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]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Janette Greenhalgh, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

James Mahon, Director, Coldingham Analytical Services, Berwickshire

Rachel Houten, Health Economic Modeller, LR*i*G, University of Liverpool

Katherine Edwards, Research Associate (Clinical Effectiveness), LR*i*G, University of Liverpool

Sarah Donegan, Lecturer in Statistics, Department of Health Data Science, University of Liverpool

Angela Boland, Director, LR*i*G, University of Liverpool

Sophie Beale, Director, HARE Research, North Yorkshire

Yenal Dundar, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Joanne McEntee, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

Michael Burkitt, Consultant Gastroenterologist and Deputy Medical Director, Manchester University NHS, Manchester

Correspondence to: Janette Greenhalgh, Senior Research Fellow (Clinical Effectiveness), Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

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.

Contributions of authors:

Janette Greenhalgh	Project lead, critical appraisal of the clinical evidence and supervision of the final report
James Mahon	Critical appraisal of the economic model
Rachel Houten	Critical appraisal of the economic model
Katherine Edwards	Critical appraisal of the clinical evidence
Sarah Donegan	Critical appraisal of the statistical evidence
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
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

Table of contents

LIST OF TABLES

LIST OF FIGURES

,

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.

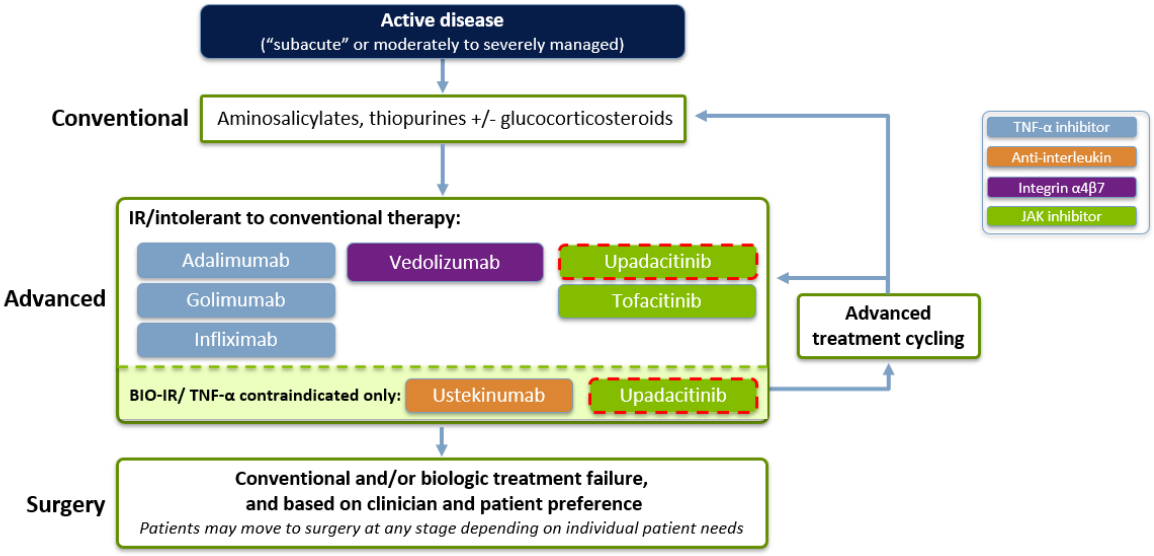

Figure 1 Treatment pathway for patients with ulcerative colitis

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) <u>Study population and trial characteristics</u>

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.

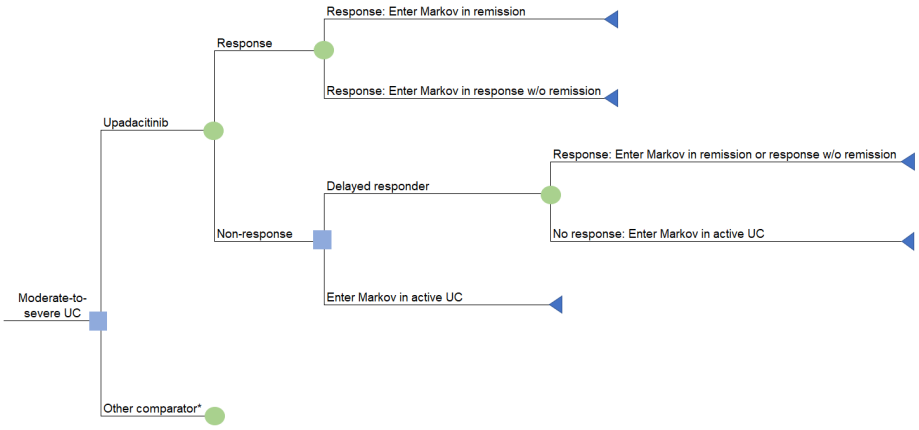

Figure 2 Company decision tree (induction phase)

Source: CS, Figure 9

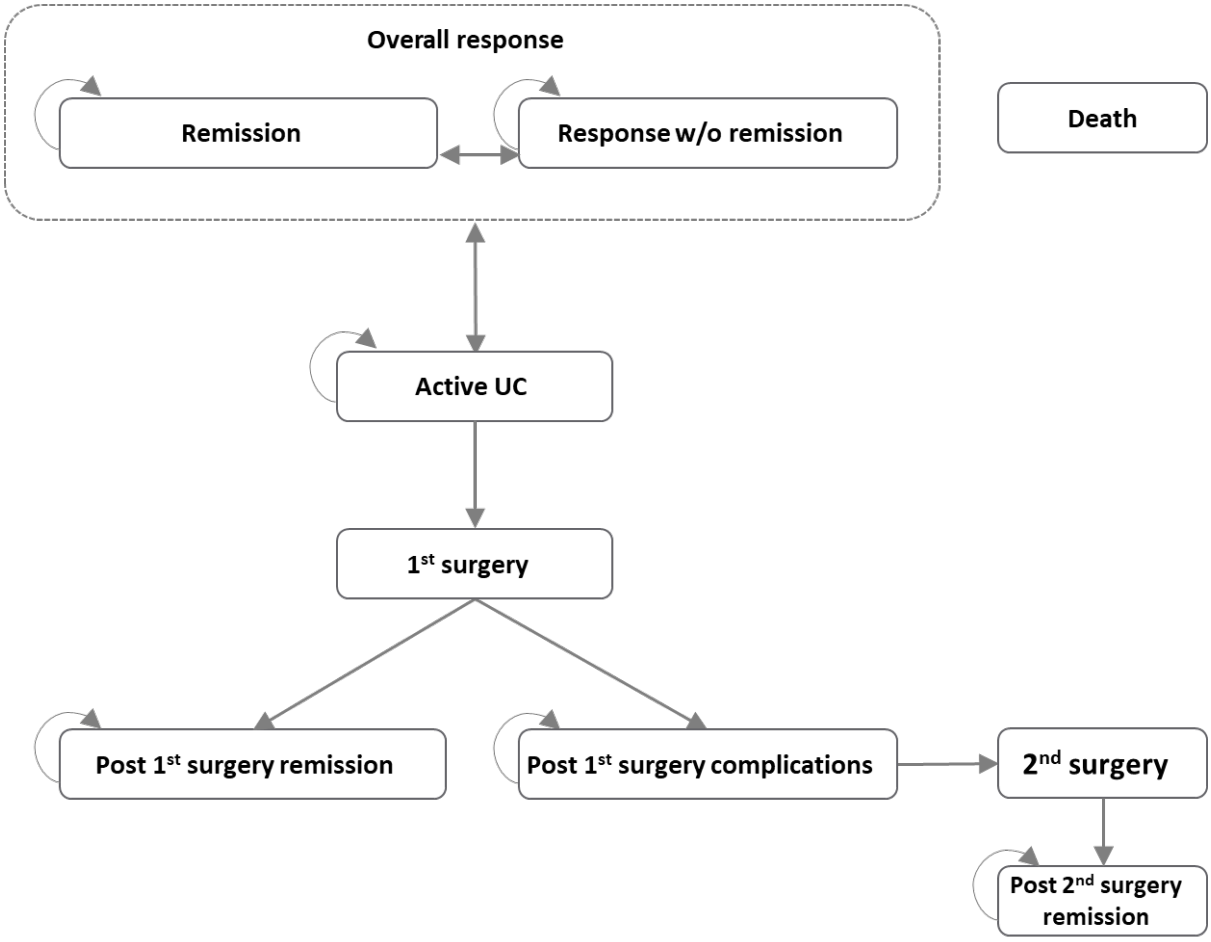

Figure 3 Company Markov model (maintenance phase, subsequent treatment and surgery)

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.

6 REFERENCES

1. Ko CW, Singh S, Feuerstein JD, Falck-Ytter C, Falck-Ytter Y, Cross RK. AGA Clinical Practice Guidelines on the Management of Mild-to-Moderate Ulcerative Colitis. Gastroenterology. 2019; 156:748-64.
2. Ordas I, Eckman L, Talamini M, Baumgart D, Sandborn W. Ulcerative colitis. Lancet. 2012; 380:1606-19.
3. National Institute for Health and Care Excellence. Ulcerative colitis. Published date: April 2020. Available from: https://cks.nice.org.uk/topics/ulcerative-colitis/background-information/prevalence/. Accessed 15 April 2022.
4. Burisch J, Jess T, Martinato M, Lakatos PL. The burden of inflammatory bowel disease in Europe. Journal of Crohn's and Colitis. 2013; 7:322-37.
5. National Institute for Health and Care Excellence. Single Technology Appraisal. Ustekinumab for treating moderately to severely active ulcerative colitis [ID1511]. Committee Papers, version 1. Published date: 2020. Available from: https://www.nice.org.uk/guidance/ta633/evidence/appraisal-consultation-committee-papers-pdf-8774360605. Accessed 15 June 2022.
6. Crohn's and colitis UK. Ulcerative colitis. Last reviewed: May 2021. Available from: https://www.crohnsandcolitis.org.uk/about-crohns-and-colitis/publications/ulcerative-colitis Accessed 15 June 2022.
7. 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; 68:s1-s106.
8. Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis. 2008; 14:1660-6.
9. Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. Gut. 1998; 43:29-32.
10. Canadian Agency for Drugs Technologies and Health (CADTH). Clinical review report for Ustekinumab (Stelara). Publication date: September 2020. Available from: https://www.cadth.ca/sites/default/files/cdr/clinical/sr0627-stelara-clinical-review-report.pdf. Accessed 15 June 2022.
11. Perler BK, Ungaro R, Baird G, Mallette M, Bright R, Shah S, *et al.* Presenting symptoms in inflammatory bowel disease: descriptive analysis of a community-based inception cohort. BMC gastroenterology. 2019; 19:1-8.
12. Devlen J, Beusterien K, Yen L, Ahmed A, Cheifetz AS, Moss AC. The burden of inflammatory bowel disease: a patient-reported qualitative analysis and development of a conceptual model. Inflammatory bowel diseases. 2014; 20:545-52.
13. Armuzzi A, Liguori G. Quality of life in patients with moderate to severe ulcerative colitis and the impact of treatment: A narrative review. Digestive and Liver Disease. 2021:803-8.
14. Danese S, Vermeire S, Zhou W, Pangan AL, Siffledeen J, Greenbloom S, *et al.* Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials. The Lancet. 2022; 339:2113-28.
15. National Institute for Health and Care Excellence. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy [TA329]. Published date: 25 February 2015. Available from: https://www.nice.org.uk/guidance/ta329/resources/infliximab-adalimumab-and-golimumab-for-treating-moderately-to-severely-active-ulcerative-colitis-after-the-failure-of-conventional-therapy-pdf-82602495307717. Accessed 15 June 2022.
16. National Institute for Health and Care Excellence. Tofacitinib for moderately to severely active ulcerative colitis [TA547]. Published date: 28 November 2018. Available from: https://www.nice.org.uk/guidance/ta547/resources/tofacitinib-for-

moderately-to-severely-active-ulcerative-colitis-pdf-82606966445509. Accessed 15 June 2022.
17. National Institute for Health and Care Excellence. Vedolizumab for treating moderately to severely active ulcerative colitis [TA342]. Published date: 5 June 2015. Available from: https://www.nice.org.uk/guidance/ta342/resources/vedolizumab-for-treating-moderately-to-severely-active-ulcerative-colitis-pdf-82602604482757. Accessed 15 June 2022.
18. National Institute for Health and Care Excellence. Ustekinumab for treating moderately to severely active ulcerative colitis [TA633]. Published date: 17 June 2020. Available from: https://www.nice.org.uk/guidance/ta633/resources/ustekinumab-for-treating-moderately-to-severely-active-ulcerative-colitis-pdf-82609076043205. Accessed 15 June 2022.
19. Abbvie. Data on File. Company budget impact analysis submission for upadacitinib for treating moderately to severely active ulcerative colitis [ID3953]. Published date: April 2022.
20. Office for National Statistics. ONS. Principal projection- England population in age groups. Published date: 12 January 2022. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections/datasets/tablea24principalprojectionenglandpopulationinagegroups Accessed 15 June 2022.
21. National Institute for Health and Care Excellence (NICE). Ustekinumab for treating moderately to severely active ulcerative colitis [TA633]. Resource impact template.; Available from: https://www.nice.org.uk/guidance/ta633/resources. Accessed 15 June 2022.
22. National Institute for Health and Care Excellence. Ulcerative colitis: management. NICE guideline [NG130]. Published: 03 May 2019. Available at: https://www.nice.org.uk/guidance/ng130 (Accessed April 2022). 2019.
23. National Institute for Health and Care Excellence (NICE). Upadacitinib for treating moderately to severely active ulcerative colitis [ID3953]. Final scope. Issue date: February 2022. Available from: https://www.nice.org.uk/guidance/gid-ta10866/documents/final-scope. Accessed 15 June 2022.
24. AbbVie. Upadacitinib. M14-234 substudy 1 and substudy 2 clinical study report. R&D/20/1294. A multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of upadacitinib (ABT-494) for induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis. Published date: 10 August 2021.
25. AbbVie. Upadacitinib. M14-675 clinical study report. R&D/21/0078. A multicenter, randomized, double-blind, placebo-controlled induction study to evaluate the efficacy and safety of upadacitinib (ABT-494) in subjects with moderately to severely active ulcerative colitis. Published date: 29 June 2021.
26. AbbVie. Upadacitinib. M14-234 substudy 3 clinical study report - interim. R&D/21/0503. A multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of upadacitinib (ABT-494) for induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis. Published date: 3 August 2021.
27. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J*, et al.* Infliximab for induction and maintenance therapy for ulcerative colitis. The New England journal of medicine. 2005; 353:2462-76.
28. Kobayashi T, Suzuki Y, Motoya S, Hirai F, Ogata H, Ito H*, et al.* First Trough Level of Infliximab at Week 2 Predicts Future Outcomes of Induction Therapy in Ulcerative Colitis: A Post-hoc Analysis of a Multicenter Prospective Randomized Controlled Trial: 1851. Official journal of the American College of Gastroenterology| ACG. 2015; 110:S787.

29. Jiang XL, Cui HF, Gao J, Fan H. Low-dose Infliximab for Induction and Maintenance Treatment in Chinese Patients With Moderate to Severe Active Ulcerative Colitis. J Clin Gastroenterol. 2015; 49:582-8.
30. Janssen Research & Development. Clinical Study Report Synopsis. Protocol REMICADEUCO3001; Phase 3. CNTO312 (infliximab). Available at: https://yoda.yale.edu/sites/default/files/nct01551290.pdf 2014; Accessed 15 April 2022.
31. Reinisch W, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S*, et al.* Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut. 2011; 60:780-7.
32. 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; 142:257-65.e1-3.
33. Suzuki Y, Motoya S, Hanai H, Matsumoto T, Hibi T, Robinson AM*, et al.* Efficacy and safety of adalimumab in Japanese patients with moderately to severely active ulcerative colitis. Journal of gastroenterology. 2014; 49:283-94.
34. Panés J, Colombel J, D'Haens G. High versus standard adalimumab induction dosing regimens in patients with moderately to severely active ulcerative colitis: results from the SERENE-UC induction study. United European Gastroenterol J. 2019; 7:118.
35. Hibi T, Imai Y, Senoo A, Ohta K, Ukyo Y. Efficacy and safety of golimumab 52-week maintenance therapy in Japanese patients with moderate to severely active ulcerative colitis: a phase 3, double-blind, randomized, placebo-controlled study-(PURSUIT-J study). Journal of gastroenterology. 2017; 52:1101-11.
36. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel J-F, Sandborn WJ*, et al.* Vedolizumab as induction and maintenance therapy for ulcerative colitis. New England Journal of Medicine. 2013; 369:699-710.
37. 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; 146:85-95.
38. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J*, et al.* Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014; 146:96-109. e1.
39. Motoya S, Watanabe K, Ogata H, Kanai T, Matsui T, Suzuki Y*, et al.* Vedolizumab in Japanese patients with ulcerative colitis: a phase 3, randomized, double-blind, placebo-controlled study. PLoS One. 2019; 14:e0212989.
40. Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J*, et al.* Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. The New England journal of medicine. 2019; 381:1201-14.
41. Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S*, et al.* Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. The New England journal of medicine. 2017; 376:1723-36.
42. AbbVie. Upadacitinib (Rinvoq). Draft Summary of Product Characteristics. 2022.
43. Food and Drug Administration (FDA). Ulcerative Colitis: Clinical trial endpoints guidance for industry: draft guidance. Published date: August 2016. Available from: https://www.fda.gov/files/drugs/published/Ulcerative-Colitis--Clinical-Trial-Endpoints-Guidance-for-Industry.pdf. Accessed 14 June 2022.
44. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Summary of opinion (post authorisation): Upadacitinib (Rinvoq). 2022; Available from: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-opinion-rinvoq-x-12-g_en.pdf. Accessed 21 June 2022.
45. Medicines and Healthcare products Regulatory Agency. Tofacitinib (Xeljanz▼): new measures to minimise risk of major adverse cardiovascular events and malignancies 2021; Available from: https://www.gov.uk/drug-safety-update/tofacitinib-xeljanzv-new-

measures-to-minimise-risk-of-major-adverse-cardiovascular-events-and-malignancies. Accessed 21 June 2022.
46. Clinicaltrials.gov. A study to evaluate the long-term safety and efficacy of upadacitinib (ABT-494) in participants with ulcerative colitis (UC). 2022; Available from: https://www.clinicaltrials.gov/ct2/show/NCT03006068 (accesed June 2022). Accessed.
47. European Medicines Agency. Janus kinase inhibitors (JAKi): status update 10 June 2022. 2022; Available from: https://www.ema.europa.eu/en/medicines/human/referrals/janus-kinase-inhibitors-jaki. Accessed 20 June 2022.
48. National Institute for Health and Care Excellence (NICE). Filgotinib for treating moderately to severely active ulcerative colitis [TA792]. Published date: 1 June 2022. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10600. Accessed 15 June 2022.
49. National Institute for Health and Care Excellence (NICE). Ozanimod for treating moderately to severely active ulcerative colitis [ID3841]. Expected publication date: 21 September 2022. 2022; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10732. Accessed 15 June 2022.
50. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Process and methods [PMG9]. Published date: 4 April 2013. . Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 Accessed 14 June 2022.
51. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ*, et al.* Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2019.
52. Abbvie. Statistical analysis plan for Substudy 2. Study M14-234. A mutli-center, randomised, double-blind, placebo-controlled study to evaluate the safety and efficacy of upadacitinib (ABT-494) for induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis, version 5.0. Published date: 13 November 2020.
53. Abbvie. Statistical analysis plan for Substudy 3. Study M14-234. A mutli-center, randomised, double-blind, placebo-controlled study to evaluate the safety and efficacy of upadacitinib (ABT-494) for induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis, version 4.0. Published date: 20 May 2021.
54. Abbvie. Statistical analysis plan for Study M14-675. A mutli-center, randomised, double-blind, placebo-controlled induction study to evaluate the safety and efficacy of upadacitinib (ABT-494) in subjects with moderately to severely active ulcerative colitis, version 6.0. Published date: 19 January 2021.
55. Abbvie. Clinical study protocol M14-675. A mutli-center, randomised, double-blind, placebo-controlled induction study to evaluate the efficacy and safety of upadacitinib (ABT-494) in subjects with moderately to severely active ulcerative colitis. Publication date: 9 October 2020.
56. Abbvie. Clinical study protocol M14-234. A mutli-center, randomised, double-blind, placebo-controlled study to evaluate the safety and efficacy of upadacitinib (ABT-494) for induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis. Published date: 9 October 2020.
57. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, Danese S, Colombel JF, Törüner M*, et al.* Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. The New England journal of medicine. 2019; 381:1215-26.
58. Sandborn WJ, Peyrin-Biroulet L, Sharara AI, Su C, Modesto I, Mundayat R*, et al.* Efficacy and safety of tofacitinib in ulcerative colitis based on prior tumor necrosis factor inhibitor failure status. Clinical Gastroenterology and Hepatology. 2022; 20:591-601. e8.

59. Dias S, Welton NJ, Sutton AJ, Ades A. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. 2011.
60. Ali T, Skup M, Yang M, Yang M, Wu E, Mulani P*, et al.* Cost-effectiveness of adalimumab in moderately to severely active ulcerative colitis: 1588. American College of Gastroenterology Conference: 77th Annual scientific meeting of the American College of Gastroenterology; 2012; Las Vegas, NV United States.
61. Arebi N, Karapiperis D, Tripolo S. Cost-effectiveness of surgery and infliximab for refractory ulcerative colitis: A single centre study using patient-level data. Journal of Crohn's and Colitis Conference: 8th Congress of the European Crohn's and Colitis Organisation, ECCO 2013; Vienna Austria.
62. Borsi A, Barthelmes J, Maier-Downing T, Kahol D, Lee JM, Bird A*, et al.* PGI11 Cost per responder and remitter analysis comparing ustekinumab to comparator treatments for moderate-to-severe ulcerative colitis in the United Kingdom. Value in Health. 2020; 23:S535.
63. Lohan C, Diamantopoulos A, LeReun C, Wright E, Bohm N, Sawyer LM. Tofacitinib for the treatment of moderately to severely active ulcerative colitis: a systematic review, network meta-analysis and economic evaluation. BMJ open gastroenterology. 2019; 6:e000302.
64. Punekar YS, Hawkins N. Cost-effectiveness of infliximab for the treatment of acute exacerbations of ulcerative colitis. Eur J Health Econ. 2010; 11:67-76.
65. Tsai H, Punekar Y, Morris J, Fortun P. A model of the long-term cost effectiveness of scheduled maintenance treatment with infliximab for moderate-to-severe ulcerative colitis. Alimentary pharmacology & therapeutics. 2008; 28:1230-9.
66. Williams JG, Alam MF, Alrubaiy L, Clement C, Cohen D, Grey M*, et al.* Comparison Of iNfliximab and ciclosporin in STeroid Resistant Ulcerative Colitis: pragmatic randomised Trial and economic evaluation (CONSTRUCT). Health Technology Assessment. 2016; 20:1-320.
67. Wilson MR, Azzabi Zouraq I, Chevrou-Severac H, Selby R, Kerrigan MC. Cost-effectiveness of vedolizumab compared with conventional therapy for ulcerative colitis patients in the UK. ClinicoEconomics and Outcomes Research. 2017; 9:641-52.
68. Wilson MR, Bergman A, Chevrou-Severac H, Selby R, Smyth M, Kerrigan MC. Cost-effectiveness of vedolizumab compared with infliximab, adalimumab, and golimumab in patients with ulcerative colitis in the United Kingdom. European Journal of Health Economics. 2018; 19:229-40.
69. Yang H, Curry A, Wang S. Cost-effectiveness of adalimumab in moderately to severely active ulcerative colitis (sub-acute) in the UK. United European Gastroenterology Journal Conference: 22nd United European Gastroenterology Week; 2014; Vienna Austria. .
70. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ. 1996; 313:275.
71. Misra R, Askari A, Faiz O, Arebi N. Colectomy rates for ulcerative colitis differ between ethnic groups: results from a 15-year nationwide cohort study. Canadian Journal of Gastroenterology and Hepatology. 2016; 2016.
72. Segal JP, McLaughlin SD, Faiz OD, Hart AL, Clark SK. Incidence and long-term implications of prepouch ileitis: an observational study. Diseases of the Colon & Rectum. 2018; 61:472-5.
73. Office for National Statistics. Dataset. National life tables: UK. . 2021; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables Accessed 14 June 2022.
74. Woehl A, Hawthorne A, McEwan P. The relation between disease activity, quality of life and health utility in patients with ulcerative colitis. Gut; 2008. British Medical

Association House, Tavistock Square, London WC1H 9JR, England: BMJ Publishing Group.
75. Arseneau KO, Sultan S, Provenzale DT, Onken J, Bickston SJ, Foley E*, et al.* Do patient preferences influence decisions on treatment for patients with steroid-refractory ulcerative colitis? Clinical Gastroenterology and Hepatology. 2006; 4:1135-42.
76. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value in Health. 2010; 13:509-18.
77. Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J*, et al.* Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. Health Technology Assessment. 2016; 20:1-610.
78. National Institute for Health and Care Excellence. British National Formulary (BNF). Last updated: 19 May 2022. Available from: https://bnf.nice.org.uk/. Accessed 15 June 2022.
79. Electronic Medicines Compendium. RINVOQ 15 mg prolonged-release tablets. Summary of Product Characteristics. . 2021; Available from: https://www.medicines.org.uk/emc/product/10972/smpc#gref Accessed 15 June 2022.
80. Abbvie. Adalimumab (Humaira). Summary of product characteristics.; Available from: https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf. Accessed 15 June 2022.
81. Janssen Biologics B.V. Golimumab (Simponi). Summary of product characteristics. . Available from: https://www.ema.europa.eu/en/documents/product-information/simponi-epar-product-information_en.pdf. Accessed 15 June 2022.
82. Janssen Biologics B.V. Infliximab (Remicade). Summary of product characteristics.; Available from: https://www.ema.europa.eu/en/documents/product-information/remicade-epar-product-information_en.pdf. Accessed 15 June 2022.
83. Pfizer. Tofacitinib (Xeljanz). Summary of product characteristics.; Available from: https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf. Accessed 15 June 2022.
84. Janssen Biologic B.V. Ustekinumab (Stelera). Summary of product characteristics.; Available from: https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf. Accessed 15 June 2022.
85. Abbvie. Vedolizumab (Entyvio). Summary of product characteristics.; Available from: https://www.ema.europa.eu/en/documents/product-information/entyvio-epar-product-information_en.pdf. Accessed 15 June 2022.
86. Department of Health. NHS reference costs 2019/20. Available from: https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/. Accessed 24 June 2022.
87. Buchanan J, Wordsworth S, Ahmad T, Perrin A, Vermeire S, Sans M*, et al.* Managing the long term care of inflammatory bowel disease patients: The cost to European health care providers. Journal of Crohn's and Colitis. 2011; 5:301-16.
88. Jones K, Burns A. Unit costs of health and social care 2021. : Personal Social Services Research Unit, Kent, UK, 185; 2021.
89. Schneider P, McNamara S, Love-Koh J, Doran T, Gutacker N. Quality-adjusted life expectancy norms for the English population. 2021; Available from: https://www.medrxiv.org/content/medrxiv/early/2021/12/14/2021.12.13.21267671.full.pdf. Accessed 15 June 2022.
90. Swinburn P, Elwick H, Bean K, Curry A, Patel S, Bodger K*, et al.* PTU-127 The impact of surgery on health related quality of life in ulcerative colitis. Gut. 2012; 61:A237-A.

91. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). MedDRA the Medical Dictionary for Regulatory Activities terminology (MedDRA). Available from: https://www.meddra.org/faq. Accessed 15 June 2022.
92. Ghosh S, Wolf DC, Sandborn W, Colombel J-F, Zhou Q, Lazar A*, et al.* Sa1208 Sustained Efficacy in Patients With Ulcerative Colitis Treated With Adalimumab: Results From ULTRA 2. Gastroenterology. 2013; 5:S-230.
93. Sandborn WJ, Wolf DC, Van Assche G, Yang M, Mulani PM, Reilly N*, et al.* Rapid onset of adalimumab and long-term efficacy among week-8 responders in adults with moderate to severe active ulcerative colitis. Inflammatory Bowel Diseases. 2011; 17:S4-S.
94. D'Haens G, Van Assche G, Wolf D, Sandborn W, Colombel J-F, Lazar A*, et al.* Mucosal Healing in Ulcerative Colitis Patients with Week 8 Response to Adalimumab: Subanalysis of ULTRA 2: 1523. Official journal of the American College of Gastroenterology| ACG. 2012; 107:S610-S1.
95. Sandborn W, Colombel JF, D'haens G, Van Assche G, Wolf D, Kron M*, et al.* One-year maintenance outcomes among patients with moderately-to-severely active ulcerative colitis who responded to induction therapy with adalimumab: subgroup analyses from ULTRA 2. Alimentary pharmacology & therapeutics. 2013; 37:204-13.
96. Panaccione R, Colombel J-F, Sandborn W, Reinisch W, D'Haens GR, Hommes DW*, et al.* Sa1229 Durable Clinical Remission and Response in Adalimumab-Treated Patients With Ulcerative Colitis. Gastroenterology. 2015; 148:S-264.
97. Colombel J-F, D'haens G, Lee W-J, Petersson J, Panaccione R. Outcomes and strategies to support a treat-to-target approach in inflammatory bowel disease: a systematic review. Journal of Crohn's and Colitis. 2020; 14:254-66.
98. Sandborn WJ, Colombel J-F, Panaccione R, Dulai PS, Rosario M, Cao C*, et al.* Deep remission with vedolizumab in patients with moderately to severely active ulcerative colitis: a GEMINI 1 post hoc analysis. Journal of Crohn's and Colitis. 2019; 13:172-81.
99. Feagan BG, Rubin DT, Danese S, Vermeire S, Abhyankar B, Sankoh S*, et al.* Efficacy of vedolizumab induction and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists. Clinical Gastroenterology and Hepatology. 2017; 15:229-39. e5.
100. Nagahori M, Watanabe K, Motoya S, Ogata H, Kanai T, Matsui T*, et al.* Week 2 Symptomatic Response with Vedolizumab as a Predictive Factor in Japanese Anti-TNFα-Naive Patients with Ulcerative Colitis: A post hoc Analysis of a Randomized, Placebo-Controlled Phase 3 Trial. Digestion. 2021; 102:742-52.
101. Van Assche G, Targan SR, Baker T, O'Brien CD, Zhang H, Johanns J*, et al.* DOP47 Sustained remission in patients with moderate to severe ulcerative colitis: Results from the Phase 3 UNIFI maintenance study. Journal of Crohn's and Colitis. 2019; 13:S054-S5.
102. Sands BE, Peyrin-Biroulet L, Marano C, O'Brien CD, Zhang H, Johanns J*, et al.* P312 Efficacy in biologic failure and non-biologic-failure populations in a Phase 3 study of ustekinumab in moderate–severe ulcerative colitis: UNIFI. Journal of Crohn's and Colitis. 2019; 13:S256-S7.
103. Alcala M, Sulleiro S, Hernando T, et al. Alcala M, Sulleiro S, Hernando T, et al. Efficacy of ustekinumab at the end of maintenance in ulcerative colitis patients receiving 6 mg/kg induction posology. data from UNIFI trial. United European Gastroenterology Journal. Conference: 28th United European Gastroenterology Week, UEG. Virtual. 8 (8 Suppl.) (pp 414). 2020.
104. Danese S, Sands BE, Sandborn WJ, et al. Efficacy of ustekinumab subcutaneous maintenance treatment by induction-dose subgroup in the UNIFI study of patients with ulcerative colitis. United European Gastroenterology Journal. Conference: 27th United European Gastroenterology Week, UEG. Spain. 7 (10) (pp 1415). 2019.

105. Panaccione R, Peyrin-Biroulet L, Danese S, Marano C, O'Brien CD, Szapary P*, et al.* 842 Impact of Response and Inflammatory Burden at Start of Maintenance Therapy on Clinical Efficacy of Ustekinumab Dosing Regimen in UC: Week 44 Results From UNIFI. Official journal of the American College of Gastroenterology| ACG. 2019; 114:S487-S8.
106. Lichtenstein G, Moore G, Soonasra A, Nduaka C, Kwok K, Wang L*, et al.* P479 Analysis of haematological changes in tofacitinib-treated patients with ulcerative colitis across Phase 3 induction and maintenance studies. Journal of Crohn's and Colitis. 2019; 13:S351-S2.
107. Dubinsky MC, Peyrin-Biroulet L, Melmed GY, Hou JK, Woodworth DA, Friedman GS*, et al.* Efficacy of tofacitinib in patients with ulcerative colitis by prior tumor necrosis factor inhibitor treatment status: results from OCTAVE induction and maintenance studies: 640. Official journal of the American College of Gastroenterology| ACG. 2017; 112:S354.
108. Sandborn W, Sands B, Steinwurz F, Vermeire S, Guo X, Maller E*, et al.* P113 Evaluation of the efficacy of tofacitinib in patients with ulcerative colitis utilizing the modified Mayo score: Data from the Octave program. Inflammatory Bowel Diseases. 2020; 26:S17-S8.
109. D'Haens GR, Sands BE, Sandborn WJ, Hibi T, Su C, Niezychowski W*, et al.* Tofacitinib has induction efficacy in moderately to severely active ulcerative colitis, regardless of prior TNF inhibitor therapy. United European Gastroenterology Journal. 2016;4(5 Supplement 1):A45-A6. 2016.
110. Hanauer S, Panaccione R, Danese S, Cheifetz A, Reinisch W, Higgins PD*, et al.* Tofacitinib induction therapy reduces symptoms within 3 days for patients with ulcerative colitis. Clinical Gastroenterology and Hepatology. 2019; 17:139-47.
111. Chiorean M, Rubin DT, Löwenberg M, Gisbert JP, Tsilkos K, Quirk D*, et al.* Improvement in Physician's Global Assessment Within 2 Weeks in Patients With Ulcerative Colitis Treated With Tofacitinib: 734. Official journal of the American College of Gastroenterology| ACG. 2018; 113:S414.
112. Danese S, Sandborn WJ, Panes J, Zhang H, Woodworth D, Marren A*, et al.* Onset of efficacy of tofacitinib for induction therapy in patients with active ulcerative colitis in two multinational, Phase 3 clinical trials. Digestive and Liver Disease. 2017;49(Supplement 2):e90-e1. 2017.
113. Sands BE, Long MD, Reinisch W, Panés J, Loftus Jr EV, Nduaka CI*, et al.* Tofacitinib for the treatment of ulcerative colitis: analysis of nonmelanoma skin cancer rates from the Ulcerative Colitis Clinical Program. Inflammatory bowel diseases. 2022; 28:234-45.
114. Vavricka S, Greuter T, Cohen B, Reinisch W, Steinwurz F, Fellmann M*, et al.* DOP85 Corticosteroid-free efficacy and safety outcomes in patients receiving tofacitinib in the OCTAVE Sustain maintenance study. Journal of Crohn's and Colitis. 2021; 15:S116-S7.
115. Reinisch W, Osterman MT, Doherty G, Marren A, Woodworth DA, Lawendy N*, et al.* P531 Efficacy of tofacitinib maintenance therapy for ulcerative colitis in remitting patients vs. patients with clinical response after 8 weeks of induction treatment. Journal of Crohn's and Colitis. 2019; 13:S378-S9.
116. Feagan BG, Vermeire S, Sandborn WJ, Reinisch W, Panés J, Tarabar D*, et al.* Tofacitinib for Maintenance Therapy in Patients With Active Ulcerative Colitis in the Phase 3 OCTAVE Sustain Trial: Results by Local and Central Endoscopic Assessments: 607. Official journal of the American College of Gastroenterology| ACG. 2017; 112:S329-S30.
117. Lichtenstein G, Cohen B, Laurent PB, et al. Impact of prior immunosuppressant and tumor necrosis factor inhibitor therapies on tofacitinib efficacy and safety in patients with ulcerative colitis. American Journal of Gastroenterology. Conference: 2018 Advances in Inflammatory Bowel Diseases. United States. 114 (Supplement 1) (pp S10). 2019.

118. Hudesman D, Torres J, Salese L, Woolcott JC, Mundayat R, Su C*, et al.* S866 Patient-Reported Outcome Improvement with Tofacitinib in the Ulcerative Colitis OCTAVE Clinical Program. Official journal of the American College of Gastroenterology| ACG. 2021; 116:S404-S5.

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