
- Indirect comparison suggests ozanimod likely to be as effective as some treatments offered after conventional therapy
- When conventional therapy is not tolerated or not working well enough, infliximab is more cost effective than ozanimod
- When compared with most other treatments ozanimod was likely to be cost effective

Patient expert perspectives

Submissions from Crohn's & Colitis UK and patient testimony

Living with ulcerative colitis

- Disease severity is wide-ranging and each individual has own experience: embarrassed, frustrated, sad and fear need for surgery or developing cancer
- Symptoms include frequent diarrhoea, abdominal pain and fatigue, anaemia, extra-intestinal manifestations, affecting ability to work, study and socialise

UC is a horrible disease, with a huge impact on personal, professional and family life

Unmet need in moderate to severe ulcerative colitis

- Range of treatments available but people who experience a lack of response face the prospect of surgery with considerable anxiety
- Dissatisfaction with current treatments, side effects from steroids extremely unpleasant, concern about long-term safety profile of other treatments including biologics
- Allowing the earlier introduction of biologic / JAK treatments to the treatment plan may increase quality of life for UC sufferers, reduce hospital admissions and the need for surgery

Upadacitinib

- An oral therapy, gives patients a treatment option to be taken at home
- Additional option with a different mode of action that may reduced likelihood of loss of response

Abbreviations: UC, ulcerative colitis

Clinical expert perspectives

Submissions from UKPCA and British Society of Gastroenterology

Aim of drug treatment for moderately to severely active ulcerative colitis

- To induce clinical, steroid-free and endoscopic remission, prevent flares, hospitalisations and surgery, and improve QoL

Unmet need

- Approximately 1/3rd people relapse during first 12 months on treatment
- In up to ~50% of patients there is a lack of response or loss of response over time
- TNF-α inhibitors are affected by primary failure of induction therapy (19-58%) and secondary loss of response (17-22%) or need for dose escalation (~40%); treatment failure even higher if given 2nd-line

Upadacitinib

- Step change – NMA suggests best performing agent for induction of clinical remission in moderate to severe UC
- Easier for patients: a once-daily oral agent, so ↓ risk of hospital derived infection and injection site reactions
- No special temperature storage conditions (vs other options such as adalimumab which needs to be stored in a fridge – less wastage)
- Like with current treatments, additional monitoring is required
- High response rates seen suggest it should not be reserved for *after* failure of anti-TNF-α, vedolizumab or ustekinumab
- Use caution in patients with risk factors for venous thromboembolism

Abbreviations: NMA, network meta-analysis; UKCPA, UK Clinical Pharmacy

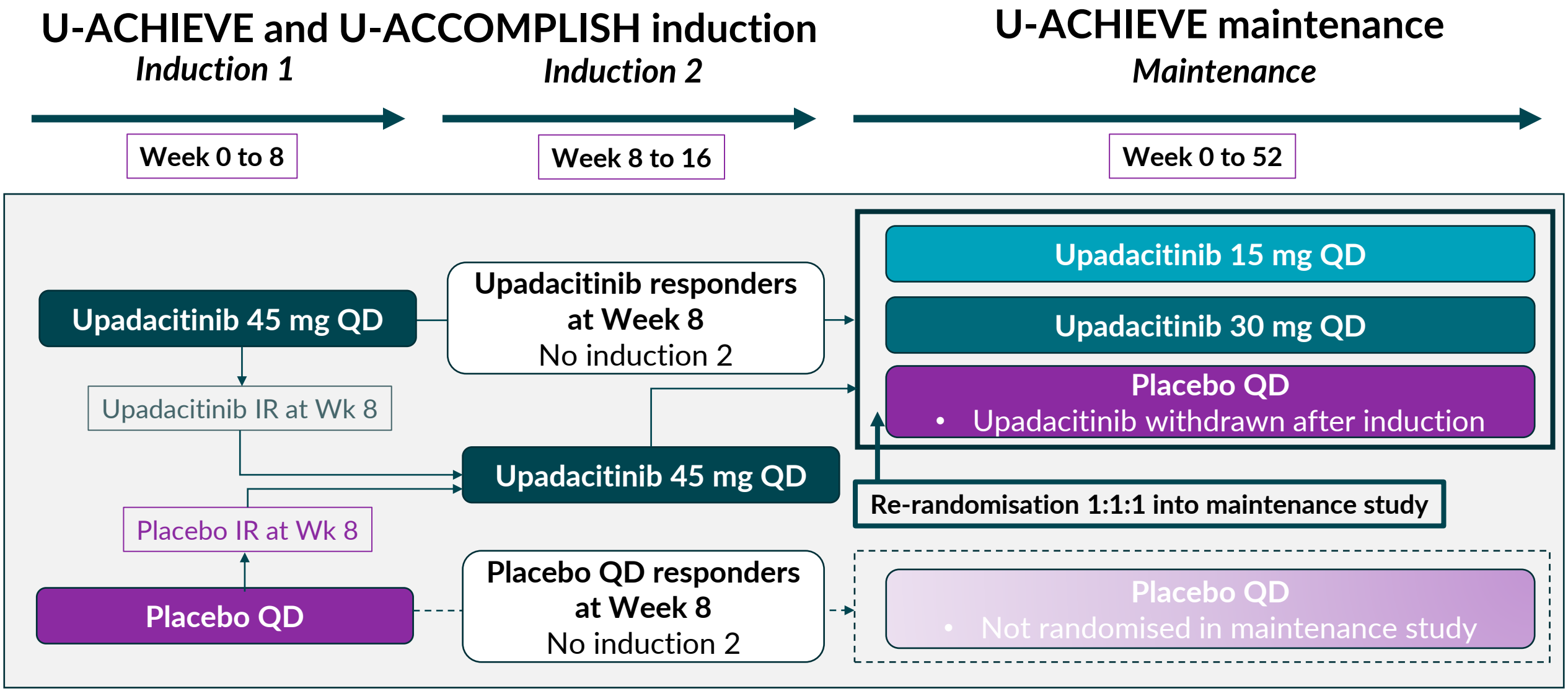
Clinical effectiveness

In clinical trials, upadacitinib is more effective than placebo for key outcomes

In indirect comparisons, NMA results show upadacitinib is more effective than comparators and has similar AEs

Clinical trial results

Key clinical trials



Note: Any IR patients at Week 16 did not enter maintenance study

Key clinical trials of upadacitinib versus placebo

	U-ACHIEVE induction	U-ACCOMPLISH induction	U-ACHIEVE maintenance
Design	Phase 3, multicentre, randomised, double-blind, placebo-controlled trial		
Population	Moderately to severely active UC with inadequate response, loss of response or intolerance to aminosalicylates, immunomodulators, corticosteroids, or biologic therapies		Moderately to severely active UC who achieved clinical response in induction studies
Intervention	Upadacitinib 45 mg		Upadacitinib 15 mg or 30 mg
Comparator(s)	Placebo		Placebo
Duration	8 weeks (+8 weeks open label if no adequate response)		52 weeks
Primary outcome	Clinical remission by adapted Mayo score at week 8		
Key secondary outcomes	Endoscopic improvement / remission Clinical response Histologic-endoscopic mucosal improvement Lack of bowel urgency / abdominal pain		Endoscopic improvement / remission Maintenance of clinical remission Corticosteroid-free maintenance of clinical remission
Locations	International including UK		
Used in model?	Yes	Yes	Yes

Abbreviations: UC, ulcerative colitis

Baseline characteristics

Endpoint	U-ACHIEVE induction		U-ACCOMPLISH induction		U-ACHIEVE maintenance		
	Upadacitinib 45 mg (n=319)	Placebo (n=154)	Upadacitinib 45 mg (n=341)	Placebo (n=174)	Upadacitinib 15 mg (n=148)	Upadacitinib 30 mg (n=154)	Placebo (n=149)
Male, %	62	63	63	62	64	56	57
Age, mean, years	44	44	42	42	43	43	43
Bio-IR, %	53	51	50	51	48	47	54
Mayo score >9, %	49	49	53	51	49	52	50
Medication use, % Yes:							
Corticosteroid	39	40	35	41	37	37	40
Immunomodulator	1	2	0	2	1	1	0
Aminosalicylates	69	67	68	69	67	69	66

NICE

Abbreviations: Bio-IR, biologic therapy-intolerant or inadequate responder; SD, standard deviation

Summary of trial efficacy data

A summary of slides 26 to 28

Upadacitinib more effective than placebo for key outcomes

Overall population:

- Primary endpoint (clinical remission) and key secondary endpoints*: significantly more people treated with upadacitinib than placebo had improvement in induction (week 8) and maintenance studies (all [redacted])

Biologic experienced and biologic naïve subpopulations:

- In line with overall population. Some differences between biologic experienced and biologic naïve but no clear trends (all CIs overlap suggesting no significant differences between subgroups)

Ranges of adjusted treatment difference (upadacitinib vs placebo) across studies and upadacitinib doses:

- Clinical remission: [redacted] to [redacted] following induction, [redacted] to [redacted] following maintenance
- Clinical response: [redacted] to [redacted] following induction, [redacted] to [redacted] following maintenance
- Endoscopic improvement: [redacted] to [redacted] following induction, [redacted] to [redacted] following maintenance
- Maintenance of clinical remission (from induction): [redacted] to [redacted]
- Corticosteroid-free maintenance of clinical remission (from induction): [redacted] to [redacted]
- Maintenance of endoscopic improvement (from induction): [redacted] to [redacted]

*Clinical response, endoscopic improvement and measured at week 52 only, maintenance of clinical remission, corticosteroid-free maintenance of clinical remission, maintenance of endoscopic improvement

Results of induction studies at Week 8

Company: please confirm you are happy that data visible in this table is correct and no longer needs to be marked AIC

Endpoint, %		U-ACHIEVE induction		U-ACCOMPLISH induction	
		Upadacitinib 45 mg		Upadacitinib 45 mg	
		Adjusted treatment difference vs placebo, % (95% CI)	p value	Adjusted treatment difference vs placebo, % (95% CI)	p value
Clinical remission (by adapted Mayo score)	Overall population	21.6 (15.8, 27.4)	<0.0001	29.0 (23.2, 34.7)	<0.0001
	Biologic experienced	[redacted]	[redacted]	[redacted]	[redacted]
	Biologic naïve	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (by adapted Mayo score)	Overall population	46.3 (38.4 to 54.2);	<0.0001	49.4 (41.7 to 57.1)	<0.0001
	Biologic experienced	[redacted]	[redacted]	[redacted]	[redacted]
	Biologic naïve	[redacted]	[redacted]	[redacted]	[redacted]
Endoscopic improvement	Overall population	29.3 (22.6 to 35.9)	<0.0001	35.1 (28.6 to 41.6)	<0.0001
	Biologic experienced	[redacted]	[redacted]	[redacted]	[redacted]
	Biologic naïve	[redacted]	[redacted]	[redacted]	[redacted]

Results of maintenance study at Week 52 (1)

Company: please confirm you are happy that data visible in this table is correct and no longer needs to be marked AIC

Endpoint, %		U-ACHIEVE maintenance			
		Upadacitinib 15 mg		Upadacitinib 30 mg	
		Adjusted treatment difference vs placebo, % (95% CI)	p value	Adjusted treatment difference vs placebo, % (95% CI)	p value
Clinical remission (by adapted Mayo score)	Overall population	30.7 (21.7 to 39.8);	<0.0001	39.0 (29.7 to 48.2)	<0.0001
	Biologic experienced	[redacted]	[redacted]	[redacted]	[redacted]
	Biologic naïve	[redacted]	[redacted]	[redacted]	[redacted]
Clinical response (by adapted Mayo score)	Overall population	44.6 (34.5 to 54.7)	<0.0001	56.6 (47.2 to 66.0)	<0.0001
	Biologic experienced	[redacted]	[redacted]	[redacted]	[redacted]
	Biologic naïve	[redacted]	[redacted]	[redacted]	[redacted]
Endoscopic improvement	Overall population	34.4 (25.1 to 43.7)	<0.0001	46.3 (36.7 to 55.8)	<0.0001
	Biologic experienced	[redacted]	[redacted]	[redacted]	[redacted]
	Biologic naïve	[redacted]	[redacted]	[redacted]	[redacted]

Results of maintenance study at Week 52 (2)

Company: please confirm you are happy that data visible in this table is correct and no longer needs to be marked AIC

Endpoint, %		U-ACHIEVE maintenance			
		Upadacitinib 15 mg		Upadacitinib 30 mg	
		Adjusted treatment difference vs placebo, % (95% CI)	p value	Adjusted treatment difference vs placebo, % (95% CI)	p value
Maintenance of clinical remission (from induction)	Overall population	37.4 (20.3 to 54.6)	<0.0001	47.0 (30.7 to 63.3)	<0.0001
	Biologic experienced	[redacted]	[redacted]	[redacted]	[redacted]
	Biologic naïve	[redacted]	[redacted]	[redacted]	[redacted]
Corticosteroid-free maintenance of clinical remission (from induction)	Overall population	35.4 (18.2 to 52.7)	<0.0001	45.1 (28.7 to 61.6)	<0.0001
	Biologic experienced	[redacted]	[redacted]	[redacted]	[redacted]
	Biologic naïve	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance of endoscopic improvement (from induction)	Overall population	42.0 (27.8 to 56.2)	<0.0001	48.6 (35.5 to 61.7)	<0.0001
	Biologic experienced	[redacted]	[redacted]	[redacted]	[redacted]
	Biologic naïve	[redacted]	[redacted]	[redacted]	[redacted]

Summary of AEs

A summary of slides 30 to 31

Upadacitinib no current concerns with safety profile but safety review underway for all JAK inhibitors

Most common AEs with upadacitinib:

- Inductions trials: blood CPK increase, acne and nasopharyngitis and leading to discontinuation, GI disorders
- Maintenance trial: nasopharyngitis, worsening of UC, and blood CPK increase and leading to discontinuation, GI disorders, infections and infestations

EAG clinical advisors:

- No concerns with safety profile of upadacitinib compared to other targeted therapies for inflammatory bowel disease; no need for additional monitoring during treatment

Note: TA792 (filgotinib) noted that cardiovascular AEs should have been included in model due to association

[redacted]

EMA safety review tofacitinib (June 2022)

Final results from a clinical trial of tofacitinib in rheumatoid arthritis showed people who were at risk of heart disease were more likely to experience a major cardiovascular problem and had a higher risk of developing cancer than those treated with medicines belonging to the class of TNF-alpha inhibitors

As a result, EMA safety committee is carrying out a review to determine whether risks associated with tofacitinib are also associated with all JAK inhibitors authorised in the EU (including upadacitinib) for the treatment of inflammatory disorders, and whether marketing authorisations for these medicines should be amended

Adverse events

Company: please confirm you are happy that data in this table is correct and no longer needs to be marked AIC

Category, %	U-ACHIEVE induction		U-ACCOMPLISH induction		U-ACHIEVE maintenance		
	Upadacitinib 45 mg (n=319)	Placebo (n=155)	Upadacitinib 45 mg (n=344)	Placebo (n=177)	Upadacitinib 15 mg (n=148)	Upadacitinib 30 mg (n=154)	Placebo (n=149)
Any AE	56	62	53	40	78	79	76
Serious adverse events	3	6	3	5	7	6	13
AE leading to discontinuation	2	9	2	5	4	6	11

- No deaths in any group
- Most common AEs with upadacitinib were blood CPK increase, acne and nasopharyngitis in induction trials and nasopharyngitis, worsening of UC, and blood CPK increase in maintenance trial
- Most common AEs leading to discontinuation were GI disorders in induction trials and GI disorders, infections and infestations in maintenance trial, all with higher rates for placebo than upadacitinib

EAG:
- Induction studies have short follow up (8 weeks)
- Clinical advisors: no concerns with safety profile of upadacitinib compared to other targeted therapies for inflammatory bowel disease; no need for additional monitoring during treatment

Abbreviations: AE, adverse event; CPK, creatine phosphokinase; GI, gastrointestinal

JAK inhibitor safety review underway by EMA

EMA safety review tofacitinib (June 2022)

Final results from a clinical trial of tofacitinib in rheumatoid arthritis showed people who were at risk of heart disease were more likely to experience a major cardiovascular problem and had a higher risk of developing cancer than those treated with medicines belonging to the class of TNF-alpha inhibitors

As a result, EMA safety committee is carrying out a review to determine whether risks associated with tofacitinib are also associated with all JAK inhibitors authorised in the EU (including upadacitinib) for the treatment of inflammatory disorders, and whether marketing authorisations for these medicines should be amended

Note: TA792 (filgotinib) noted that cardiovascular AEs should have been included in model due to association

Company has ongoing study that may provide data:

- U-ACTIVATE is a multicentre, long-term extension study to evaluate the safety, tolerability, and efficacy of upadacitinib in patients with UC up to Week 288. The study population includes patients who previously participated in completed or ongoing trials, including U-ACHIEVE and U-ACCOMPLISH induction studies, and U-ACHIEVE maintenance study

[redacted]

Summary of key issue – no direct evidence vs comparators

Trial demonstrates effectiveness, but only vs placebo

A summary of slide 33

Clinical evidence:

- Upadacitinib studied versus placebo in clinical trial, so no direct comparison against relevant comparators
- Not uncommon for this to be the case in clinical studies

Is committee satisfied that a lack of direct evidence versus relevant comparators is not unique to upadacitinib?

Tech team recommendation: company's approach is acceptable – issue is not unique to this appraisal and conducing placebo-controlled trial in line with NICE methods.

Key issue: Lack of direct evidence for the comparison of upadacitinib versus relevant comparators

EAG

- Clinical effectiveness evidence for upadacitinib is from placebo-controlled trials with no direct evidence for comparison of upadacitinib versus any relevant comparators in NICE scope
- Company NMAs generate indirect clinical effectiveness evidence for the comparisons

Company technical engagement response

- Approach in line with NICE manual; placebo controlled clinical trial design adopted in several comparator trials for therapies that have been assessed and recommended by NICE for use in UC
- Acknowledges lack of direct evidence for the comparison of upadacitinib versus relevant comparators and that the use of indirect evidence is a source of uncertainty
- Large number of relevant treatment options means that even if upadacitinib had a comparator in the control arm, this would not provide direct evidence against all relevant comparators

Stakeholder comments – UKPCA

- Lack of direct evidence between majority of relevant comparators– issue not unique to upadacitinib
- To-date only direct comparison is VARSITY trial of vedolizumab versus adalimumab

Is committee satisfied that a lack of direct evidence versus relevant comparators is not unique to upadacitinib?

Abbreviations: UC, ulcerative colitis; UKCPA, UK Clinical Pharmacy

Indirect treatment comparison

Summary of NMA methods

A summary of slide 36

Company did 9 NMAs for outcomes of clinical remission, clinical response and serious infection

Included studies:

- 2 RCTs of upadacitinib and 18 RCTs of comparators (5 of infliximab, 4 adalimumab, 3 golimumab, 2 vedolizumab, 1 ustekinumab, 3 tofacitinib); all vs placebo
- Considered bio exposed and bio naïve subpopulation for efficacy and overall population for safety
- Considered induction and maintenance studies separately

NMA outcomes:

- Odds ratio vs placebo: values closer to 1 suggest smaller difference from placebo
- SUCRA (surface under the cumulative ranking) score, which is used to rank treatments. Higher SUCRA scores correlates with better efficacy or better safety
- Predicted absolute outcome rate, which shows the predicted probability of the outcome being considered. Higher rates correlate with better efficacy, whereas lower rates correlate with better safety
- Pairwise comparisons (slides in back up): median odds ratio (OR) and credible intervals presented for each comparator versus upadacitinib, where OR of <1, favours upadacitinib

Company NMA methods

Performed 9 NMAs:

Population	Induction phase data (duration: 6-10 weeks)	Maintenance phase data (duration: 44-54 weeks)
Bio-naïve	Clinical remission, Clinical response	Clinical remission, Clinical response
Bio-experienced	Clinical remission, Clinical response	Clinical remission, Clinical response
Overall population	Serious infection	-

- NMAs included 20 RCTs (5 of infliximab, 4 adalimumab, 3 golimumab, 2 vedolizumab, 1 ustekinumab, 3 tofacitinib, 2 upadacitinib); all with common comparator – placebo
- Base case models: random effects used for all analyses except clinical response in the bio-naïve population in induction, where fixed effects with baseline-risk adjustment used
- Bio-naïve defined as: patients who had an inadequate response or intolerance to conventional therapy but had not failed biologic therapy
- Bio-exposed defined as: patients who had an inadequate response or intolerance to conventional therapy or a biologic treatment
- Sensitivity analyses of these did not materially change the results

Abbreviations: IR, inadequate response; NMA, network meta-analysis; RCT, randomised controlled trial

Summary of NMA results

A summary of slides 38 to 50

Upadacitinib point estimates often more effective than comparators, sometimes with statistical significance, but with similar low risk of serious infection

Efficacy endpoints of clinical remission and clinical response:

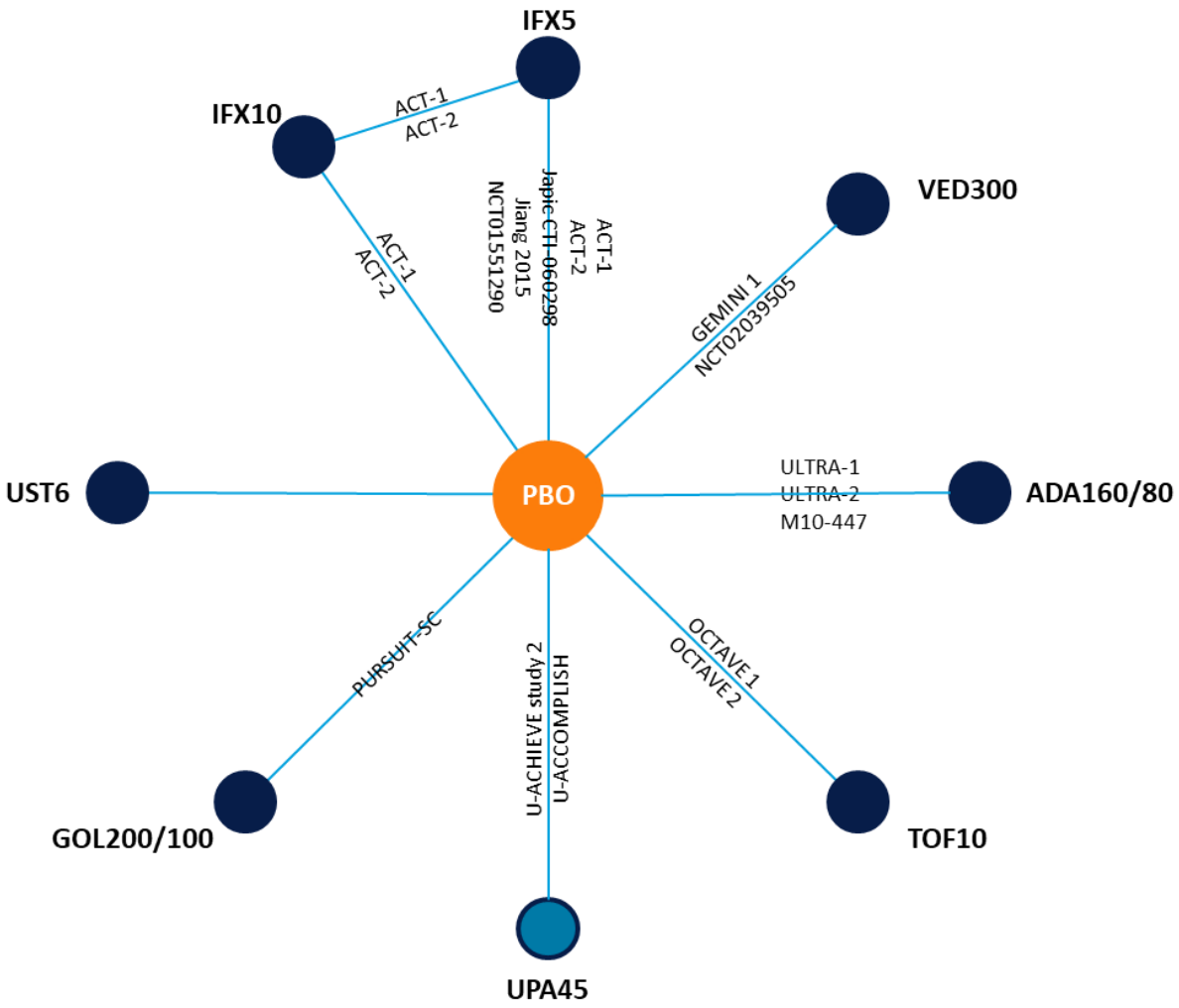
- Induction: upadacitinib is more effective than all comparators (bio naïve and bio exposed)
    - Credible intervals non-overlapping for some comparisons, so difference is statistically significant
- Maintenance: upadacitinib is more effective than most comparators in achieving clinical remission and clinical response, with some difference being statistically significant. Taking account of company and EAG analyses of pairwise comparisons, a 3 comparisons favoured tofacitinib:
    - bio naïve subpopulation – in maintenance phase, tofacitinib 5 mg or 10 mg is more effective than upadacitinib for clinical remission, and for other comparisons upadacitinib is the same or more effective
    - bio exposed subpopulation – in maintenance phase, tofacitinib 10 mg is [redacted] for clinical response, and for other comparisons upadacitinib is more effective for clinical remission and more effective than most comparators for clinical response

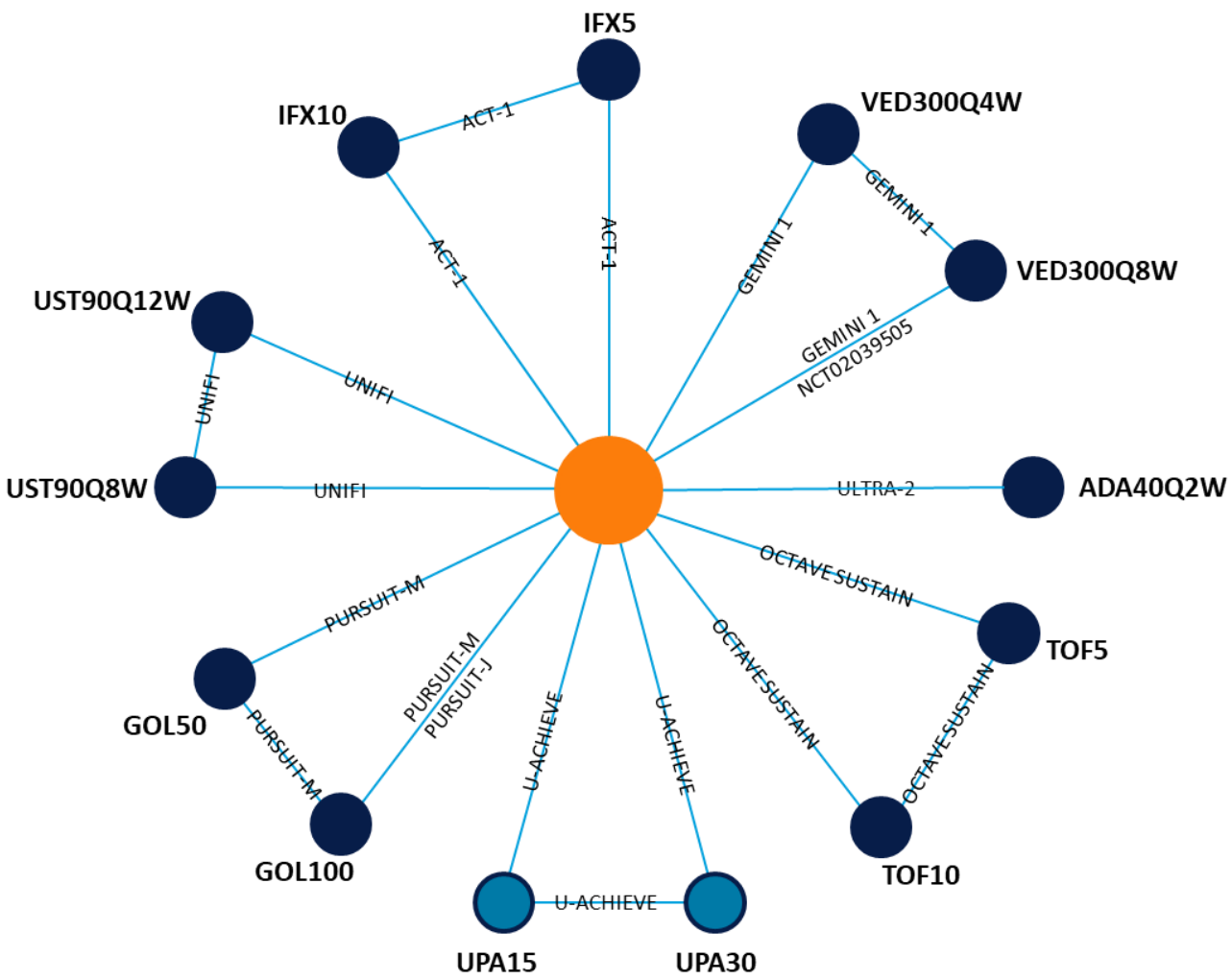
Safety endpoint of serious infections:

- Induction (only): upadacitinib has a low risk of serious infections ([redacted] probability). [redacted]

Company NMAs: bio-naïve

- **Induction:**
  - (1) Clinical remission, (2) Clinical response
- **Maintenance:**
  - (3) Clinical remission, (4) Clinical response





Abbreviations: NMA, network meta-analysis

NMA 1: clinical remission in bio-naïve induction

Upadacitinib has highest probability of clinical remission

- Random effects model

Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Upadacitinib 45 mg	[redacted]	[redacted]	[redacted]
Infliximab 5 mg/kg	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg	[redacted]	[redacted]	[redacted]
Golimumab 200/100 mg	[redacted]	[redacted]	[redacted]
Infliximab 10 mg/kg	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg	[redacted]	[redacted]	[redacted]
Ustekinumab 6 mg/kg	[redacted]	[redacted]	[redacted]
Adalimumab 160/80 mg	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

*SUCRA ranking score: higher value = better efficacy

Abbreviations: NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve

NMA 2: clinical response in bio-naïve induction

Upadacitinib has highest probability of clinical response

- Fixed effects adjusted model

Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Upadacitinib 45 mg	[redacted]	[redacted]	[redacted]
Ustekinumab 6 mg/kg	[redacted]	[redacted]	[redacted]
Infliximab 10 mg/kg	[redacted]	[redacted]	[redacted]
Infliximab 5 mg/kg	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg	[redacted]	[redacted]	[redacted]
Adalimumab 160/80 mg	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg	[redacted]	[redacted]	[redacted]
Golimumab 200/100 mg	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

*SUCRA ranking score: higher value = better efficacy

Abbreviations: NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve

NMA 3: clinical remission in bio-naïve maintenance

Upadacitinib 30 mg has 3rd highest probability of clinical remission

- Random effects model

Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Tofacitinib 10 mg	[redacted]	[redacted]	[redacted]
Tofacitinib 5 mg			
Upadacitinib 30 mg			
Vedolizumab 300 mg Q4W			
Vedolizumab 300 mg Q8W			
Upadacitinib 15 mg			
Golimumab 100 mg			
Golimumab 50 mg			
Ustekinumab 90 mg Q8W			
Ustekinumab 90 mg Q12W			
Infliximab 10 mg/kg			
Infliximab 5 mg/kg			
Adalimumab 40 mg Q2W			
Placebo			

*SUCRA ranking score: higher value = better efficacy

 Abbreviations: NMA, network meta-analysis; QxW, every x weeks; SUCRA, surface under the cumulative ranking curve

NMA 4: clinical response in bio-naïve maintenance

Upadacitinib 30 mg has highest probability of clinical response

- Random effects model

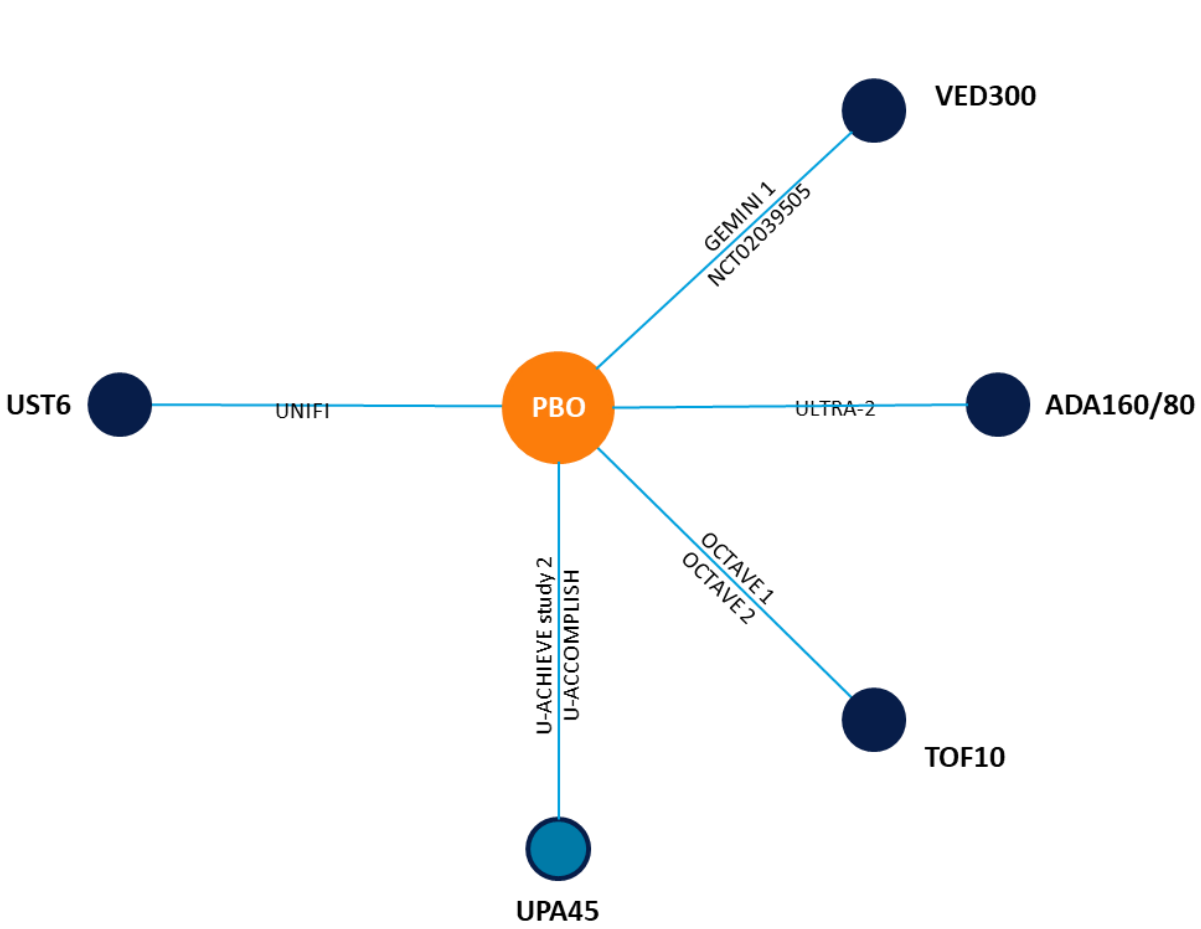
Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg			
Vedolizumab 300 mg Q8W			
Upadacitinib 15 mg			
Tofacitinib 5 mg			
Vedolizumab 300 mg Q4W			
Ustekinumab 90 mg Q8W			
Ustekinumab 90 mg Q12W			
Golimumab 100 mg			
Infliximab 10 mg/kg			
Golimumab 50 mg			
Infliximab 5 mg/kg			
Adalimumab 40 mg Q2W			
Placebo			

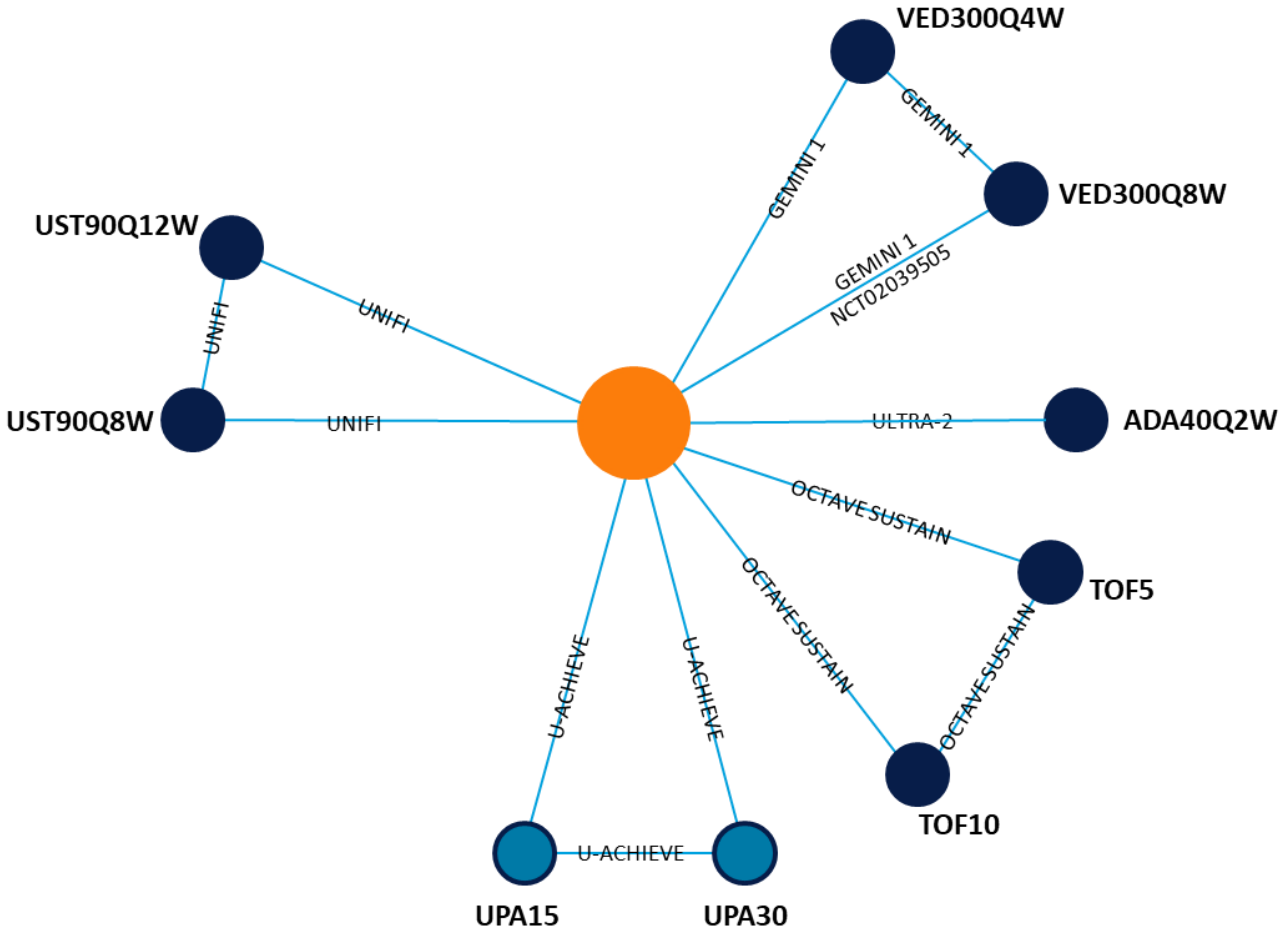
*SUCRA ranking score: higher value = better efficacy

 Abbreviations: NMA, network meta-analysis; QxW, every x weeks; SUCRA, surface under the cumulative ranking curve

Company NMAs: bio-exposed

- **Induction:**
  (5) Clinical remission, (6) Clinical response
- **Maintenance:**
  - (7) Clinical remission, (8) Clinical response





Abbreviations: NMA, network meta-analysis

NMA 5: clinical remission in bio-exposed induction

Upadacitinib has highest probability of clinical remission

- Random effects model

Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Upadacitinib 45 mg	[redacted]	[redacted]	[redacted]
Ustekinumab 6 mg/kg	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg	[redacted]	[redacted]	[redacted]
Adalimumab 160/80 mg	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

*SUCRA ranking score: higher value = better efficacy

Abbreviations: NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve

NMA 6: clinical response in bio-exposed induction

Upadacitinib has highest probability of clinical response

- Random effects model

Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Upadacitinib 45 mg	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg	[redacted]	[redacted]	[redacted]
Ustekinumab 6 mg/kg	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg	[redacted]	[redacted]	[redacted]
Adalimumab 160/80 mg	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

*SUCRA ranking score: higher value = better efficacy

Abbreviations: NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve

NMA 7: clinical remission in bio-exposed maintenance

Upadacitinib has highest probability of clinical remission

- Random effects model

Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg			
Vedolizumab 300 mg Q8W			
Vedolizumab 300 mg Q4W			
Tofacitinib 10 mg			
Ustekinumab 90 mg Q8W			
Adalimumab 40 mg Q2W			
Tofacitinib 5 mg			
Ustekinumab 90 mg Q12W			
Placebo			

*SUCRA ranking score: higher value = better efficacy

 Abbreviations: NMA, network meta-analysis; QxW, every x weeks; SUCRA, surface under the cumulative ranking curve

NMA 8: clinical response in bio-exposed maintenance

Upadacitinib 30 mg has highest probability of clinical response

- Random effects model

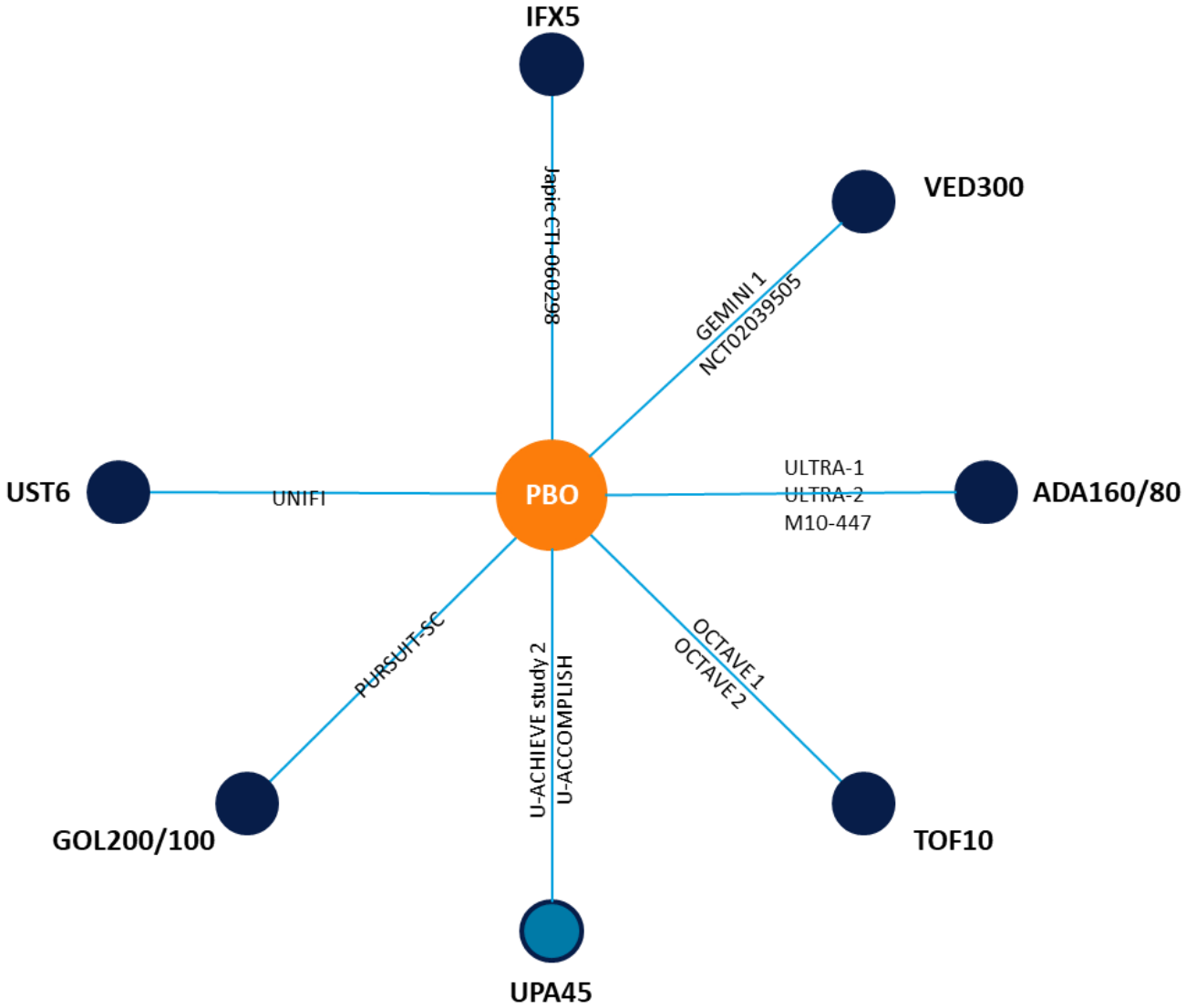
Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg			
Upadacitinib 15 mg			
Tofacitinib 5 mg			
Vedolizumab 300 mg Q8W			
Vedolizumab 300 mg Q4W			
Ustekinumab 90 mg Q8W			
Adalimumab 40 mg Q2W			
Ustekinumab 90 mg Q12W			
Placebo			

*SUCRA ranking score: higher value = better efficacy

 Abbreviations: NMA, network meta-analysis; QxW, every x weeks; SUCRA, surface under the cumulative ranking curve

Company NMA: overall population

- **Induction:** (9) Serious infection



Abbreviations: NMA, network meta-analysis

NMA 9: serious infections in overall induction

Upadacitinib has a low risk of serious infections

- Random effects model

Treatment	Odds ratio vs placebo Median (95% CrI)	SUCRA ranking score*	Predicted absolute outcome rate, median (95% CrI)
Golimumab 200/100 mg	[redacted]	[redacted]	[redacted]
Ustekinumab 6 mg/kg	[redacted]	[redacted]	[redacted]
Vedolizumab 300 mg	[redacted]	[redacted]	[redacted]
Infliximab 5 mg/kg	[redacted]	[redacted]	[redacted]
Tofacitinib 10 mg	[redacted]	[redacted]	[redacted]
Upadacitinib 45 mg	[redacted]	[redacted]	[redacted]
Adalimumab 160/80 mg	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

*SUCRA ranking score: higher value = better safety

Abbreviations: NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve

EAG's comments on company NMA results

- Induction NMAs: upadacitinib best performing vs placebo for clinical remission and clinical response
- Maintenance NMAs:
    - Upadacitinib 30mg ranked within top 3 for all outcomes
    - Upadacitinib 15mg ranked within top 4 for all outcomes (apart from maintenance/bio-naïve/clinical remission where it ranked 6th with a non-statistically significant odds ratio versus placebo)
- Company used random effects models for all NMAs except for induction/bio-naïve/response comparison where company used fixed effects adjusted (FEA) NMA model
- At clarification, company provided pairwise comparisons and EAG presented these alongside its own analyses. These identified some comparisons with other treatments that did not favour upadacitinib:
    - Maintenance/bio-exposed population, upadacitinib 15 mg: for clinical response point estimates favoured tofacitinib 10 mg
    - Maintenance phase/bio-naïve population, upadacitinib 30 mg: for clinical remission point estimates favoured tofacitinib 10 mg and tofacitinib 5 mg
- Conclusion from company's and EAG's NMAs:
    - Upadacitinib induction & maintenance treatments compared favourably with all comparators in bio-naïve and bio-exposed populations for clinical remission and clinical response
    - For most comparisons, point estimates similar, and all results that were statistically significantly different favoured upadacitinib. For many comparisons, no statistically significant differences

Abbreviations: NMA, network meta-analysis; RCT, randomised controlled trial

Summary of key issue – NMA statistical issues

A summary of slides 52 to 53

NMAs results plausible but with some uncertainty

Unresolvable issue of unclear impact:

- EAG raised 3 issues with the NMA method but was unable to suggest an alternative approach
  - consistency assumption could not be tested formally – reliability of NMA unknown
  - maintenance phase NMA results less reliable than those of induction phase – trial design and descriptions of the intervention and placebo treatments of the trials included raise unresolvable issues
  - company and EAG preferred approaches to generating NMA results differ; however, outputs similar
- EAG suggested clinical opinion is sought on plausibility and robustness of NMA results – if 3 issues of no major concern, then company NMA results should be used to inform decision making
  - Company cited 2 new published NMAs and clinical opinion to support findings that upadacitinib is consistently more effective than comparators

UKPCA and British Society of Gastroenterology: also cited evidence from the 2 new published NMAs noting these "*reached the same conclusions for moderate-severe UC… Upadacitinib ranked highest in both NMA for clinical remission and response*"

Is committee satisfied that the results of the company's NMA are plausible and suitable for decision making?

Tech team recommendation: NMAs results are plausible, so we consider upadacitinib is effective in UC, but the EAG has identified unresolvable issues which adds uncertainty.

Abbreviations: UKCPA, UK Clinical Pharmacy

Key issue: Network meta-analysis statistical issues

EAG

- Identified 3 methodological issues which cast doubt on the robustness of NMA results:
  - for all networks (induction and maintenance), the consistency assumption could not be tested formally
  - maintenance phase NMA results less reliable than those of induction phase – trial design and descriptions of the intervention and placebo treatments of the trials included raise unresolvable issues
  - company and EAG preferred approaches to generating NMA results differ; however, outputs similar
- EAG unable to suggest an alternative approach – effect of these issues on cost effectiveness is not known
- Suggest clinical opinion is sought on the plausibility and robustness of NMA results
- If 3 issues are of no major concern, then company NMA results should be used to inform decision making

Company technical engagement response

- Upadacitinib consistently shown to be most efficacious at inducing and maintaining clinical response and remission in both biologic-exposed and biologic-naïve populations, in 4 separate NMAs – Company's, EAG's, and NMAs published by Burr (2022) & Lasa (2022) (see next slide)
- Notes submission from British Society of Gastroenterology: *'The rapidity of response to treatment is impressive with upadacitinib'* and *'In addition, the high remission rates at 8 weeks are impressive'*
- Clinical advice: the RCTs included in NMAs were appropriate sources of clinical data for decision-making
- Clinical statements included: *'had 7 patients on upadacitinib in UC, all are still on drug, which is unique. Upadacitinib for the treatment of UC is as effective as most effective (infliximab) and more durable'*

References: Burr NE, et al. Gut 2022;71:1976–1987. Lasa JS, et al. Lancet Gastroenterol Hepatol 2022; 7: 161–70.
Abbreviations: RCT, randomised controlled trial; UC, ulcerative colitis; UKCPA, UK Clinical Pharmacy

Key issue: Network meta-analysis statistical issues

Stakeholder comments – UKPCA and British Society of Gastroenterology

- 2 peer reviewed published NMAs of biologics and small molecule drugs have broadly reached the same conclusions as company / EAG NMAs for moderate to severe UC:

Published NMA	Conclusions
Burr et al 2022 (28 trials)	• Upadacitinib 45 mg once daily ranked first for clinical remission in all patients, patients naïve to anti-TNF-α drugs and patients previously exposed
Lasa et al 2022 (29 trials)	• Upadacitinib best performing agent for efficacy outcomes in the overall population • Upadacitinib was more likely to be associated with non-serious AEs than comparators (but not serious AEs)

- These published NMAs also include filgotinib which has now been approved by NICE
- In clinical practice, in addition to generally sequencing the therapies, a key question is how to sequence the 3 JAK inhibitors licensed (tofacitinib, filgotinib and upadacitinib)
  - These 2 NMAs could inform the current appraisal

Is committee satisfied that the results of the company's NMA are plausible and suitable for decision making?

References: Burr NE, et al. Gut 2022;71:1976–1987. Lasa JS, et al. Lancet Gastroenterol Hepatol 2022; 7: 161–70.
Abbreviations: RCT, randomised controlled trial; UC, ulcerative colitis; UKCPA, UK Clinical Pharmacy

Cost effectiveness

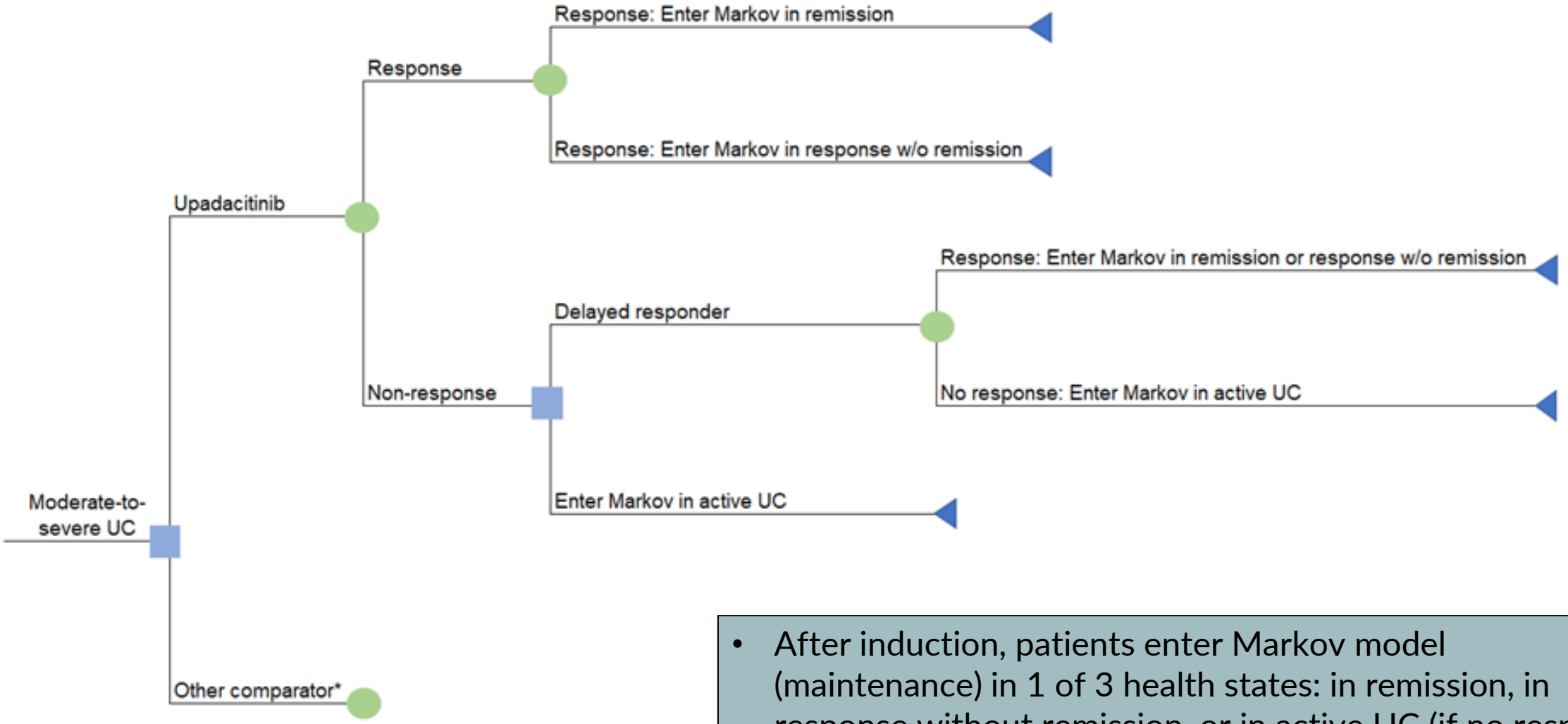
Company's hybrid decision tree (induction) and Markov model (maintenance) generally in line with previous appraisals

Company and EAG differ in base case assumptions relating to modelled treatment pathway and source for utility values

Key issues where company and EAG differ generally do not have big impact on ICER

Company's model structure (1)

- **Induction – decision tree:**

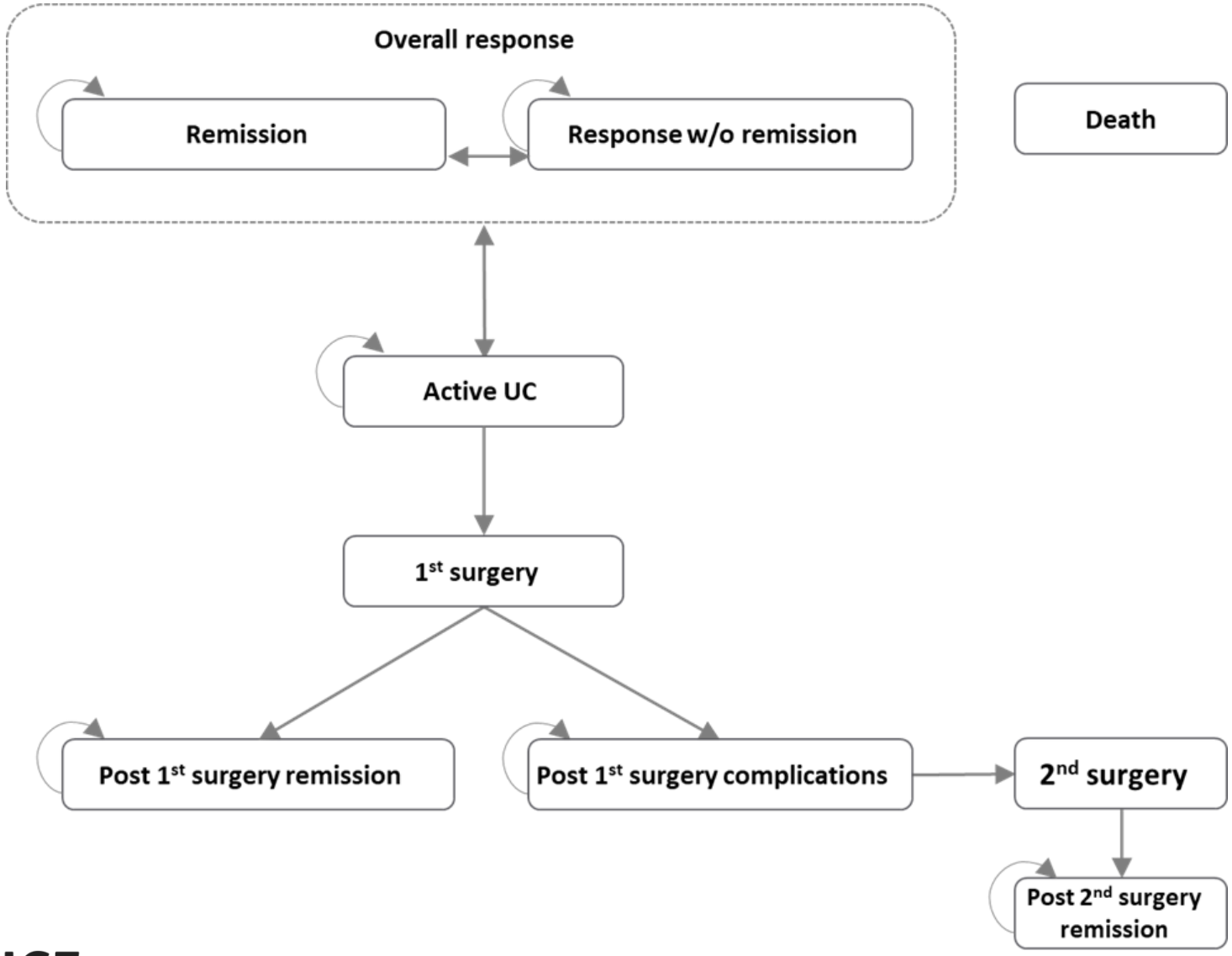


- After induction, patients enter Markov model (maintenance) in 1 of 3 health states: in remission, in response without remission, or in active UC (if no response)

Abbreviations: CT, conventional therapy; UC, ulcerative colitis; w/o without

Company's model structure (2)

- **Maintenance phase – Markov model:**



- At the end of each 4-week cycle, responders either remain on maintenance treatment (in remission or in response without remission), lose response and transition to active UC (where they receive surgery), or die

Upadacitinib affects **costs** by:

- More people with response /remission - fewer in 'active UC' accruing costs associated with this health state

Upadacitinib affects **QALYs** by:

- More people with response /remission - fewer in 'active UC' losing QALYs associated with this health state

Abbreviations: CT, conventional therapy; UC, ulcerative colitis; w/o without

Company's model *continued*
Model features generally in line with previously appraisals

Assumptions:

- Base case: patients who do not achieve a response after induction, discontinue treatment and enter maintenance in 'active UC'
- Scenario analyses for: a further line of (non-CT) treatment after treatment failure; and spontaneous remission

Features of model are generally in line with previous UC appraisals:

- Lifetime horizon (consistent with most previous appraisals)
- Model structure is hybrid decision tree-Markov model (consistent with previous appraisals)
- Cycle length of 4 weeks (previous appraisals consider 2 to 8 weeks)
- Treatment waning effect – no (consistent with previous appraisals)
- Source of utilities was published literature (consistent with most recent TA633 of ustekinumab)
- Source of costs consistent with previous appraisals and updated to most recent year
- Discounting: costs and QALYs accrued after the first year are discounted at an annual rate of 3.5%
- Adverse effects of treatment considered serious infection (consistent with previous appraisals, although TA792 (filgotinib) noted that cardiovascular AEs should also have been included)
- Stopping rule – no (consistent with recent appraisals)
- Spontaneous remission – no (consistent with previous appraisals)

Abbreviations: CT, conventional therapy; UC, ulcerative colitis; w/o without

Summary of company and ERG base case assumptions and key scenarios after technical engagement

Assumption	Company base case	ERG base case	Company and EAG agree?
Modelled treatment pathway (induction or maintenance)	Non-responders enter 'active UC' health state • Scenario analyses of second line treatment option, and time horizons of 2 years and 5 years	Non-responders enter 'on subsequent treatment' health state • Scenario analysis of company's base case but assuming higher rates of surgery	No
Source of utility values for response, remission and active UC health states	Published evidence (Woehl 2008) • Scenario analyses of other published evidence sources and upadacitinib trial-based data	Upadacitinib trial-based data (higher values than in published evidence)	No
Upadacitinib given at 70:30 ratio of 15 mg (standard) to 30 mg (high) maintenance doses	Adopts 70:30 ratio	Adopts 70:30 ratio	Yes

Abbreviations: UC, ulcerative colitis

How company incorporated evidence into model

Input	Company	EAG comment
Baseline characteristics	Upadacitinib induction trials	Agrees with approach
Efficacy estimates	Induction phase – NMA results Maintenance phase – NMA results	Has concerns with maintenance phase NMAs but has not been able to identify more certain estimates
Adverse events	Modelled serious infections only due to high costs, consistent with TA547 and TA633 Induction phase only – NMA results	Agrees with approach
Utilities	From Woehl et al (2008), except surgery and post-surgery complications (Arseneau 2006) • Adjusted for age and gender • Applied disutility for effect of serious infections on HRQoL	Not in line with NICE reference case. Prefers EQ-5D data from upadacitinib trials • Effect of serious infections on HRQoL already incorporated
Costs and resource use	From published literature, previous NICE submissions, NHS Reference Costs for 2019/20 and BNF Includes drug acquisition, administration, management of adverse events, surgery, and background disease management	Number of consultant contacts in response / remission health states are likely overestimated but negligible effect on cost effectiveness results
Mortality	UK general population (ONS data), with 30% excess risk of death for surgery health states	Agrees with approach

Abbreviations: BNF, British National Formulary; NMA, network meta-analysis; ONS, Office for National Statistics SC, subcutaneous

Description of Company's modelled health states

Health state	Definition
Remission	Full Mayo score of 0-2 points with no individual subscore >1
Response without remission	• Not meeting remission definition, and • Decrease from baseline in Mayo score of ≥30% and ≥3 points, and • Decrease from baseline in the rectal bleeding subscore of ≥1, or an absolute rectal bleeding subscore of 0 or 1
Active ulcerative colitis	Full Mayo score of 6-12 (remission or remission without response not achieved)
First surgery	First surgical intervention to resolve UC (assumed duration of 6 months); could include acute complications
Post-first surgery remission	No chronic complications from first surgery
Post-first surgery complications	Chronic complications from first surgery such as wound infection, bowel obstruction, intra-abdominal abscess, or anastomotic leak
Second surgery	Second surgical intervention due to pouch failure (assumed duration of 6 months); could include acute complications
Post-second surgery remission	No chronic complications from second surgery
Death	Absorbing state

Abbreviations: UC, ulcerative colitis

Summary of key issue – modelled treatment pathway (1)

Company and EAG differ although does not have big impact on ICER

A summary of slides 63 to 69

Company vs EAG approach:

- Company consider only 1 line of treatment. If this fails, patients enter 'active UC' health state
  - Consistent with newest appraisal at time of submisssion – TA633 (ustekinumab) – however, here committee would have preferred additional health states in the model to account for patients who had long-term treatment with corticosteroids
  - Different approach in recent filgotinib appraisal (TA792) – model included a 'last line of conventional therapy' for people who failed advanced treatment and were in active UC – committee considered model appropriate
- Company explored adding 2nd line of treatment (ustekinumab) after failure in a scenario analysis – no big impact on ICER
- EAG note that by the end of 2 years, most patients who received any treatment end up in 'active UC' health state. The only way to leave then is by having surgery or dying, and surgery rates are low
  - Company's model treatment pathway does not reflect NHS clinical practice and results in most modelled patients, regardless of treatment, ending up in active UC health state for many decades with no active treatment and with low HRQoL
  - Instead models 'On subsequent treatment' health state for any subsequent therapy (but not surgery), which more accurately reflects NHS practice

Summary of key issue – modelled treatment pathway (2)

Company and EAG differ although does not have big impact on ICER

A summary of slides 63 to 69

Company disagrees with EAG's approach in 3 areas:

- (a) Inclusion of further drug after failure
  - In EAG model, people who fail treatment move to a 'basket of treatments' instead of active UC
  - Company notes that when modelling treatment sequences, each additional line of treatment introduces uncertainty. It has explored a 2nd line treatment option in a scenario analysis
- (b) Validity of efficacy estimates for further drug treatment after failure:
  - Company disagrees with the way EAG has incorporated efficacy estimates into its model when considering people receiving 'basket of treatments' and disagrees that surgery is not included
- (c) Utility values unrealistic particularly in longer term
  - Company notes that any reduction in quality of life that patients who fail treatment may experience is not taken into account for people receiving 'basket of treatments'
- Overall impact of EAG's preferred approach on ICER – upadacitinib dominates

Which modelled health state most reflects NHS clinical practice for patients who lose response, 'active UC' (company) or 'on subsequent treatment' (EAG)?

Tech team recommendation: company's approach in line with recent appraisals, pros and cons to both company and EAG approach. Company and EAG base cases differ on this issue, but has little impact on ICER overall

Key issue: Modelled treatment pathway not a good reflection on NHS practice

Background

- Company's model considers only 1 line of treatment, so patients who have not had an adequate response (induction) or who stop responding (maintenance) enter the active UC health state
- Same maintenance treatment pathway used in models that informed previous NICE appraisals (TA342 [vedolizumab] and TA633 [ustekinumab]), but committee have expressed a preference for modelling of subsequent therapy (TA633) including conventional therapy 9TA792 [filgotinib])
  - Annual probability of 1st and 2nd surgery of 0.5% from Misra et al (2016) and proportion of surgeries that resulted in post-surgery complications (33.5%) from UK clinical audit

ERG comments

- Company's modelled treatment pathway does not reflect NHS clinical practice and results in most patients, regardless of treatment, ending up in active UC health state for many decades with no active treatment
  - By the end of 2 years, most patients (bio-naïve or bio-exposed) who received any treatment end up in active UC health state
  - The only way for a patient to leave the active UC state is by having surgery or dying
  - As only 1 in ~200 (0.5%) patients in active UC health state have surgery each year, this means that most people in the active UC health state remain there until they die
  - Patients in active UC health state experience a low HRQoL (0.41) and are likely to be hospitalised

Abbreviations: HRQoL, health-related quality of life; UC, ulcerative colitis

Key issue: Modelled treatment pathway not a good reflection on NHS practice

ERG comments *continued*

- Clinical advice: patients with active UC treated in NHS clinical practice are either offered surgery within 12 months or are prescribed the treatment which previously gave them the best symptom alleviation, even if the patient was not considered to have responded to this treatment
- EAG has modelled an alternative pathway that more closely represents NHS clinical practice, to replace the company's 'active ulcerative colitis' heath state:

EAG's alternative 'On subsequent treatment' modelled heath state
• Patients who have achieved remission on a treatment after having failed to achieve remission on earlier treatment(s), and • Patients who have failed to achieve long-term remission on any drug and are unwilling or unsuitable for surgery and therefore are indefinitely prescribed the treatment which gave them the most symptom alleviation (without achieving remission) • Patients can receive a basket of biologic treatments, but not surgery

- This approach negates the need for the second-line therapy option within the company model (scenario analysis) or the introduction of a model with multiple lines of biologic treatments
  - Proportions of treatments used in EAG modelled pathway based on company's market share data
  - Efficacy assumptions based on NMA results for those treatments (response, remission)

Abbreviations: UC, ulcerative colitis

Key issue: Modelled treatment pathway not a good reflection on NHS practice

Company technical engagement response

- Company model suitable for addressing NICE decision problem and is aligned with previous appraisals in UC
  - Scope of appraisal is not to determine the most cost-effective treatment sequence among hundreds of possible permutations
- Provides new scenarios including those considering shorter time horizons of 2 years and 5 years, time points at which a large proportion of the patient cohort has entered the active UC health state
  - Upadacitinib remained dominant or highly cost effective versus all comparators in both the bio-naïve and bio-exposed scenarios – expected since clinical and quality-of-life benefits from upadacitinib treatment are accrued in the remission and response health states
  - Incremental benefit of upadacitinib derived from disease control through clinically important outcomes documented in clinical trials – BSG submission describes it as a step change in management
- Concerns about EAGs approach regarding: (a) treatment sequencing; (b) efficacy estimates; (c) utility values (more detail on next slides)

ERG critique

- Clinical advice: company's model does not capture current experience of NHS patients and describes a treatment pathway that may be considered unethical by patients and health care professionals

Abbreviations: BSG, British Society of Gastroenterology; UC, ulcerative colitis

Key issue: Modelled treatment pathway
(a) inclusion of further drug after failure:

Background
- Company consider only 1 line of treatment. If this fails, patients enter 'active UC' health state
- Consistent with newest appraisal at time of submisssion – TA633 (ustekinumab) – however, here committee would have preferred additional health states in the model to account for patients who had long-term treatment with corticosteroids
- Different approach in recent filgotinib appraisal (TA792)– model included a 'last line of conventional therapy' for people who failed advanced treatment and were in active UC – committee considered model appropriate

Company technical engagement response
- Choice of treatment after 1st biologic is complex clinical decision and individualised to patient
- When modelling treatment sequences, each additional line introduces uncertainty into decision making
- Company's model allows treatment sequencing to be explored in a scenario analysis

ERG critique
- While 'basket of treatments' is not perfect, clinical advice is that it more accurately represents NHS clinical practice than company's model
- Lifetime time horizon and including subsequent treatments in line with NICE reference case
- 'Basket of treatments' is not treatment sequencing
- Clinical advice: most patients do not spend long in 'active UC', instead managed with drug treatments

Abbreviations: UC, ulcerative colitis

Key issue: Modelled treatment pathway
(b) validity of efficacy estimates for further drug treatment:

Company technical engagement response

- EAG approach lacks face validity:
  - Assumes bio exposed population has same levels of clinical efficacy and utility as bio-naïve population
  - Assumes patients who have failed all treatments default back to 'the best one' and achieve same level of efficacy as first time they received it before failing
  - No consideration of surgery from this 'basket' health state, so not aligned with clinical practice, and assumes that patients will be on drug treatment until death
- Clinical experts state, and trial data show, that each additional line of treatment has a reduction in efficacy
  - Use of bio-naïve efficacy data inaccurate, overestimates effectiveness of subsequent biologic treatment
  - Since EAG's 'on subsequent treatment' health state includes all treatments, this benefits treatments with worse efficacy as it will be beneficial to fail 1st treatment in sequence
  - Also cancels out any benefit gained by more effective treatment, such as upadacitinib, when calculating ICERs, as upadacitinib is included in 'basket of treatments'
- Biologic-exposed population in upadacitinib UC trials included subjects who had ≥1 biologic previously of whom 37.5%, 37.9%, 19.5% and 5% had failed 1, 2, 3 or ≥4 biologics, respectively
  - Therefore, bio-exposed population data used in company's model is representative of clinical efficacy across multiple lines of biologic treatments and is a conservative interpretation of cost effectiveness

Abbreviations: UC, ulcerative colitis

Key issue: Modelled treatment pathway
(b) validity of efficacy estimates for further drug treatment:

ERG critique

- EAG has produced a scenario where treatment efficacy data for the bio-exposed population (where available) have been used to estimate the efficacy of the basket of treatments
- Clinical advice: surgery is a rare event for people who start on biologic therapy and inclusion in the model is therefore unlikely to make a significant difference to the estimates of cost effectiveness
  - Cost of surgery and the utility benefit from surgery mean that surgery is a highly cost effective treatment option
  - More patients treated with a comparator end up in basket of treatment health state than patients treated with upadacitinib, so if surgery was incorporated into basket of treatments health state, the ICERs per QALY gained for the comparison of upadacitinib versus all treatments would increase
- Modelling a basket of treatments is not without limitations; however, EAG consider that this approach more closely reflects NHS practice than company's modelling approach, and therefore provides more reliable ICERs per QALY gained
  - Proportions of treatments used in EAG modelled pathway based on company's market share data
  - Efficacy assumptions based on NMA results for those treatments (response, remission)

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; UC, ulcerative colitis

Key issue: Modelled treatment pathway
(c) utility values after treatment failure:

Background
- Company's base case model uses an 'active UC' health state after treatment failure, while the EAG model uses an alternative 'on subsequent treatment' health state it its base case

Company technical engagement response
- Utility value applied to EAG's 'on subsequent treatment' health state is a weighted average of values for remission and response without remission from upadacitinib UC trials. As such, all patients in the EAG model have a utility value at least equal to the utility value associated with response to treatment until death
- Company considers that patients who lose response to treatment (relapse) would have experienced a decrease in their quality of life due to disease symptoms, more aligned with the 'active UC' health state
  - Clinicians noted: 'If untreated, a 40-50% reduction in quality of life would be expected for moderate-to-severe UC. Work will be severely impacted …increased impact on joblessness, social life, relationships'

ERG critique
- Clinical advice: in contrast to company model outcomes, most NHS patients who are treated with pharmacological treatment do not have 'active UC'
  - Therefore, they will not incur the QALYs (and costs) modelled by the company for patients with active UC – EAG considers the use of remission and response utility values is appropriate

Which modelled health state most reflects NHS clinical practice for patients who lose response, 'active UC' (company) or 'on subsequent treatment' (EAG)?

Abbreviations: QALY, quality-adjusted life year; UC, ulcerative colitis

Summary of key issue – utility values

A summary of slides 71 to 72

Company and EAG have different preferences although does not have a big impact on ICER

Company vs EAG approach:

- Company use utility values from published sources and explore impact of alternative using alternative published sources for the data and using upadacitinib trial data = all have little impact on ICER
    - In most recent appraisal at time of submisssion – TA633 (ustekinumab) – the NICE committee noted patient expert's reflections on utility values, stating that it is possible some effects on quality of life (such as feeling out of control) may not be captured in trials
- EAG uses higher utility values, from upadacitinib trail base data in its preferred base case – in line with NICE reference case. Impact of EAG's preferred approach – small increase in ICER
- Note: in previous appraisals, the committee have questioned use of utility data from published sources when trial data is available (e.g. TA547 [tofacitinib] and TA633 [ustekinumab]), and in TA633 noted the Woehl et al. 2008 data had been a source of controversy in all the previous appraisals

Which source of utilities data does the committee prefer?

Tech team recommendation: company and EAG base cases differ on this issue, and previously company approach has been preferred, but it has little impact on ICER overall, so choice does not have big impact.

Key issue: Company choice of utility values

ERG comments

- In line with NICE reference case, EAG provides scenario using EQ-5D data collected in 3 upadacitinib trials – this is adopted as EAG preferred base case
- Clinical opinion needed to determine most realistic utility values for use in company model

Health state	Subgroup	Company preferred: published utility values (Woehl 2008)	EAG preferred: upadacitinib trial-based utility values
Remission	Bio-naïve	0.87	[redacted]
Response without remission		0.76	[redacted]
Active UC		0.41	[redacted]
Remission	Bio-exposed	0.87	[redacted]
Response without remission		0.76	[redacted]
Active UC		0.41	[redacted]

Company technical engagement response

- Clinical experts and company consider utility data collected in a trial is likely to underestimate true quality of life burden experienced by patients with UC, especially in active UC health state with limited trial follow-up
  - *'being in a trial [benefits] QoL … patients feel rewarded by increased interactions with a dedicated team'*
  - *'would like to see multiple years of QoL data… reasonable to use observational data where this not available'*

Abbreviations: QoL, quality of life; UC, ulcerative colitis

Key issue: Company choice of utility values

Company technical engagement response *continued*

- In TA633 (ustekinumab), the NICE committee noted patient expert's reflections on utility values, stating that it is possible some effects on quality of life (such as feeling out of control) may not be captured in trials
  - Also reflected in the statements on patient experience of UC in Crohn's and Colitis UK's TE submission
- New scenarios to support company submission, testing several utility data sources: Swinburn et al (2012), Vaizey et al (2014), and utility data collected in upadacitinib UC trials
  - Upadacitinib remained dominant or highly cost effective versus all comparators in these scenario analyses in both the bio-naïve and bio-exposed populations

Tech team note

- In several previous appraisals, the committee have questioned use of utility data from published sources when trial data is available (e.g. TA547 [tofacitinib] and TA633 [ustekinumab]), and in TA633 noted the Woehl et al. 2008 data had been a source of controversy in all the previous appraisals

Which source of utilities data does the committee prefer?

Abbreviations: UC, ulcerative colitis

Company's model – intervention and comparators

- **Intervention:**
  - Induction: upadacitinib 45 mg once daily
  - Maintenance: upadacitinib 15 mg ('standard') and 30 mg ('high') once-daily
- **Comparators:**

Comparator	Bio-naïve population	Bio-exposed population
Adalimumab (and biosimilar)	Included	Included
Golimumab	Included	Excluded
Infliximab (and biosimilar)	Included	Excluded
Tofacitinib	Included	Included
Ustekinumab	Included	Included
Vedolizumab†	Included	Included

†Data for vedolizumab IV applied to vedolizumab SC

- All comparator drugs assumed to be prescribed in 70:30 ratio of 'standard' to 'high' maintenance doses
  - Consistent with the assumption made in TA633 (ustekinumab) that 30% of patients have escalated doses of maintenance treatment
- Upadacitinib also assumed to be prescribed in 70:30 ratio of 'standard' to 'high' maintenance doses – *Key issue resolved after TE*

Abbreviations: IV, intravenous; NMA, network meta-analysis; SC, subcutaneous

Summary of key issue – high / low doses of upadacitinib

Note: issue now resolved

A summary of slide 75

Company presented high/low maintenance dose as 2 separate analyses, EAG considered there would be a mix of doses in practice, company agreed

Upadacitinib maintenance doses:

- Company initially presented separate analyses for 15 mg and 30 mg maintenance doses of upadacitinib
- EAG assumed a 70:30 ratio of these upadacitinib doses would be used, in line with what was being assumed for standard and high doses of comparators
- Company agreed and presented subsequent analyses adopting 70:30 ratio for upadacitinib maintenance dosing

Tech team recommendation: no further discussion needed.

Key issue: high and low doses of upadacitinib maintenance treatments – *resolved after technical engagement*

EAG comments

- All comparator drugs assumed to be prescribed in 70:30 ratio of 'standard' to 'high' maintenance doses in company's model
- Assumption reasonable for comparators treatments, but results in inconsistency for comparison with upadacitinib
- Clinical advice to EAG is that whilst the proportion of patients who will be prescribed high dose upadacitinib maintenance therapy in clinical practice is currently unknown, an assumption of 70:30 ratio of standard to high maintenance doses is not unreasonable
- EAG prefers results from company scenario using this ratio for all treatments is relevant to decision makers

Company technical engagement response

- Provided updated probabilistic base-case analyses with a 70:30 dose split between the 15 mg and 30 mg upadacitinib maintenance doses to align with comparators
- Clinical advisors to company considered this assumption was plausible
- Deterministic analysis of 15 mg and 30 mg were conducted for completeness and as recognition that the Committee may find these useful as supporting information for decision making.

Summary of additional issue – surgery rates

A summary of slides 77 to 79

Company and EAG have different preferences, which has a moderate impact on ICER in company's preferred base case only
However, no surgery in EAG's preferred approach so not relevant here

Company vs EAG approach:

- Note: EAG's preferred model uses an alternative 'on subsequent treatment' health state in its base case which does not include surgery as an option (was not possible with the modelling), so this issue relates only to company's preferred model where people enter the 'active UC' health state
- EAG and company differ in the rates of surgery that should be assumed for patients who leave the company's modelled 'active UC' health state
    - Company assumes 0.5% of patients in 'active UC' health state will have surgery each year
    - EAG prefers to assume that ~50% of patients in 'active UC' health state will have surgery because 0.5% assumed by company relates to *all* patients with UC (not just those in active UC)
- EAG notes that new published evidence provided by company that colectomy rates are declining, provide further support for EAG's preferred model where an 'on subsequent treat' health state is used

Which source of surgery data does the committee prefer?

Tech team recommendation: In company's base case (only), the issue has a moderate impact on ICER overall but upadacitinib remains a cost-effective treatment so choice does not have big impact. If committee prefers the EAG base case and modelled treatment pathway (see earlier key issue) then no further discussion needed.

Additional issue: Surgery rates assumed by EAG higher than assumed by company

EAG comments

- In the company model, 0.5% of patients in the active UC health state receive surgery each year
  - The company converted this rate to a probability per cycle of 1st surgery for patients in the active UC health state. The same rate was also used for the probability of a patient undergoing a 2nd revision surgery after being left with complications following the 1st surgery
- Clinical advice to EAG is that:
  - ~50% of patients who do not respond to active treatments will undergo surgical procedures, and
  - the other ~50% of patients are offered surgery but choose not to have it – these patients are likely to continue the treatment that provided best symptom alleviation, even if it did not constitute response
- EAG considers that, in the company's modelled treatment pathway, the rate of surgical procedures used for patients in the active UC health state is too low - 0.5% is the rate for *all* people with UC (not just those in active UC)
  - Assessed impact of using higher surgery rates for patients in active UC state, by running scenarios using a 50% annual rate of 1st surgery and a 100% annual rate of 2nd revision surgery

Company technical engagement response

- EAG's scenario analysis in which 50% of patients with active UC progress to surgery each year conflicts with published literature
  - Clinical expert opinion: lifetime risk of colectomy associated with UC is ~25%

Abbreviations: UC, ulcerative colitis

Additional issue: Surgery rates assumed by EAG higher than assumed by company

Company technical engagement response *continued*

- Company's assumption that 0.5% of patients in the active UC health state receive surgery each year is based on based on HES data, is further validated by clinical expert opinion, and is the most reliable data source to inform the probability of surgery in the model
- There has been a reduction in colectomy rates over time, likely due to more advanced treatments, indicating that the surgical rates assumed by the company could be higher than they would be in 2022
  - Worsley et al (2020) showed that patients with UC, admitted for active disease during 2013-2016 had significantly lower cumulative probability of colectomy compared to patients admitted during 2003-2007 or 2008-2012 (based on HES data)
  - Another study looked at the reduction of surgery for UC, showing that between 2005 and 2018 yearly colectomy rates per 100 UC patients fell from 1.47 to 0.44 ($p<0.001$) (Jenkinson 2021)
  - Therefore, the EAG scenario for surgery is not relevant for this decision problem

EAG comments after technical engagement

- To estimate a colectomy rate, the company used HES data from patients who were admitted to hospital and had a UC diagnosis, but the 'active UC' health state in the company model represents patients who are not responding to pharmacological therapy, have a low quality of life and high resource use

Abbreviations: HES, Hospital Episode Statistics; UC, ulcerative colitis

Additional issue: Surgery rates assumed by EAG higher than assumed by company

EAG comments after technical engagement *continued*

- Clinical advice to the EAG is that all patients in the active UC health state (unless contraindicated) would be offered surgery in NHS clinical practice, of these ~50% would be ineligible or choose not to have surgery
- The Jenkinson (2021) study identified by the company highlights how increasingly rare colectomy rates have become for patients with UC since the introduction of biological therapies in the NHS
  - This provides evidence to support the EAG's 'basket of treatments' modelling approach as it indicates that most patients with UC are managed with pharmacological therapy
- EAG's preferred model using 'on subsequent treatment' health state does not include surgery as an option as it was not possible with the modelling

Which source of surgery data does the committee prefer?

Abbreviations: HES, Hospital Episode Statistics; UC, ulcerative colitis

Key issues

Issue	Resolved?	Tech team view	ICER impact
No direct evidence vs comparators – *influenced by confidence in NMA results*	No – cannot be resolved	Company approach acceptable	Unknown
NMA statistical issues – *plausibility and suitability of NMA results*	No – for discussion	NMAs results plausible but some uncertainty	Unknown
Modelled treatment pathway – *does not represent NHS practice*	No – for discussion	Choice does not have big impact	Small
Utility values – *trial utilities available, but not used in company base case*	No – for discussion	Choice does not have big impact	Small
High and low doses of upadacitinib maintenance treatments - *different doses with different costs available; what is used in NHS?*	Yes	No further discussion needed	Small

Abbreviations: ICER, incremental-cost effectiveness ratio; NMA, network meta-analysis

Additional issue after technical engagement

Issue	Resolved?	Tech team view	ICER impact
Surgery rates – *only relates to company base case (not EAGs)*	No – for discussion	Choice does not have big impact	Moderate 

Abbreviations: ICER, incremental-cost effectiveness ratio; NMA, network meta-analysis

NICE National Institute for Health and Care Excellence

Thank you.