NICE National Institute for Health and Care Excellence

Cost-comparison evaluation

Upadacitinib for previously treated moderately to severely active Crohn's disease [ID4027]

Committee Papers

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COST-COMPARISON EVALUATION

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Contents:

The following documents are made available to stakeholders:

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

1. **Company submission** from AbbVie:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

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

4. **Expert personal perspectives** from:
   a. James Lindsay, professor of inflammatory bowel disease – clinical expert, nominated by AbbVie
   b. Ruth Rudling, advanced clinical pharmacist – clinical expert, nominated by UKCPA
   c. Greg Collins, policy lead – patient expert, nominated by Crohn's & Colitis UK *(*see item 3a)*
   d. Derek Fraser – patient expert, nominated by Crohn's & Colitis UK
   e. Peter Irving, consultant gastroenterologist – clinical expert, nominated by AbbVie

5. **External Assessment Report** prepared by Kleijnen Systematic Reviews Ltd

6. **External Assessment Group response to factual accuracy check of EAR**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Upadacitinib for previously treated moderately to severely active Crohn's disease [ID4027]

Document B

Company evidence submission

October 2022

File name	Version	Contains confidential information	Date
2c. ID4027_Upadacitinib CD_NICE_DocB_Final_Fully redacted	**V1**	**Yes (AiC/CiC)**	**05 October 2022**

Contents

Tables and figures

Abbreviations

ADA	adalimumab
AE	adverse event
AESI	adverse events of special interest
AO	as observed
AP	abdominal pain
AZA	azathioprine
BF	biologic failure
BID	twice daily
Bio-IR	biologic inadequate response/intolerance
BMI	body mass index
BSC	best supportive care
BSG	British Society of Gastroenterology
CCF	conventional care failure
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CEA	cost-effectiveness analysis
CI	confidence interval
COVID-19	Coronavirus Disease 2019
CMH	Cochran-Mantel-Haenszel
CRD	Centre for Reviews and Dissemination
CrI	credible interval
CSR	clinical study report
DIC	deviance information criteria
EIM	extraintestinal manifestation
EQ-5D	EuroQol-5 Dimensions health questionnaire
FACIT-F	The Functional Assessment of Chronic Illness Therapy – Fatigue
FAS	full analysis set
FCP	fecal calprotectin
FDA	Food and Drug Administration

FE	fixed effects
GI	gastrointestinal
HBI	Harvey Bradshaw Index
Hct	haematocrit
HCRU	healthcare resource use
HR	hazard ratio
HRQoL	health-related quality of life
hs-CRP	high-sensitivity C-reactive protein
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICER	incremental cost-effectiveness ratio
IFX	infliximab
IL	interleukin
IMM	immunomodulators
IR	inadequate response
IRT	interactive response technology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	indirect treatment comparison
ITT	intention to treat
IV	intravenous
JAK	Janus kinase
LS	least squares
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MoA	mechanism of action
MP	mercaptopurine
MTX	methotrexate
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NRI-C	non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19
NSAID	non-steroidal anti-inflammatory drug
OL	open-label
PAS	Patient Access Scheme
PBO	placebo
PRO	patient-reported outcome
p.o.	per os (orally)
QxW	every x weeks
QD	once daily
QoL	quality of life
RD	risk difference
RE	random effects
SA	safety analysis
SAE	serious adverse event

SC	subcutaneous
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	stool frequency
SLR	systematic literature review
SMC	Scottish Medicines Consortium
SPC	Summary of Product Characteristics
STRIDE	The Selecting Therapeutic Targets in Inflammatory Bowel Disease
SS1	sub-study 1
SUCRA	Surface Under the Cumulative Ranking
TA	technology appraisal
TEAE	treatment-emergent adverse event
TNF	tumour necrosis factor
TSD	technical support document
UPA	upadacitinib
UST	ustekinumab
VAS	visual analogue scale
VDZ	vedolizumab

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

B.1.1 Decision problem

The population considered in this appraisal is people with moderately to severely active Crohn's disease (CD) in whom tumour necrosis factor (TNF)-alpha inhibitors are deemed unsuitable; or where biological treatment is not tolerated or not working well enough.

The anticipated license for upadacitinib in this indication is expected to be [redacted]. As such, the submission represents a sub-population to that specified in the NICE pre-invitation scope and licensed indication. The submission covers the anticipated licensed doses of upadacitinib for CD, i.e., oral induction dose of 45 mg once daily for 12 weeks followed by an oral maintenance dose of 15 mg or 30 mg once daily based on individual patient presentation. The decision problem addressed in this appraisal is outlined in Table 1.

Upadacitinib currently holds marketing authorisation in Great Britain (GB) for rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, atopic dermatitis, and ulcerative colitis (UC) (1). NICE has recommended upadacitinib in[1]: severe active rheumatoid arthritis (TA665) (2); moderate active rheumatoid arthritis (TA744) (3); active psoriatic arthritis (TA768) (4); and ankylosing spondylitis (TA829) (5). Appraisals of upadacitinib in non-radiographic axial spondyloarthritis (ID3958) (6) and ulcerative colitis (ID3953) (7) are ongoing. The SMC has accepted upadacitinib for use in[1]: active psoriatic arthritis (SMC2361) (8); severe active rheumatoid arthritis (SMC2315) (9); moderate to severe atopic dermatitis in adults and adolescents aged 12 years and older (SMC2417) (10). An appraisal of upadacitinib in ulcerative colitis (SMC2510) and moderate to severe rheumatoid arthritis (SMC2495) are ongoing (11).

[1] Restrictions apply to the NICE and SMC recommendations in each indication.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with previously treated moderately to severely active CD	People with moderately to severely active CD in whom TNF-alpha inhibitors are deemed unsuitable; or where biological treatment is not tolerated or not working well enough (BF population)	The proposed positioning of upadacitinib focuses on part of the technology's marketing authorisation to optimise the cost effectiveness of upadacitinib, accordingly a cost-comparison case can be made only for this population. The design of the UPA trials included non-Bio-IR† and Bio-IR populations‡, which align with the CCF (people who have had an inadequate response to conventional care) and BF (people who have had an inadequate response to ≥1 prior biologic) populations used in previous NICE appraisals. In line with the anticipated positioning of UPA, data for the BF population are presented in the main submission and CCF data are provided in the appendices for completeness.
Intervention	UPA	As per scope	NA
Comparator(s)	• TNF-alpha inhibitors (IFX and ADA) • VDZ • UST For people for whom TNF-alpha inhibitor, VDZ, and UST have been ineffective, are contraindicated, or are not tolerated: • BSC	• VDZ • UST	The anticipated positioning for upadacitinib is aligned with that of UST and VDZ for patients in whom TNF-alpha inhibitors are deemed unsuitable; or where biological treatment is not tolerated or not working well enough. TNF-alpha inhibitors are therefore not relevant comparators in this population. The scope includes BSC as a comparator for those who have failed or are contraindicated to all currently available biologic therapies (TNF-alpha inhibitors [ADA, IFX], UST and/or VDZ). BSC is not considered an appropriate comparator; in clinical practice, if a biologic therapy has failed or is contraindicated, the individual will be offered an alternative biologic therapy.
Outcomes	• Disease activity (remission, response, relapse) • Mucosal healing • Surgery • Hospitalisation rates • Adverse effects of treatment • Health-related quality of life	• Disease activity (remission, response, relapse) • Endoscopic outcomes • Hospitalisation rates • Adverse effects of treatment • Health-related quality of life	Mucosal healing does not have a set definition (e.g., it may be considered the absence of ulceration or any improvement in ulceration). Therefore, the term 'endoscopic outcomes' is used for clarity in this submission and includes multiple outcomes indicative of mucosal healing. Full definitions of the endoscopic outcomes used in the upadacitinib clinical trials are provided at the relevant points in the submission. Surgery was an outcome in the UPA maintenance study (U-ENDURE). However, the usefulness of the data is limited given the low number of events in the study population. The 52-week maintenance treatment duration may not be sufficient to capture any noticeable effect on surgery rate.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	If evidence allows: • Location of CD (ileal, colonic, perianal)	• People who have had an inadequate response to conventional care (CCF) • People who have received ≥1 previous biologic therapy and had an inadequate response (BF)	Separate analyses were conducted in the CCF and BF populations due to the anticipated positioning of UPA (i.e., in the BF population).§ CCF data are presented in appendices for completeness. Due to low subject numbers the analysis of outcomes by CD location was deemed untenable. This was validated with clinical experts who noted that disease location is not a clinically relevant distinction and patients are generally not stratified by this subgroup during treatment plan development. Furthermore, as the UPA trials were not powered to determine differences by CD location, stratification by CCF and BF population would make data interpretation challenging (12).
Special considerations including issues related to equity or equality	The availability and cost of biosimilar and generic products should be taken into account	No biosimilars are available for the comparators (UST and VDZ) considered in the submission	NA

Abbreviations: ADA, adalimumab; BF, biologic failure; Bio-IR, biologic inadequate response/intolerance; BSC, best supportive care; CD, Crohn's disease; CCF, conventional care failure; IFX, infliximab; NA, not applicable; TNF, tumour necrosis factor; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab. †Subjects who had an inadequate response or intolerance to conventional therapy (defined as one or more of the following: aminosalicylates, oral locally acting steroids [e.g., budesonide, beclomethasone], systemic corticosteroids [prednisone or equivalent], or immunomodulators). This population may include patients who had received biologic therapy in the past but stopped therapy based on reasons other than inadequate response (IR) or intolerance (e.g., change in reimbursement coverage, well-controlled disease); ‡Subjects with documented intolerance or inadequate response (either failure to respond to induction treatment, or loss of response to maintenance therapy) to one or more biologics for CD (infliximab, adalimumab, certolizumab, natalizumab, vedolizumab, and/or ustekinumab). §The BF population is considered to include those contraindicated to TNF-alpha inhibitors.

B.1.2 Description of the technology being evaluated

Details of the technology being appraised in the submission are provided in Table 2. The draft summary of product characteristics (SmPC) for upadacitinib is provided in Appendix C (13).

Table 2: Technology being evaluated

UK approved name and brand name	Upadacitinib (RINVOQ®)
Mechanism of action	The JAK family of enzymes (intracellular tyrosine kinases) contains four members, JAK1, JAK2, JAK3 and TYK2, which function as dimers to phosphorylate and activate STATs (14, 15) and potentiate inflammatory cytokine signals (16). UPA is a selective and reversible oral JAK inhibitor which has been engineered to have greater affinity for JAK1(17). The JAK1 selectivity of UPA has the potential to reduce off-target side effects related to JAK2 and JAK3 inhibition (18). Pro-inflammatory cytokines (including IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 and IFN- γ) transduce signals via the JAK1 pathway and are understood to play a role in the pathogenesis of CD (19, 20). JAK1 inhibition with UPA modulates the signalling of JAK-dependent cytokines and thus reduces the inflammatory burden which, in turn, reduces the signs and symptoms associated with CD.
Marketing authorisation/CE mark status	A marketing authorisation application was filed with the EMA in [redacted]. CHMP positive option is anticipated in [redacted] with marketing authorisation expected to be granted by the European Commission in [redacted]. A marketing authorisation application was filed with the MHRA in [redacted] with marketing authorisation in Great Britain expected to be granted in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication for UPA is as follows: [redacted] This submission covers a subpopulation of this indication: • People with moderately to severely active CD in whom TNF-alpha inhibitors are deemed unsuitable; or where biological treatment is not tolerated or not working well enough

Method of administration and dosage	UPA is administered orally and available as 15 mg, 30 mg and 45mg prolonged-release tablets (21, 22).
	Induction
	• 45 mg once daily for 12 weeks.
	Maintenance
	• 15 mg or 30 mg once daily based on individual patient presentation:
	  ○ A dose of 30 mg once daily is recommended for patients who have not achieved adequate therapeutic benefit after the initial 12-week induction. For these patients, UPA should be discontinued if there is no evidence of therapeutic benefit after 24 weeks of treatment.
	  ○ A dose of 30 mg once daily may be appropriate for patients with high disease burden or those who do not show adequate therapeutic benefit with 15 mg once daily.
	  ○ The lowest effective dose for maintenance should be used.
	  ○ For patients ≥65 years of age, the recommended maintenance dose is 15 mg once daily.
	  ○ In patients who are responding to induction or maintenance treatment with UPA, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Additional tests or investigations	UPA treatment should be interrupted in patients with ALC <0.5 x 10^9 cells/L, ANC <1 x 10^9 cells/L, or Hb levels <8 g/dL; UPA treatment can be restarted once these levels are restored. UPA should be temporarily interrupted if drug-induced liver injury is suspected. Patients should be managed according to international clinical guidelines for hyperlipidaemia. As such, routine blood workup would be performed on patients with active disease who are eligible to receive UPA. However, patients would receive these tests as part of routine clinical practice and so additional tests or investigations beyond this would not be needed for patients receiving UPA.
List price and average cost of a course of treatment	UPA is commercially available as a pack of 28 x 15 mg tablets at a list price of £805.56 per pack, and as pack of 28 x 30 mg tablets at a list price of £1,281.54 per pack. UPA is also anticipated to be commercially available as a pack of 28 x 45 mg tablets at a list price of [redacted] per pack. Average cost of course of treatment (1 year): [redacted]
Patient access scheme (if applicable)	There is a simple PAS agreed with NHS England which is reflected in the submission. The PAS equates to an approximate [redacted] discount for each 15 mg, 30 mg, and 45 mg packet. This [redacted] the per packet cost to [redacted] for a 28 x 15 mg packet, to [redacted] for a 28 x 30 mg packet, and to [redacted] for a 28 x 45 mg packet.

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CD, Crohn's disease; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; Hb, haemoglobin; IFN, interferon; IL, interleukin; JAK, Janus kinase; MHRA, Medicines and Healthcare Products Regulatory Agency; PAS, Patient Access Scheme; STAT, signal transducer and activator of transcription; TYK, tyrosine kinase; UPA, upadacitinib.

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

B.1.3.1 Disease burden

CD is a chronic relapsing systemic inflammatory bowel disease (IBD) that can cause inflammation and mucosal ulceration to the entire gastrointestinal tract (from the mouth to the anus), but most commonly affects the distal small intestine. Inflammation affects the whole thickness of the bowel wall (23, 24). The pathogenesis of CD involves the complex interaction of immunological, microbiological, environmental, and genetic factors (23, 25, 26).

Presenting symptoms can be heterogeneous and insidious; common CD symptoms include abdominal pain, diarrhoea, fatigue, weight loss, and blood or mucus in stools (26, 27). Individuals with CD typically suffer from recurrent relapses, with acute exacerbations interspersed with periods of remission (28-30). The symptoms of CD can significantly adversely affect individuals' lives, negatively impacting educational achievements, work productivity, mental health, and quality of life (QoL) (31-36).

Psychological disorders are more prevalent in people with CD compared with matched controls; 60% of people with CD have been reported to experience mental health problems, such as depression and anxiety, when symptoms are active (35-37). Additionally, increased disease activity has been reported to negatively affect individuals' feelings about relationships; people with CD may experience embarrassment and feel socially restricted as a result of symptoms (38).

Symptoms can also lead to extensive use of health services for disease management (33-35, 39). Timely intervention is required to promote mucosal healing and reduce the risk of long-term complications, e.g., development of fibrotic strictures leading to bowel obstruction and penetrating disease resulting in the development of an abscess and/or fistula (abnormal connection between the inflamed intestine and other body sites) (40, 41). Inadequate treatment of mucosal inflammation leads to disease progression and increased likelihood of surgery (42).

B.1.3.2 Epidemiology

The prevalence of CD in the UK in 2021 was 0.35 and 0.44 in men and women, respectively (43). Given the latest population estimates (44), there are an estimated 178,797 people aged ≥18 years with CD in England and 186,067 in England and Wales. Approximately 40% of people with CD in the UK are estimated to have moderately to severely active disease at any time post diagnosis (45, 46). Based on these data, the estimated total prevalent number of people with moderately to severely active CD in England was approximately 71,519 in 2022. In England and Wales, this figure is estimated to be 74,427 people.

It is estimated that [redacted] of patients with moderately to severely active CD are eligible for biologic treatment (47) (more details on the pathway of care, including biologic treatment, are presented in Section B.1.3.4). The proportion of these patients who have failed at least one prior biologic therapy is 66% (48).

In 2021, there were approximately 6,458 diagnosed incident cases of CD (based on a rate of 9 cases per 100,000) (49). Most individuals are diagnosed between 17 and 40 years of age, with incidence peaking at 14.3 per 100,000 person years in this age category in England (49).

B.1.3.3 Economic burden of CD

In 2006, IBD treatment cost the NHS in excess of £700 million (50). The medical requirements of people with CD place a significant burden on healthcare resources, with the average annual cost of care for treating CD in the UK estimated to be £6,156 per person (51). CD is associated with higher rates of primary care visits and emergency attendances compared with matched controls (35). In 2020–2021, there were 132,648 finished consultant episodes and 123,138 hospital admissions related to CD in England (ICD code K50 as the primary diagnosis; note that these data may be slightly different to a 'typical' year due to the impact of COVID-19) (52). Additionally, many people with CD require surgery, which contributes to their healthcare resource use (HCRU); the risk of surgery 5 and 10 years after diagnosis of CD has been reported to be 33.3% and 46.6%, respectively (27, 53, 54). Compared with remission, relapse or flare-up is associated with higher costs for treatment, adverse events and complications (total cost per year: £10,513 versus £1,800 for relapse versus remission) (51), while worsening disease severity is associated with increasing healthcare costs (55).

In addition, CD negatively affects the educational achievements and work productivity of individuals (31). In a study of the long-term impact of CD and ulcerative colitis on the career aspirations, opportunities and choices of individuals aged 16–25 in the UK (N=91), 67% reported that their IBD had delayed or was delaying their education and/or training, while 69% felt IBD prevented them from reaching their full educational potential (31). Similarly, in individuals with CD who were in paid employment (N=744), 40% stated that CD prevented them from pursuing their job of choice, 59% had to reduce working hours due to CD, and 54% reported that CD had an impact on their career progression (31). The negative effect of CD on careers translates into a perceived loss of earning for individuals (31). In a retrospective analysis of people with IBD (N=233), 50% of employed people with CD had some loss of employment days, with a median loss of earnings of £299 over a 6-month period (55). Similarly, significantly higher loss of productivity costs has been reported for the caregivers of people with CD aged ≤18 years compared with controls, highlighting that the indirect costs of CD can extend to caregivers (56).

B.1.3.4 Current pathway of care

CD is not medically or surgically curable. Treatment choices are made according to clinical judgement and individual preference (57). The aim of medical treatment in CD has been focused on maintaining a symptom-free remission state whilst controlling inflammation, reducing risk of complications, and minimising surgery to preserve the patient's nutritional independence by maintaining sufficient intestinal luminal length. Endoscopic outcomes, such as mucosal healing, are now recognised as an important treatment target (evident from the recent update in British Society of Gastroenterology [BSG] guidance) (57-59). This is because mucosal healing is associated with better long-term outcomes, such as reduced risk of relapse, decreased hospitalisation rates, steroid-free remission in follow-up examination, resection free intervals and improved QoL (60, 61).

The treatment guidelines that are considered relevant for moderately to severely active CD in UK clinical practice are listed below:

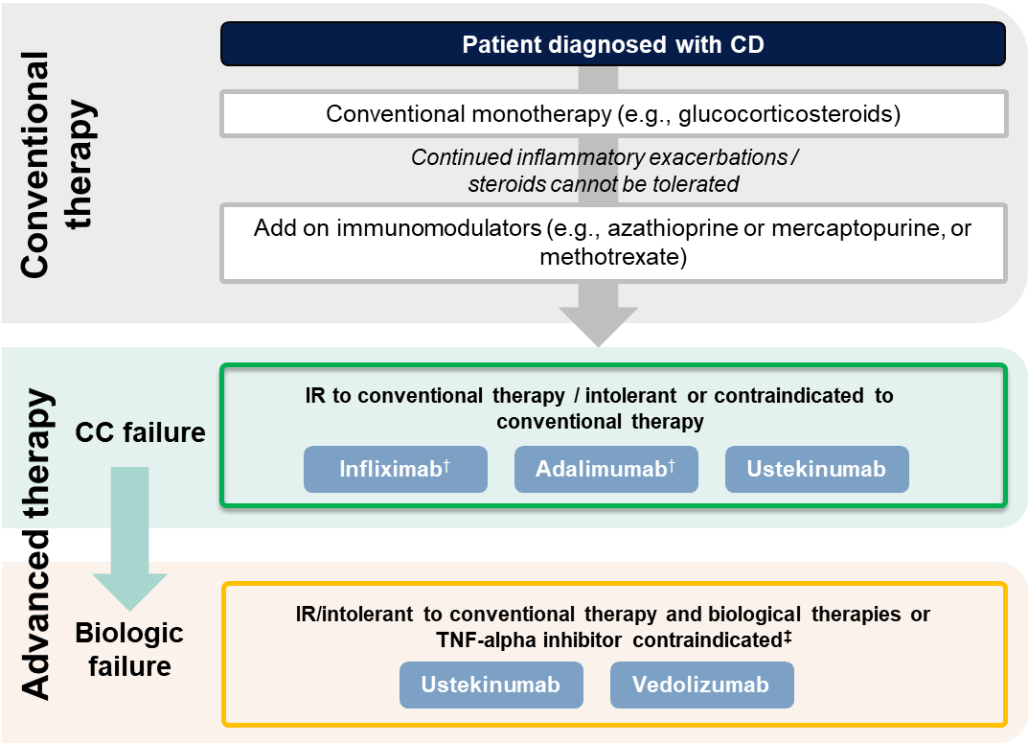
- Crohn's disease: management (NICE guidance, NG129, 2019) (62)
- BSG consensus guidelines on the management of IBD in adults (2019) (57)
- European Crohn's and Colitis Organisation Guidelines on Therapeutics in Crohn's Disease: Medical Treatment (2020) (63)

In England, current NICE guidelines (NG129) for adults recommend initial pharmacotherapy with conventional care to induce remission (initial presentation or during a flare-up), which typically includes corticosteroids (e.g., prednisolone) or aminosalicylates, typically followed by immunomodulators (IMM), such as azathioprine, to maintain remission. IMM can also be given in addition to corticosteroids in the presence of continued inflammatory exacerbations (62). Of note, aminosalicylates are rarely used in UK clinical practice (64) and other treatment guidelines do not recommend their use for CD (57, 63).

Advanced therapies (i.e., biologics in the current pathway of care) are introduced if there is a poor response to initial therapy with conventional care, or if the conventional care therapy is not tolerated, or is contraindicated. Figure 1 summarises the treatment options for patients with moderately to severely active CD who have failed

conventional care (green box) or biologics (orange box) or for whom specific therapies, e.g., TNF-alpha inhibitors, are contraindicated. Guidance from the BSG generally aligns with NICE guidance (57).

Figure 1: Treatment pathway based on CD management guidance by NICE



Abbreviations: CC, conventional care; CD, Crohn's disease; IR, inadequate response/treatment failure; TNF, tumour necrosis factor. Figure adapted from NICE guidance. Source: NICE (2019), Crohn's disease: management (NG129) (62). †Biosimilars are also available. ‡TNF-alpha contraindicated people with CD are considered as part of the biologic failure population. For severe disease, stronger immunosuppressive add-on therapies, such as azathioprine and methotrexate, are used (65).

NICE recommends starting biologic therapy treatment with the least expensive option. After 12 months of treatment with a biologic therapy, clinicians are recommended to assess individuals to determine if they are responding and should continue on the same therapy (62). BSG guidance recommends that the choice between TNF-alpha inhibitor treatment, ustekinumab and vedolizumab should be made on an individual basis, considering individual preference, cost, likely adherence, safety data and speed of response to the drug (57).

Ultimately, clinical management of CD depends on disease activity, site, behaviour of disease (inflammatory, fistulising or stricturing), response to previous treatments, side effect profiles of treatments, patient preference, and extra-intestinal manifestations, such as uveitis and arthritis (57, 62, 66).

Surgery is another treatment option for people with CD (62); the most common reasons for surgery include poor response to drug or nutritional treatment, strictures, and fistulas. The benefits of surgery can include relief from pain, reduction of symptoms (e.g., diarrhoea, vomiting and fatigue), reduction or cessation of treatments which may cause side effects (e.g. steroids), and prevention of delayed growth (67). However, avoidance of surgery is preferable because surgery is not curative and use of biologic therapies may still be required (68). Furthermore, multiple surgeries for CD can result in short bowel syndrome, in which the intestine is shortened and nutrient absorption is impaired (69).

B.1.3.4.1 Dosing of biologic therapies

Dosing of currently available biologic treatments requires induction therapy, where the drug is administered at a higher dose initially to reduce inflammation and improve CD symptoms (i.e., achieve remission). Following induction, a standard dose is administered at regular intervals to maintain control of the disease. There is clinical flexibility for dose escalation of biologics (i.e., IL-12/23 [ustekinumab] and integrin α4β7 [vedolizumab] inhibitors) (70, 71). Specifically, ustekinumab may be initiated at a standard dose (Q12W) or a higher dose (Q8W), and may also be increased from the standard dose (Q12W) to a higher dose during treatment (Q8W) (71, 72). Vedolizumab may also be increased from the standard dose (Q8W) to a higher dose (Q4W) during treatment (70). Vedolizumab SC as maintenance treatment is administered as 108 mg Q2W with no recommended dose escalation (73). Feedback from clinical experts indicates that dose escalation may be necessary in 30% and 92.5% of individuals receiving vedolizumab or ustekinumab, respectively (12).

B.1.3.5 Limitations in current treatment pathway

CD is not always adequately controlled by currently available conventional and biologic therapies; it is estimated that there are approximately 4,000 people in the UK who have had an inadequate response to currently available conventional and biologic therapies[2] (45). Approximately 50% of people with moderately to severely active CD do not respond to or cannot tolerate conventional treatment (74). Although biologic

[2] Figure estimated before the introduction of ustekinumab.

therapies offer additional treatment options, individuals may still experience disease flares resulting in the appearance or worsening of disease symptoms, such as abdominal pain and fatigue, which may require dose escalation, therapy change or treatment with additional therapies, such as corticosteroids (72, 75-78).

Primary non-response to treatment is an issue with biologic therapies. Up to 30% of individuals do not respond to TNF-alpha inhibitor therapy (e.g., infliximab, adalimumab, and their biosimilars) (76). A loss of response rate of approximately 30% at 52 weeks has been reported for vedolizumab (integrin α4β7 inhibitor) and ustekinumab (IL-12/23 inhibitor) (72, 78). Furthermore, in an international online survey (Canada, France, Germany, Italy, Spain, UK and USA) of people with CD, loss of response to prior treatment was reported in 69% of individuals (48).

Another key limitation of existing treatments is their association with adverse side effects leading to potentially increased HCRU and costs. For example, long-term exposure to corticosteroids (often used alongside biologic therapies) may result in an increased risk of numerous adverse events, including infection, psychological disturbances, diabetes, hypertension and osteoporosis (79). TNF-alpha inhibitors are associated with an increased risk of malignancy, demyelination and infection, including tuberculous infection (70, 72, 76).

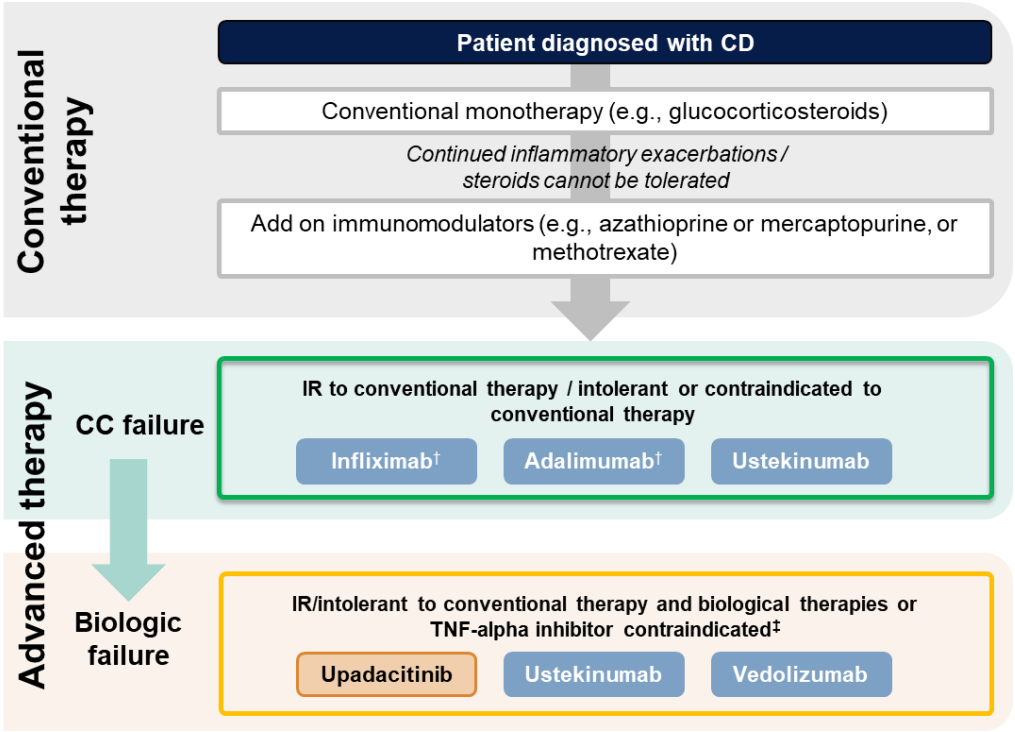
A further limitation of existing treatments is the development of anti-drug antibodies, which may lead to a loss of clinical efficacy (51, 70). The rates of anti-drug antibody development with TNF-alpha inhibitors are high; anti-drug antibody rates of 28.5% and 62.8% have been reported for adalimumab and infliximab, respectively (80).

B.1.3.6 Upadacitinib for the treatment of CD

The proposed positioning of upadacitinib is for people with moderately to severely active CD in whom TNF-alpha inhibitors are deemed unsuitable; or where biological treatment is not tolerated or not working well enough. This is in line with the NICE recommendations for the clinical pathway in moderately to severely active CD (see Section B.1.3.4) and is similar to that of ustekinumab and vedolizumab (Figure 1).

Upadacitinib fulfils an important unmet need by providing a novel therapeutic option for the management of CD patients with an incomplete response to currently available biologic therapies (Figure 2); it will be the first JAK inhibitor and the only oral advanced therapy available for CD. As an oral advanced therapy, upadacitinib can rapidly improve symptoms that significantly impact on the lives of people with CD.

Figure 2: Proposed positioning of upadacitinib in UK treatment pathway for CD



Abbreviations: CC, conventional care; CD, Crohn's disease; IR, inadequate response/treatment failure; TNF, tumour necrosis factor. Figure adapted from NICE guidance. Source: NICE (2019), Crohn's disease: management (NG129) (62). † Biosimilars are also available. ‡ TNF-alpha contraindicated people with CD are considered as part of the biologic failure population, in line with CEM and BIM. For severe disease, stronger immunosuppressive add-on therapies, such as azathioprine, are used (65).

B.1.4 Equality considerations

No equality issues associated with the use of upadacitinib in this indication have been identified or are foreseen.

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

B.2.1 Clinical outcomes and measures

There are two biologic treatments for CD that would be displaced by the introduction of upadacitinib. The relevant NICE technology appraisals for the treatment of adult patients with moderately to severely active CD after prior therapy are:

- TA456: Ustekinumab for moderately to severely active Crohn's disease after prior therapy (published 2017) (45)
- TA352: Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy (published 2015) (46)

B.2.1.1 Clinical outcomes used in the cost-effectiveness analyses

B.2.1.1.1 Clinical effectiveness

Key outcomes evaluated in RCTs to assess efficacy of treatments for CD include clinical response and clinical remission, with CD disease activity historically using the CDAI score. The definitions of clinical response and remission were consistent across the ustekinumab and vedolizumab CD RCTs and are presented in Table 3. More details of these severity measures are presented in Appendix K.

Table 3: Definitions of clinical response and remission in VDZ and UST trials

Endpoint	Definitions used across UST and VDZ RCTs (as well as UPA RCTs)
Clinical remission	CDAI score <150
Clinical response	Decrease of ≥100 points in CDAI from baseline (CR-100) Decrease of ≥70 points in CDAI from baseline (CR-70)

Abbreviations: CDAI, Crohn's Disease Activity Index; RCT, randomised controlled trial; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

The ustekinumab and vedolizumab submissions used two definitions of clinical response. CR-100 (decrease of ≥100 points in CDAI from baseline) was used as a definition of clinical response in both the vedolizumab and ustekinumab clinical trials. In the cost-effectiveness analysis, vedolizumab used CR-70 as the definition of clinical response (to aid comparison with other treatments) while ustekinumab used CR-100 in the base-case analysis, with CR-70 used in a scenario.

Although CDAI is not commonly used as a measure to assess disease severity in UK clinical practice, it is the measure most frequently used in clinical trials for this indication, including in the vedolizumab and ustekinumab trials (57, 81, 82). In UK clinical practice, the Harvey Bradshaw Index (HBI), a simplified and less comprehensive tool than the CDAI is more frequently used to measure disease severity due to its ease of use (83). Studies have shown that results from the HBI correlate with CDAI results (83, 84). Furthermore, committees accepted the use of CDAI in the ustekinumab and vedolizumab submissions given its historic use in assessing response to other biologic treatments, as well as it being a clinically valid and comprehensive tool for CD assessment.

B.2.1.1.2 Safety

In addition to clinical response and remission, the incidence of AEs and discontinuation rates were included in the cost-effectiveness models. Both ustekinumab and vedolizumab appraisals incorporated AEs (selected based on expert opinion and sourced using the same criteria) in their cost-effectiveness analyses. Ustekinumab excluded AEs in a scenario analysis to assess the impact on the incremental cost-effectiveness ratio (ICER), which was negligible. Discontinuation rates due to lack of efficacy were included and based on clinical trial data. Vedolizumab also included discontinuations due to AEs. Discontinuation rates or AE rates did not have a major impact on ICERs across the different populations. Table 4 summarises the key clinical outcome measures in the relevant NICE TAs.

B.2.1.2 Key clinical drivers of the cost-effectiveness analyses

In both the appraisals listed (TA456 and TA352), sensitivity and scenario analyses were conducted to identify key drivers of cost effectiveness. For vedolizumab (TA352) in comparison with TNF-alpha inhibitors (infliximab and adalimumab), the variables with the largest impact on the ICER were the transition probabilities (particularly for remission), the vedolizumab/infliximab/adalimumab efficacy data, and health state costs. For ustekinumab (TA456) the variables with the largest impact on the ICER were treatment duration (largest impact; versus adalimumab) as well as efficacy and extent of resource use for the moderate-to-severe health state (versus adalimumab and vedolizumab).

Table 4: Clinical outcomes and measures appraised in published NICE guidance for the comparator(s)

	Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER	Committee's preferred assumptions	Uncertainties raised by ERG
NICE TA456 (45)	Treatment response	CDAI-100 and CDAI-70	**Base case:** CDAI-100 **Scenario:** CDAI-70 Response rates sourced from UST trials	Substantial - induction efficacy had one of the largest impacts	The committee accepted that the use of the CDAI was acceptable given its historic use in assessing response to other biological treatments	NA
	Remission	CDAI	Remission rates sourced from UST trials (CDAI <150)	Substantial - induction efficacy had one of the largest impacts	The ERG had concerns regarding the transition probabilities used in the model, including those used for remission rates, which may have led to an overestimation of the cost-effectiveness of ustekinumab	Considerable uncertainty due to a combination of trial design, NMA inputs, and constraints imposed by calibration method
	Surgery	Annual rate	Annual rate of 7% sourced from HES data	Moderate – amending the annual surgery rate had a small impact	In the ERG model, the cost of surgery was only applied in the cycle of transition to surgery to avoid double counting of surgery costs	The model did not capture the change in disease course that surgery may cause
	AEs of treatment and surgical complications	AE rates from clinical trials	**Base case:** AEs included **Scenario:** AEs excluded Selected AEs based on expert opinion and sourced using the same criteria as TA352	No impact	Not discussed in detail; inferred that base case was accepted by ERG	NA
	Mortality	All-cause mortality	All-cause mortality rate sourced from ONS life tables for England and Wales, with no differential mortality for CD patients (as this approach was criticised in TA352)	Unclear/not assessed	Committee did not investigate the impact of CD-related mortality	NA
	Treatment discontinuation	Discontinuation due to lack of efficacy	Applied using data from IM-UNITI trial for UST and trials of comparators (ACCENT I for IFX and GEMINI II for VDZ). Percentage of patients who discontinued	Unclear/not assessed	The ERG preferred for discontinuation due to lack of efficacy to also be possible in the maintenance phase of the model rather than induction alone	In the model, once patients have discontinued, they move onto conventional care for the remainder of the time horizon or until death. This may underestimate the true proportion of patients

	Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER	Committee's preferred assumptions	Uncertainties raised by ERG
			converted into instantaneous rate followed by a per-cycle probability of discontinuation occurring using an exponential formula			discontinuing as the rate is only applied to patients in the moderate to severe state. Furthermore, it was not possible to know the percentage of patients in the moderate to severe state over time from the study data
NICE TA352 (46)	Treatment response	CDAI-70	Clinical response: CDAI-70	Substantial	The ERG preferred the use of assessment at week 10 rather than week 6 as was submitted in the base case	Definition of response may have limited relevance to English clinical practice as CDAI scores are not routinely used
	Remission	CDAI	CDAI <150 used to assess remission rates	Substantial	The ERG noted that the proportion of patients in remission who were on conventional non-biologic therapies was greater in GEMINI II than in the economic model, which underestimated efficacy of these treatments. This was because the model used data from the maintenance phase in patients who initially responded to VDZ rather than patients on placebo, and that the observed data for the placebo arm of the GEMINI II trial should be used instead.	Use of the ERG's preferred assumption may underestimate the efficacy of conventional non-biologic therapies
	Treatment discontinuation	Discontinuation due to lack of response or AEs	As not all trials reported discontinuation data, the data used in the model reflect trials that did report discontinuation due to AEs	Minimal	Discontinuation due to lack of efficacy in the maintenance phase was not included in the model and the ERG believed it should be incorporated It was assumed that there was no increase in relapse after withdrawal of biological treatment in patients in the remission or mild disease health states, which was not aligned with clinical expert opinion received by the ERG	NA
	Surgery	Rate and costs of surgery	As surgery was included as a health state and	Use of the updated surgery	Surgery was modelled as a single health state and may be overly simplistic as	NA

	Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER	Committee's preferred assumptions	Uncertainties raised by ERG
			postsurgical health states were not modelled, the incidence of surgical complications was included within the surgery health state	costs resulted in a minimal reduction in the ICER (reduction from £21,620 to £20,344 per QALY)	subsequent surgery is likely to depend on the type of initial surgery. However, the ERG recognised that this was likely due to a lack of data and believed the impact on results would be minimal The ERG used the rates from the GEMINI trial rather than the HES-based estimates used in the company's submission. The ERG advised that the costs of surgery should be decreased following an analysis of HES data	
	Mortality	Annual mortality rate calculated using ONS mortality rates and then adjusted for each model health state according to the published literature to give a relative risk	Starting annual mortality rate of 0.0015 (UK general population rate)	Minimal	The ERG believed that the same excess risk mortality should be applied to all CD health states	The model predicted better survival for patients on biologic vs conventional therapy. However, the study used by the company in its model did not show any statistical differences in the excess mortality rates according to disease severity at baseline, or in mortality between patients who did or did not receive IFX.
	AEs	AE rates from clinical trials	Selected AEs based on expert opinion	Minimal	No further critique was provided by the ERG	It was not clear if all or only Grade 3 or 4 AEs were included in the model. The ERG found the calculations to be simplistic and likely to be inaccurate as they did not account for trial duration. It was also unclear why the incidence of serious AEs was not used in the model.

Abbreviations: AE, adverse event; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; ERG, Evidence Review Group; HES, Hospital Episode Statistics; ICER; incremental cost-effectiveness ratio; IFX, infliximab; NA, not applicable; ONS, Office for National Statistics; QALY, quality-adjusted life year; TA; technology appraisal, UST, ustekinumab; VDZ, vedolizumab.

B.2.2 Resource use assumptions

Resource use considered in the relevant NICE technology appraisals listed in Section B.2.1 is shown in Table 5.

Table 5: Resource use considered in relevant NICE technology appraisals

	Resource use costs considered	Committee comments
TA456 (45)	• Drug acquisition (intervention, comparators, conventional care)	• The ERG did not agree with the company's assumption that patients on biologic therapy would receive concomitant conventional care therapies at 50% of the dose, although this was not expected to impact the ICER • The ERG felt that there was a mismatch between the effectiveness data and the cost data used (as the costs did not reflect what was actually received by patients in the conventional care arm of the UNITI trials), although this was not expected to impact the ICER
	• Treatment administration o VDZ, IFX and induction UST are administered as IV infusion o Maintenance UST and all ADA are administered by SC injection	• No concerns
	• Surgery (combining cost of surgical procedures and surgical complications) o Resource use estimates gathered via Delphi panel o Clinicians divided surgical procedure resource use according to length of stay and this was used to calculate a weighted average cost (20% day case; 10% <5 days; 70% >5 days) o Costs of surgical complications were added to the weighted surgery cost to give a total surgery cost	• The ERG noted that additional surgical costs were included in health state costs and all patients in all health states may undergo surgery independent of the separate surgery health state • This led to the potential for double counting of surgery costs given the separate surgery health state, although the company stated that the Delphi panel were aware of the separate surgery health state and felt the additional costs were appropriate • The additional costs were excluded in a scenario analysis and the ERG felt this was more representative of clinical practice, and preferred the base case costs used in TA352 • There were no concerns regarding the costs of surgical complications
	• Adverse reactions • Five AEs were included: serious infection, TB, hypersensitivity, injection site reactions, and lymphoma	• The company used an injection site reaction cost of £5,240 which the ERG noted was considerably higher than the £1,363 value used in TA352 • An alternative injection site reaction cost of £1,621 was applied by the ERG

	Resource use costs considered	Committee comments

TA352 (46)	• Drug acquisition (intervention, comparators, conventional care)
	  ○ Patients on biologic therapy were also assumed to require conventional therapy
		• The calculated drug acquisition costs were conditional on the treatment regimen assumed within the company's model. The ERG had some concerns with the treatment regimen assumed, notably for VDZ and ADA for the induction phase
		• The ERG also noted that the drug acquisition cost for IFX is conditional on the patient weight. The ERG believes that using the mean weight is not appropriate and that the distribution of patients within weight band should be used instead; it is unclear whether the drug acquisition for IFX would be affected
		• The ERG questioned the arbitrary (not justified in the company submission) assumption that whilst patients are receiving biologic therapy, the costs associated with conventional non-biologic therapy will be halved (concomitant therapy)
		  ○ A scenario was submitted during CQs with 100% of patients on biologic therapy also receiving conventional therapy; the impact on ICERs was minimal

	• IV drug administration	• The ERG was satisfied with the administration cost estimate assumed by the company
	• Surgery ○ Included cost of treating surgical complications (wound infection, prolonged ileus/bowel obstruction, intraabdominal abscess, anastomotic leak)	• The company included an additional cost for complications due to surgery. It is unclear from the Bodger study whether the costs associated with complications due to surgery are already included in the health state cost • There were no details on which resources were included in the health states

	• Adverse events
	  ○ Five AEs were included: serious infection, TB, hypersensitivity, injection site reactions, and lymphoma
	  ○ It was assumed that all patients with these AEs required hospitalisation
		• The ERG noted that the latest NHS reference costs were not included, but the ERG had no comments following CQs and was satisfied with the inclusion of serious AEs requiring hospitalisation only

Abbreviations: ADA, adalimumab; AE, adverse event; CQs, clarification questions; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; IFX, infliximab; IV, intravenous; SC, subcutaneous; TB, tuberculosis; UST, ustekinumab; VDZ, vedolizumab.

B.3 Clinical effectiveness

Evidence for upadacitinib in moderately to severely active CD patients

The Phase 3 pivotal induction studies (U-EXCEL and U-EXCEED) and maintenance study (U-ENDURE) provide the clinical evidence for upadacitinib for the treatment of moderately to severely active CD.

- U-EXCEL and U-EXCEED were Phase 3, multicentre, randomised, double-blind 12-week induction studies that evaluated the efficacy and safety of upadacitinib 45 mg QD versus placebo in adults with moderately to severely active CD
- U-EXCEL enrolled subjects with either inadequate response/intolerance to prior biologic therapy (Bio-IR) or with inadequate response/intolerance to conventional therapy (non-Bio-IR) for CD, while U-EXCEED enrolled subjects with only a documented inadequate response or intolerance to ≥1 biologic therapy for CD (Bio-IR)
    - Subjects in the double-blind upadacitinib 45 mg arms who did not achieve clinical response at Week 12 subsequently received upadacitinib 30 mg QD for 12 weeks (i.e., until Week 24) in an extended induction period. Subjects who received double-blind placebo and did not achieve clinical response subsequently received upadacitinib 45 mg QD for 12 weeks (i.e., until Week 24)
- U-ENDURE is a Phase 3, multicentre, randomised, double-blind maintenance study (with an ongoing open-label extension phase) to evaluate the efficacy and safety of upadacitinib 30 mg or 15 mg QD in subjects with moderately to severely active CD. The study enrolled subjects who achieved clinical response in U-EXCEL or U-EXCEED
- Subjects who achieved clinical response to upadacitinib 45 mg after 12 weeks of induction treatment (at either Week 12 or Week 24) in U-EXCEL or U-EXCEED were rerandomised 1:1:1 to receive upadacitinib 30 mg QD, upadacitinib 15 mg QD, or placebo

Definition of subpopulation of interest

The naming convention used to describe the population of interest in the pivotal upadacitinib clinical trials in CD (Bio-IR) is different from that used in previous TAs for this indication (biologic failure [BF]). The definition of this specific population is as follows: subjects with documented intolerance or IR (either failure to respond to induction treatment, or loss of response to maintenance therapy) to one or more biologics for CD (infliximab, adalimumab, certolizumab, natalizumab, vedolizumab, and/or ustekinumab). This population is analogous to the BF population which has been described in previous submissions. Consequently, the Bio-IR naming convention is used in the context of the upadacitinib clinical trials only, whilst through the remainder of the submission (i.e., the NMA and cost comparison model), BF is used for consistency with previous TAs.

The population referred to in previous TAs as conventional care failure (CCF) is referred to as non-Bio-IR in the upadacitinib clinical trials; data on this population are presented in Appendix J for completeness†.

Efficacy

- In the induction studies (U-EXCEL and U-EXCEED), a significantly greater proportion of patients achieved the co-primary endpoints (CDAI clinical remission‡ and endoscopic response§) with upadacitinib 45 mg compared with placebo
- Symptomatic improvements were observed as early as Week 2 (CDAI clinical response) and Week 4 (CDAI clinical remission) with upadacitinib 45 mg
- Significantly more patients receiving upadacitinib achieved endoscopic remission at Week 12 compared with the placebo group in both U-EXCEL and U-EXCEED
- In the maintenance study (U-ENDURE), symptomatic and endoscopic improvements were observed after 52 weeks of treatment with upadacitinib 30 mg or 15 mg
- Rates of steroid-free remission (discontinuation of corticosteroids and achievement of CDAI clinical remission) were significantly higher with upadacitinib versus placebo in both induction studies (U-EXCEL and U-EXCEED) and the maintenance study (U-ENDURE)
- Improvements in HRQoL (assessed using EQ-5D-5L) with upadacitinib were observed as early as Week 4 in the induction studies and persisted to Week 52 of the maintenance study

Safety

- Across the induction (U-EXCEL and U-EXCEED) and maintenance (U-ENDURE) studies, upadacitinib was generally safe and well-tolerated with no new safety risks observed compared with the known safety profile of upadacitinib

Indirect treatment comparison

- In induction NMAs in the BF population, upadacitinib demonstrated superior efficacy to ustekinumab and vedolizumab (as well as to placebo) for CDAI clinical remission and CDAI clinical response
- In the maintenance NMA in the BF population, upadacitinib generally showed superior efficacy to comparators for CDAI clinical remission (the only efficacy outcome assessed)
- In the safety NMAs, upadacitinib showed comparable rates of serious AEs and discontinuation due to AEs compared with all comparators, including placebo

‡CDAI clinical remission defined as CDAI score <150. §Endoscopic response defined as decrease in SES-CD of >50% from baseline of the induction study or for subjects with an SES-CD of 4 at baseline, ≥2-point reduction from baseline, as scored by central reviewer. †Non-Bio-IR: Subjects who had an inadequate response or intolerance to conventional therapy, defined as one or more of the following: aminosalicylates, oral locally acting steroids [e.g., budesonide, beclomethasone], systemic corticosteroids [prednisone or equivalent], or immunomodulators. This population may also include subjects who had received biologic therapy in the past but stopped therapy based on reasons other than inadequate response or intolerance (e.g., change in reimbursement coverage, well-controlled disease); however, the majority of subjects had not received a prior biologic therapy (in U-EXCEL, 8.5% and 9.2% of the upadacitinib and placebo non-Bio-IR groups had received a prior biologic; in U-ENDURE, 14.6% of the upadacitinib 30 mg group and 11.1% of the upadacitinib groups had received a prior biologic; no patients in the placebo group of U-ENDURE had received a prior biologic). This population is analogous to the CCF population which has been described in previous submissions.

B.3.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant clinical evidence on the efficacy and safety of upadacitinib and relevant comparators for the treatment of people aged ≥16 years with moderately to severely active CD; the aim was to identify data to facilitate indirect comparison (via NMA) between upadacitinib and comparators. An overview of the methodology, including search strategy, PRISMA flow diagram, list of included studies and list of excluded studies at full text review is provided in Appendix D.

The SLR identified clinicaltrial.gov entries for the upadacitinib clinical trials; however, data for upadacitinib were derived from clinical study reports (CSRs).

B.3.2 List of relevant clinical effectiveness evidence

A summary of the clinical effectiveness evidence for upadacitinib is provided in Table 6, Table 7 and Table 8.

In all of the clinical trials, upadacitinib was compared against placebo. No head-to-head data were available for upadacitinib versus ustekinumab and vedolizumab (the comparators of interest for this submission). Therefore, an NMA was performed to indirectly compare upadacitinib with ustekinumab and vedolizumab (see Section B.3.9).

Table 6: Clinical effectiveness evidence – U-EXCEL (induction study)

Study	U-EXCEL (M14-433)				
Study design	Phase 3, multicentre, randomised, double-blind, placebo-controlled induction study				
Population	Adults with moderately to severely active CD who had inadequately responded to or were intolerant to prior biologic therapy (Bio-IR population), or who had inadequately responded to or were intolerant to conventional therapy (non-Bio-IR population)				
Intervention(s)	Part 1: UPA 45 mg QD p.o. for 12 weeks† Part 2: UPA 45 mg or 30 mg QD p.o. for 12 weeks‡				
Comparator(s)	PBO QD p.o.				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if the trial is used in the economic model**	Yes	✓
	No			No	
Reported outcomes specified in the decision problem	• Disease activity (remission, response) • Endoscopic outcomes • Hospitalisation rates • Adverse effects of treatment • Health-related quality of life				

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CD, Crohn's disease; CSR, clinical study report; non-Bio-IR, conventional therapy inadequate response/intolerance; PBO, placebo; p.o., per os (orally); QD, once daily; UPA, upadacitinib.
Source: U-EXCEL CSR (85). †Part 1 refers to the initial induction period of 12 weeks into which all eligible subjects were enrolled. ‡Part 2 refers to the extended treatment period of 12 weeks that only included clinical non-responders from Part 1.

Table 7: Clinical effectiveness evidence – U-EXCEED (induction study)

Study	U-EXCEED (M-14-431)				
Study design	Phase 3, multicentre, randomised, double-blind, placebo-controlled induction study				
Population	Adults with moderately to severely active CD who had inadequately responded to or were intolerant to prior biologic therapy (Bio-IR population)				
Intervention(s)	Part 1: UPA 45 mg QD p.o. for 12 weeks† Part 2: UPA 45 mg QD p.o. for 12 weeks‡ Part 3: UPA 45 mg or 30 mg QD p.o. for 12 weeks§				
Comparator(s)	PBO QD p.o.				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if the trial is used in the economic model**	Yes	✓
	No			No	
Reported outcomes specified in the decision problem	• Disease activity (remission, response) • Endoscopic outcomes • Hospitalisation rates • Adverse effects of treatment • Health-related quality of life				

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CD, Crohn's disease; PBO, placebo; p.o., per os (orally); QD, once daily; UPA, upadacitinib.
Source: U-EXCEED CSR (86). †Part 1 refers to the initial 12-week double-blind induction period into which all eligible subjects were enrolled until sufficient subject numbers were achieved. ‡Part 2 refers to the open-label 12-week induction period that was included to ensure sufficient subject numbers for the U-ENDURE maintenance study. §Part 3 refers to the extended treatment period of 12 weeks that only included clinical non-responders from Part 1 and Part 2.

Table 8: Clinical effectiveness evidence – U-ENDURE (maintenance study)

Study	U-ENDURE (M14-430)				
Study design	Phase 3, multicentre, randomised, double-blind, placebo-controlled maintenance study				
Population	Adults with moderately to severely active CD who achieved clinical response and completed the induction studies U-EXCEL or U-ENDURE (includes Bio-IR and non-Bio-IR populations)				
Intervention(s)	UPA 15 mg QD p.o. UPA 30 mg QD p.o.				
Comparator(s)	PBO QD p.o.				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if the trial is used in the economic model**	Yes	✓
	No			No	
Reported outcomes specified in the decision problem	• Disease activity (remission, response) • Endoscopic outcomes • Hospitalisation rates • Adverse effects of treatment • Health-related quality of life				

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CD, Crohn's disease; CSR, clinical study report; non-Bio-IR, conventional therapy inadequate response/intolerance; PBO, placebo; p.o., per os (orally); QD, once daily; UPA, upadacitinib.
Source: U-ENDURE CSR (87)

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

B.3.3.1 Upadacitinib randomised controlled trials

B.3.3.1.1 Induction studies (U-EXCEL and U-EXCEED)

U-EXCEL and U-EXCEED were Phase 3, randomised, double-blind induction studies that evaluated the efficacy and safety of upadacitinib 45 mg QD versus matched placebo in adults with moderately to severely active CD (85, 86). The population of U-EXCEL comprised subjects with an inadequate response or intolerance to prior biologic therapy (Bio-IR) or with an inadequate response or intolerance to conventional therapy (non-Bio-IR). The population of U-EXCEED comprised subjects with an inadequate response or intolerance to prior biologic therapy (Bio-IR). These populations were defined as follows:

- **Bio-IR population:** included subjects with a documented inadequate response or intolerance to one or more prior biologic therapies for CD (infliximab, adalimumab,

certolizumab, natalizumab, vedolizumab, and/or ustekinumab) (see Appendix J for full details of inclusion criteria).

- **Non-Bio-IR population**: included subjects with a documented inadequate response or intolerance to one or more prior conventional therapies for CD, defined as oral locally acting steroids (budesonide, beclomethasone); IV or oral corticosteroids (prednisone or equivalent); and/or immunosuppressants (azathioprine, mercaptopurine, methotrexate, tacrolimus). The non-Bio-IR population included subjects who may have received a prior biologic therapy for up to 1 year but discontinued for reasons other than intolerance or inadequate response, e.g., a change in insurance or achieving well-controlled disease.

B.3.3.1.1.1 U-EXCEL

U-EXCEL consisted of two parts:

- **Part 1:** randomised, double-blind, placebo-controlled induction period
- **Part 2:** extended induction period for non-responders from Part 1

In Part 1, subjects were randomised in a 2:1 ratio to receive either upadacitinib 45 mg QD or matched placebo for 12 weeks. Randomisation was stratified by baseline corticosteroid use (yes or no), endoscopic disease severity (SES-CD <15 or ≥15), and number of prior biologic treatments (0, 1, >1). At Week 12, subjects who achieved a clinical response were eligible to enter the 52-week U-ENDURE maintenance study (see Section B.3.3.1.2). Clinical response was defined as ≥30% decrease in average daily very soft or liquid stool frequency (SF) and/or ≥30% decrease in average daily abdominal pain (AP) score (both not worse than baseline) (note that this is different from the definition of clinical response as a trial endpoint, see Section B.3.3.3).

Subjects who did not achieve a clinical response at Week 12 of Part 1 were enrolled in Part 2, a 12-week extended induction period. The objectives of Part 2 were to offer blinded upadacitinib induction treatment to placebo non-responders from Part 1 and evaluate delayed response in subjects who did not initially respond to upadacitinib during Part 1.

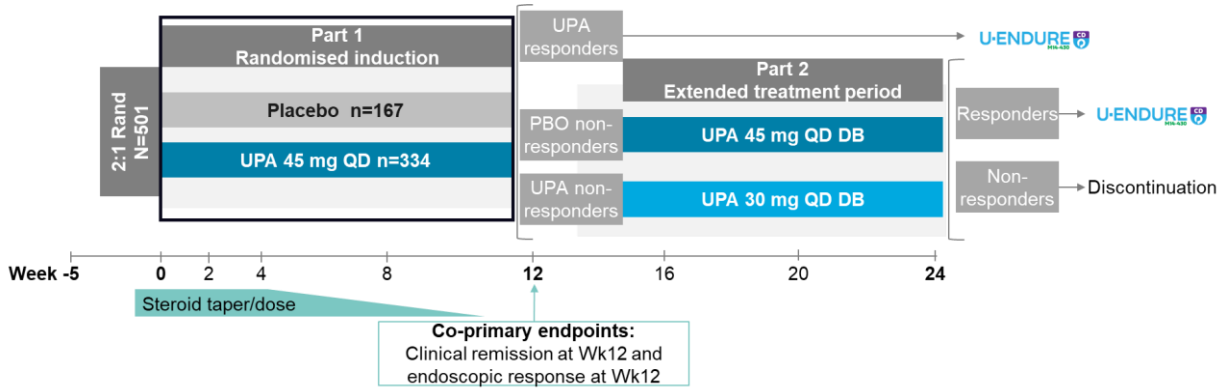
Treatment allocation in Part 2 was as follows:

- **Cohort 1 (subjects who received placebo in Part 1)**: double-blind induction treatment with upadacitinib 45 mg QD for 12 weeks (i.e., until Week 24)
- **Cohort 2 (subjects who received upadacitinib in Part 1)**: double-blind upadacitinib 30 mg QD for 12 weeks (i.e., until Week 24)

At Week 24, subjects who achieved clinical response in Part 2 were also eligible to enter U-ENDURE (see Section B.3.3.1.2). Subjects who did not achieve clinical response were discontinued from the programme and received standard or care at the investigator's discretion. Data collected from subjects in Part 2 were not part of the primary efficacy analyses for U-EXCEL and are presented in Appendix J.

The study design for U-EXCEL is summarised in Figure 3.

Figure 3: U-EXCEL study design



Abbreviations: DB, double blind; OL, open label; QD, once daily; Rand, randomisation; UPA, upadacitinib.

B.3.3.1.1.2 U-EXCEED

U-EXCEED was divided into three parts:

- **Part 1:** randomised, double-blind, placebo-controlled induction period
- **Part 2:** open-label, single arm active induction period
- **Part 3:** extended induction period for non-responders from Part 1 or Part 2

In Part 1, subjects were randomised in a 2:1 ratio to receive either upadacitinib 45 mg QD or matched placebo for 12 weeks. Randomisation was stratified by baseline corticosteroid use (yes or no), endoscopic disease severity (SES-CD <15 or ≥15), and number of prior biologic treatments (>1 or ≤1).

Once Part 1 enrolment was completed, subjects were enrolled in Part 2 to receive open-label upadacitinib 45 mg QD for 12 weeks. The objective of Part 2 was to have sufficient subjects with a clinical response who could be re-randomised in the double-blind maintenance phase of the 52-week U-ENDURE study, while also minimising unnecessary exposure to placebo. Data collected from subjects in Part 2 were not part of the primary efficacy analyses for U-EXCEED and are not presented in this submission.

At Week 12 in Part 1 and Part 2, subjects who achieved clinical response were eligible to enter the 52-week U-ENDURE maintenance study (see Section B.3.3.1.2). Clinical response was defined as ≥30% decrease in average daily very soft or liquid SF and/or ≥30% decrease in average daily AP score (both not worse than baseline). Subjects who did not achieve clinical response were eligible to enter Part 3 of U-EXCEED, an extended 12-week induction period with three cohorts. The objectives of Part 3 were to offer blinded upadacitinib induction treatment to placebo non-responders from Part 1 and to evaluate delayed clinical response to upadacitinib in subjects who did not initially respond to upadacitinib during Part 1 or Part 2.

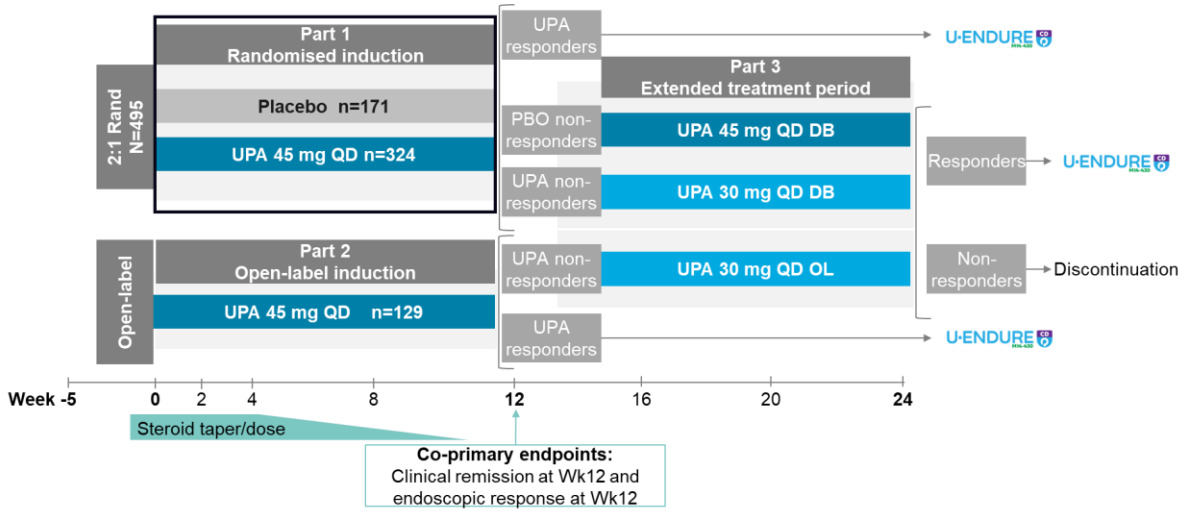
Treatment allocation for each cohort in Part 3 was as follows:

- **Cohort 1 (subjects who received placebo in Part 1):** double-blind induction treatment with upadacitinib 45 mg QD for 12 weeks (i.e., until Week 24)
- **Cohort 2 (subjects who received upadacitinib 45 mg in Part 1):** double-blind upadacitinib 30 mg QD for 12 weeks (i.e., until Week 24)
- **Cohort 3 (subjects who received upadacitinib 45 mg in Part 2):** open-label upadacitinib 30 mg QD for 12 weeks (i.e., until Week 24)

Subjects in Cohort 1 and Cohort 2 remained blinded to their treatment allocation to avoid unmasking the treatment received in Part 1. At Week 24, subjects who achieved clinical response were eligible to enter U-ENDURE. Subjects without clinical response were discontinued from the program and received standard of care at the investigator's discretion. Data collected from subjects in Part 3 were not part of the primary efficacy analyses for U-EXCEED.

The study design for U-EXCEED is summarised in Figure 4.

Figure 4: U-EXCEED study design



Abbreviations: DB, double blind; OL, open label; QD, once daily; Rand, randomisation; UPA, upadacitinib.

Efficacy and safety analyses for U-EXCEL and U-EXCEED were performed using the ITT1 and SA1 populations, respectively. These populations are defined in Table 9 and all analysis sets from the induction studies are defined in Appendix J.

Table 9: Definitions of analysis sets – U-EXCEL and U-EXCEED

Analysis set	*Definition*
ITT1	• ITT population for Part 1 (12-week double-blind induction period), which included all randomised subjects who received ≥1 dose of study drug in Part 1 • Population used for all efficacy and baseline analyses for Part 1
SA1	• Safety population for Part 1, which included all subjects who received ≥1 dose of study drug in Part 1

Abbreviations: ITT, intention to treat; SA, safety analysis.
Note: For safety populations, subjects were assigned to a treatment group based on the 'as treated' treatment group, which was determined by the most frequent dose regimen received in the analysis period.

B.3.3.1.2 Maintenance study (U-ENDURE)

U-ENDURE comprised two substudies, Substudy 1 (maintenance phase) and Substudy 2 (long-term extension). Long-term extension data are not presented in this submission and therefore 'U-ENDURE' is used to refer to the 52-week maintenance phase of the trial (i.e., Substudy 1).

The U-ENDURE population included subjects who achieved clinical response and completed U-EXCEL or U-EXCEED. As such, the population comprised both Bio-IR and non-Bio-IR subjects.

For U-ENDURE, baseline was defined as the baseline visit of the induction studies (U-EXCEL and U-EXCEED) and Week 0 was defined as the first study visit of U-ENDURE. At Week 0, all subjects were enrolled in U-ENDURE in a blinded fashion to one of 3 cohorts according to their induction treatment history in U-EXCEL or U-EXCEED, as shown in Table 10.

Table 10: U-ENDURE study cohorts

Cohort	Induction treatment and response	U-ENDURE treatment allocation	Analysis set(s)
1	• Clinical response to upadacitinib 45 mg at Week 12 • Clinical response to upadacitinib 45 mg at Week 24 following no clinical response to placebo at Week 12	Randomised 1:1:1 to receive one of the following: • Upadacitinib 30 mg QD • Upadacitinib 15 mg QD • Placebo QD	Primary population for efficacy and safety analyses: • ITT1 (efficacy) • SA1 (safety) (see Table 11 for further details)
2	• Clinical response to placebo at Week 12	• Non-randomised placebo QD	• ITT2 (efficacy) • SA2 (safety) • Data from Cohort 2 are not reported further in this submission
3	• Clinical response to upadacitinib 30 mg at Week 24 following no clinical response to upadacitinib 45 mg at Week 12	• Non-randomised upadacitinib 30 mg QD	• ITT3 (efficacy) • SA3 (safety) • Data from Cohort 3 are not reported further in this submission

Abbreviations: ITT, intention to treat; QD, once daily; SA, safety analysis.
Source: U-ENDURE CSR (87)

Randomisation in Cohort 1 was stratified by Bio-IR and non-Bio-IR status from the induction studies, as well as by patient-reported outcome (PRO) clinical remission and endoscopic response status on entry to U-ENDURE. In line with the study protocol, all primary and secondary efficacy endpoints were analysed in Cohort 1 (ITT1 population, see Table 11), which was planned to include the first 501 patients who were randomised and received at least one dose of study drug. Safety analyses were also conducted in Cohort 1, using the SA1 population (Table 11).

Table 11: Definitions of analysis sets – U-ENDURE

Analysis set	*Definition*
ITT	• All subjects who received ≥1 dose of study drug in U-ENDURE
ITT1	• Subset of ITT population who were the first 502 subjects randomised in Cohort 1 • Primary analysis population in Cohort 1 for efficacy and baseline analyses
SA	• All subjects who received ≥1 dose of study drug in U-ENDURE
SA1	• Subset of SA population who were in Cohort 1 • Primary analysis population in Cohort 1 for safety analyses

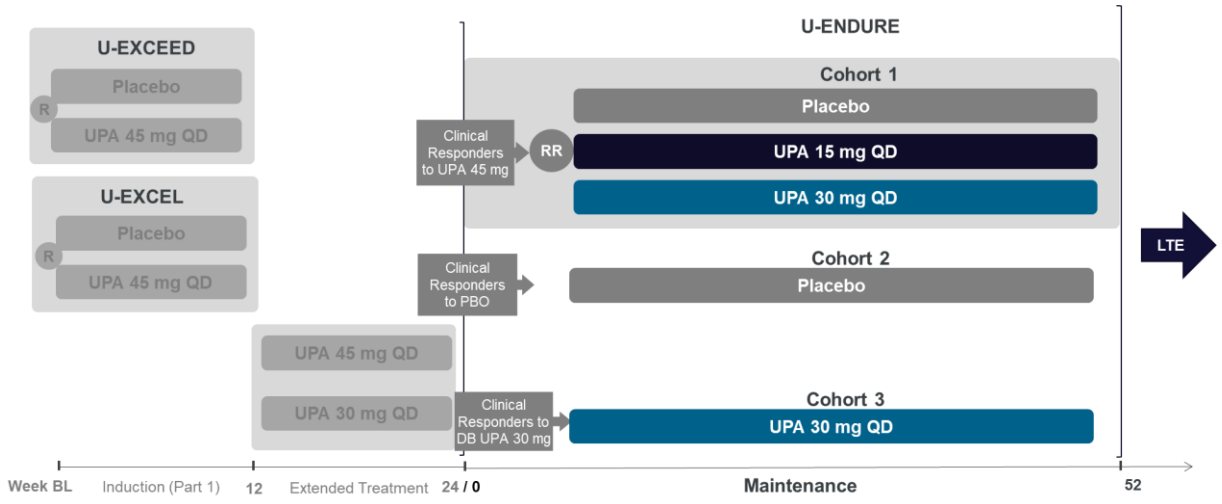
Abbreviations: ITT, intention to treat; SA, safety analysis.

Subjects with persistent symptoms or worsening CD were permitted to discontinue at any time. Subjects were discontinued from the study if they withdrew consent or if they were deemed unsuitable to continue for any reason by the investigator.

At or after Week 4 of U-ENDURE, subjects who met the criteria for inadequate response and required medical treatment were eligible to receive rescue therapy with open-label upadacitinib 30 mg QD from that point forward until the end of follow-up.

The study design for U-ENDURE is summarised in Figure 5.

Figure 5: U-ENDURE study design



Abbreviations: BL, baseline; DB, double-blind; LTE, long-term extension; PBO, placebo; QD, once daily; RR, re-randomisation; UPA, upadacitinib.

B.3.3.2 Comparative summary of trial methodology

An overview of the methodology of the three pivotal upadacitinib studies informing this submission is presented in Table 12.

Table 12: Comparative summary of trial methodology

Trial no. (acronym)	M14-433 (U-EXCEL)	M14-431 (U-EXCEED)	M14-430 (U-ENDURE)
Study objective	To evaluate the efficacy and safety of upadacitinib versus placebo as induction therapy in a Bio-IR and non-Bio-IR population aged ≥18 and ≤75 years with moderately to severely active CD	To evaluate the efficacy and safety of upadacitinib versus placebo as induction therapy in a Bio-IR population aged ≥18 and ≤75 years with moderately to severely active CD	To evaluate the efficacy and safety of two doses of upadacitinib 15 mg and 30 mg QD versus placebo as maintenance therapy in a population with moderately to severely active CD who responded to upadacitinib induction treatment in U-EXCEL or U-EXCEED
Trial design	Phase 3, multicentre, randomised, double-blind, placebo-controlled induction study		Phase 3, multicentre, randomised, double-blind, placebo-controlled maintenance and long-term extension study (note: this submission covers the 52-week maintenance phase only)
Method of randomisation	All subjects were assigned a unique identification number by the IRT at the screening visit and kept the same unique identification number throughout the study. The IRT also assigned each eligible subject a randomisation number that encoded the subject's treatment group assignment according to the randomisation schedule		All subjects kept the same unique identification number that they were assigned in U-EXCEL or U-EXCEED. For randomisation in U-ENDURE, the IRT assigned each subject a randomisation number that encoded the subject's treatment group assignment according to the randomisation schedule
	In Part 1, subjects were randomised in a 2:1 ratio to UPA 45 mg QD or matching placebo. Randomisation was stratified by baseline corticosteroid use (yes or no), endoscopic disease severity (SES-CD <15 and ≥15), and number of prior biologic treatments (0, 1 and >1)	In Part 1, subjects were randomised in a 2:1 ratio to UPA 45 mg QD or matching placebo. Randomisation was stratified by baseline corticosteroid use (yes or no), endoscopic disease severity (SES-CD <15 and ≥15), and number of prior biologic treatments (>1 and ≤1)	Cohort 1 subjects were randomised in a 1:1:1 ratio to receive either upadacitinib 30 mg QD, upadacitinib 15 mg QD, or matching placebo. Randomisation was stratified by prior induction study population ([1] U-EXCEL non-bio-IR, [2] U-EXCEL bio-IR or U-EXCEED Part 1/Part 3, or [3] U-EXCEED Part 2); PRO clinical remission (yes/no), and endoscopic response status (yes/no) at Week 12 or 24 of U-EXCEL or U-EXCEED
Method of blinding (care provider, patient and outcome assessor)	All personnel with direct oversight of the conduct and management of the trial (with the exception of the Drug Supply Management Team), the investigator, study site personnel, and subject remained blinded to each subject's treatment throughout the study. To maintain the blind, UPA and placebo tablets provided for the study were identical in appearance. The IRT provided access to unblinded subject treatment information in case of medical emergency		

<table>
<tr><th>Trial no. (acronym)</th><th colspan="2">M14-433 (U-EXCEL)</th><th>M14-431 (U-EXCEED)</th><th>M14-430 (U-ENDURE)</th></tr>
<tr><td rowspan="3">Eligibility criteria for participants</td><td colspan="3">Key inclusion criteria (see Appendix J for full details):
• Male or female aged ≥18 and ≤75 years or minimum age of adult consent according to local regulations at baseline
• Confirmed diagnosis of CD for ≥3 months prior to baseline
• SES-CD (excluding the presence of narrowing component) ≥6 (or ≥4 for subjects with isolated ileal disease)
• Average daily very soft or liquid SF ≥4.0 and/or average daily AP score ≥2.0 at baseline</td><td rowspan="2">Key inclusion criteria (see Appendix J for full details):
• Clinical response in U-EXCEL or U-EXCEED
• Completed Week 12 (for subjects who achieved response at Week 12) or Week 24 (for subjects who achieved response at Week 24) visit and procedures in U-EXCEL or U-EXCEED
Note: the final endoscopy for U-EXCEL and U-EXCEED may be missing if the endoscopy could not be performed during the COVID-19 pandemic</td></tr>
<tr><td colspan="2">• IR or intolerance to ≥1 conventional and/or biologic therapies: oral locally acting steroids (budesonide, beclomethasone), IV or oral corticosteroids (prednisone), immunosuppressants (AZA, MP, MTX, tacrolimus), and/or biologic therapies for CD (IFX, ADA, CER, VDZ, UST)
• Demonstration of intolerance requires no minimum dose or duration of use</td><td>• IR or intolerance to ≥1 biologic therapy (IFX, ADA, CER, VDZ, UST)
• Demonstration of intolerance requires no minimum dose or duration of use</td></tr>
<tr><td colspan="3">Key exclusion criteria (see Appendix J for full details):
• Subjects who had received any of the following within 8 weeks prior to baseline: ADA, CER, GOL, IFX, NAT, VDZ
• Subjects who had received UST within 12 weeks prior to baseline
• Subjects with JAK inhibitor (e.g. TOF, BAR, FIL) exposure within 30 days of baseline (subjects who received a JAK inhibitor before study entry could be enrolled if they had not had IR or loss of response)
• Subjects who had been on CD-related antibiotics or oral aminosalicylates who had not been on stable doses of these medications for ≥14 days prior to baseline or had discontinued these medications within 14 days of baseline
• Subjects on corticosteroids receiving prednisone or equivalent dose >30 mg/day or budesonide >9 mg/day or who had not been on the current course for ≥14 days prior to baseline and on a stable dose for ≥7 days prior to baseline
• Subjects on MTX who had not been on the current course for ≥42 days prior to baseline and had not been on a stable dose for ≥28 days prior to baseline
• Subjects with ongoing known complications of CD: abdominal or peri-anal abscess; symptomatic bowel strictures; >2 entire missing segments of the terminal ileum, right colon, transverse colon, sigmoid and left colon, or rectum; fulminant colitis; toxic megacolon</td><td>Key exclusion criteria (see Appendix J for full details):
• Hypersensitivity to upadacitinib or its excipients, or an AE in U-EXCEL or U-EXCEED that, in the investigator's judgement, made the subject unsuitable for the maintenance study
• Not in compliance with prior and concomitant medication requirements throughout U-EXCEL or U-EXCEED
• High-grade colonic dysplasia or malignancy diagnosed at the endoscopy performed at the final visit of U-EXCEL or U-EXCEED</td></tr>
</table>

Trial no. (acronym)	M14-433 (U-EXCEL)	M14-431 (U-EXCEED)	M14-430 (U-ENDURE)
Settings and locations where the data were collected	209 sites in 42 countries: Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Chile, China, Croatia, Czech Republic, Denmark, Egypt, France, Germany, Greece, Hungary, Israel, Italy, Japan, Latvia, Lithuania, Malaysia, Mexico, Netherlands, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Turkey, Ukraine, UK, and USA (including Puerto Rico)	229 sites in 39 countries: Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Brazil, Canada, Chile, China, Croatia, Czech Republic, Denmark, Egypt, Estonia, France, Germany, Greece, Hungary, Israel, Italy, Japan, Malaysia, Mexico, Netherlands, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, Slovenia, South Africa, South Korea, Spain, Switzerland, Taiwan, Turkey, UK, and USA (including Puerto Rico)	277 sites in 43 countries: Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Chile, China, Croatia, Czech Republic, Denmark, Egypt, Estonia, France, Germany, Greece, Hungary, Israel, Italy, Japan, Latvia, Lithuania, Malaysia, Mexico, Netherlands, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Turkey, Ukraine, UK, and USA (including Puerto Rico)
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x])	All subjects received one oral tablet daily to be taken with or without food at approximately the same time each day, beginning at the baseline visit Induction period (Part 1, 2:1 randomisation): • Intervention: UPA 45 mg QD (n=350) • Comparator: PBO QD (n=176) Subjects who did not achieve clinical response at Week 12 enrolled in Part 2 (extended induction period) and received blinded treatment with either UPA 45 mg QD (n=57) or UPA 30 mg QD (n=59) according to the treatment received in Part 1	All subjects received one oral tablet daily to be taken with or without food at approximately the same time each day, beginning at the baseline visit Induction period (Part 1, 2:1 randomisation): • Intervention: UPA 45 mg QD (n=324) • Comparator: PBO QD (n=171) Subjects in Part 2 received open-label UPA 45 mg QD (n=129). In Part 3, subjects who did not achieve clinical response with UPA 45 mg or placebo in Part 1 received blinded UPA 30 mg QD (n=69) or 45 mg QD (n=78), respectively. Subjects who did not achieve a clinical response to UPA 45 mg in Part 2 received open-label UPA 30 mg (n=14) in Part 3.	All subjects received one oral tablet daily to be taken with or without food at approximately the same time each day, beginning at Week 0 Maintenance period (Cohort 1, 1:1:1 randomisation): • Intervention: UPA 30 mg QD (n=168) or UPA 15 mg QD (n=169) • Comparator: PBO QD (n=165) Cohort 2 comprised subjects who achieved clinical response with 12-week induction treatment with PBO in U-EXCEL or U-EXCEED; these subjects continued to receive PBO (n=130) Cohort 3 comprised subjects who did not achieve clinical response with 12-week induction treatment with UPA 45 mg QD, but who achieved clinical response after 12 weeks of extended induction treatment with UPA 30 mg QD in U-EXCEL or U-EXCEED; these subjects continued to receive UPA 30 mg QD (n=51)
Permitted and disallowed	Permitted concomitant therapy CD-related medications (antibiotics, aminosalicylates, and/or MTX):		Permitted concomitant therapy CD-related medications (antibiotics, aminosalicylates, and/or MTX):

Trial no. (acronym)	M14-433 (U-EXCEL)	M14-431 (U-EXCEED)	M14-430 (U-ENDURE)
concomitant medications	• Subjects receiving a stable dose of these medications were permitted to continue for the duration of the study • Dose initiation/increases were not permitted • Dose reduction was permitted in the event of moderate-to-severe treatment-related toxicities Corticosteroids: • Subjects who entered the study on oral corticosteroids were not permitted to change dose during the first 4 weeks of induction treatment • Dose reduction was permitted in the event of moderate-to-severe treatment-related toxicities • At Week 4, these subjects had their corticosteroid dose reduced according to a tapering schedule • Subjects who did not achieve a clinical response at Week 12 and entered Part 2 without completing the steroid taper resumed the corticosteroid taper at Week 16, according to the tapering schedule • Locally acting (rectal/suppository) or systemic corticosteroids for any reason were prohibited during the study and were considered a protocol deviation • Use of inhaled or topical (except rectal/suppository) corticosteroids was not restricted • Subjects were not permitted to be on both budesonide (for CD) and prednisone (or equivalent) simultaneously		• Subjects receiving CD-related antibiotics may discontinue treatment starting at Week 0 • All subjects receiving a stable dose of CD-related antibiotics (who did not discontinue), aminosalicylates, or MTX at Week 0 maintained their concomitant treatments and respective doses to the end of the study • Dose reduction was permitted in the event of moderate-to-severe treatment-related toxicities • Dose initiation/increases were not permitted, with the exception of IR and need for rescue therapy Corticosteroids: • At Week 0, subjects taking oral corticosteroids at baseline of U-EXCEL or U-EXCEED, and who initiated but had not completed tapering, continued to have their corticosteroid dose reduced according to a tapering schedule • Initiation of locally acting (rectal or suppository) or systemic corticosteroids was prohibited during the maintenance period, with the exception of demonstrated inadequate response and need for rescue therapy • Use of inhaled or topical (except rectal or suppository) corticosteroids was not restricted • Subjects were not permitted to be on both budesonide (for CD) and prednisone (or equivalent) simultaneously Rescue therapy (see Appendix J for full details) • Subjects who demonstrate IR and require medical treatment may receive rescue therapy with open-label UPA 30 mg QD

Trial no. (acronym)	M14-433 (U-EXCEL)	M14-431 (U-EXCEED)	M14-430 (U-ENDURE)
	Disallowed concomitant therapy • Any biologic therapy, including but not limited to: ADA, etanercept, IFX, abatacept, anakinra, rituximab, NAT, tocilizumab, GOL, CER, UST, belimumab, secukinumab, VDZ • Systemic use of known strong CYP3A inhibitors or inducers • Traditional Chinese medicine • Live vaccines • JAK inhibitors • Cyclosporin, tacrolimus, thalidomide, mycophenolate mofetil, AZA, MP • NSAIDs, except topical NSAIDs and low dose aspirin for cardiovascular protection • Rectal therapy with any therapeutic enemas or suppositories, with the exception of those required for endoscopy • Any parenteral nutrition and exclusive enteral nutrition • Cytapheresis treatment (in Japan and China only) • Cannabis		
Primary outcomes (including scoring methods and timings of assessments)	Co-primary endpoints (see Section B.3.3.3 for interpretation): • CDAI clinical remission at Week 12: CDAI score >150 • PRO clinical remission at Week 12: average daily very soft or liquid SF ≤2.8 and average daily AP score ≤1.0 and both not greater than baseline • Endoscopic response at Week 12: decrease in SES-CD of >50% from baseline of induction study (or for subjects with SES-CD of 4 at baseline, ≥2-point reduction from baseline), as scored by central reviewer Assessment: • CDAI clinical remission: CDAI scores were calculated using an Hct value from the same visit laboratory work for all visits (Week 2, 4, 8, and 12 for Part 1 and Week 16, 20, and 24 for Part 2, as well as at any premature discontinuation visit; diary information collected during screening was used to calculate baseline CDAI) • PRO clinical remission: subjects were provided with an electronic diary at screening visit and trained on how to record CD symptoms, including very soft/liquid SF and AP. The diary was reviewed by site personnel at each visit (Week 2, 4, 8, and 12 for Part 1 and Week 16, 20, and 24 for Part 2, as well as at any premature discontinuation visit) and SF/AP data from the 7 days prior to each visit were used • Endoscopic response: endoscopy was performed at screening and at Week 12 or premature discontinuation visit. For subjects in Part 2, endoscopy was also performed at		Co-primary endpoints (see Section B.3.3.3 for interpretation): • CDAI clinical remission at Week 52: CDAI score >150 • PRO clinical remission at Week 52: average daily very soft or liquid SF ≤2.8 and average daily AP score ≤1.0 and both not greater than baseline • Endoscopic response at Week 52: decrease in SES-CD of >50% from baseline of induction study (or for subjects with SES-CD of 4 at baseline, ≥2-point reduction from baseline), as scored by central reviewer Assessment: • CDAI clinical remission: CDAI scores were calculated using an Hct value from the same visit laboratory work for all visits (Week 0, 4, 12, 22, 32, 42, and 52), as well as at any premature discontinuation visit • PRO clinical remission: subject electronic diaries were reviewed by site personnel at Week 0 and each subsequent study visit (Week 4, 12, 22, 32,

Trial no. (acronym)	M14-433 (U-EXCEL)	M14-431 (U-EXCEED)	M14-430 (U-ENDURE)
	Week 24 or premature discontinuation visit. Endoscopic scoring was performed by a central reviewer		42, and 52) as well as at any premature discontinuation visit • Endoscopic response: endoscopy was performed at Week 0 and at Week 52 or premature discontinuation visit (endoscopy at premature discontinuation was required for subjects who completed Week 8). Endoscopic scoring was performed by a central reviewer
Other outcomes used in the economic model/specified in the scope	• CDAI clinical remission at Week 4 • Discontinuation of corticosteroid use and CDAI clinical remission at Week 12 • CDAI clinical response at Week 2 and Week 12 • Endoscopic remission at Week 12 • CD-related hospitalisation during induction period • EQ-5D-5L at Week 4 and Week 12		• Discontinuation of corticosteroid use and CDAI clinical remission at Week 52 • Discontinuation of corticosteroid use for CD ≥90 days prior to Week 52 and achievement of CDAI clinical remission at Week 52 in subjects taking corticosteroids for CD at induction baseline • CDAI clinical response (CR-100) at Week 52 • Endoscopic remission at Week 52 • CDAI clinical remission and endoscopic remission at Week 52 • CD-related hospitalisation during 52-week maintenance period • EQ-5D-5L at Week 52
Pre-planned subgroups	• Bio-IR and non-Bio-IR • Prior TNF-alpha inhibitor failure	• Prior TNF-alpha inhibitor failure	• Prior TNF-alpha inhibitor failure

Abbreviations: ADA, adalimumab; AZA, azathioprine; AP, abdominal pain; BAR, baricitinib; bio-IR, biologic inadequate response/intolerance; CD, Crohn's Disease; CDAI, Crohn's Disease Activity Index; CER, certolizumab pegol; EQ-5D-5L, EuroQol-5 Dimensions 5-level; FIL, filgotinib; GOL, golimumab; Hct, haematocrit; IFX, infliximab; IR, inadequate response; IRT, interactive response technology; JAK, Janus kinase; MTX, methotrexate; MP, mercaptopurine; NAT, natalizumab; non-Bio-IR, conventional therapy inadequate response/intolerance; NSAID, non-steroidal anti-inflammatory; PBO, placebo; QD, once daily; SES-CD, Simplified Endoscopic Score for Crohn's Disease; SF, stool frequency; TNF; tumour necrosis factor; TOF, tofacitinib; UK, United Kingdom; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab; USA, United States of America.

B.3.3.3 Trial endpoints

The co-primary and secondary endpoints for U-EXCEL, U-EXCEED, and U-ENDURE are presented in Table 13. Definitions and interpretations of these endpoints are provided in Table 14. Both induction (U-EXCEL, U-EXCEED) and maintenance (U-ENDURE) trials utilised two different co-primary endpoints to address regional differences in regulatory requirements (CDAI is specifically required for FDA) (Table 13). Clinical remission was assessed using PRO and CDAI for the EMA/FDA, respectively, as defined in Table 14.

The main body of this submission presents results for CDAI outcomes; CD clinical trials have historically used this measure and its use is consistent with outcomes reported in the ustekinumab and vedolizumab clinical trials for CD (57, 81, 82).

PRO outcomes are presented in Appendix J for completeness.

Table 13: Primary and secondary efficacy endpoints in U-EXCEL, U-EXCEED and U-ENDURE

	U-EXCEL	U-EXCEED	U-ENDURE
Co-primary efficacy endpoint	• Proportion of subjects with CDAI clinical remission at Week 12 and proportion of subjects with endoscopic response at Week 12 (US/FDA) • Proportion of subjects with PRO clinical remission at Week 12 and proportion of subjects with endoscopic response at Week 12 (EU/EMA)		• Proportion of subjects with CDAI clinical remission at Week 52 and proportion of subjects with endoscopic response at Week 52 (US/FDA) • Proportion of subjects with PRO clinical remission at Week 52 and proportion of subjects with endoscopic response at Week 52 (EU/EMA)
Key secondary endpoints	• CDAI clinical remission at Week 4 • Discontinuation of corticosteroid use and CDAI clinical remission at Week 12 • CDAI clinical response at Week 2 and Week 12 • Endoscopic remission at Week 12 • CD-related hospitalisation during induction period		• Discontinuation of corticosteroid use and CDAI clinical remission at Week 52 • CDAI clinical response at Week 52 • Endoscopic remission at Week 52 • CDAI clinical remission and endoscopic remission at Week 52 • CD-related hospitalisation during 52-week maintenance period
Other efficacy endpoints	• EQ-5D-5L at Week 4 and Week 12		• EQ-5D-5L at Week 52

Abbreviations: CD, Crohn's Disease; CDAI, Crohn's Disease Activity Index; EMA, European Medicines Agency; EQ-5D-5L, EuroQol-5 Dimensions 5-level; EU, European Union; FDA, Food and Drug Administration; PRO, patient-reported outcome; US, United States.

Table 14: Definition of disease-specific endpoints used in U-EXCEL, U-EXCEED and U-ENDURE

Endpoint	Definition and interpretation
CDAI clinical remission	Clinical remission defined as CDAI score <150 CDAI score interpretation: • 150 to 220 = mild-to-moderate disease • 220 to 450 = moderate-to-severe disease • >450 = severe/fulminant disease (89)
PRO clinical remission	Average daily very soft or liquid SF ≤2.8 and average daily AP score ≤1.0 and both not greater than baseline
Clinical response (CDAI-100)	Decrease of ≥100 points in CDAI from baseline
Clinical response	≥60% decrease in average daily very soft or liquid SF and/or ≥35% decrease in average daily AP score and both not greater than baseline
Endoscopic remission	SES-CD ≤4 and ≥2-point reduction from baseline and no subscore >1 in any individual variable, as scored by central reviewer
Endoscopic response	Decrease in SES-CD of >50% from baseline of the induction study or for subjects with an SES-CD of 4 at baseline, ≥2-point reduction from baseline, as scored by central reviewer
EQ-5D-5L (index value and VAS) (90)	EQ-5D-5L index value: EQ-5D-5L health states (defined on the EQ-5D-5L descriptive system, which comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression) converted into a single index value to facilitate the calculation of quality-adjusted life years EQ-5D-5L VAS: records the respondent's self-rated health on a 20 cm vertical, VAS with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'

Abbreviations: AP, abdominal pain; CDAI, Crohn's Disease Activity Index; EQ-5D-5L, EuroQol-5 Dimensions 5-level; PRO, patient-reported outcome; SES-CD, Simplified Endoscopic Score for Crohn's Disease; SF, stool frequency; VAS, visual analogue scale.

B.3.3.4 Baseline characteristics and demographics

The baseline characteristics from the pivotal induction (U-EXCEL, U-EXCEED) and maintenance (U-ENDURE) trials are summarised in Table 15. The baseline demographics and clinical characteristics of subjects were well balanced between the treatment groups of each trial and were generally similar across the studies.

Table 15: Characteristics of study participants across treatment groups (ITT1 population)

Characteristic	U-EXCEL		U-EXCEED		U-ENDURE		
	UPA 45 mg (N=350)	PBO (N=176)	UPA 45 mg (N=324)	PBO (N=171)	UPA 30 mg (N=168)	UPA 15 mg (N=169)	PBO (N=165)
Demographics							
Sex, n (%)							
Female	161 (46.0)	82 (46.6)	155 (47.8)	75 (43.9)	75 (44.6)	67 (39.6)	77 (46.7)
Male	189 (54.0)	94 (53.4)	169 (52.2)	96 (56.1)	93 (55.4)	102 (60.4)	88 (53.3)
Age, mean years (SD)	39.7 (13.71)	39.3 (13.63)	38.4 (13.71)	37.5 (12.12)	37.0 (13.27)	38.1 (13.46)	38.1 (13.03)
Age category, n (%)							
18 to <40 years	193 (55.1)	91 (51.7)	187 (57.7)	96 (56.1)	101 (60.4)	102 (60.4)	97 (58.8)
40 to <65 years	142 (40.6)	80 (45.5)	122 (37.7)	71 (41.5)	60 (35.7)	62 (36.7)	62 (37.6)
≥65 years	15 (4.3)	5 (2.8)	15 (4.6)	4 (2.3)	7 (4.2)	5 (3.0)	6 (3.6)
Race, n (%)							
White	258 (73.7)	130 (73.9)	230 (71.0)	126 (73.7)	114 (67.9)	118 (69.8)	119 (72.1)
Black or African American	17 (4.9)	4 (2.3)	19 (5.9)	6 (3.5)	7 (4.2)	6 (3.6)	11 (6.7)
Asian	73 (20.9)	36 (20.5)	69 (21.3)	38 (22.2)	45 (26.8)	43 (25.4)	35 (21.2)
American Indian or Alaska Native	0	0	1 (0.3)	1 (0.6)	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0	0	0	0
Multiple	2 (0.6)	6 (3.4)	5 (1.5)	0	2 (1.2)	2 (1.2)	0
Ethnicity, n (%)							
Hispanic or Latino	27 (7.7)	8 (4.5)	24 (7.4)	8 (4.7)	13 (7.7)	11 (6.5)	9 (5.5)
Not Hispanic or Latino	323 (92.3)	168 (95.5)	300 (92.6)	163 (95.3)	155 (92.3)	158 (93.5)	156 (94.5)
BMI (kg/m^2), mean (SD)	24.47 (5.96)	25.61 (6.97)	24.16 (5.98)	23.90 (6.19)	24.17 (6.56)	24.10 (6.04)	24.64 (6.65)
Disease characteristics							
CD duration (years), mean (SD)	9.30 (9.47)	8.10 (7.99)	12.05 (9.54)	10.93 (7.99)	9.30 (8.42)	10.59 (8.91)	10.34 (8.95)

Characteristic	U-EXCEL		U-EXCEED		U-ENDURE		
	UPA 45 mg (N=350)	PBO (N=176)	UPA 45 mg (N=324)	PBO (N=171)	UPA 30 mg (N=168)	UPA 15 mg (N=169)	PBO (N=165)
CDAI	n=350	n=176	n=322	n=171	n=168	n=168	n=164
Mean (SD)	292.42 (81.25)	293.85 (85.38)	306.64 (89.42)	308.08 (84.27)	312.13 (75.38)	300.78 (90.77)	308.42 (82.29)
Range	62.0–543.8	89.5–530.0	102.0–627.0	112.0–545.0	153.8–543.8	102.0–657.0	114.4–509.0
SES-CD, mean (SD)	13.7 (7.29)	13.6 (6.95)	15.2 (7.82)	14.9 (7.75)	15.5 (8.10)	15.8 (7.64)	14.8 (7.71)
CD location per SES-CD, n (%)							
Ileal only	58 (16.6)	27 (15.3)	48 (14.8)	23 (13.5)	20 (11.9)	22 (13.0)	24 (14.5)
Colonic only	121 (34.6)	57 (32.4)	112 (34.6)	68 (39.8)	70 (41.7)	62 (36.7)	67 (40.6)
Ileal-colonic	171 (48.9)	92 (52.3)	164 (50.6)	80 (46.8)	78 (46.4)	85 (50.3)	74 (44.8)
Average daily very soft or liquid SF, mean (SD)	5.19 (2.61)	5.09 (2.84)	n=323 5.73 (3.36)	n=171 6.09 (3.34)	n=168 5.54 (2.79)	n=168 5.38 (3.26)	n=165 5.60 (2.80)
Average daily AP score†	1.89 (0.68)	1.91 (0.69)	n=323 1.85 (0.69)	n=171 1.80 (0.68)	n=168 1.94 (0.60)	n=168 1.84 (0.70)	n=165 1.95 (0.66)
hs-CRP (mg/L), mean (SD)	n=341 15.97 (20.47)	n=176 16.19 (22.08)	n=319 20.86 (25.97)	n=163 18.98 (24.02)	n=164 20.63 (26.09)	n=164 19.53 (23.01)	n=162 19.25 (24.53)
FCP (µg/g), mean (SD)	n=319 2,170.2 (3,991.7)	n=171 1,792.1 (2,773.8)	n=298 2,286.6 (3,880.36)	n=159 2,184.7 (3,148.34)	n=148 2,663.3 (4,321.0)	n=151 3,200.5 (5,315.4)	n=156 1,866.8 (2,655.8)
Draining fistulas, n (%)	17 (4.9)	6 (3.4)	27 (8.4)	16 (9.4)	11 (6.5)	17 (10.1)	8 (4.8)
Non-draining fistulas, n (%)	25 (7.1)	13 (7.4)	31 (9.6)	16 (9.4)	8 (4.8)	20 (11.9)	17 (10.3)
Treatment history							
Baseline corticosteroid use, n (%)	126 (36.0)	64 (36.4)	108 (33.3)	60 (35.1)	63 (37.5)	63 (37.3)	61 (37.0)
Baseline immunosuppressant use, n (%)	13 (3.7)	3 (1.7)	24 (7.4)	13 (7.6)	9 (5.4)	5 (3.0)	11 (6.7)
Biologic use/failure status, n (%)							
Bio-IR	161 (46.0)	78 (44.3)	NA	NA	127 (75.6)	124 (73.4)	126 (76.4)
Non-Bio-IR	189 (54.0)	98 (55.7)			41 (24.4)	45 (26.6)	39 (23.6)
Prior exposure to biologic therapy among non-Bio-IR subjects, n (%)	N=189 16 (8.5)	N=98 9 (9.2)	NA	NA	n=41 6 (14.6)	n=45 5 (11.1)	n=39 0
Biologics failure history, n (%)	n=161	n=78			n=127	n=124	n=126
1‡	58 (36.0)	28 (35.9)	126 (38.9)	68 (39.8)	43 (33.9)	52 (41.9)	52 (41.3)
2	52 (32.3)	24 (30.8)	92 (28.4)	55 (32.2)	35 (27.6)	31 (25.0)	32 (25.4)
≥3	51 (31.7)	26 (33.3)	106 (32.7)	48 (28.1)	49 (38.6)	41 (33.1)	42 (33.3)

Characteristic	U-EXCEL		U-EXCEED		U-ENDURE		
	UPA 45 mg (N=350)	PBO (N=176)	UPA 45 mg (N=324)	PBO (N=171)	UPA 30 mg (N=168)	UPA 15 mg (N=169)	PBO (N=165)
Prior TNF-alpha inhibitor failure, n (%)	n=161 157 (97.5)	n=78 75 (96.2)	308 (95.1)	164 (95.9)	n=127 123 (96.9)	n=124 117 (94.4)	n=126 118 (93.7)
Prior vedolizumab/natalizumab failure, n (%)	n=161 49 (30.4)	n=78 25 (32.1)	99 (30.6)	47 (27.5)	n=127 43 (33.9)	n=124 39 (31.5)	n=126 38 (30.2)
Prior ustekinumab failure, n (%)	n=161 64 (39.8)	n=78 33 (42.3)	118 (36.4)	57 (33.3)	n=127 49 (38.6)	n=124 41 (33.1)	n=126 48 (38.1)
CD-related medication taken prior to baseline, (%)							
Adalimumab	107 (30.6)	58 (33.0)	216 (66.7)	120 (70.2)	92 (54.5)	72 (42.6)	80 (48.5)
Certolizumab	1 (0.3)	3 (1.7)	7 (2.2)	5 (2.9)	1 (0.6)	5 (3.0)	2 (1.2)
Certolizumab pegol	10 (2.9)	5 (2.8)	33 (10.2)	16 (9.4)	14 (8.3)	11 (6.5)	14 (8.5)
Infliximab	133 (38.0)	58 (33.0)	225 (69.4)	117 (68.4)	99 (58.9)	99 (58.6)	85 (51.5)
Risankizumab	0	1 (0.6)	NA	NA	4 (2.4)	2 (1.2)	0
Ustekinumab	72 (20.6)	36 (20.5)	122 (37.7)	58 (33.9)	50 (29.8)	44 (26.0)	50 (30.3)
Vedolizumab	52 (14.9)	26 (14.8)	104 (32.1)	48 (28.1)	45 (26.8)	43 (25.4)	39 (23.6)

Abbreviations: AP, abdominal pain; Bio-IR, biologic inadequate response/intolerance; BMI, body mass index; CD, Crohn's Disease; CDAI, Crohn's Disease Activity Index; CSR, clinical study report; FCP, faecal calprotectin; hs-CRP, high sensitivity C-reactive protein; NA, not applicable; non-Bio-IR, conventional therapy inadequate response or intolerance; PBO, placebo; SD, standard deviation; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency; TNF, tumour necrosis factor; UPA, upadacitinib. Source: U-EXCEL CSR (85); U-EXCEED CSR (86); U-ENDURE CSR (87). † AP score: 0 = no pain; 1 = mild; 2 = moderate; 3 = severe. ‡ U-EXCEED included patients who had an inadequate response or intolerance to biologic therapy, with the eligibility criteria stating that demonstration of intolerance required no minimum dose or duration of use. Therefore, a small proportion of the trial population (1 patient in the placebo arm) failed <1 prior biologic.

B.3.3.5 Expert elicitation/opinion

Expert opinion was gathered through review of this submission document by 3 clinical and 2 economic experts. The criteria for selecting suitable experts were expertise and experience of treating CD in the UK (clinicians) and specialised technical expertise in economic evaluation and health technology assessment (health economic experts).

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

B.3.4.1 Participant flow in the relevant randomised controlled trials

See Appendix D for details of participant flow.

B.3.4.2 Definitions of subject population analysis sets

Definitions of subject population analysis sets for the induction (U-EXCEL and U-EXCEED) and maintenance (U-ENDURE) studies are presented in Table 9 and Table 11, respectively, and in Appendix D.

Analyses of the co-primary endpoints and secondary endpoints for Part 1 (12-week induction period) were performed using the ITT1 analysis sets from U-EXCEL and U-EXCEED. Similarly, analyses of the co-primary and secondary endpoints for Cohort 1 (52-week maintenance period) were performed using the ITT1 analysis set from U-ENDURE. Subject numbers for each data set are presented in Appendix D.

B.3.4.3 Statistical analysis

A summary of the statistical analysis methods used in U-EXCEL, U-EXCEED, and U-ENDURE is provided in Table 16.

For all trials, a multiple testing procedure was used to provide strong control of the type I error rate at alpha = 0.05 (2-sided) across analyses comparing upadacitinib 45 mg (U-EXCEL, U-EXCEED) or upadacitinib 30 mg and 15 mg (U-ENDURE) with placebo for the co-primary endpoints and ranked secondary endpoints. Specifically, testing used a sequence of hypothesis testing for the co-primary endpoints followed by the ranked secondary endpoints (see rankings in Appendix J). If both co-primary endpoints achieved statistical significance, continued testing followed a pre-specified

weight of alpha allocation between individual hypotheses, as well as between families of hypotheses.

In handling missing data for analysis of the co-primary endpoints, the primary approach was non-responder imputation while incorporating MI to handle missing data due to COVID-19 (NRI-C). The NRI-C categorised any subjects who did not have an evaluation during a pre-specified visit window (either due to missing assessment or early withdrawal from the study) as a non-responder for the visit. The only exception was that subjects with missing data due to COVID-19 infection or logistical restriction were handled by MI and the subjects were categorised as responders or non-responders based on MI imputed values. In U-EXCEL and U-EXCEED, at/after the CD-related corticosteroids intercurrent event and on/after the date of initiation of CD-related confounding medications after premature discontinuation of the study drug, subjects were considered non-responders. In U-ENDURE, subjects were considered non-responders at/after the occurrence of the CD-related rescue medications intercurrent event or on/after the date of initiation of CD-related confounding medications after premature discontinuation of the study drug. As observed (AO) analysis was used for some endpoints, including CD-related hospitalisation; in AO analysis, values were not imputed for missing evaluations and therefore a subject without an evaluation on a scheduled visit was excluded from the analysis for that visit. AO included all values collected in the study.

Table 16: Summary of statistical analysis approach in U-EXCEL, U-EXCEED, and U-ENDURE

	U-EXCEL	U-EXCEED	U-ENDURE
Statistical analysis	• Comparison between treatment groups for the co-primary efficacy endpoints was performed using the CMH test and stratified by baseline corticosteroid use (yes or no), endoscopic disease severity (SES-CD <15 or ≥15) and number of prior biologics with IR or intolerance (0, 1, or >1)	• Comparison between treatment groups for the co-primary efficacy endpoints was performed using the CMH test and stratified by baseline corticosteroid use (yes or no), endoscopic disease severity (SES-CD <15 or ≥15) and number of prior biologics used (>1 or ≤1)	• Comparison between treatment groups for the co-primary efficacy endpoints was performed using the CMH test and stratified by prior induction study population: (1) U-EXCEL non-bio-IR, (2) U-EXCEL bio-IR or U-EXCEED Part 1/Part 3, or (3) U-EXCEED Part 2; PRO clinical remission (yes or no); and endoscopic response status (yes or no) at: ○ Week 12 or 24 of U-EXCEL or U-EXCEED, or ○ Week 24 for subjects who received blinded induction treatment with UPA 45 mg QD for 12 weeks during the extended induction period of U-EXCEED (Cohort 1 of Part 3) or U-EXCEL (Cohort 1 of Part 2)
	Co-primary efficacy endpoints were tested at a two-sided significance level of 0.05 and a CMH-based two-sided 95% CI for the difference between treatment groups was calculated • Continuous secondary efficacy variables with repeated measurements were analysed using a MMRM model • Continuous secondary efficacy variables which were collected at only one post-baseline visit (such as SES-CD) were analysed using an ANCOVA model • Categorical secondary efficacy variables were analysed using the CMH test controlling for stratification variables		
Sample size, power calculation	• Assumptions used for sample size calculations were based on 16-week clinical and endoscopic data from the Phase 2 CELEST study (M13-740) of UPA		• The sample size for Cohort 1 was based on the expected proportion of subjects who achieve clinical remission at Week 52 and the expected proportion of subjects who achieve endoscopic response at Week 52 • Assumptions used for sample size calculations were based on 52-week clinical and endoscopic data from the Phase 2 CELEST study (M13-740) of UPA and available published data on other investigational JAK inhibitors

	U-EXCEL	U-EXCEED	U-ENDURE
	• For EU/EMA regulatory purposes: assuming a PRO clinical remission rate of 15% in the PBO group and 33% in the UPA group at Week 12, a total sample size of 501 subjects randomised in a 2:1 ratio (334 in the UPA group and 167 in the PBO group) was deemed adequate to detect ≥18% treatment difference in clinical remission rates at Week 12 using Fisher's exact test with ≥95% power at a 0.05 two-sided significance level • For US/FDA regulatory purposes: assuming a CDAI clinical remission rate of 15% in the PBO group and 33% in the UPA group at Week 12, a total sample size of 501 subjects randomised in a 2:1 ratio (334 subjects in the UPA group and 167 in the PBO group) was deemed adequate to detect ≥18% treatment difference in clinical remission rates at Week 12 using Fisher's exact test with ≥95% power at a 0.05 two-sided significance level • For both EU/US purposes: assuming an endoscopic response rate of 11.5% in the PBO group and 28.5% in the UPA group at Week 12, the sample sizes presented above were deemed adequate to detect ≥17% treatment difference in endoscopic response rates at Week 12 using Fisher's exact test with ≥95% power at a 0.05 two-sided significance level	• For EU/EMA regulatory purposes: assuming a rate of 12% for PRO clinical remission in the PBO group and 29% in the UPA group at Week 12, a total sample size of 495 subjects randomised in a 2:1 ratio (330 subjects in the UPA group and 165 in the PBO group) was deemed adequate to detect ≥17% treatment difference in clinical remission rates at Week 12 using Fisher's exact test with ≥95% power at a 0.05 two-sided significance level • For US/FDA regulatory purposes: assuming a rate of 20% for CDAI clinical remission in the PBO group and 40% in the UPA group at Week 12, a sample size of 495 subjects was deemed adequate to detect ≥20% treatment difference in clinical remission rates at Week 12 using Fisher's exact test with ≥95% power at a 0.05 two-sided significance level • For both EU/US purposes: assuming an endoscopic response rate of 10% in the PBO group and 25% in the UPA group at Week 12, the sample size presented above was deemed adequate to detect ≥15% treatment difference in endoscopic response rates at Week 12 using Fisher's exact test with ≥95% power at a 0.05 two-sided significance level	• For EU/EMA regulatory purposes: assuming a Week 52 PRO clinical remission rate of 42% for one of the UPA dose groups and 17% for the PBO group, a total sample size of 501 subjects randomised in a 1:1:1 ratio (167 subjects each in UPA 30 mg QD, UPA 15 mg QD, and PBO groups) will have approximately 99% power to detect ≥25% treatment difference in clinical remission rates at Week 52 between the treatment groups and PBO using Fisher's exact test at a 0.025 two-sided significance level • For US/FDA regulatory purposes: assuming a Week 52 CDAI clinical remission rate of 50% for one of the UPA dose groups and 22% for the PBO group, a sample size of 501 subjects would have approximately 99% power to detect ≥28% treatment difference in clinical remission rates at Week 52 between the treatment groups and PBO using Fisher's exact test at a 0.025 two-sided significance level • Assuming an endoscopic response rate of 35% for one of the UPA dose groups and 17% for the PBO group, the sample size presented above would have approximately 94% power to detect ≥28% difference in clinical remission rates at Week 52 between the treatment groups and PBO using Fisher's exact test at a 0.025 two-sided significance level
Data management, subject withdrawals	The non-responder imputation while incorporating multiple imputation (MI) to handle missing data due to COVID-19 (NRI-C) was the primary approach for missing data handling in the analyses of the co-primary efficacy endpoints. The NRI-C categorised any subjects who did not have an evaluation during a pre-specified visit window (either due to missing assessment or due to early withdrawal from the study) as a non-responder for the visit. The only exception is that subjects with missing data due to COVID-19 infection or logistical restriction were handled by MI and the subjects will be characterised as responders or non-responders based on MI imputed values		

	U-EXCEL	U-EXCEED	U-ENDURE
	• In addition, at and after the CD-related corticosteroids intercurrent event and on/after the date of initiation of CD-related confounding medications after premature discontinuation of the study drug, subjects were considered non-responders and were not imputed by MI		• In addition, on/after the date of initiation of CD-related confounding medications after premature discontinuation of study drug and the CD-related rescue medications intercurrent event, subjects were considered non-responders and were not imputed by MI
	For binary efficacy endpoints (e.g., hospitalisation), missing data were handled as follows: • As observed (AO) analysis: AO analysis did not impute values for missing evaluations and therefore a subject without an evaluation on a scheduled visit was excluded from the AO analysis for that visit. AO included all values collected in the study		

Abbreviations: ANCOVA, analysis of covariance; AO, as observed; Bio-IR, biologic inadequate response/intolerance; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; EU, EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; MAR, missing at random; MI, multiple imputation; MMRM, mixed-effect model repeat measurement; non-Bio-IR, conventional therapy inadequate response/intolerance; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; PRO, patient-reported outcome; SES-CD, Simple Endoscopic Score for Crohn's disease; UPA, upadacitinib; US, United States.

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

A summary of quality assessment results for the upadacitinib trials is provided in Table 17. A complete quality assessment for each trial is provided in Appendix D.

Table 17: Quality assessment results for RCTs

	U-EXCEL	U-EXCEED	U-ENDURE
Randomisation			
Was randomisation carried out appropriately?	Yes	Yes	Yes
Baseline comparability			
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Yes	Yes
Blinding			
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Follow-up			
Were there any unexpected imbalances in dropouts between groups?	No	No	No
Selective Reporting			
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Analysis			
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes

Abbreviations: RCT, randomised controlled trial.

B.3.6 Clinical effectiveness results of the relevant studies

Summary

Key results from upadacitinib induction studies (U-EXCEL and U-EXCEED)

- In both induction studies, a significantly greater proportion of subjects in the upadacitinib 45 mg arm achieved the co-primary endpoints of CDAI clinical remission and endoscopic response at Week 12 compared with the placebo arm
- Greater efficacy with upadacitinib 45 mg compared with placebo was observed as early as Week 2 for CDAI clinical response and Week 4 for CDAI clinical remission
- Endoscopic remission rates were significantly higher with upadacitinib versus placebo at Week 12 of U-EXCEL and U-EXCEED
- Subjects treated with upadacitinib 45 mg had significant improvements in HRQoL (assessed using EQ-5D-5L) at Week 4 and Week 12 compared with placebo
- Clear treatment effects were also observed in the Bio-IR population

Key results from upadacitinib maintenance study (U-ENDURE)

- In the overall population of U-ENDURE, a significantly greater proportion of subjects in the upadacitinib 30 mg and 15 mg groups achieved the co-primary endpoints of CDAI clinical remission and endoscopic response at Week 52 compared with the placebo group
- Significantly more patients achieved endoscopic remission at Week 52 with both doses of upadacitinib versus placebo
- Significant improvements in EQ-5D-5L VAS from induction baseline to Week 52 were observed with both doses of upadacitinib
- Upadacitinib was effective in the overall population and in the Bio-IR population

This section presents the results from the pivotal upadacitinib induction (U-EXCEL and U-EXCEED) and maintenance (U-ENDURE) studies. As described in Section B.3.3.3, CDAI outcomes are presented across all studies as this endpoint has been used in previous trials of treatments for CD and therefore facilitates indirect treatment comparisons (81, 82). PRO outcomes (defined using SF and AP scores) are not used in the model but are presented in Appendix J for completeness. Upadacitinib met all co-primary endpoints (CDAI clinical remission or PRO clinical remission in addition to endoscopic response) across the induction and maintenance studies.

All study outcome definitions are presented in Section B.3.3.3 and provided in the footnotes of the results tables. Data are presented for the anticipated licensed doses of upadacitinib (45 mg for induction therapy and 30 mg or 15 mg for maintenance therapy).

B.3.6.1 U-EXCEL

B.3.6.1.1 Co-primary efficacy outcome: proportion of subjects with CDAI clinical remission and endoscopic response at Week 12

In U-EXCEL, the co-primary endpoints of CDAI clinical remission and endoscopic response were met for upadacitinib 45 mg QD compared with placebo (85).

At Week 12, a significantly greater proportion of subjects in the upadacitinib 45 mg arm achieved CDAI clinical remission (see definition in Table 14) compared with the placebo arm ([redacted]) (Table 18). A clear treatment effect was observed in the Bio-IR population, with a greater proportion of patients achieving CDAI clinical remission with upadacitinib than with placebo ([redacted]) (Table 18).

Table 18: CDAI clinical remission at Week 12 (NRI-C) – overall and Bio-IR (U-EXCEL ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
All subjects								
UPA 45 mg	[redacted]							
PBO	[redacted]							
[redacted]								
UPA 45 mg	[redacted]							
PBO	[redacted]							

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib. Source: U-EXCEL CSR (85). Note: CDAI clinical remission defined as CDAI score <150. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

At Week 12, a significantly greater proportion of subjects achieved endoscopic response (see definition in Table 14) in the upadacitinib 45 mg arm compared with the placebo arm ([redacted]) (Table 19). A clear treatment effect was also observed in the Bio-IR population, with a greater proportion of patients achieving endoscopic response with upadacitinib than with placebo ([redacted]) (Table 19).

Table 19: Endoscopic response at Week 12 (NRI-C) – overall and Bio-IR (U-EXCEL ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
All subjects								
UPA 45 mg	[redacted]							
PBO	[redacted]							
[redacted]								
UPA 45 mg	[redacted]							
PBO	[redacted]							

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; SES-CD, Simple Endoscopic Score – Crohn's Disease; UPA, upadacitinib.
Source: U-EXCEL CSR (85). Note: endoscopic response defined as decrease in SES-CD of >50% from baseline of the induction study or for subjects with an SES-CD of 4 at baseline, ≥2-point reduction from baseline, as scored by central reviewer. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.3.6.1.2 Secondary efficacy outcomes – U-EXCEL

B.3.6.1.2.1 CDAI clinical remission at Week 4

At Week 4 of U-EXCEL, a significantly greater proportion of patients achieved CDAI clinical remission in the upadacitinib arm compared with the placebo arm ([redacted]) (Table 20). A between-treatment difference of [redacted] was observed in the Bio-IR population for upadacitinib versus placebo (Table 20).

Table 20: CDAI clinical remission at Week 4 (NRI-C) – overall and Bio-IR (U-EXCEL ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
All subjects								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
[redacted]								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.
Source: U-EXCEL CSR (85). Note: CDAI clinical remission defined as CDAI score <150. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.3.6.1.2.2 CDAI clinical response (CR-100) at Week 2 and Week 12

At Week 2, a significantly greater proportion of patients achieved CDAI clinical response (see definition in Table 14) with upadacitinib compared with placebo ([redacted]) (Table 21). A between-treatment difference of [redacted] was observed in the Bio-IR population (Table 21).

Table 21: CDAI clinical response (CR-100) at Week 2 (NRI C) – overall and Bio-IR (U-EXCEL ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
All subjects								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
Prior biologic failure status								
[redacted]								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.
Source: U-EXCEL CSR (85). Note: CR-100 defined as decrease of ≥100 points in CDAI from baseline. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

At Week 12, a significantly greater proportion of patients achieved CDAI clinical response (CR-100) with upadacitinib compared with placebo ([redacted]) (Table 22). A between-treatment difference of [redacted] for upadacitinib versus placebo was observed in the Bio-IR (Table 22).

Table 22: CDAI clinical response (CR-100) at Week 12 (NRI-C) – overall and Bio-IR (U-EXCEL ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
All subjects								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
[redacted]								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.
Source: U-EXCEL CSR (85). Note: CR-100 is defined as decrease of ≥100 points in CDAI from baseline. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.3.6.1.2.3 Endoscopic remission at Week 12

At Week 12, a significantly greater proportion of patients achieved endoscopic remission (see definition in Table 14) in the upadacitinib arm compared with the placebo arm ([redacted]) (Table 23). A between-treatment difference of [redacted] was observed for upadacitinib versus placebo in the Bio-IR population (Table 23).

Table 23: Summary of achievement of endoscopic remission at Week 12 (NRI-C) – overall and Bio-IR (U-EXCEL ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
All subjects								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
[redacted]								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.
Source: U-EXCEL CSR (85). Note: endoscopic remission defined as SES-CD ≤4 and ≥2-point reduction from baseline and no subscore >1 in any individual variable, as scored by central reviewer. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.3.6.1.2.4 Discontinuation of corticosteroid use and CDAI clinical remission at Week 12

Among subjects who were taking corticosteroids for CD at baseline, a significantly greater proportion discontinued corticosteroid use and achieved CDAI clinical remission at Week 12 with upadacitinib compared with placebo ([redacted]; [redacted]) (Table 24). A clear treatment effect was also observed in the Bio-IR population, with a between-treatment difference for upadacitinib versus placebo of [redacted] (Table 24).

Table 24: Discontinuation of corticosteroid use for CD and achievement of CDAI clinical remission at Week 12 in subjects taking corticosteroids for CD at baseline (NRI-C) – overall and Bio-IR (U-EXCEL ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI[†]	Missing due to COVID-19, n	Diff.	Adj. diff. (%)[‡]	95% CI[§]	P value
All subjects								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
Bio-IR								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.
Source: U-EXCEL CSR (85). Note: CDAI clinical remission defined as CDAI score <150. [†]95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. [§]95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.3.6.1.2.5 CD-related hospitalisation

Table 25 shows the occurrence of CD-related hospitalisations during the 12-week induction period of U-EXCEL. No significant difference was observed between the upadacitinib and placebo arms ([redacted]). A between-treatment difference of [redacted] in favour of upadacitinib was observed in the Bio-IR population (Table 25).

Table 25: CD-related hospitalisations during the 12-week induction period (AO) – overall and Bio-IR (U EXCEL ITT1 population)

Population Treatment	Responder				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.‡	Adj. diff. (%)	95% CI§	P value
All subjects								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
[redacted]								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: AO, as observed; Bio-IR, biologic inadequate response/intolerance; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; non-Bio-IR, conventional therapy inadequate response/intolerance; NR, not reported; PBO, placebo; UPA, upadacitinib. Source: U-EXCEL CSR (85). Note: For all subjects in the ITT1 population, occurrence of hospitalisation due to CD was a binary variable. The value was 'yes' for subjects who had at least one hospitalisation due to CD during the 12-week induction period and 'no' for subjects who did not have any hospitalisation during the 12-week induction period. †95% CI for response rate is based on the normal approximation to the binomial distribution. ‡Risk difference = UPA – PBO. §95% CI for treatment difference was based on normal approximation of the binomial proportions. P-value was calculated according to the Chi-squared test or Fisher's exact test if more than 20% of the cells have expected counts of less than 5.

B.3.6.1.2.6 EQ-5D-5L at Week 4 and Week 12

Statistically significant improvements in the EQ-5D-5L index value and EQ-5D VAS were observed with upadacitinib compared with placebo. At Week 4, the improvement from baseline (LS mean) was [redacted] in the upadacitinib arm and [redacted] in the placebo arm with a statistically significant between-treatment difference of [redacted] (Table 26). At Week 12, the improvement from baseline was [redacted] and [redacted] in the upadacitinib and placebo arms, respectively, resulting in a significant between-treatment difference of [redacted] (Table 26).

Similar results were observed for the EQ-5D VAS score; at Week 4, subjects in the upadacitinib arm had a greater improvement from baseline compared with the placebo arm (LS mean [redacted]); a between-treatment difference of [redacted] (Table 26). At Week 12, the improvement from baseline was [redacted] and [redacted] with upadacitinib and placebo, respectively, resulting in a significant between-treatment difference of [redacted] (Table 26).

Table 26: Change from baseline in EQ-5D-5L index value and EQ-5D VAS at Weeks 4 and 12 (MMRM) (U-EXCEL ITT1 population)

Outcome Timepoint Treatment	Within group change from baseline					Between group difference vs PBO		
	N	Baseline mean	Visit mean	LS mean	95% CI	LS mean	95% CI	P value
EQ-5D-5L index value								
Week 4								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Week 12								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
EQ-5D VAS								
Week 4								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Week 12								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			

Abbreviations: CI, confidence interval; CSR, clinical study report; EQ-5D-5L, EuroQol-5 Dimensions 5-level; LS, least squares; MMRM, mixed effect model repeat measurement; PBO, placebo, SES-CD, Simple Endoscopic Score for Crohn's Disease; UPA, upadacitinib; VAS, visual analogue scale.
Source: U-EXCEL CSR (85). MMRM was the mixed effect model repeat measurement with baseline value, stratification factors (baseline corticosteroid use [yes or no], endoscopic disease severity [SES-CD <15 or ≥15], and number of prior biologics failed [0, 1, or >1]), treatment visit, treatment-by-visit interaction included in the model. An unstructured covariance matrix was used.

B.3.6.2 U-EXCEED

B.3.6.2.1 Co-primary efficacy outcome: proportion of subjects with CDAI clinical remission and endoscopic response at Week 12

In U-EXCEED, the co-primary endpoint of CDAI clinical remission and endoscopic response at Week 12 was met. At Week 12, a significantly greater proportion of subjects achieved CDAI clinical remission in the upadacitinib arm compared with the placebo arm ([redacted] vs [redacted]) (Table 27). A clear treatment effect with upadacitinib versus placebo was also observed in the ≤1 biologic failure and >1 biologic failure populations, with between-treatment differences of [redacted] respectively (Table 27).

Table 27: CDAI clinical remission at Week 12 (NRI-C) – overall and by prior biologic failure status (U-EXCEED ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
All subjects								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
Prior biologic failure status								
[redacted]								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
[redacted]								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.
Source: U-EXCEED CSR (86). Note: CDAI clinical remission defined as CDAI score <150. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

At Week 12, a significantly greater proportion of subjects achieved endoscopic response in the upadacitinib arm compared with the placebo arm ([redacted]) (Table 28). A clear treatment effect with upadacitinib versus placebo was also observed in the ≤1 biologic failure and >1 biologic failure populations, with between-treatment differences of [redacted] respectively (Table 28).

Table 28: Endoscopic response at Week 12 (NRI-C) – overall and by prior biologic failure status (U-EXCEED ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
All subjects								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
Prior biologic failure status								
[redacted]								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
[redacted]								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib. Source: U-EXCEED CSR (86). Note: endoscopic response defined as decrease in SES-CD of >50% from baseline of the induction study or for subjects with an SES-CD of 4 at baseline, ≥2-point reduction from baseline, as scored by central reviewer. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.3.6.2.2 Secondary efficacy outcomes – U-EXCEED

B.3.6.2.2.1 CDAI clinical remission at Week 4

At Week 4, approximately [redacted] of subjects in the upadacitinib arm achieved CDAI clinical remission. A significantly greater proportion of subjects achieved CDAI clinical remission with upadacitinib compared with placebo at this timepoint ([redacted]) (Table 29). A significant difference in favour of upadacitinib was also observed at Week 2 (see Appendix J).

Table 29: CDAI clinical remission at Week 4 (NRI-C; U-EXCEED ITT1 population)

Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.
Source: U-EXCEED CSR (86). Note: CDAI clinical remission defined as CDAI score <150. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.3.6.2.2.2 CDAI clinical response (CR-100) at Week 2 and Week 12

Significantly greater proportions of patients achieved CDAI clinical response with upadacitinib compared with placebo at Week 2 and Week 12 ([redacted], respectively: both [redacted]) (Table 30).

Table 30: CDAI clinical response (CR-100) at Week 2 and Week 12 (NRI-C; U-EXCEED ITT1 population)

Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
Week 2								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
Week 12								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CR-100, clinical response 100; COVID-19, Coronavirus Disease 2019; CR-100, clinical response 100; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.
Source: U-EXCEED CSR (86). Note: CR-100 defined as decrease of ≥100 points in CDAI from baseline. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.3.6.2.2.3 Endoscopic remission at Week 12

At Week 12, a significantly greater proportion of patients achieved endoscopic remission in the upadacitinib arm compared with the placebo arm ([redacted]) (Table 31).

Table 31: Endoscopic remission at Week 12 (NRI-C; U-EXCEED ITT1 population)

Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI	Missing due to COVID-19, n	Diff.	Adj. diff. (%)	95% CI	P value
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CI, confidence interval; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib. Source: U-EXCEED CSR (86). Note: endoscopic remission defined as SES-CD ≤4 and ≥2-point reduction from baseline and no subscore >1 in any individual variable, as scored by central reviewer. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.3.6.2.2.4 Discontinuation of corticosteroid use and CDAI clinical remission at Week 12

Among subjects taking corticosteroids for CD at baseline, a significantly greater proportion discontinued corticosteroids and achieved CDAI clinical remission with upadacitinib compared with placebo at Week 12 ([redacted]) (Table 32).

Table 32: Discontinuation of corticosteroid use and achievement of CDAI clinical remission at Week 12 in subjects taking corticosteroids for CD at baseline (NRI-C; U-EXCEED ITT1 population)

Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib. Source: U-EXCEED CSR (86). Note: CDAI clinical remission defined as CDAI score <150. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.3.6.2.2.5 CD-related hospitalisation

Table 33 shows CD-related hospitalisations occurring during the 12-week induction period of U-EXCEED. No significant differences were observed between the treatment groups (Table 33).

Table 33: CD-related hospitalisation during the 12-week induction period (AO; U-EXCEED ITT1 population)

Treatment	Responder				Response rate difference vs PBO			
	N	n (%)	95% CI	Missing due to COVID-19, n	Diff.	Adj. diff. (%)	95% CI	P value
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: AO, as observed; CI, confidence interval; COVID-19, coronavirus disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; PBO, placebo; UPA, upadacitinib. Source: U-EXCEED CSR (86). Note: For all subjects in the ITT1 population, occurrence of hospitalisation due to CD was a binary variable. The value was 'yes' for subjects who had at least one hospitalisation due to CD during the 12-week induction period and 'no' for subjects who did not have any hospitalisation during the 12-week induction period. †95% CI for response rate is based on the normal approximation to the binomial distribution. ‡Risk difference = UPA – PBO. §95% CI for treatment difference was based on normal approximation of the binomial proportions. P-value was calculated according to the Chi-squared test or Fisher's exact test if more than 20% of the cells have expected counts of less than 5.

B.3.6.2.2.6 EQ-5D-5L at Week 4 and Week 12

Significant improvements in the EQ-5D-5L index value and EQ-5D VAS score were observed with upadacitinib compared with placebo at both Week 4 and Week 12. At Week 4, the improvement from baseline (LS mean) was [redacted] in the upadacitinib arm and [redacted] in the placebo arm; a significant between-treatment difference of [redacted] (Table 34). At Week 12, the improvement from baseline was [redacted] and [redacted] with upadacitinib and placebo, respectively; a between-treatment difference [redacted] (Table 34).

Similar results were observed for the EQ-5D VAS score. At Week 4, subjects in the upadacitinib arm had a greater improvement from baseline compared with the placebo arm (LS mean [redacted]); a between-treatment difference of [redacted] (Table 34). At Week 12, the improvement from baseline was [redacted] and [redacted] with upadacitinib and placebo, respectively; a between-treatment difference of [redacted] (Table 34).

Table 34: Change from baseline in EQ-5D-5L index value and EQ-5D VAS at Weeks 4 and 12 (MMRM; U-EXCEED ITT1 population)

Score Timepoint Treatment	Within group change from baseline					Between group difference vs PBO		
	N	Baseline mean	Visit mean	LS mean	95% CI	LS mean	95% CI	P value
EQ-5D-5L index value								
Week 4								
UPA 45 mg	[redacted]							
PBO	[redacted]							
Week 12								
UPA 45 mg	[redacted]							
PBO	[redacted]							
EQ-5D VAS								
Week 4								
UPA 45 mg	[redacted]							
PBO	[redacted]							
Week 12								
UPA 45 mg	[redacted]							
PBO	[redacted]							

Abbreviations: CI, confidence interval; CSR< clinical study report; EQ-5D-5L, EuroQol-5 Dimensions 5-Levels; LS, least squares; MMRM, mixed effect model repeat measurement; PBO, placebo; SES-CD, Simple Endoscopic Score for Crohn's disease; UPA, upadacitinib; VAS, visual analogue scale.
Source: U-EXCEED CSR (86). MMRM was the mixed effect model repeat measurement with baseline value, stratification factors (baseline corticosteroid use [yes or no], endoscopic disease severity [SES-CD <15 or ≥15], and number of prior biologics failed [>1 or ≤1]), treatment visit, treatment-by-visit interaction included in the model. An unstructured covariance matrix was used.

B.3.6.3 U-ENDURE

B.3.6.3.1 Co-primary efficacy outcome: proportion of subjects with CDAI clinical remission and endoscopic response at Week 52

In U-ENDURE, the co-primary endpoints of CDAI clinical remission and endoscopic response at Week 52 were met. A significantly greater proportion of subjects achieved CDAI clinical remission with upadacitinib 30 mg and upadacitinib 15 mg compared with placebo ([redacted]) (Table 35). In the Bio-IR population, the between-treatment difference with upadacitinib 30 mg and upadacitinib 15 mg versus placebo was [redacted] and [redacted] respectively (Table 35).

Table 35: CDAI clinical remission at Week 52 (NRI-C) – overall and Bio-IR (U-ENDURE ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
All subjects								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							
[redacted]								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NA, not applicable; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib. Source: U-ENDURE CSR (87). Note: CDAI clinical remission defined as CDAI score <150. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

At Week 52, a significantly greater proportion of patients achieved endoscopic response with upadacitinib 30 mg and 15 mg compared with placebo ([redacted]) (Table 36). In the Bio-IR population, the between-treatment difference with upadacitinib 30 mg and upadacitinib 15 mg versus placebo was [redacted] and [redacted], respectively (Table 36).

Table 36: Endoscopic response at Week 52 (NRI-C) – overall and Bio-IR (U-ENDURE ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI[†]	Missing due to COVID-19, n	Diff.	Adj. diff. (%)[‡]	95% CI[§]	P value
All subjects								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							
[redacted]								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NA, not applicable; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.
Source: U-ENDURE CSR (87). Note: endoscopic response defined as decrease in SES-CD of >50% from baseline of the induction study or for subjects with an SES-CD of 4 at baseline, ≥2-point reduction from baseline, as scored by central reviewer. [†]95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. [§]95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.3.6.3.2 Secondary efficacy outcomes – U-ENDURE

B.3.6.3.2.1 CDAI clinical response (CR-100) at Week 52

At Week 52, [redacted] receiving upadacitinib 30 mg achieved CDAI clinical response (CR-100); a significantly greater proportion than those receiving placebo ([redacted]) (Table 37). In the upadacitinib 15 mg arm, [redacted] of patients achieved CDAI clinical response, which was also significantly greater than the placebo arm ([redacted]) (Table 37).

Table 37: CDAI clinical response (CR-100) at Week 52 (NRI-C; U-ENDURE ITT1 population)

Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CR, clinical response; CSR, clinical study report; ITT, intention to treat; NA, not applicable; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.
Source: U-ENDURE CSR (87). Note: CR-100 defined as decrease of ≥100 points in CDAI from baseline. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.3.6.3.2.2 Endoscopic remission at Week 52

Statistically significantly more patients achieved endoscopic remission at Week 52 with upadacitinib 30 mg or 15 mg compared with placebo ([redacted]) (Table 38).

Table 38: Endoscopic remission at Week 52 (NRI-C; U-ENDURE ITT1 population)

Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CR, clinical response; CSR, clinical study report; ITT, intention to treat; NA, not applicable; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; SES-CD, Simple Endoscopic Score for Crohn's Disease; UPA, upadacitinib. Source: U-ENDURE CSR (87). Note: endoscopic remission defined as SES-CD ≤4 and ≥2-point reduction from baseline and no subscore >1 in any individual variable, as scored by central reviewer. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.3.6.3.2.3 CDAI clinical remission and endoscopic remission at Week 52

At Week 52, almost [redacted] receiving upadacitinib 30 mg achieved both CDAI clinical remission and endoscopic remission; a significantly greater proportion than in the placebo arm [redacted] (Table 39). In the upadacitinib 15 mg arm, [redacted] of subjects achieved this outcome, which was also significantly greater than the placebo arm ([redacted]) (Table 39).

Table 39: CDAI clinical remission and endoscopic remission at Week 52 (NRI-C; U-ENDURE ITT1 population)

Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CR, clinical response; CSR, clinical study report; ITT, intention to treat; NA, not applicable; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; SES-CD, Simple Endoscopic Score for Crohn's Disease; UPA, upadacitinib. Source: U-ENDURE CSR (87). Note: CDAI clinical remission defined as CDAI score <150. endoscopic remission defined as SES-CD ≤4 and ≥2-point reduction from baseline and no subscore >1 in any individual variable, as scored by central reviewer. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.3.6.3.2.4 Discontinuation of corticosteroid use and CDAI clinical remission at Week 52

Table 40 shows the proportion of subjects who were steroid-free for at least 90 days prior to Week 42 and achieved CDAI clinical remission at Week 52. The proportion of patients achieving this outcome was [redacted] in the upadacitinib 30 mg arm and [redacted] in the upadacitinib 15 mg arm, which was significantly better than in the placebo arm ([redacted]; [redacted]) (Table 40).

Table 40: Without corticosteroid use for CD ≥90 days prior to Week 52 and achievement of CDAI clinical remission at Week 52 (NRI-C; U-ENDURE ITT-1 population)

Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							

Abbreviations: CD, Crohn's Disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NA, not applicable; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.
Source: U-ENDURE CSR (87). Note: CDAI clinical remission defined as CDAI score <150. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

Table 41 shows the proportion of subjects who were receiving corticosteroids for CD and induction baseline and who were steroid-free for ≥90 days prior to Week 52 and achieved CDAI clinical remission at Week 52. The proportion of subjects achieving this outcome was the same with both maintenance doses of upadacitinib ([redacted]) and statistically significantly better than the placebo arm ([redacted] both p<0.0001) (Table 41).

Table 41: Discontinuation of corticosteroid use for CD ≥90 days prior to Week 52 and achievement of CDAI clinical remission at Week 52 in subjects taking corticosteroids for CD at induction baseline (NRI-C; U-ENDURE ITT1 population)

Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							

Abbreviations: CD, Crohn's Disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NA, not applicable; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.
Source: U-ENDURE CSR (87). Note: CDAI clinical remission defined as CDAI score <150. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.3.6.3.2.5 CD-related hospitalisation during the 52-week maintenance period

Table 42 shows the occurrence of CD-related hospitalisations during the 52-week maintenance period. No statistically significant differences were observed between the treatment groups (Table 42).

Table 42: CD-related hospitalisation during the 52-week maintenance period (AO; U-ENDURE ITT1 population)

Treatment	Responder					Incidence rate diff. vs PBO		
	N	n (%)	Time at risk (PY)	Incidence rate (n/100PY)	95% CI†	Diff.‡	95% CI§	P value
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AO, as observed; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CR, clinical response; CSR, clinical study report; ITT, intention to treat; NA, not applicable; NR, not reported; PBO, placebo; PY, patient-years; UPA, upadacitinib.
Source: U-ENDURE CSR (87). †95% CI for incidence rate is based on the normal approximation to binomial distribution. ‡Incidence rate difference = UPA – PBO. §95% CI for incidence rate difference and p value are based on the normal approximation to Poisson distribution.

B.3.6.3.2.6 EQ-5D-5L at Week 52

Statistically significant improvements in the EQ-5D-5L index value and EQ-5D VAS were observed with upadacitinib 30 mg compared with placebo at Week 52. The improvement from baseline (LS mean) was [redacted] in the upadacitinib 30 mg arm and [redacted] in the placebo arm, with a statistically significant between-treatment difference of [redacted] (Table 43). The improvement from baseline with upadacitinib 15 mg was [redacted], which was not statistically significantly different from placebo (LS mean difference [redacted]) (Table 43).

Similar results were observed for the EQ-5D VAS score. Subjects in the upadacitinib 30 mg arm had a significantly greater improvement from baseline compared with the placebo arm (LS mean [redacted]), giving a between-treatment difference of [redacted] (Table 43). Similarly, the improvement from baseline with upadacitinib 15 mg was [redacted], which was significantly different from placebo (LS mean difference [redacted]) (Table 43).

Table 43: Change from induction baseline in EQ-5D-5L at Week 52 (MMRM; U-ENDURE ITT1 population)

Outcome Treatment	Within group change from baseline					Between group difference vs PBO		
	N	Baseline mean	Visit mean	LS mean	95% CI	LS mean	95% CI	P value
EQ-5D-5L index value								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							
EQ-5D VAS								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CI, confidence interval; CSR, clinical study report; DB, double-blind; EQ-5D-5lL, EuroQol-5 dimensions-5 Levels; LS, least squares; MMRM, mixed effect model repeat measurement; non-Bio-IR, conventional therapy inadequate response/intolerance; OL, open-label; PBO, placebo, PRO, patient-reported outcome; UPA, upadacitinib; VAS, visual analogue scale.
Source: U-ENDURE CSR (87). Note: MMRM is the mixed effect model repeat measurement with induction baseline value, Week 0 value, stratification factors (prior induction population [non-Bio-IR, DB bio-IR, OL bio-IR), PRO clinical remission [yes/no], and endoscopic response status [yes/no]), treatment visit, visit, treatment-by-visit interaction included in the model. Induction baseline was defined as the last non-missing observation prior to the first dose of study drug in U-EXCEL/U-EXCEED. An unstructured covariance matrix was used.

Additional outcomes beyond those presented in Section B.3.6.3 are presented in Appendix J and listed below:

- CDAI clinical remission at Week 2
- PRO clinical remission at Week 52
- CDAI clinical remission at Week 52 in subjects who achieved CDAI clinical remission at Week 0
- PRO clinical remission in subjects at Week 52 in subjects who achieved PRO clinical remission at Week 0
- PRO clinical remission and endoscopic remission at Week 52
- Change from induction baseline in FACIT-F total score at Week 52
- Change from induction baseline in IBDQ total score at Week 52
- Resolution of EIMs at Week 52 in subjects with any EIMs at induction baseline
- Without corticosteroids/discontinuation of corticosteroids and CDAI clinical remission at Week 52

B.3.7 Subgroup analysis

As described in Section B.1, this submission presents evidence for upadacitinib in the BF (Bio-IR) population, a subpopulation of the anticipated licensed population for upadacitinib. Data on the CCF (non-Bio-IR) subpopulation are presented in Appendix J for completeness.

In addition, subgroup data are presented for subjects with prior TNF-alpha inhibitor failure (failed 1 or >1 TNF-alpha inhibitor) and for subjects who had draining fistulas at baseline (see Appendix E).

B.3.8 Meta-analysis

The absence of head-to-head data prevented a standard meta-analysis of RCTs from being performed. Instead, a comprehensive network meta-analysis (NMA) was conducted; this enabled comparisons with other biologic therapies included in the NICE scope and allowed for more precise estimates of treatment effects to be calculated compared with a naïve comparison of trials. The NMA is presented in Section B.3.9.

B.3.9 Indirect and mixed treatment comparisons

B.3.9.1 Methodology

Full details of the methodology for the indirect/mixed treatment comparison are provided in Appendix D. A brief overview of the methodology is presented in Section B.3.9.1.

B.3.9.1.1 Analysis scope

As discussed in Section B.3.1, an SLR was conducted to identify all relevant clinical evidence on the efficacy and safety of upadacitinib and comparators for the treatment of moderately to severely active CD in adults. In the absence of head-to-head RCTs between all comparators specified in the NICE scope, an NMA was performed to assess the relative efficacy of upadacitinib compared with relative comparators (ustekinumab, vedolizumab) in adults with moderately to severely active CD who experienced BF. The Bio-IR population in the upadacitinib clinical trials is considered

analogous to the BF population (see Section B.3.3.1 for more details). NMAs were also performed for the non-Bio-IR population (considered analogous to the CCF population) and results are presented in Appendix L. The methodology of the SLR that identified studies used in the NMAs is described in Appendix D.

B.3.9.1.2 Study selection for NMA

As described in Appendix D, a total of 290 records met the inclusion criteria of the clinical SLR, reporting on 71 original studies. After applying the inclusion/exclusion criteria, 10 unique trials reported by 11 records were included in the NMA. A list of all studies excluded from the NMA (including reason for exclusion) is available in Appendix D.

The interventions and doses of interest included in the NMAs for the induction and maintenance phases are presented in Appendix D. For each of the interventions, only licensed UK doses were included in the analysis. A summary of the trials used to conduct the NMA is presented in Table 44.

Table 44: Summary of trials used in the NMA

Study	Active treatment(s)	CCF/ BF	Induction CDAI remission	Induction CR-100	Maintenance CDAI remission
			Week data was collected		
U-EXCEL†	UPA45	Both	12	12	NA
U-EXCEED†	UPA45	BF	12	12	NA
U-ENDURE†	UPA15; UPA30	Both	NA	NA	52
UNITI 1 (81, 91)	UST	BF	6	6	NA
UNITI 2 (81, 91)	UST	CCF	6	6	NA
IM-UNITI (81, 91)	UST Q8W; Q12W	Both	NA	NA	44
GEMINI 2 (82, 92)	Ind: VDZ IV; Maint: VDZ IV Q4W; VDZ IV Q8W	Both	6	6	52
GEMINI 3 (92, 93)	VDZ IV	Both	6	6	
VISIBLE 2 (94, 95)	VDZ SC	Both	NA	NA	52
Watanabe et al (2020) (96)	Ind: VDZ IV; Maint: VDZ IV Q8W	Both	10	10	60

Abbreviations: ADA, adalimumab; BF, biologic failure; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; CR-100, clinical response ≥100-point decrease from baseline in CDAI score; IFX, infliximab; Ind, induction; IV, intravenous; Maint, maintenance; NA, not applicable; NMA, network meta-analysis; QxW, every x weeks; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
† CSR data used in NMA.

B.3.9.1.3 Outcomes of interest

Outcomes assessed using NMA included CDAI clinical remission and CDAI clinical response (CR-100), as defined in Table 45. The definitions for these outcomes used in the NMA align with those used in the upadacitinib clinical trials (see Section B.3.3.3). CDAI outcomes were of interest as they facilitate comparison with comparator therapies. Furthermore, these outcomes have historically been used in CD clinical studies and their use in the NMA is consistent with clinical trials of ustekinumab and vedolizumab in CD (unlike endoscopic outcomes, which were not universally assessed in the ustekinumab and vedolizumab trials) (57, 81, 82). CDAI outcomes were generally assessed after an induction phase of 4 to 12 weeks and a maintenance phase of 44 to 60 weeks (see Appendix D for more details).

Table 45: CDAI outcomes assessed in NMA

Outcome	Definition
CDAI clinical remission	Clinical remission was defined as CDAI score <150 points at endpoint measurement
CDAI-100 clinical response (CR-100)	Clinical response (≥100 CDAI response) was defined as a ≥100-point decrease from baseline in CDAI score at endpoint measurement

Abbreviations: CDAI, Crohn's Disease Activity Index; CR, clinical response; NMA< network-meta-analysis. Note: CR-100 defined as decrease of ≥100 points in CDAI from baseline.

In the NMAs, CDAI clinical remission and CDAI clinical response (CR-100) were assessed for induction trials, while CDAI clinical remission was assessed for maintenance trials (clinical response was not generally reported in the maintenance trials as only patients with a clinical response at the end of induction continued to the maintenance trials). Outcomes were assessed by CCF and BF subgroups (Table 46).

Table 46: Trials reporting CDAI outcomes used in the NMA

Population	CCF		BF	
Treatment phase	**Induction**	**Maintenance**	**Induction**	**Maintenance**
Studies reporting CDAI outcomes	• GEMINI 2 • GEMINI 3 • U-EXCEL • UNITI-2 • Watanabe et al. (2020)	• GEMINI 2 • IM-UNITI • U-ENDURE • VISIBLE 2 • Watanabe et al. (2020)	• GEMINI 2 • GEMINI 3 • U-EXCEL • U-EXCEED • UNITI-1 • Watanabe et al. (2020)	• GEMINI 2 • IM-UNITI • U-ENDURE • VISIBLE 2 • Watanabe et al. (2020)

Abbreviations: BF, biologic failure; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index.

In addition to CDAI outcomes, NMAs were conducted for serious AEs and discontinuation due to AEs. Most trials did not report safety outcomes by subpopulation (CCF or BF) and therefore safety NMAs were conducted in the overall population only (Table 47, for full methods and results, see Appendix D).

Table 47: Trials reporting safety outcomes assessed in the NMA

Study	Active treatment(s)	Induction/ Maintenance	Serious AE	Discontinuation due to AE
GEMINI 2	Ind: VDZ IV; Maint: VDZ IV Q4W; VDZ IV Q8W	Both	✓	✓
GEMINI 3	VDZ IV	Ind.	✓	✓
IM-UNITI	UST Q8W; UST Q12W	Maint.	✓	✓
U-ENDURE	UPA 15; UPA 30	Maint.	✓	✓
U-EXCEED	UPA 45	Ind.	✓	✓
U-EXCEL	UPA 45	Ind.	✓	✓
UNITI 1	UST	Ind.	✓	✓
UNITI 2	UST	Ind.	✓	✓
VISIBLE 2	VDZ SC	Maint.	✓	✓
Watanabe et al. 2020	Ind: VDZ IV; Maint: VDZ IV Q8W	Both	✓	✓

Abbreviations: ADA, adalimumab; AE, adverse event; IFX, infliximab; Ind., induction; IV, intravenous; Maint., maintenance; QxW, every x weeks; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

B.3.9.1.4 Summary of trials included in NMA

A summary of the trials included in the base case and sensitivity analysis NMAs, as well as the reporting of outcomes from each study considered for inclusion, is detailed in Appendix D.

B.3.9.1.5 Overview of NMA methodology

A Bayesian NMA approach was selected to indirectly compare upadacitinib with relevant comparators using an evidence base of published RCTs. Binary outcomes were modelled with a binomial likelihood and a risk difference (RD) link (NICE decision support unit [DSU] technical support document [TSD] 2 (97, 98)). An NMA feasibility assessment was performed based on the included RCTs; full details of the methodology and feasibility assessment are presented in Appendix D.

B.3.9.1.5.1 Model selection

Model selection was made after comparing model fit statistics, leverage plots, and density plots of posterior SDs for each set of two risk difference models (FE and RE; see Appendix D for more details). Due to heterogeneity in reported placebo rates in the included trials, a risk difference approach was utilised rather than an unadjusted approach as this approach was less sensitive to differences in placebo response rates; see Section B.3.9.1.5.3 for further information. FE models were selected for all outcomes in the base case; justification for this approach is provided in Appendix D with the main reason being the small number of trials eligible for inclusion in each network leading to implausible estimates of the between-study standard deviation when RE models were used.

B.3.9.1.5.2 Upadacitinib post-hoc CDAI 220–450 inclusion criterion

For robust NMAs, a key assumption is that populations are sufficiently similar and comparable across the included trials. All trials included in the NMAs applied a similar CDAI score inclusion criterion, except for the upadacitinib studies. Instead of the CDAI score, the upadacitinib induction trials (U-EXCEL and U-EXCEED) used two key CD symptoms of abdominal pain and stool frequency as inclusion criteria (both are components of CDAI; see Appendix K for full details). To align with the CDAI score inclusion criterion (220–450) applied in the other CD trials in the NMA, post-hoc

analyses were conducted to obtain upadacitinib trial results in a population with a baseline CDAI score of 220–450.

After applying the post-hoc inclusion analysis, approximately 80% of patients were retained in each arm of the upadacitinib trials. In general, baseline CDAI values for the whole population and for the post-hoc CDAI 220–450 restricted population of U-EXCEL and U-EXCEED were comparable to the values observed in other CD trials (Table 48). As the trials had a re-randomisation design, only patients who were included in the induction trials (and had a clinical response) moved to the maintenance trials. Therefore, only the baseline CDAI scores for the induction studies are presented in Table 48. Baseline characteristics and treatment efficacy also remained similar between the whole trial population and the post-hoc CDAI 220–450 restricted population (see Appendix C). Therefore, data from the CDAI 220–450 restricted population from the upadacitinib trials was used in the base case NMA to maximise the potential comparability of the trial populations.

Table 48: CDAI inclusion criteria and mean baseline CDAI scores of included BF induction populations

Trial	CDAI inclusion criterion	Treatment arm	CDAI score, mean (SD)	Treatment arm	CDAI score, mean (SD)
U-EXCEL	None	PBO	299 (97)	UPA 45	302 (85)
U-EXCEL (CDAI restricted)	220–450	PBO	313 (62)	UPA 45	317 (58)
U-EXCEED	None	PBO	308 (84)	UPA 45	307 (89)
U-EXCEED (CDAI restricted)	220–450	PBO	318 (58)	UPA 45	315 (59)
GEMINI 2*	220–450	PBO	325 (78)	VDZ IV	327 (71)
GEMINI 3	220–400	PBO	306 (55)	VDZ IV	316 (53)
Watanabe 2020*	220–450	PBO	295 (65)	VDZ IV	304 (63)
UNITI-1	220–450	PBO	319 (60)	UST	328 (62)

Abbreviations: BF, biologic failure; CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; IV, intravenous; PBO, placebo; SD, standard deviation; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
*indicates that baseline CDAI is only reported for the overall population and not by CCF/BF subgroup.

B.3.9.1.5.3 Risk-difference approach

The risk-difference approach was selected to minimise the impact of different placebo rates which were observed across the included trials (efficacy data for the placebo groups across the different trials are presented in Appendix D) and because of the intuitive presentation of results when generated on the risk-difference scale. The implications of this approach are discussed in further detail in section B.3.9.3.1.

B.3.9.1.6 Sensitivity analysis methodology

Sensitivity analyses were conducted using RE NMA (FE was used in all base case analyses) and the results are presented in Appendix L. Overall, the RE NMA results were comparable to the FE model results, although there were larger CrIs across most comparisons. This is to be expected as the RE NMA incorporates between-study differences in its efficacy estimates.

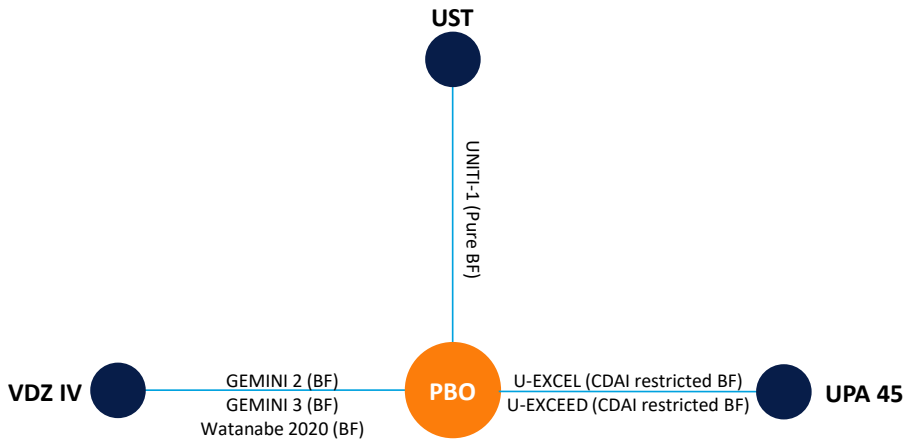
B.3.9.1.7 NMA networks

Separate analyses were performed for the induction and maintenance trials for the BF population. In all networks, placebo was the common comparator. NMAs were also performed for the CCF population and are presented in Appendix L.

B.3.9.1.7.1 BF population

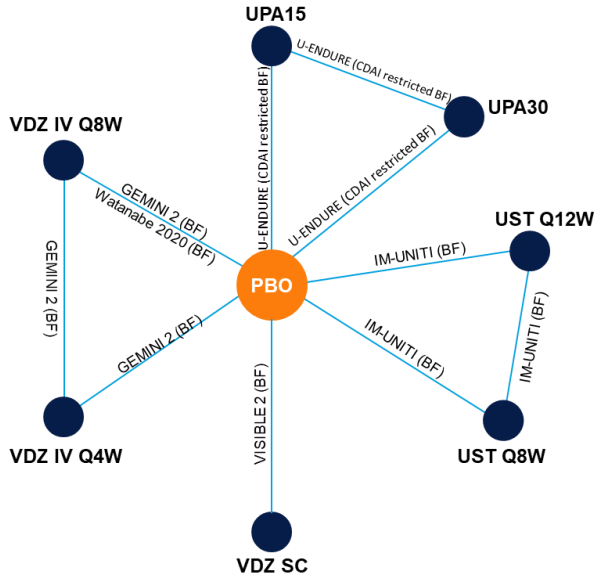
The BF population networks for the induction and maintenance phases are presented in Figure 6 and Figure 7, respectively.

Figure 6: Network diagram of included induction studies in the BF population



Abbreviations: BF, biologic failure; IV, intravenous; PBO, placebo; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

Figure 7: Network diagram of included maintenance studies in the BF population



Abbreviations: BF, biologic failure; IV, intravenous; PBO, placebo; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

B.3.9.2 Results

The following sections report results from the NMA for CDAI outcomes, which have been used to inform the assumption that upadacitinib is likely to provide similar or greater health benefits than its comparators. The results are reported as RD with credible intervals (CrI, 95% CrIs presented throughout). Please note that 'significance' in these results is defined by CrIs not crossing zero; these analyses should not be interpreted in a frequentist manner. In addition, safety outcomes are presented to support comparison of upadacitinib with relevant active comparators.

For each combination of outcome and NMA, league tables of the relative effect estimate for all possible pair-wise comparisons are presented.

Additional results for base-case analysis are presented in Appendix L:

- Relative effect estimates for each relevant comparator versus placebo on the RD scale
- Predicted absolute outcomes for each treatment
- Surface Under the Cumulative RAnking (SUCRA) values for each treatment (99)[3]

[3] SUCRA would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst

B.3.9.2.1 Base-case analysis – induction CDAI-100 clinical response (CR-100)

Table 49 presents the base-case NMA results for CDAI clinical response (CR-100) with induction upadacitinib versus comparators in a BF population.

The NMA results show a RD of [redacted] for upadacitinib versus placebo, showing that there is a [redacted] greater probability of CDAI clinical response in patients receiving upadacitinib versus placebo.

Table 49: Results for CDAI clinical response (CR-100) in BF induction NMA (FE model)

	VDZ IV	UPA	UST	PBO
PBO	[redacted]	[redacted]	[redacted]	
UST	[redacted]	[redacted]		[redacted]
UPA	[redacted]		[redacted]	[redacted]
VDZ IV		[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failure; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

B.3.9.2.2 Base case analysis – induction CDAI clinical remission

Table 50 presents the base case NMA results for CDAI clinical remission with induction upadacitinib versus comparators in a BF population.

The NMA results show a RD of [redacted] for upadacitinib versus placebo, showing that there is a [redacted] greater probability of CDAI clinical remission in patients receiving upadacitinib versus placebo.

Table 50: Results for CDAI clinical remission in BF induction NMA (FE model)

	VDZ IV	UPA	UST	PBO
PBO	[redacted]	[redacted]	[redacted]	
UST	[redacted]	[redacted]		[redacted]
UPA	[redacted]		[redacted]	[redacted]
VDZ IV		[redacted]	[redacted]	[redacted]

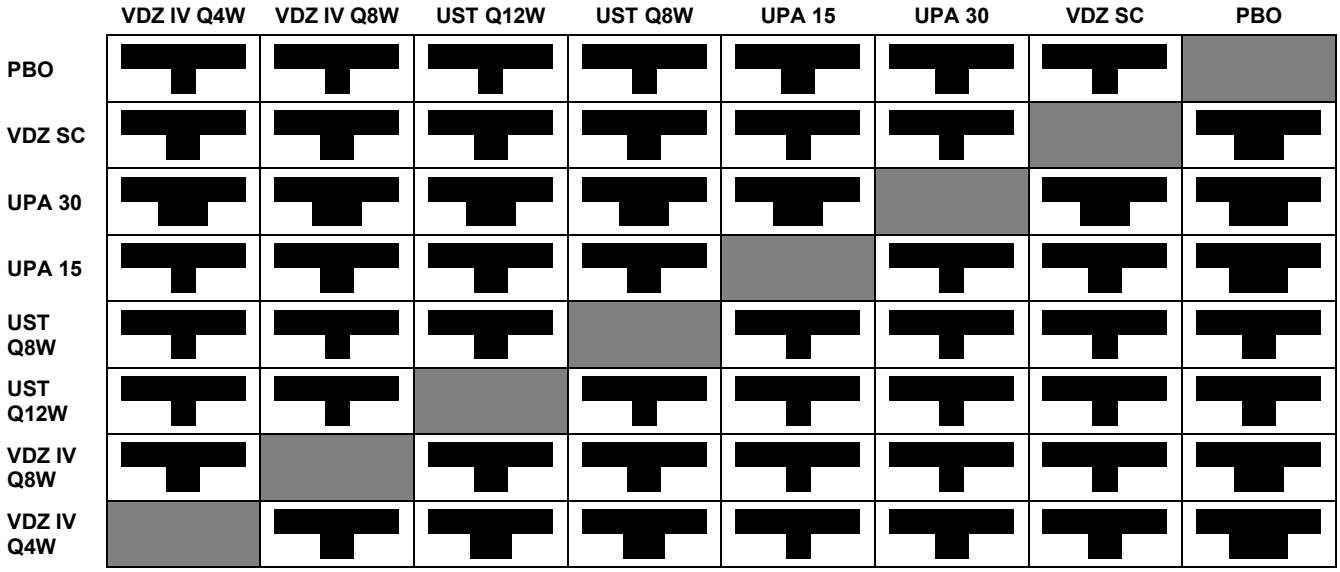
Abbreviations: BF, biologic failure; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

B.3.9.2.3 Base case analysis – maintenance CDAI clinical remission

Table 51 presents the base case NMA results for CDAI clinical remission with maintenance upadacitinib versus comparators in a BF population.

The NMA results show a RD of [redacted] for upadacitinib 30 mg and [redacted] for upadacitinib 15 mg versus placebo, showing that there is a [redacted] and [redacted] greater probability of CDAI clinical remission in patients receiving upadacitinib 30 mg and 15 mg versus placebo, respectively.

Table 51: Results for CDAI clinical remission in BF maintenance NMA (FE model)



Abbreviations: BF, biologic failure; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; QxW, every x weeks; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

B.3.9.2.4 Base case analysis – safety outcomes

Due to reporting limitations, safety events were taken as defined/reported in the relevant publications and not stratified by CCF or BF subgroup. Therefore, outcomes presented in this section are for the overall population (still with the CDAI 220–450 restriction, as described in Section B.3.9.1.5.2) and are presented for the induction and maintenance periods.

B.3.9.2.4.1 Serious AEs (induction)

Table 52 presents the base case NMA results for serious AEs with induction upadacitinib versus comparators in an overall population.

The NMA results show a RD of [redacted] with upadacitinib versus placebo, showing that the rate of serious AEs was comparable between upadacitinib and placebo.

Table 52: Results for serious AEs in induction NMA (FE model)

	VDZ IV	UPA	UST	PBO
PBO	[redacted]	[redacted]	[redacted]	
UST	[redacted]	[redacted]		[redacted]
UPA	[redacted]		[redacted]	[redacted]
VDZ IV		[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

B.3.9.2.4.2 Serious AEs (maintenance)

Table 53 presents the results for serious AEs with maintenance upadacitinib versus placebo in an overall population (still with the CDAI 220–450 restriction, as described in Section B.3.9.1.5.2).

The NMA results show a RD of [redacted] with upadacitinib 30 mg versus placebo and [redacted] with upadacitinib 15 mg versus placebo, showing that the rate of serious AEs was comparable between both upadacitinib doses and placebo. The results also showed a trend towards fewer serious AEs with any active treatment compared with placebo.

Table 53: Results for serious AEs in maintenance NMA (FE model)

	VDZ IV Q4W	VDZ IV Q8W	UST Q12W	UST Q8W	UPA 15	UPA 30	VDZ SC	PBO
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV Q4W		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; QxW, every x weeks; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered ‘significant’ (no ‘significant’ results were observed in this NMA).

B.3.9.2.4.3 Discontinuation due to AEs (induction)

Table 54 presents the base case NMA results for discontinuation AEs with induction upadacitinib versus comparators in an overall population (still with the CDAI 220–450 restriction, as described in Section B.3.9.1.5.2).

The NMA results show a RD of [redacted] for upadacitinib versus placebo, showing that the rate of discontinuation due to AEs was comparable between upadacitinib and placebo.

Table 54: Results for discontinuation due to AEs in induction NMA (FE model)

	VDZ IV	UPA	UST	PBO
PBO	[redacted]	[redacted]	[redacted]	
UST	[redacted]	[redacted]		[redacted]
UPA	[redacted]		[redacted]	[redacted]
VDZ IV		[redacted]	[redacted]	[redacted]

Abbreviations: CCF, conventional care failure; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

B.3.9.2.4.4 Discontinuation due to AEs (maintenance)

Table 53 presents the base case NMA results for discontinuation AEs with maintenance upadacitinib versus comparators in an overall population (still with the CDAI 220–450 restriction, as described in Section B.3.9.1.5.2).

The NMA results show a RD of [redacted] for upadacitinib 30 mg and [redacted] for upadacitinib 15 mg versus placebo, showing that the rate of discontinuation due to AEs was comparable between both doses of upadacitinib and placebo.

Table 55: Results for discontinuation due to AEs in maintenance NMA (FE model)

	VDZ IV Q4W	VDZ IV Q8W	UST Q12W	UST Q8W	UPA 15	UPA 30	VDZ SC	PBO
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
VDZ SC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV Q4W		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; QxW, every x weeks; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered ‘significant’.

B.3.9.3 Uncertainties in the indirect and mixed treatment comparisons

B.3.9.3.1 RD NMA method

The NMAs used in this submission utilised the RD method, which was used in this instance as it is recommended where baseline risk-adjusted models are deemed inappropriate due to lack of convergence or face validity (97).

Like baseline risk adjustment, RD NMA is also recognised as valid framework by NICE (DSU TSD2, Section 3.7 (97)). It has been used in publications and prior submissions to NICE (100, 101). Cameron et al. (2018) (102) found that use of an NMA on the RD scale represents a viable alternative approach to account for the presence of cross-study differences in placebo response rates. Per NICE DSU TSD2 (98, 103), RD NMA could be used as an alternative method to log-odds NMA when there are imbalances in the number of studies with low placebo response rates across pairwise contrasts in the network. The RD model code utilised was adapted from Dias et al. (2018) (98), which was based on modelling frameworks by Warn et al. (2002) (104).

In TA521, RD was used to adjust for cross-trial differences (100). Rather than calculating relative effects as ratios (such as odds ratios produced by traditional logit-link NMA frameworks), absolute probabilities of treatment response were subtracted across interventions in RD models to minimise the potential impacts of overly low or high placebo efficacy. This may help to minimise bias when there are imbalances in the number of studies with low placebo response rates across pairwise contrasts in the network. TA521 concluded that baseline-risk adjusted models and risk difference NMAs should yield less biased estimates of effect than the unadjusted NMA analyses on the relative scale.

Due to the general paucity of data in the relevant CD evidence networks leading to poor performance of baseline-risk adjusted logit-link NMAs, RD NMAs provided an attractive option to minimise impacts of placebo heterogeneity on NMA-produced treatment effect estimates.

Criticism of RD models stems from potential model instability, leading to lack of convergence and sensitivity to starting values (102). However, the RD models in the

CD NMA analysis in this submission converged and had appropriate fit (more details on model fit are presented in Appendix D). Appropriate vague prior distributions were utilised which corresponded to the RD scale. Starting values were utilised which are dispersed across the probability space.

In summary, the RD models addressed placebo rate variation of the sort observed in the biologic CD trials, yielded reasonable estimates, passed diagnostic tests based on their convergence and fit, are accepted by NICE, have been used in prior submissions, and have appeared in the published academic literature.

B.3.9.4 Conclusion

Induction upadacitinib was found to have superior efficacy to ustekinumab, vedolizumab, and placebo for CDAI clinical remission and clinical response. As maintenance therapy, upadacitinib was also superior to its comparators. Safety outcomes (serious AEs and discontinuation due to AEs) were comparable between upadacitinib and the comparators, including placebo.

B.3.10 Adverse reactions

The primary safety data for upadacitinib in this submission is taken from CSRs. AEs were coded using MedDRA version 24.0. In this section, 'Crohn's disease' refers to worsening of underlying CD compared with baseline.

B.3.10.1 U-EXCEL and U-EXCEED

The following section presents safety data from U-EXCEL and U-EXCEED separately; pooled safety data are presented in Appendix J.

B.3.10.1.1 TEAEs

TEAEs in U-EXCEL and U-EXCEED were defined as events that began or worsened either on or after the first dose of the study drug and:

- Within 30 days after the last dose of the study drug for subjects who did not participate in U-ENDURE
- Within 30 days after the last dose of the study drug in U-EXCEL or U-EXCEED and before the first dose of the study drug in U-ENDURE if the subject enrolled in U-ENDURE

An overview of TEAEs and deaths reported in U-EXCEL and U-EXCEED is presented in Table 56. Data are presented for the SA1 population, which included all subjects who received ≥1 dose of study drug in the double-blind induction period (Part 1) of the trials, and for the SA2 population, which included all subjects who received at least one dose of open-label upadacitinib 45 mg in Part 2. Results are presented for the anticipated licensed induction dose of upadacitinib only (i.e., 45 mg QD). A summary of TEAEs occurring in ≥5% of subjects in the upadacitinib or placebo arms of U-EXCEL or U-EXCEED is presented in Table 57.

Table 56: Overview of TEAEs and deaths during the 12-week double-blind and open-label induction periods (U EXCEL and U-EXCEED SA1 and SA2 populations)

Event, n (%)	U-EXCEL			U-EXCEED		
	Part 1 (DB)		Part 2 (OL)	Part 1 (DB)		Part 2 (OL)
	UPA 45 mg N=350	PBO N=176	UPA 45 mg N=57	UPA 45 mg N=324	PBO N=171	UPA 45 mg N=129
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE related to COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE related to study drug (assessed by investigator)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to withdrawal of study treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE resulting in death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths occurring ≤30 days after last dose of study drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths occurring >30 days after last dose of study drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths due to COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: COVID-19, Coronavirus Disease 2019; CSR, clinical study report; DB, double-blind; OL, open-label; PBO, placebo; SA, safety analysis; TEAE, treatment-emergent adverse event; UPA, upadacitinib.
Source: U-EXCEL (85) and U-EXCEED (86) CSRs. Note: In U-EXCEL, TEAEs in the induction period (Part 1) were defined as events that begin either on or after the first dose of the study drug in Part 1 and until (i) the first dose of study drug in U-ENDURE (if applicable), or (ii) until the first dose of study drug in Part 2 (if applicable), or (iii) within 30 days after the last dose administration of the study drug in Part 1, whichever is earlier. TEAEs for Part 2 were defined as events that began either on or after the first dose of study drug in Part 2 and until (i) first dose of study drug in U-ENDURE (if applicable) or (ii) within 30 days after the last dose of study drug in Part 2, whichever is earlier. In U-EXCEED, TEAEs for Part 1/Part 2 were defined as events that began either on or after the first dose of the study drug in Part 1/Part 2 and until (i) the first dose of study drug in U-ENDURE (if applicable), or (ii) until the first dose of study drug in Part 3 (if applicable), or until (iii) within 3 days after the last dose administration of the study drug in Part 1, whichever is earlier. Subjects are counted once in each row, regardless of the number of events they may have had.

Table 57: TEAEs reported in ≥5% of subjects in any treatment group of U-EXCEL or U EXCEED during the 12-week double-blind and open-label induction periods (U-EXCEL and U-EXCEED SA1 and SA2 populations)

TEAE by MedDRA 24.0 preferred term, n (%)	U-EXCEL			U-EXCEED		
	Part 1 (DB)		Part 2 (OL)	Part 1 (DB)		Part 2 (OL)
	UPA 45 mg N=350	PBO N=176	UPA 45 mg N=57	UPA 45 mg N=324	PBO N=171	UPA 45 mg N=129
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acne	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Worsening of CD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CD, Crohn's disease; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; SA, safety analysis; TEAE, treatment-emergent adverse event; UPA, upadacitinib.
Source: U-EXCEL (85) and U-EXCEED (86) CSRs. Note: In U-EXCEL, TEAEs in the induction period (Part 1) were defined as events that begin either on or after the first dose of the study drug in Part 1 and until (i) the first dose of study drug in U-ENDURE (if applicable), or (ii) until the first dose of study drug in Part 2 (if applicable), or (iii) within 30 days after the last dose administration of the study drug in Part 1, whichever is earlier. TEAEs for Part 2 were defined as events that began either on or after the first dose of study drug in Part 2 and until (i) first dose of study drug in U-ENDURE (if applicable) or (ii) within 30 days after the last dose of study drug in Part 2, whichever is earlier. In U-EXCEED, TEAEs for Part 1/Part 2 were defined as events that began either on or after the first dose of the study drug in Part 1/Part 2 and until (i) the first dose of study drug in U-ENDURE (if applicable), or (ii) until the first dose of study drug in Part 3 (if applicable), or until (iii) within 3 days after the last dose administration of the study drug in Part 1, whichever is earlier. Subjects are counted once in each row, regardless of the number of events they may have had.

B.3.10.1.2 Adverse events of special interest

Adverse events of special interest (AESI) were prespecified in the statistical analysis plan (SAP) for U-EXCEL and U-EXCEED. These events were selected based on safety concerns reported for other JAK inhibitors, as well as upadacitinib data from preclinical studies. An overview of AESI in U-EXCEL and U-EXCEED is presented in Table 58. Overall, rates were comparable between the upadacitinib and placebo treatment arms. Anaemia was more frequently reported in the upadacitinib arm of U-EXCEL compared with placebo, but comparable rates were observed between the treatment arms in U-EXCEED (Table 58). Rates of serious infections were [redacted] in all

treatment groups, except for the open-label upadacitinib arm of U-EXCEED ([redacted]). Herpes zoster infection rates ranged from [redacted] in the upadacitinib arms of U-EXCEL and U-EXCEED, while no such infections were reported in the placebo group (Table 58). No cases of active TB or malignancies were reported in any of the trial arms.

Table 58: Overview of treatment-emergent AESI during the 12-week double-blind and open-label induction periods (U-EXCEL and U-EXCEED SA1 and SA2 populations)

Treatment-emergent AESI, n (%)	U-EXCEL			U-EXCEED		
	Part 1 (DB)		Part 2 (OL)	Part 1 (DB)		Part 2 (OL)
	UPA 45 mg N=350	PBO N=176	UPA 45 mg N=57	UPA 45 mg N=324	PBO N=171	UPA 45 mg N=129
Anaemia	[redacted]					
Hepatic disorders	[redacted]					
CPK elevations	[redacted]					
Lymphopenia	[redacted]					
Herpes zoster	[redacted]					
Serious infections	[redacted]					
Neutropenia	[redacted]					
Adjudicated cardiovascular events						
Opportunistic infections excluding TB and herpes zoster						
Renal dysfunction						
Adjudicated GI perforations						
Active TB						
Malignancies (all types)						
Malignancies excluding NMSC						
NMSC						
Lymphoma						
Adjudicated thrombotic events						

Abbreviations: AESI, adverse events of special interest; CPK, creatine phosphokinase; CSR, clinical study report; DB, double-blind; GI, gastrointestinal; NMSC, non-melanoma skin cancer; OL, open-label; PBO, placebo; SA, safety analysis; TB, tuberculosis; UPA, upadacitinib. Source: U-EXCEL (85) and U-EXCEED (86) CSRs. Note: In U-EXCEL, TEAEs in the induction period (Part 1) were defined as events that begin either on or after the first dose of the study drug in Part 1 and until (i) the first dose of study drug in U-ENDURE (if applicable), or (ii) until the first dose of study drug in Part 2 (if applicable), or (iii) within 30 days after the last dose administration of the study drug in Part 1, whichever is earlier. TEAEs for Part 2 were defined as events that began either on or after the first dose of study drug in Part 2 and until (i) first dose of study drug in U-ENDURE (if applicable) or (ii) within 30 days after the last dose of study drug in Part 2, whichever is earlier. In U-EXCEED, TEAEs for Part 1/Part 2 were defined as events that began either on or after the first dose of the study drug in Part 1/Part 2 and until (i) the first dose of study drug in U-ENDURE (if applicable), or (ii) until the first dose of study drug in Part 3 (if applicable), or until (iii) within 3 days after the last dose administration of the study drug in Part 1, whichever is earlier.

B.3.10.2 U-ENDURE

B.3.10.2.1 TEAEs

In U-ENDURE, TEAEs were defined as events that began either on or after the first dose of study drug in the maintenance phase and until (i) the first dose of study drug in the long-term extension phase (if applicable), or (ii) the first dose of open-label upadacitinib 30 mg QD rescue therapy (if applicable), or (iii) within 30 days after the last dose administration of the double-blinded drug in the maintenance phase, whichever is earlier. An overview of TEAEs and deaths occurring during U-ENDURE is presented in Table 59. A summary of TEAEs occurring in ≥5% of patients in U-ENDURE is presented in Table 60.

Table 59: Overview of TEAEs and deaths during the 52-week maintenance period (U-ENDURE SA1 population)

Event, n (%)	UPA 30 mg N=229	UPA 15 mg N=221	PBO N=223
Any TEAE	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
TEAE related to study drug (assessed by investigator)	[redacted]	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]
TEAE leading to withdrawal of study treatment	[redacted]	[redacted]	[redacted]
TEAE resulting in death	[redacted]	[redacted]	[redacted]
Deaths occurring ≤30 days after last dose of study drug	[redacted]	[redacted]	[redacted]
Deaths occurring >30 days after last dose of study drug	[redacted]	[redacted]	[redacted]
Deaths due to COVID-19	[redacted]	[redacted]	[redacted]

Abbreviations: COVID-19, coronavirus disease 2019; CSR, clinical study report; PBO, placebo; SA, safety analysis; TEAE, treatment-emergent adverse event; UPA, upadacitinib.
Source: U-ENDURE CSR (87). Note: TEAEs were defined as events that began either on or after the first dose of study drug in the maintenance phase and until (i) the first dose of study drug in the long-term extension phase (if applicable), or (ii) the first dose of open-label upadacitinib 30 mg QD rescue therapy (if applicable), or (iii) within 30 days after the last dose administration of the double-blinded drug in the maintenance phase, whichever is earlier.

Table 60: TEAEs reported in ≥5% of subjects during the 52-week maintenance period (U-ENDURE SA1 population)

Event, n (%)	UPA 30 mg N=229	UPA 15 mg N=221	PBO N=223
Any TEAE	[redacted]	[redacted]	[redacted]
Crohn's disease	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Acne	[redacted]	[redacted]	[redacted]

Abbreviations: COVID-19, coronavirus disease 2019; PBO, placebo; SA, safety analysis; TEAE, treatment-emergent adverse event; UPA, upadacitinib.
Source: U-ENDURE CSR (87). Note: TEAEs were defined as events that began either on or after the first dose of study drug in the maintenance phase and until (i) the first dose of study drug in the long-term extension phase (if applicable), or (ii) the first dose of open-label upadacitinib 30 mg QD rescue therapy (if applicable), or (iii) within 30 days after the last dose administration of the double-blinded drug in the maintenance phase, whichever is earlier. Subjects are counted once in each row, regardless of the number of events they may have had.

B.3.10.2.2 Adverse events of special interest

An overview of treatment-emergent AESI during the 52-week maintenance phase of U-ENDURE is presented in Table 61. Rates of serious infections were similar across the treatment groups, with the lowest rate ([redacted]) observed in the upadacitinib 15 mg group and the highest rate ([redacted]) observed in the upadacitinib 30 mg group (Table 61). Rates of anaemia and lymphopenia were higher in the placebo group than in both of the upadacitinib groups. Adjudicated GI perforations, malignancy, MACE, and VTE were infrequent and most of these events were considered by the investigator to either be unrelated to the study drug or not unexpected in a CD population (87). No events of active TB or lymphoma were reported in any treatment groups (Table 61).

Table 61: Overview of treatment-emergent AESI during the 52-week maintenance period (U-ENDURE SA1 population)

Event, n (%)	UPA 30 mg N=229	UPA 15 mg N=221	PBO N=223
Anaemia	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]
Serious infections	[redacted]	[redacted]	[redacted]
Hepatic disorders	[redacted]	[redacted]	[redacted]
CPK elevations	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Adjudicated GI perforations	[redacted]	[redacted]	[redacted]
Renal dysfunction	[redacted]	[redacted]	[redacted]
Malignancies (all types)	[redacted]	[redacted]	[redacted]
Malignancies excluding NMSC	[redacted]	[redacted]	[redacted]
Opportunistic infections excluding TB and herpes zoster	[redacted]	[redacted]	[redacted]
Adjudicated thrombotic events	[redacted]	[redacted]	[redacted]
VTE	[redacted]	[redacted]	[redacted]
Other venous thrombosis	[redacted]	[redacted]	[redacted]
Arterial thromboembolic events (non-cardiac, non-neurologic)	[redacted]	[redacted]	[redacted]
Active TB	[redacted]	[redacted]	[redacted]
NMSC	[redacted]	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]	[redacted]
Adjudicated cardiovascular events	[redacted]	[redacted]	[redacted]
MACE	[redacted]	[redacted]	[redacted]
Other cardiovascular events	[redacted]	[redacted]	[redacted]
Undetermined/unknown cause of death	[redacted]	[redacted]	[redacted]

Abbreviations: AESI, adverse event of special interest; CPK, creatine phosphokinase; GI, gastrointestinal; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PBO, placebo; TB, tuberculosis; UPA, upadacitinib; VTE, venous thromboembolic event.
Source: U-ENDURE CSR (87). Note: MACE was defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. VTE was defined as deep vein thrombosis or pulmonary embolism (fatal and non-fatal). TEAEs were defined as events that began either on or after the first dose of study drug in the maintenance phase and until (i) the first dose of study drug in the long-term extension phase (if applicable), or (ii) the first dose of open-label upadacitinib 30 mg QD rescue therapy (if applicable), or (iii) within 30 days after the last dose administration of the double-blinded drug in the maintenance phase, whichever is earlier.

B.3.11 Conclusions about comparable health benefits and safety

The clinical benefits of upadacitinib compared with placebo have been demonstrated in two pivotal induction studies (U-EXCEL and U-EXCEED) and one pivotal maintenance study (U-ENDURE). In the NMA, upadacitinib was superior to vedolizumab and ustekinumab for CDAI clinical remission and clinical response (CR-100) in the induction period. For the maintenance period, upadacitinib was superior to its comparators for CDAI clinical remission (the only efficacy outcome assessed in the maintenance period). In NMAs for serious AEs and discontinuation due to AEs, upadacitinib showed comparable results to all comparators, including placebo.

B.3.11.1 Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

B.3.11.1.1 Efficacy

Upadacitinib is an oral treatment and, if approved, will be the first oral advanced therapy for CD. In clinical trials, upadacitinib has demonstrated that it is an effective and well-tolerated treatment for adults with moderately to severely active CD.

Across the three pivotal trials (U-EXCEL and U-EXCEED for induction, U-ENDURE for maintenance), upadacitinib met all co-primary endpoints of clinical remission (defined either by CDAI or PROs) and endoscopic response. In the overall populations of the upadacitinib arms, a significantly greater proportion of subjects achieved clinical remission and endoscopic response compared with placebo. A clear treatment effect was also observed in the BF subpopulation. Analysis of secondary efficacy outcomes demonstrated that upadacitinib is associated with higher rates of endoscopic remission than placebo at Week 12 of U-EXCEL and U-EXCEED. This effect was maintained to Week 52 of U-ENDURE.

Upadacitinib can rapidly improve symptoms that have a substantial impact on the lives of people with CD. In the induction studies, CDAI clinical remission was achieved as early as Week 4 in approximately [redacted] of subjects receiving upadacitinib ([redacted] in U-EXCEL and [redacted] in U-EXCEED; both significantly higher than placebo). In addition to

the clinical efficacy, statistically significant improvements in QoL (EQ-5D-5L) were observed in the upadacitinib arm at Week 4 in both induction studies.

The early (Week 2 and Week 4) onset of efficacy of upadacitinib is important for people with CD who experience a wide range of symptoms, including abdominal pain/distension, fatigue, and bowel obstruction or diarrhoea (23, 26, 27), as well a substantial impact on their QoL and daily activities (105, 106). Furthermore, CD is a progressive condition and disease duration correlates with accumulated bowel damage, meaning that an early treatment effect is important to achieve disease control and prevent structural damage (107). The time to response for currently available biologics is reported to range from 2 to 19 weeks in most patients (108), meaning that symptoms and QoL impairments are prolonged with the potential for more bowel damage to occur. Given that a proportion of patients will not respond to a specific (or any) biologic therapy, this length of time to onset can delay treatment switching (potentially to a more effective therapy) and achievement of improvements for patients.

In addition to its early efficacy onset, upadacitinib has demonstrated sustained efficacy in terms of clinical symptoms, endoscopic disease activity, and QoL measures. This durable effect is an area of unmet need with current CD biologic therapies as loss of response to biologic therapy has been reported in 66% of individuals (48). As described above, the primary efficacy endpoints of U-ENDURE were met and both upadacitinib maintenance doses (30 mg and 15 mg QD) demonstrated significantly better rates of clinical remission and endoscopic response compared with placebo at Week 52. Endoscopic remission rates at Week 52 were also significantly better with both doses of upadacitinib versus placebo. Meeting both clinical and endoscopic treatment targets over 52 weeks suggest that upadacitinib may facilitate long-term CD control. For example, improvements in endoscopic outcomes may reduce the future relapse rate, risk of penetrating complications, and surgery (61, 109) compared with people with severe ulcerations; mucosal healing has recently been recognised in UK clinical guidance as an important target for clinicians and people with CD (57).

Across all key secondary endpoints in U-ENDURE, both doses of upadacitinib showed statistically significant improvements compared with placebo, including for endoscopic remission and CDAI clinical response. QoL improvements were also maintained, with

statistically significant improvements in EQ-5D-5L observed with upadacitinib 30 mg and numerical improvements with upadacitinib 15 mg.

Finally, one of the key treatment aims in CD is the reduction or discontinuation of corticosteroids due to their association with AEs, including bone loss, mood disorders, insomnia, hypertension, elevated blood glucose, and hypoadrenalism (110). Corticosteroids are used as concomitant or bridging therapy in CD. However, in U-EXCEL, [redacted] of patients who were receiving corticosteroids for CD at baseline achieved clinical remission and were able to discontinue corticosteroids at Week 12 (i.e., achieved steroid-free remission), with similar treatment effects observed in the overall and Bio-IR, as well as in the upadacitinib arm of U-EXCEED. The effect of upadacitinib on steroid-free remission was maintained to Week 52 of U-ENDURE (approximately [redacted] steroid-free remission rate in both upadacitinib arms versus [redacted] in placebo).

B.3.11.1.2 Safety

Across the induction and maintenance studies, upadacitinib was generally safe and well-tolerated. The results of the upadacitinib CD trials did not identify any new safety risks compared with the known safety profile of upadacitinib, which has been established across six other indications with 19 Phase 3 trials and more than 5,000 patients.

In the 12-week induction and extended induction periods of U-EXCEL and U-EXCEED, upadacitinib 45 mg QD was well tolerated. Rates of serious AEs, severe AEs, and AEs leading to discontinuation of study drug were comparable between the upadacitinib 45 mg and placebo groups. One death was reported across the induction studies (in U-EXCEED) but was not considered to be related to the study drug. The most frequent AEs, occurring in ≥5% of subjects in the upadacitinib groups in either U-EXCEL or U-EXCEED, were acne, anaemia, nasopharyngitis, headache, CD, and upper respiratory tract infection.

Maintenance treatment with upadacitinib 30 mg or 15 mg QD for 52 weeks was also well tolerated. In the SA1 analysis set (representing Cohort 1), rates of overall AEs, serious AEs, severe AEs, and AEs leading to discontinuation of study drug were lower

in the upadacitinib groups than in the placebo group. The most frequent AEs, occurring in ≥5% of subjects in either of the upadacitinib groups, were worsening of CD, arthralgia, and pyrexia (CD worsening was reported more frequently in subjects receiving placebo compared with upadacitinib, which may reflect improvement in underlying CD among upadacitinib recipients). Rates of serious infection were comparable across the treatment groups. Herpes zoster, hepatic disorders, neutropenia, and creatine phosphokinase (CPK) elevations were reported more frequently in the upadacitinib 30 mg group than in the upadacitinib 15 mg and placebo groups. Anaemia and lymphopenia were more commonly reported in the placebo group than in the upadacitinib groups.

B.3.11.1.3 Indirect treatment comparison

In the absence of head-to-head RCTs between upadacitinib and the comparators specified in the NICE scope, a series of NMAs were performed to assess the relative efficacy of upadacitinib compared with relevant comparators (ustekinumab, vedolizumab) in people with moderately to severely active CD in the BF population. In the induction analyses, upadacitinib was superior to ustekinumab and vedolizumab for CDAI clinical remission and clinical response (CR-100). In the maintenance analyses, upadacitinib was generally superior to the comparators for CDAI clinical remission (the only outcome assessed). The safety NMAs, which were conducted for serious AEs and discontinuation due to AEs, showed that upadacitinib had a comparable safety profile to the comparators, including placebo.

B.3.11.2 Strengths and limitations of the clinical evidence base for the technology

B.3.11.2.1 Trial design

The U-EXCEL and U-EXCEED induction studies and the U-ENDURE maintenance study were large, multinational, placebo-controlled, well-conducted and methodologically robust studies with relevant and appropriate eligibility criteria. The upadacitinib clinical trial programme enrolled a total of [redacted]

B.3.11.2.2 Intervention and comparators

Upadacitinib is an oral therapy and offers advantages through its mode of administration, including increased flexibility for patients in the timing and location of administration, and minimal invasiveness. Clinicians have noted that IV treatment is often delayed due to limited IV capacity in clinics (12); oral therapy is advantageous in this regard because it can be taken as soon as required. All currently available advanced therapies for CD are administered either IV or SC and therefore upadacitinib would be the first oral advanced therapy for CD in the UK.

The upadacitinib trials included treatment arms with different doses of upadacitinib; however, this submission only presents results for upadacitinib doses that are expected to be licensed in UK clinical practice, i.e., 45 mg QD for induction and 30 mg or 15 mg QD for maintenance. All three studies were placebo-controlled, which facilitates indirect treatment comparison with multiple other comparator treatments through the respective placebo arms.

B.3.11.2.3 Patient characteristics

Baseline subject characteristics in the upadacitinib clinical trials were representative of the moderately to severely active CD population in the UK. Demographics and clinical characteristics were generally well balanced across the treatment arms of each trial, as well as across the three trials. Furthermore, based on clinical expert opinion (64), the Bio-IR and non-Bio-IR populations of the upadacitinib clinical trials are broadly representative of populations seen in UK clinical practice, namely those with prior biologic therapy experience (BF population) and those with no prior biologic therapy experience (CCF population), respectively.

B.3.11.2.4 Outcomes

U-EXCEL, U-EXCEED, and U-ENDURE provide efficacy and safety data of direct relevance to the anticipated license for upadacitinib in CD. A key strength of the trials is that the co-primary endpoints determine improvements in both clinical symptoms (determined by CDAI/PRO clinical remission) and in mucosal healing (determined by endoscopic response). Although CDAI is not widely used to measure disease severity in UK clinical practice, it remains relevant because it is linked to the HBI, which is

commonly used as a disease severity measure in the UK (88). Use of the CDAI also facilitated comparison of upadacitinib with ustekinumab and vedolizumab as it was the assessment method used in these trials. Inclusion of endoscopic response as a primary endpoint reflects a paradigm shift in CD treatment with mucosal healing now considered a key treatment goal due to its association with improved long-term outcomes (57-59). For UK clinical practice, endoscopic outcomes may be more informative than CDAI for quantifying disease severity; however, as they are less frequently reported in trials of other therapies, there are limitations when making comparisons using these outcomes. Therefore, including both CDAI and endoscopic outcomes in the upadacitinib trials provides clinically relevant data that can be used to draw meaningful comparisons with other CD therapies.

B.3.11.2.5 Safety

Upadacitinib was generally well tolerated in clinical trials; however, as upadacitinib is administered orally, it can be easily stopped if AEs occur. AEs are also likely to be of limited duration as a short half-life of approximately 9–14 hours (13).

B.3.11.2.6 Limitations

As described above, the upadacitinib trial populations broadly represent the moderately to severely active CD population in the UK. However, as the three trials were multinational, some of the subjects may have received prior treatment with a therapy that is not approved in the UK.

A limitation of the upadacitinib trials is that they were all placebo-controlled, meaning that no head-to-head data with active comparators were available. This limitation was addressed by performing indirect treatment comparisons with NMAs conducted in the CCF and BF populations.

A limitation of U-ENDURE (maintenance study) is the re-randomised responder-withdrawal design, which meant that subjects with a clinical response to upadacitinib 45 mg in the induction period could be re-randomised to placebo for maintenance; as a result, a proportion of subjects receiving placebo in U-ENDURE had previous exposure to upadacitinib. However, this has also been a limitation of pivotal maintenance trials of other advanced therapies for CD (81, 82).

The NMAs performed for induction upadacitinib versus comparators showed that upadacitinib tended to show improved efficacy versus comparators ([redacted] improvement versus placebo for CDAI clinical response and [redacted] improvement versus placebo for CDAI clinical remission in the BF populations, respectively).

B.3.12 Ongoing studies

Publications of primary and post-hoc analyses from the three upadacitinib trials (U-EXCEL, U-EXCEED, and U-ENDURE) are expected within the next 12 months. No results from other studies are expected.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Upadacitinib is an oral therapy and is administered once-daily as a modified-release tablet for both the induction and maintenance doses. It is expected to be prescribed in secondary care with all administrations taking place at home. The comparator therapies, ustekinumab and vedolizumab, are administered either IV or SC. All IV infusions are administered in a hospital setting. The first dose of SC therapy is administered by a trained nurse and incurs an associated cost; no additional costs to the NHS are assumed for subsequent SC doses as these are typically self-administered (see Section B.4.2.2). Therefore, despite requiring more frequent administration than its IV and SC comparators, upadacitinib requires fewer resources due to being an oral therapy.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

A cost comparison analysis was conducted to evaluate the cost to the NHS of using upadacitinib versus ustekinumab and vedolizumab for people with moderately to severely active CD in whom TNF-alpha inhibitors are deemed unsuitable; or where biological treatment is not tolerated or not working well enough. A cost-comparison model was developed in Microsoft Excel to facilitate comparison between the therapies.

The model time horizon is 1 year, in line with clinical practice and NICE guidance, which states that patients should be reassessed at 12 months to determine whether continuing with biologic treatment is appropriate (111). This also aligns with the duration of the upadacitinib clinical trials, which assessed maintenance outcomes up to 52 weeks. Year 1 includes all induction treatment and associated costs, as well as maintenance therapy once the induction period is completed.

It has been noted during previous appraisals that a treatment continuation assessment means that it will be deemed appropriate for at least some patients to continue treatment beyond 1 year. Therefore, in Section B.4.4, a sensitivity analysis is presented that considers the cost of a patient continuing their treatment beyond Year 1. This time horizon is described as 'Year 2+' for the purposes of this submission and shows the costs of each year of treatment beyond Year 1.

In the model, upadacitinib is compared against ustekinumab and vedolizumab as these treatments are approved in the target BF and TNF-alpha inhibitor-contraindicated populations and would be displaced by the introduction of upadacitinib (See Section B.1.3.6). The BF population is considered to include those contraindicated to TNF-alpha inhibitors. Data on CCF patients from the upadacitinib clinical trials are presented for completeness in Appendix J.

Costs were not discounted in the analysis in line with the user guide for cost-comparison appraisals (112).

B.4.2.2 Intervention and comparators' acquisition costs

Ustekinumab is administered intravenously (IV) in the induction period and subcutaneously (SC) in the maintenance period. Vedolizumab administration is IV in the induction period and either IV or SC in the maintenance period. Both the IV and SC regimens of vedolizumab were considered in this analysis.

Ustekinumab IV dosing is weight-based. An average dose of 390 mg, equating to three 130 mg vials, was calculated based on trial population data presented in the ustekinumab SmPC (71). Dosing of ustekinumab SC, vedolizumab SC, and vedolizumab IV is not weight dependent. The weight characteristics of the model

population, which were used to calculate the ustekinumab IV induction dose, are presented in Table 62 and are based on the upadacitinib trial populations (113).

Table 62: Population characteristics for cost comparison model

Characteristic	Model input	UST induction dose by weight
Mean weight (kg)	[redacted]	NA
Weight <55 kg	[redacted]	260 mg
Weight >55 kg and ≤85 kg	[redacted]	390 mg
Weight >85 kg	[redacted]	520 mg

Abbreviations: IV, intravenous; NA, not applicable; SmPC, Summary of Product Characteristics; UST, ustekinumab.
Source: AbbVie data on file (113), ustekinumab IV SmPC (72)

Upadacitinib, ustekinumab, and IV vedolizumab are all available as either standard dose or high dose maintenance therapy. The proportion of patients on the standard and high doses is based on UK clinical expert input (114) and is shown in Table 63.

Table 63: Proportion of patients on standard and high dose maintenance therapy in cost comparison model

Intervention	Proportion of patients on standard dose maintenance therapy	Proportion of patients on high dose maintenance therapy
UPA	70.0%	30.0%
UST	7.5%	92.5%
VDZ IV	70.0%	30.0%
VDZ SC	100%	NA

Abbreviations: IV, intravenous; NA, not applicable; SC, subcutaneous; UPA, upadacitinib; UST ustekinumab; VDZ, vedolizumab.

The acquisition costs of upadacitinib and comparators are presented in Table 64. The table also presents the dosing schedule used in the model for each treatment.

Table 64: Acquisition costs of the intervention and comparator technologies

	UPA (PAS price)	UST (list price)	VDZ IV (list price)	VDZ SC (list price)
Pharmaceutical formulation	Modified-release tablet	90 mg solution for injection in pre-filled syringe (1mL) 130 mg concentration for solution for infusion vial (26 mL)	300 mg powder for concentrate for solution for infusion vials	300 mg powder for concentrate for solution for infusion vials 108 mg solution for injection in pre-filled pen/syringe (0.68 mL)
(Anticipated) care setting	Prescribed in secondary care	Secondary care	Secondary care	Secondary care
Acquisition cost per unit	45 mg: [redacted]; 30 mg: [redacted]; 15 mg: [redacted]	130 mg (IV): £2,147 90 mg (SC): £2,147	300 mg: £2,050	108 mg: £512.50
Acquisition cost (excluding VAT): Year 1†	Induction: [redacted] Maintenance: [redacted] **Total:** [redacted]	Induction: £6,441.00 Maintenance: £12,559.95 **Total: £19,000.95**	Induction: £6,150.00 Maintenance: £13,940.00 **Total: £20,090.00**	Induction: £6,150.00 Maintenance: £9,737.50 **Total: £15,887.50**
Method of administration	Oral	IV, SC	IV	IV, SC
Recommended dose	Induction: 45 mg Maintenance: 15 mg or 30 mg	Induction: ~6 mg/kg IV at Week 0 (390 mg on average) Maintenance: 90 mg	Induction: 300 mg IV Maintenance: 300 mg IV	Induction: 300 mg IV Maintenance: 108 mg SC
Dosing frequency	Induction and maintenance: QD	Induction: Week 0 Maintenance (standard dose): Q12W from Week 8 Maintenance (high dose): Q8W	Induction: Weeks 0, 2, and 6 Maintenance (standard dose): Q8W from Week 14 Maintenance (high dose): Q4W	Induction: Weeks 0, 2, and 6 Maintenance: Q2W from Week 14
Dose adjustments	A dose of 30 mg once daily may be appropriate for patients with high disease burden or those who do not show adequate therapeutic benefit with 15 mg once daily (see Table 63 for details)	Patients who lose response with standard dosing may benefit from moving to the high dose (see Table 63 for details)	Patients with a decrease in their response on standard dose may benefit from moving to the high dose (see Table 63 for details)	NA
Average length of a course of treatment	NA	NA	NA	NA

Abbreviations: IV, intravenous; NA, not applicable; PAS, Patient Access Scheme; QD, once daily; QxW, once every x weeks; SC, subcutaneous; VAT, value-added tax.
†For Year 2+ data, please refer to Section B.4.4

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

A systematic literature review was undertaken to identify studies reporting healthcare resource use and costs associated with upadacitinib and relevant comparators. A total of 6 studies relevant to UK decision-making were identified and full details are reported in Appendix G.

Upadacitinib is administered as oral tablets for induction and maintenance doses; as such, there are no associated administration costs. Ustekinumab is administered via IV infusion for the induction and maintenance doses. Vedolizumab is administered by IV infusion for induction and then either IV or SC for maintenance therapy. Infusions (IV) were administered in a hospital setting; SC administrations assumed a cost for the first dose only (training by a nurse) and no additional cost to the NHS for subsequent doses (as these are typically self-administered).

Administration costs of IV, SC, and oral treatments are shown in Table 60.

Table 65: Administration costs used in cost comparison model

	IV	SC	Oral
First administration	£291.00	£44.00	£0.00
Subsequent administration	£291.00	£0.00	£0.00

Abbreviations: IV, intravenous; SC, subcutaneous
Source: IV costs were sourced from the National Tariff Payment System 2022/23 HRG code FD02H Inflammatory Bowel Disease without Interventions, with CC Score 0. SC costs were sourced from the Unit Costs of Health and Social Care 2021. Personal Social Services Research Unit. Cost per working hour or band 5 nurse. See Section 10.1, page 108 (115).

Table 66: Resource costs of the intervention and comparator technologies (Year 1)

Intervention		IV administration			SC administration			Reference	
		Induction	Maintenance	Total	Induction	Maintenance	Total		
UPA	Number of units	0.00	0.00	**0.00**	0.00	0.00	**0.00**	NA	NA
	Costs	£0.00	£0.00	**£0.00**	£0.00	£0.00	**£0.00**		
UST	Number of units	1.00	0.00	**1.00**	0.00	5.85	**5.85**	**IV costs:** National Tariff Payment System 2022/23 HRG code FD02H Inflammatory Bowel Disease without Interventions, with CC Score 0 **SC costs:** Unit Costs of Health and Social Care 2021. Personal Social Services Research Unit. Cost per working hour or band 5 nurse. See Section 10.1, page 108 (115).	
	Costs	£291.00	£0.00	**£291.00**	£0.00	£44.00	**£44.00**		
VDZ IV	Number of units	3.00	6.80	**9.80**	0.00	0.00	**0.00**		
	Costs	£873.00	£1,978.80	**£2,851.80**	£0.00	£0.00	**£0.00**		
VDZ SC	Number of units	3.00	0.00	**3.00**	0.00	19.00	**19.00**		
	Costs	£873.00	£0.00	**£873.00**	£0.00	£44.00	**£44.00**		

Abbreviations: HRG, Healthcare Resource Group; IV, intravenous; NA, not applicable; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

B.4.2.4 Adverse reaction unit costs and resource use

As described in Section B.3.9.2.4, results of the NMA analyses for serious AEs and discontinuation due to AEs showed similar AE rates between upadacitinib, ustekinumab, and vedolizumab. Therefore, it was assumed that the costs associated with treatment AEs would be similar for all therapies and AE costs were excluded from the analysis.

B.4.2.5 Miscellaneous unit costs and resource use

No other unit costs and resource use were considered.

B.4.2.6 Clinical expert validation

Several key assumptions in the model were validated with clinical experts (12, 64):

- Proportion of patients receiving standard and high doses of upadacitinib
- Proportion of patients receiving standard and high doses of ustekinumab
- Exclusion of extended induction from the base case analysis

B.4.2.7 Uncertainties in the inputs and assumptions

Key model inputs are summarised in Table 67; these assumptions (patient weight and proportion of patients on standard versus high dose) are considered key because they affect the required dose of upadacitinib for each patient and thus impact the associated costs. Model assumptions are presented in Table 68.

Table 67: Summary of key model inputs

Input	UPA	UST	VDZ IV	VDZ SC	Reference
Mean weight (kg)	[redacted]	[redacted]	[redacted]	[redacted]	Section B.4.2.2
Weight <55 kg (%)	[redacted]	[redacted]	[redacted]	[redacted]	
Weight >55 kg and ≤85 kg (%)	[redacted]	[redacted]	[redacted]	[redacted]	
Weight >85 kg (%)	[redacted]	[redacted]	[redacted]	[redacted]	
Dose escalation (% patients on standard/high)	70/30	7.5/92.5	70/30	NA	Section B.4.2.2

Abbreviations: IV, intravenous; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

Table 68: Key assumptions of the analysis

Base case assumption	Rationale	Relevant sensitivity analysis
AEs are equivalent between UPA and comparators.	An NMA was conducted on key safety outcomes (see Section B.3.9.2.4) and no clinically meaningful difference in AE rates was identified between UPA and its comparators. The AE rates are therefore not considered as there would be no incremental difference between comparators.	NA
In the maintenance period, 70% of patients receive the standard dose (15 mg) of upadacitinib.	A 70%/30% split across the standard and high doses of UPA aligns with the approach used and accepted across IBD indications (including UC) (116). As there is a lack of precedent in CD, this approach was validated by clinicians who confirmed it was acceptable for CD (12).	Scenario analyses were conducted with different proportions of patients receiving the high dose of UPA (e.g., 100% on standard dose; 0% on standard dose).
In the maintenance period, 92.5% of patients receive the high UST dose.	Feedback from clinical experts indicated that the majority of patients (92.5%) receive the higher frequency/dose escalated Q8W dose of UST in the maintenance period (12).	Scenario analyses were conducted with different proportions of patients requiring the high dose of UST (70%, 80%, and 100%).
Extended induction was not included in the base case analysis.	According to the expected license for UPA (13), patients who do not respond to UPA in the first 12-week induction period could go on to receive a further 12 weeks of 30 mg UPA treatment (extended induction). However, this is expected to be a minority of patients based on the clinical response rate in the first 12-week induction period in the UPA trials (85, 86). Furthermore, clinical experts indicated that patients with an inadequate response would be more likely to switch to a different advanced therapy/biologic than receive extended induction (64). Therefore, extended induction was excluded from the base case and instead included in a scenario analysis.	A scenario analyses was conducted to include an extended induction period for all treatments.

Abbreviations: AE, adverse event; CD, Crohn's disease; NMA, network meta-analysis; UPA, upadacitinib; UST, ustekinumab.

B.4.3 Base case results

In the analysis presented below, the upadacitinib PAS price is compared to the list prices for ustekinumab and vedolizumab. As PAS prices are confidential, it was not feasible to perform cost comparison analyses using PAS prices for all therapies.

In the base case, the total costs with upadacitinib were [redacted] (Table 69). Upadacitinib was associated with lower costs than ustekinumab and vedolizumab (IV and SC), for which costs ranged from £16,805 to £22,942.

Table 69: Base case results

Technology	Total costs
UPA (PAS price)	[redacted]
UST (list price)	£19,336
VDZ IV (list price)	£22,942
VDZ SC (list price)	£16,805

Abbreviations: IV, intravenous; PAS, Patient Access Scheme; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

B.4.4 Sensitivity and scenario analyses

A series of analyses were performed to evaluate the sensitivity of the model results to individual inputs when all other inputs remained constant. These include:

- Sensitivity analysis 1: Year 2+ costs (see Section B.4.2.1 for justification)
- Sensitivity analysis 2a: proportion of UPA patients on 15 mg QD dose set to 100%, proportion of UPA patients on 30 mg QD dose set to 0%
- Sensitivity analysis 2b: proportion of UPA patients on 15 mg QD dose set to 0%, proportion of UPA patients on 30 mg QD dose set to 100%
- Sensitivity analysis 3a: proportion of UST patients on 90 mg Q12W (standard) dose set to 0%, proportion of UST patients on 90 mg Q8W (high) dose set to 100%
- Sensitivity analysis 3b: proportion of UST patients on 90 mg Q12W (standard) dose set to 20%, proportion of UST patients on 90 mg Q8W (high) dose set to 80%
- Sensitivity analysis 3c: proportion of UST patients on 90 mg Q12W (standard) dose set to 30%, proportion of UST patients on 90 mg Q8W (high) dose set to 70%
- Sensitivity analysis 4: extended induction (patients who do not achieve clinical response with first induction therapy receive a second round of induction therapy; this reflects the expected license for UPA (13))

In Sensitivity analysis 4 (extended induction), the extended induction dose of ustekinumab is 90 mg and is administered at Week 8. The maintenance dose of ustekinumab is 90 mg and is also administered at Week 8, meaning that any patients

requiring extended induction of ustekinumab effectively receive a double maintenance dose. The vedolizumab extended induction includes an additional 300 mg IV dose at week 10. However, in the model the cost of the extended induction dose is only considered as part of the extended induction analysis.

The results for these sensitivity analyses are presented in Table 70, Table 71, Table 72, Table 73, Table 74, and Table 75. Across all scenarios, upadacitinib was associated with lower costs versus ustekinumab and vedolizumab (IV and SC).

Table 70: Sensitivity analysis 1 results (Year 2+ costs, per year)

Technology	Total costs
UPA (PAS price)	[redacted]
UST (list price)	£13,607
VDZ IV (list price)	£19,781
VDZ SC (list price)	£13,325

Abbreviations: IV, intravenous; PAS, Patient Access Scheme; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

Table 71: Sensitivity analysis 2a results (100% on UPA 15 mg)

Technology	Total costs
UPA (PAS price)	[redacted]
UST (list price)	£19,336
VDZ IV (list price)	£22,942
VDZ SC (list price)	£16,805

Abbreviations: IV, intravenous; PAS, Patient Access Scheme; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

Table 72: Sensitivity analysis 2b results (0% on UPA 15 mg)

Technology	Total costs
UPA (PAS price)	[redacted]
UST (list price)	£19,336
VDZ IV (list price)	£22,942
VDZ SC (list price)	£16,805

Abbreviations: IV, intravenous; PAS, Patient Access Scheme; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

Table 73: Sensitivity analysis 3a results (0% on UST standard dose)

Technology	Total costs
UPA (PAS price)	[redacted]
UST (list price)	£19,658
VDZ IV (list price)	£22,942
VDZ SC (list price)	£16,805

Abbreviations: IV, intravenous; PAS, Patient Access Scheme; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

Table 74: Sensitivity analysis 3b results (20% on UST standard dose)

Technology	Total costs
UPA (PAS price)	[redacted]
UST (list price)	£18,799
VDZ IV (list price)	£22,942
VDZ SC (list price)	£16,805

Abbreviations: IV, intravenous; PAS, Patient Access Scheme; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

Table 75: Sensitivity analysis 3c costs (30% on UST standard dose)

Technology	Total costs (Y1)
UPA (PAS price)	[redacted]
UST (list price)	£18,370
VDZ IV (list price)	£22,942
VDZ SC (list price)	£16,805

Abbreviations: IV, intravenous; PAS, Patient Access Scheme; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

Table 76: Sensitivity analysis 4 costs (extended induction)

Technology	Total costs
UPA (PAS price)	[redacted]
UST (list price)	£21,527
VDZ IV (list price)	£24,581
VDZ SC (list price)	£19,146

Abbreviations: IV, intravenous; PAS, Patient Access Scheme; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

B.4.5 Subgroup analysis

No subgroup analyses were considered as part of the cost comparison.

B.4.6 Interpretation and conclusions of economic evidence

The economic analysis presented in this submission compared the costs of treatment with upadacitinib versus ustekinumab and vedolizumab in people with moderately to severely active CD in whom TNF-alpha inhibitors are deemed unsuitable; or where biological treatment is not tolerated or not working well enough. This is a subpopulation of the population specified in the decision problem in Table 1.

Upadacitinib was shown to be a cost saving intervention versus ustekinumab and vedolizumab in the population of interest over a 1-year time horizon. In the base case, the total costs of treatment with upadacitinib were [redacted]. Upadacitinib was associated with lower costs than ustekinumab and vedolizumab (IV and SC), for which costs ranged from £16,805 to £22,942. These savings are derived from the lower acquisition and administration costs of upadacitinib versus ustekinumab and vedolizumab. As upadacitinib is administered as an oral tablet, it has no associated administration costs. In contrast, ustekinumab and vedolizumab are administered intravenously or subcutaneously and incur associated resource costs for administration.

The analysis is relevant to clinical practice in England and Wales because ustekinumab and vedolizumab are positioned for the treatment of BF patients according to NICE clinical guidance, as shown in the pathway in Section B.1.3.4.

A key strength of the model was that the analysis was robust to variation in inputs, including dose escalation of upadacitinib and ustekinumab, as shown in sensitivity analyses.

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B.6 Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Price details of treatments included in the submission

Appendix I: Checklist of confidential information

Appendix J: Additional supporting data from the upadacitinib clinical trial programme

Appendix K: Additional supportive data – CD disease measures

Appendix L: Additional NMA results

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Upadacitinib for previously treated moderately to severely active Crohn's disease [ID4027]

Summary of Information for Patients (SIP)

October 2022

File name	Version	Contains confidential information	Date
5. ID4027_Upadacitinib CD_NICE_SIP_Final	V1	No	5 October 2022

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

RESPONSE: **Generic name**: Upadacitinib **Brand name:** RINVOQ®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

RESPONSE: The population considered in the appraisal is people with moderately to severely active Crohn's disease (CD) in whom tumour necrosis factor (TNF)-alpha inhibitors are deemed unsuitable; or where biological treatment is not tolerated or not working well enough. Upadacitinib does not currently have marketing authorisation (approval) in the UK for treating CD. The anticipated dates for approval and indicated population are confidential and are presented in Section B.1.2 of the company submission (Document B).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

RESPONSE: Marketing authorisation from the Medicines and Healthcare Product Regulatory Agency (MHRA) for upadacitinib in CD is pending approval. Please see the upadacitinib CD NICE submission (Document B, Section B.1.2, Table 2) for further details on the anticipated dates for approval.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

RESPONSE:
AbbVie collaborates with a range of stakeholders with an interest in CD.

This includes collaboration with patient groups to support improvements in health and care for individuals with inflammatory bowel disease, for both CD and ulcerative colitis (UC).

Where this includes any Transfer of Value, for example to support the development of information for patients and their families, this is declared on an annual basis and is available at: https://www.abbvie.co.uk/our-company/policies-disclosures.html

Two patient groups relevant to CD, Crohn's and Colitis UK (CCUK) and IBD Relief, received Transfers of Value from AbbVie in 2020 and 2021, respectively.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

RESPONSE:
Condition that the medicine plans to treat:

CD is a chronic, lifelong inflammatory bowel disease where parts of the digestive system become inflamed (1). It is caused by the immune system attacking the gut, resulting in inflammation and painful ulcers anywhere in the digestive tract, but most commonly in the last segment of the small intestine and/or the large bowel (2, 3). As a result of the inflammation, people with CD most commonly suffer with abdominal pain, diarrhoea, fatigue, weight loss, and blood or mucus in the stool (4, 5).

The severity of CD activity is classified based on several symptoms, including the frequency of liquid/very soft stools, abdominal pain, and use of anti-diarrhoea medication. The amount of inflammation on the mucosa (lining of the gut) can be assessed using endoscopy and is also used to measure CD severity. This submission is for upadacitinib in people who have moderately to severely active CD. There are an estimated 71,519 people living with moderately to severely active Crohn's disease in England as of 2022.

Symptoms:

Some people with CD can experience additional symptoms outside the digestive system due to uncontrolled inflammation. These are called extraintestinal manifestations, with up to 40% of people with CD developing extraintestinal manifestations associated with the skin, bone and connective tissue, eyes, and liver (e.g., joint inflammation, mouth sores/ulcers, eye inflammation, and bone loss).

The symptoms and severity of CD vary from person to person, can change over time, and become worse during periods where treatments prescribed to control the disease lose their ability to control the inflammation (6-9).

CD can cause irreversible damage to the bowel wall when the inflammation is not adequately controlled (10, 11). In addition, the symptoms of CD can have a significant impact on individuals' lives, negatively impacting educational achievements, work productivity, mental health, and quality of life (12-17). The fatigue, pain, anxiety, and depression experienced by people with CD may all contribute to the impact of the disease on quality of life and ability to perform daily activities (18, 19).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

RESPONSE:

CD may be difficult to diagnose as it can have similar symptoms to other conditions. As a first step, doctors will evaluate the individual's medical history (e.g., start of symptoms, blood or mucus [or both] in stool, cramps, incontinence) and conduct physical examinations, e.g., abdominal examination, inspection for fistulas (an abnormal connection or passageway that connects two organs or vessels that do not usually connect), rectal examination (with a camera), and presence of extraintestinal manifestations.

Doctors may carry out additional examinations with imaging procedures, such as endoscopy (a detailed look at the inside of the gastrointestinal tract), tissue biopsies (taking a small sample of body tissue for examination), and laboratory blood tests (to measure the presence of biomarkers, i.e., a biological molecule found in blood that is a sign of a normal or abnormal process, or of a condition or disease) (2).

No additional tests are required to determine whether a person is eligible to receive treatment with upadacitinib.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

RESPONSE:

Overview

CD is a lifelong condition and there are currently no medical or surgical treatments to cure it. There are several different therapies available to manage CD and they are designed to suppress the immune system's response, which contributes to the inflammation. In certain situations, a special diet may be prescribed. Surgery may also be required to remove the affected area of bowel where the inflammation has caused damage and when drug therapies are no longer effective in treating the symptoms (20).

Drug therapies are classed into two different types:

- **Conventional care** with steroids/immunomodulator drugs (drugs which modulate the immune system; e.g., prednisolone) are typically used for milder disease (referred to as conventional care/therapy) (8)
- **Advanced therapies** (includes biologics, which refers to a type of protein that is made in the laboratory and blocks parts of the immune system contributing to the inflammation (21)). These therapies are typically used for moderate-to-severe disease (8). There are several types of biologic therapies, which work differently based on the parts of the immune system they block (see **Error! Reference source not found.** for more details) (22).

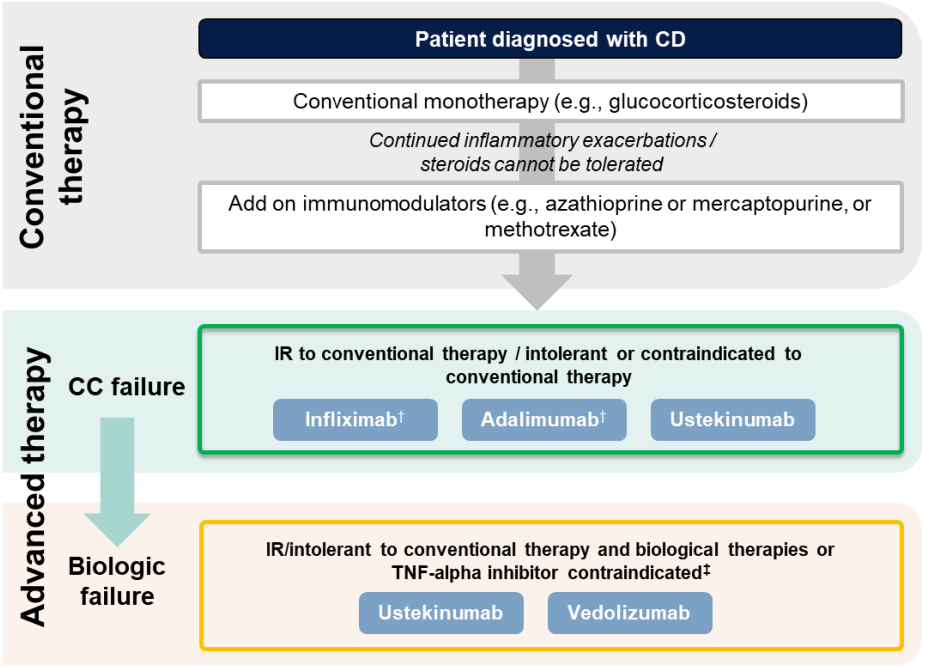
NICE UK clinical guidelines for the management of CD

In England, current NICE guidance for adults recommends initial treatment with conventional care (steroids and immunomodulators) to induce remission. Biologic therapies are introduced if there is a poor response to initial therapy with conventional care, if the therapy is not tolerated, or is contraindicated (i.e., specific medical reasons for not using a particular treatment (23)).

Typically, a TNF-alpha inhibitor (adalimumab, infliximab) is prescribed as a first biologic for bio-naïve individuals (those who have not previously been treated with a biologic therapy). For people who have failed or have had an inadequate response to previous biologic therapy, the second or later biologic used is typically ustekinumab or vedolizumab (which are not TNF-alpha inhibitors). Both ustekinumab or vedolizumab are also typically used if an individual has a contraindication to TNF-alpha inhibitors (**Error! Reference source not found.**) (20).

Surgery is another treatment option for people with CD (20); the most common reasons for surgery include poor response to drug treatment, strictures (an area of narrowing in the intestines), and fistulas.

Figure 1: Current treatment pathway for adults with moderately to severely active CD, based on management guidance from NICE

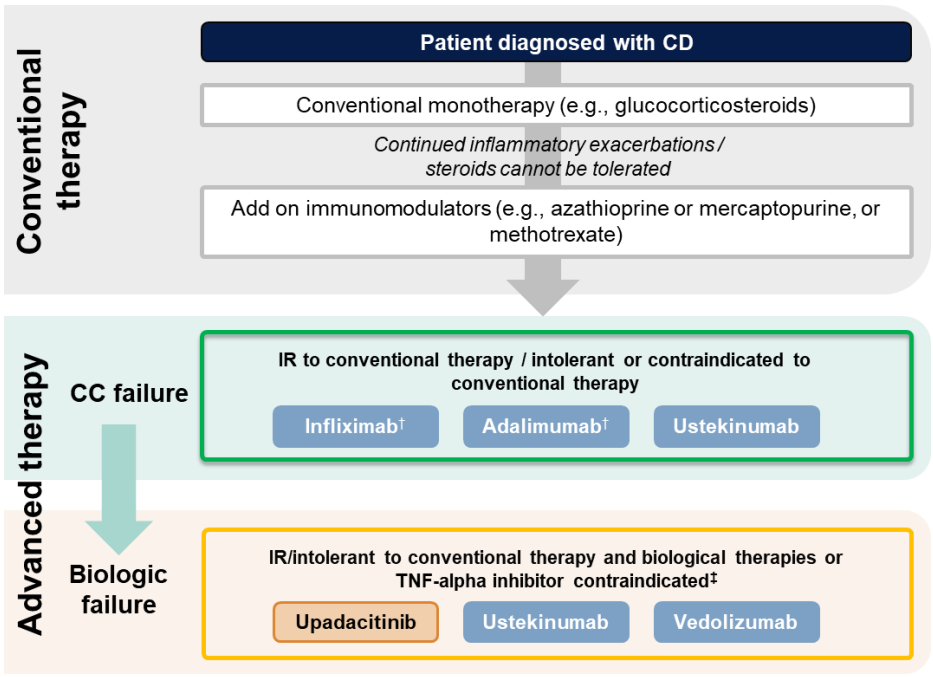


Abbreviations: CC, conventional care; CD, Crohn's disease; IR, inadequate response/treatment failure; TNF, tumour necrosis factor. Figure adapted from NICE guidance. Source: Crohn's disease: management (NG129). 2019. NHS England, Clinical Commissioning Policy. 2020 (24). † Biosimilars are also available (24). ‡ TNF-alpha contraindicated people with CD are considered as part of the biologic failure population.

Upadacitinib for the management of CD

If approved, upadacitinib can provide a novel treatment option in UK clinical practice for people with moderately to severely active CD who have previously received a biologic therapy or for those who have a contraindication (i.e., a specific reason that a treatment should not be used) for TNF-alpha inhibitors. This group of people is termed 'biologic failure' and is shown in the yellow box in Figure 2.

Figure 2: Upadacitinib in the treatment pathway for adults with moderately to severely active CD



Abbreviations: CC, conventional care; CD, Crohn's disease; IR, inadequate response/treatment failure; TNF, tumour necrosis factor.
Figure adapted from NICE guidance. Source: NICE. Crohn's disease: management (NG129). 2019. NHS England, Clinical Commissioning Policy. 2020. (24). † Biosimilars are also available (24). ‡ TNF-alpha contraindicated people with CD are considered as part of the biologic failure population.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

RESPONSE:

CD has a negative impact on physical and psychological wellbeing, social performance, and working capacity, thereby worsening the quality of life of people with the condition (13-15).

A UK-based survey of 167 people was conducted in 2021 to determine the physical and emotional impact of inflammatory bowel disease (including CD and UC) on people aged 18 years or over. The survey was developed with input from people living with inflammatory bowel disease, in order to ensure that the content was fully relevant to their lived experience (26).

Survey respondents highlighted that disease flares had a significant impact on their ability to perform daily tasks. In total, 90% of respondents reported that they were unable to participate in spontaneous activities, 86% were unable to travel on public transport, 81% were unable to socialise with friends, 75% were unable to go on holiday and 70% were unable to leave home

during a flare. Fatigue was reported as a significant burden (74% of people with inflammatory bowel disease reported experiencing fatigue daily) as was the increased need for toilet visits, which affected daily activities of 79% of respondents (26).

Survey respondents were also concerned about the impact of their condition on future life events, such as having children and getting married (25% and 19% of respondents expressed concern, respectively) (26).

Inflammatory bowel disease was also reported to have a significant emotional impact on those affected, with 64% reporting anxiety, 58% reporting low mood and 56% reporting low self-confidence because of their condition (26).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

RESPONSE:

Upadacitinib is a tablet taken by mouth once a day. It is produced slightly differently from biologic therapies and is therefore sometimes known as an 'advanced therapy'.

Upadacitinib functions as an inhibitor of Janus kinases (JAKs), which are proteins in the body. There are four JAKs (JAK1, JAK2, JAK3, and TYK2) and they are important in many functions, including cell survival and immune responses. JAKs play a key role in the signalling within the body that results in inflammation in CD (27, 28). Upadacitinib specifically inhibits JAK1; this selectivity is important because inhibiting the other JAKs may cause unwanted side effects due to their widespread functions (29). If approved, upadacitinib will be the first oral advanced therapy and the first JAK inhibitor for the treatment of CD.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

RESPONSE:

Upadacitinib is not intended to be used in combination with any other medicines. The efficacy and safety of upadacitinib in combination with immunosuppressants, including biologics, have not been evaluated.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

RESPONSE:

Upadacitinib is a tablet taken by mouth and is taken in two phases: (1) induction phase (an initial short-term dosing schedule to control disease symptoms) and (2) maintenance phase (a long-term dosing schedule to maintain control of symptoms).

In the induction phase, the recommended dose is 45 mg upadacitinib once daily for 12 weeks. After 12 weeks, individuals move to a maintenance dose of either 15 mg or 30 mg upadacitinib once daily. The dose depends on the individual's condition; the 30 mg dose may be appropriate for people with a high disease burden or for whom the 15 mg dose has not been sufficiently effective. A dose of 15 mg is recommended for people aged 65 years and older.

If an individual does not have sufficient benefits from upadacitinib 45 mg at the end of the 12-week induction period, they may receive 30 mg upadacitinib once daily for a further 12 weeks. This is sometimes called an 'extended induction' period. If they still do not experience sufficient benefits after this time (24 weeks of treatment in total), treatment with upadacitinib should be discontinued.

People receiving upadacitinib can take the medicine in their own home/place of residence because it is administered orally. No training from healthcare professionals is required. This differs from currently available biologic therapies for CD, which are delivered in intravenous (i.e., via a drip) and subcutaneous (i.e., by injection) formulations and require some degree of healthcare professional input (e.g., training from a nurse) (30-35).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

RESPONSE:

The Phase 3 induction trials (U-EXCEL and U-EXCEED) and Phase 3 maintenance trial (U-ENDURE) provide the evidence for upadacitinib for the treatment of moderately to severely active CD in adults (36-38).

U-EXCEL and U-EXCEED were double-blinded†, randomised, multicentre, 12-week induction trials that evaluated the efficacy and safety of upadacitinib 45 mg once daily versus placebo (which contains no active drug ingredient) in adults. In both trials, participants were assigned to one of the treatment groups (upadacitinib or placebo) in a blinded fashion. U-EXCEL enrolled 526 participants who had either not received a biologic therapy before (bio-naïve) or who had received a biologic therapy before, but it had stopped working (biologic failure). U-EXCEED enrolled 495 participants with a biologic failure treatment history. People who achieved a clinical response to induction treatment with upadacitinib progressed to the maintenance trial (U-ENDURE) (36, 37).

U-ENDURE is a double-blinded†, partially randomised, multicentre maintenance trial in adults with moderately to severely active CD. A total of 502 participants were re-randomised (from the

induction trials) to receive 52 weeks of maintenance treatment with upadacitinib 30 mg, upadacitinib 15 mg, or placebo. Although the 52-week maintenance phase is complete, U-ENDURE is an ongoing trial and will provide further long-term evidence on upadacitinib in moderately to severely active CD (38).

†Neither the participants nor the researchers knew which treatment or intervention participants were receiving until the trial was complete.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

RESPONSE:

Randomised controlled trial data showed that upadacitinib is superior to placebo for treating people with moderately to severely active CD. Upadacitinib showed improvements in disease activity, endoscopic outcomes, and quality of life. The data showing these benefits of upadacitinib come from two induction trials (U-EXCEL and U-EXCEED) and one maintenance trial (U-ENDURE) (36-38).

The upadacitinib trials assessed co-primary endpoints of clinical remission (assessed using clinical measures of CD symptoms) and endoscopic response (assessed via endoscopy). The use of these co-primary endpoints is important as they represent a combination of clinical symptom and endoscopic endpoints, which ensure that improvement in disease symptoms is also accompanied by healing of the gut mucosa (the layer of cells lining the gut). While improvement of clinical symptoms is important in CD, improvement of the gut mucosa is associated with improved long-term outcomes (e.g., reduced risk of relapse, decreased hospitalisations rates, steroid-free remission, fewer surgeries) (39-41).

In the induction trials (U-EXCEL and U-EXCEED), the co-primary endpoints and most of the key secondary efficacy endpoints were met. Upadacitinib treatment (45 mg once daily) resulted in resolution of clinical symptoms as early as Week 4 and endoscopic improvements were observed at Week 12. When participants with a history of biologic failure (where a biologic therapy fails to work or maintain effectiveness) were analysed, upadacitinib improved CD symptoms and the gut mucosa in this group of participants† (36, 37).

The results from the maintenance trial (U-ENDURE) support continued treatment with upadacitinib 30 mg or 15 mg once daily for participants who responded to induction treatment with upadacitinib 45 mg. The co-primary endpoints were met, with upadacitinib resulting in improvements in CD symptoms and the gut mucosa at Week 52 compared with placebo. These benefits were also observed in the biologic failure population† (38).

Similar to other pivotal trials of biologic therapies for CD (42-46), the upadacitinib trials only compared against placebo rather than another biologic therapy. In absence of a direct comparison between different biologics (in one trial), a data analysis can be performed to compare treatments indirectly between their own trials. This is done by creating a 'network' where treatments are compared via a treatment they have in common, in this case placebo, and is called a network meta-analysis (47).

For the upadacitinib NICE submission, the network meta-analysis allowed comparison of treatment effectiveness between upadacitinib and the comparator therapies (ustekinumab and

vedolizumab). Overall, the network meta-analysis results suggest that upadacitinib has superior efficacy to ustekinumab and vedolizumab for improving symptoms of CD in people for whom a previous biologic therapy has failed to work/maintain effectiveness or for whom TNF-alpha inhibitors are not suitable. This effect was observed for both induction and maintenance treatment.

†The benefits of upadacitinib in the induction and maintenance phases were also observed in people who had failed conventional care but not received a prior biologic (bio-naïve) but this population does not form part of the target population in the NICE submission.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

RESPONSE:

Use of upadacitinib demonstrated improvements in quality of life in both induction trials (U-EXCEL, U-EXCEED) and in the maintenance trial (U-ENDURE). Quality of life was assessed using a general measure (EQ-5D-5L health questionnaire) and a disease-specific measure (IBDQ questionnaire). Improvements were observed from Week 4 onwards. More details are provided in Section B.3 of the company submission (Document B).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

RESPONSE:

Like all medicines, upadacitinib is associated with side effects and adverse events; however, these are considered manageable, mild to moderate in severity, and no worse than those associated with other medicines used to treat CD.

Induction treatment with upadacitinib 45 mg and maintenance treatment with upadacitinib 30 mg or 15 mg was generally well tolerated (36-38).

In the induction trials (U-EXCEL and U-EXCEED), the overall rates of adverse events during the 12-week induction period were similar among the upadacitinib and placebo treatment groups. The most commonly reported adverse events (occurring in 5% or more of participants) with upadacitinib in the induction trials were acne, nasopharyngitis (common cold), and anaemia. The rates of serious adverse events were also comparable, with the highest serious adverse event rate reported in the placebo arm of U-EXCEED. The rate of adverse events leading to withdrawal of trial treatment was less than 6% in all arms and was highest in the placebo arm of U-EXCEL. No deaths within 30 days of the last dose of trial treatment were reported (36, 37).

In the maintenance trial (U-ENDURE), the overall rates of adverse events over 52 weeks were comparable between upadacitinib and placebo. The most commonly reported adverse events (occurring in 5% or more of participants) with upadacitinib were worsening of CD and arthralgia (joint pain/stiffness). Rates of serious adverse events were comparable for upadacitinib and placebo, as were rates of adverse events leading to discontinuation of trial treatment. No deaths occurred in any of the treatment groups during the maintenance period (38).

Across the upadacitinib clinical trials, no new safety risks were identified. The overall safety profile of upadacitinib was consistent with its known profile in the management of other conditions, including rheumatoid arthritis and psoriatic arthritis, for which upadacitinib is an approved treatment (48, 49).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

RESPONSE:

Mode of administration:
Upadacitinib is an oral medicine and can be taken at home without needing support or training from a healthcare professional (which is required for some intravenous and subcutaneous treatments). This may be more convenient than approved biologic treatments and minimise the travel and time commitment needed from people receiving upadacitinib because they do not need to travel to hospital to receive treatment, as they may need to do for other medicines.

Effectiveness of upadacitinib:
The clinical benefits of upadacitinib have been demonstrated in two induction trials (U-EXCEL and U-EXCEED) (36, 37) and one maintenance trial (U-ENDURE) (38).

Upadacitinib showed significant improvements in clinical symptoms as early as 2 weeks after the start of induction treatment. Mucosal improvements were observed from Week 12; improvement of the gut mucosa is important to achieve in CD and is associated with improved long-term outcomes, such as reduced risk of disease relapse, decreased hospitalisation rates, steroid-free remission and fewer bowel resections (39-41). In addition, current disease management guidance by the British Society of Gastroenterology recognises the importance of different treatment goals, with a recent focus on endoscopic outcomes, such as mucosal healing (absence of inflammation and ulcers on the mucosa), in addition to controlling clinical symptoms (50). Improvements in quality of life were observed from an early stage of treatment (Week 4) and were also observed at the last assessment point of the maintenance trial, showing sustained quality of life benefits with upadacitinib. Upadacitinib also improved fatigue at Week 12 of the induction trials, and this continued to the end of the maintenance trial. Finally, people who received upadacitinib were able to achieve steroid-free remission, meaning that their CD symptoms resolved, and they were also able to stop using steroids quickly (via a step-wise reduction in steroid dose, known as a taper). This is important because steroids are often used to treat CD but there are serious side effects associated with their long-term use, including increased risk of infections, diabetes, high blood pressure, and bone loss (51).

Upadacitinib may be used for the treatment of moderately to severely active CD in people with prior biologic failure

Evidence from the trials shows that upadacitinib is effective in people for whom a previous biologic therapy failed to work/maintain effectiveness or who were not suitable for TNF-alpha inhibitors (known as 'biologic failure'). A substantial proportion of participants in the trials had a history of biologic treatment failure, with 45% of participants in U-EXCEL and 75% of participants in U-ENDURE having failed at least one biologic (U-EXCEED only included participants who were considered to have experienced biologic failure). Upadacitinib was effective in this biologic failure population, showing that it is beneficial for participants who are sometimes considered difficult to treat because they have already tried biologic therapies†.

†The benefits of upadacitinib in the induction and maintenance phases were also observed in people who had failed conventional care but not received a prior biologic (bio-naïve) but this population does not form part of the target population in the NICE submission.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

RESPONSE:

Upadacitinib is associated with some side effects (adverse events); however, there are generally considered manageable and occur infrequently.

In the induction trials (U-EXCEL and U-EXCEED), the most frequently reported adverse events in the upadacitinib group were acne, nasopharyngitis (common cold), and anaemia. Acne occurred more frequently in the upadacitinib group compared with the placebo group. The frequency of nasopharyngitis and anaemia was similar in the upadacitinib and placebo groups. Rates of serious adverse events and adverse events leading to discontinuation of treatment were comparable across the upadacitinib and placebo groups.

In the maintenance trial (U-ENDURE), the most frequently reported adverse events were worsening of CD and arthralgia (joint pain/stiffness). The highest frequency of CD worsening was observed in the placebo group while rates of arthralgia were similar across the upadacitinib and placebo groups. Rates of serious adverse events were similar in the upadacitinib and placebo groups. Rates of adverse events leading to discontinuation of treatment were slightly higher in the upadacitinib groups than in the placebo group.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

RESPONSE:

As part of the company submission, an analysis (network meta-analysis) was performed to indirectly compare upadacitinib with ustekinumab and vedolizumab, the other two therapies used for people with CD and biologic failure. The results showed that upadacitinib had superior efficacy to ustekinumab and vedolizumab. An economic model was developed to compare the costs to the NHS of using upadacitinib with the costs of using ustekinumab and vedolizumab (cost-comparison model). Vedolizumab is available as either intravenous (IV) or subcutaneous (SC) treatments and both treatments were compared in the model (vedolizumab IV and vedolizumab SC).

Since upadacitinib demonstrated that it can provide similar or greater clinical benefits than existing therapies, the cost-comparison model did not incorporate any clinical data. Rather, the model was designed to calculate the cost of upadacitinib to the NHS and compare it with the cost of existing NICE-approved treatments. The key aspects of the model are summarised below.

Data used in the model

- Acquisition costs of the treatments (i.e., the purchase price): for ustekinumab and vedolizumab, this is the cost of the drugs listed in the British National Formulary. For upadacitinib, the price used is subject to a confidential discount that the company has agreed with the NHS.
- Administration costs of the treatments: ustekinumab and vedolizumab are administered either intravenously or subcutaneously, which is associated with administration costs for healthcare professionals' time. As upadacitinib is an oral medicine, it does not have any administration costs.
- Upadacitinib, ustekinumab, and vedolizumab IV all have standard and escalated (high) doses in the maintenance phase. These doses have different costs and the model distributes people across the doses (different proportions of people on the standard and high doses were assessed in scenario analyses).

Time frame considered

- In the model, a treatment duration of one year is considered, comparing cost for the first year of treatment ('Year 1'). For example, Year 1 of upadacitinib consisted of 12 weeks of induction and then maintenance for the remainder of the year. As some people will be on treatment for longer than one year, the cost for following years was also compared ('Year 2+', i.e., maintenance treatment only).

Results

- The results of the cost-comparison analysis showed that upadacitinib was associated with lower costs than ustekinumab, vedolizumab IV, and vedolizumab SC in Year 1 and for Year 2+

Uncertainty

- The model assumes that upadacitinib has comparable efficacy to ustekinumab and vedolizumab. This assumption is based on data from a network meta-analysis, which is a widely used approach to compare treatments when no head-to-head comparisons are available, but is also sensitive to differences between the participants in the included trials.
- Scenario analyses were performed to change the proportions of people receiving different doses (standard or escalated) of the treatments and the results consistently showed that upadacitinib was associated with lower costs than the other treatments considered (ustekinumab, intravenous vedolizumab, and subcutaneous vedolizumab).

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

RESPONSE:

Mode of administration

At present, all biologic therapies available for moderately to severely active CD are administered either intravenously or subcutaneously, which requires individuals with CD to attend clinic and/or receive appropriate training from a healthcare professional for self-administration. Upadacitinib is the first oral (tablet taken by mouth) advanced treatment for CD and also the first JAK inhibitor available for CD (pending approval). It can be taken at home without the need for administration support from healthcare professionals and without placing a time/travel burden on people receiving treatment.

Loss of response with biologic therapy

Upadacitinib is considered to be non-biologic advanced therapy, meaning that it is produced differently from the available biologic therapies. Therefore, upadacitinib is unlikely to be affected by the formation of antibodies that can lead to a reduced treatment response.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

RESPONSE:

No equality issues associated with the use of upadacitinib in this indication have been identified or are foreseen.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

RESPONSE:

Further information on CD:

- Crohn's and Colitis UK (https://crohnsandcolitis.org.uk/info-support/information-about-crohns-and-colitis/all-information-about-crohns-and-colitis?parent=4107&page=1&tags=&category=&sort=)
- IBD relief (https://www.ibdrelief.com/learn)

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

RESPONSE:

- **Adverse event:** an unwanted side effect that may occur as a result of taking a particular therapy
- **Biologic failure population:** Individuals for whom a previous biologic therapy failed to work/maintain effectiveness or who have a specific contraindication (reason a medicine cannot be used) to TNF-alpha inhibitors
- **Biomarker:** A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease
- **Bio-naïve population:** Individuals with moderate-to-severe CD who have had an inadequate response, are intolerant, or are contraindicated to conventional care, and have not received a prior biologic therapy
- **Fistula:** An abnormal connection or passageway that connects two organs or vessels that do not usually connect
- **JAKs (Janus kinases):** proteins that play a key role in the signalling in the body that causes inflammation in CD
- **MHRA (Medicines and Healthcare Products Regulatory Agency):** part of the UK Department for Health and Social Care and responsible for ensuring that medicines are safe for use in the UK

- **Network meta-analysis:** an analysis used to compare the effectiveness of different treatments when no data directly comparing the treatments are available (e.g., from a randomised controlled trial)
- **Relapse:** The return of a disease, or the signs and symptoms of a disease after a period of improvement
- **Refractory disease:** A disease or condition that does not respond to treatment
- **Remission:** Reduction or disappearance of the signs and symptoms of a disease

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Upadacitinib for previously treated moderately to severely active Crohn's disease

[ID4027]

Clarification questions

October 2022

File name	Version	Contains confidential information	Date
ID4027 upadacitinib CD EAG clarification letter_responses [fully redacted]	V1	Yes [AiC/CiC]	11 November 2022

Section A: Clarification on effectiveness data

Literature searches

A 1. Please provide the full strategies used for the searches of ClinicalTrials.gov, World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and all conference proceedings.

Company response

The search strategy was to manually enter the term 'Crohn's disease' and intervention names in each of the websites listed in Appendix D.1.1.3 of the company submission (CS) (e.g., Crohn's disease AND upadacitinib).

A 2. No literature searches appear to have been conducted for health-related quality of life (HRQoL) data. Please explain why these searches are not included in the company submission (CS), and provide if necessary.

Company response

HRQoL literature searches were not included within the CS as HRQoL data are not within the scope of the cost-comparison approach undertaken by the company for this appraisal. This is substantiated by the NICE reference case presented in the NICE manual for health technology appraisals (Table 4.1 (1)). As upadacitinib demonstrated at least equal efficacy and safety to comparators, and in actuality demonstrated superior efficacy in the population of interest [biologic failure (BF)], a HRQoL systematic review and network meta-analysis (NMA) was not required (as HRQoL is driven by the health state that a patient is in).

Although not required for this appraisal, the company conducted an internal systematic literature review (SLR) to assess HRQoL in patients with moderately to severely active Crohn's disease (CD). Searches for English-language publications were conducted on July 14, 2022. For transparency, the report of this SLR has been included in the reference pack.

HRQoL data from the upadacitinib clinical trials are presented in the CS; EQ-5D-5L data are provided in Section B.3.6, while FACIT-F and IBDQ data are presented in Appendix J (Section J.6).

Decision problem

A 3. Priority question. The company's decision problem defined the population of interest as "People with moderately to severely active CD [Crohn's Disease] in whom TNF-alpha inhibitors are deemed unsuitable; or where biological treatment is not tolerated or not working well enough (BF population)". The use of the conjunction 'or' in the population definition appears to specify two distinct populations: one appears to be the BF (Biologic Failure) population, which must have been previously treated, agreeing with the National Institute for Health and Care Excellence (NICE) scope. However, the decision problem also defines an additional population, where TNF-alpha inhibitors are 'deemed unsuitable', which suggests that it is unnecessary for the patients to have been previously treated. This implies that there may be participants that have not been previously treated included in the decision problem, even though this is not in accordance with the NICE scope ('previously treated moderately to severely active CD').

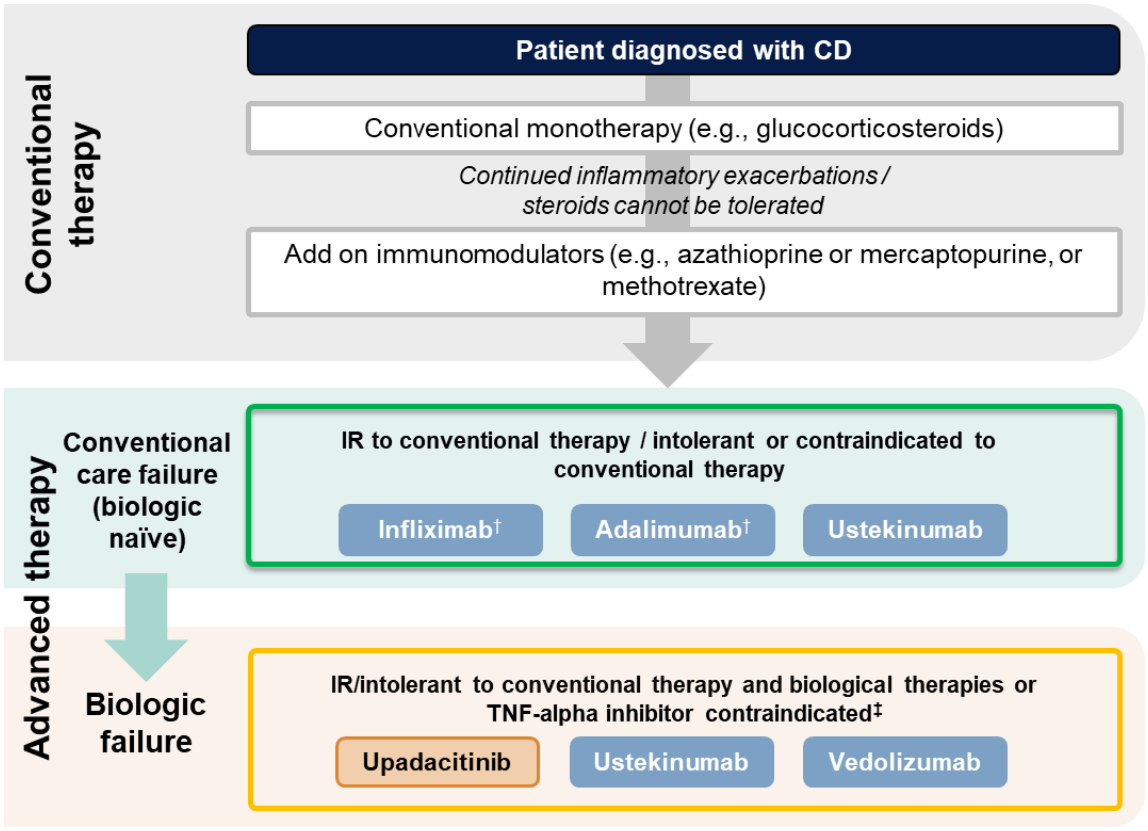
a) Please clarify whether the decision problem includes people who have not been previously treated.

b) If those for whom TNF-alpha inhibitors are deemed unsuitable must also have been previously treated, are they intended to be part of the BF population?

Company response

All patients in the BF target population have been previously treated with a biologic (likely to be a TNF-alpha inhibitor, as explained below) or with at least conventional care if they are contraindicated to TNF-alpha inhibitors. Figure 1 shows the treatment pathway for CD in the UK, which is based on guidance by NICE. The proposed positioning of upadacitinib is shown for reference.

Figure 1: CD treatment pathway based on guidance by NICE, including upadacitinib



Abbreviations: CC, conventional care; CD, Crohn's disease; IR, inadequate response/treatment failure; TNF, tumour necrosis factor. Figure adapted from NICE guidance. Source: NICE (2019), Crohn's disease: management (NG129) (2). †Biosimilars are also available. ‡TNF-alpha contraindicated people with CD are considered as part of the biologic failure population. For severe disease, stronger immunosuppressive add-on therapies, such as azathioprine and methotrexate, are used (3).

As shown in the figure, all patients with moderately to severely active CD receive conventional care, unless they are contraindicated to conventional care. In the event of conventional care failure, patients receive a first-line biologic therapy. This group of patients are considered the conventional care failure (CCF) or 'biologic naïve' population because they have received previous treatment with conventional care but no biologic therapy. It is important to note that in UK clinical practice, TNF-alpha inhibitors (either infliximab or adalimumab) are typically used as the first-line biologic therapy, in line with NICE guidance, which also recommends starting biologic therapy with the least expensive option (2, 4).

If first-line biologic therapy fails, patients receive second-line biologic therapy; this group of patients is the BF (biologic failure) population. In clinical practice, a therapy class switch is normally preferred when moving to second-line biologics, meaning that after a patient has received a TNF-alpha inhibitor (e.g., adalimumab) as a first-line

biologic treatment, they will typically not switch to another TNF-alpha inhibitor (e.g., infliximab). Therefore, the vast majority of patients receive either ustekinumab or vedolizumab in the BF population. This is also the target positioning of upadacitinib.

In summary, patients in the BF population are 'previously treated' because they have already received conventional care and a prior biologic therapy, typically a TNF-alpha inhibitor. Patients who are contraindicated to TNF-alpha inhibitors are also 'previously treated' because they will have received either conventional care or a biologic. Those for whom TNF-alpha inhibitors are contraindicated are considered part of the BF population, which is consistent with previous appraisals in CD, such as ustekinumab (TA456) (5) and vedolizumab (TA352) (6), as well as in broader immunology indications, e.g., ixekizumab in active psoriatic arthritis (TA537) (7).

For completeness, clinical upadacitinib data in CCF patients is presented in Appendix J (Section J.4 – clinical trial data) and Appendix L (Section L.1.1) of the CS.

A 4. Priority question. The decision problem defined a population that have previously used biologics ('people … where biological treatment is not tolerated or not working well enough (BF population)'), and the company has stated that the trial evidence relating to patients who have previously been treated with conventional treatments will not be fully considered. This represents a further discrepancy between the NICE scope and the decision problem, because the NICE scope makes no such distinction according to the nature of previous treatment. Please explain the rationale for the differing population in the NICE scope and the decision problem in terms of the nature of previous treatment.

Company response

The division of the CD population into BF and CCF populations is an established approach and has been accepted by NICE, as discussed in more detail below. The CS positions upadacitinib for use in the BF population. As stated in CS Section B.1.1, this represents a subpopulation to that specified in the NICE pre-invitation scope and licensed indication for upadacitinib.

It is important to note that the CCF and BF populations have both failed conventional care. The CCF population has failed conventional care only, while the BF population has failed conventional care and then also experienced biologic therapy failure.

The division of the moderately to severely active CD population into the CCF and BF subpopulations is an established approach to analyses in this disease area and has been used for previous CD submissions to NICE, including ustekinumab (TA456) (5) and vedolizumab (TA352) (6). Furthermore, the subpopulation analyses were predefined for the upadacitinib clinical trials (where applicable – U-EXCEL and U-ENDURE enrolled CCF and BF subjects while U-EXCEED enrolled BF subjects only). For completeness, clinical upadacitinib data in CCF patients are presented in Appendix J (Section J.4 – clinical trial data) and Appendix L (Section L.1.1 – NMA data) of the CS. The data align with the results in the BF population, i.e., upadacitinib demonstrated better efficacy than placebo for the co-primary outcomes in the clinical trials and showed at least equivalent efficacy to comparators in NMAs.

A 5. Priority question. The comparators listed in the NICE final score are TNF-alpha inhibitors [Infliximab (IFX) and Adalimumab (ADA)], best supportive care, and the biologics vedolizumab (VDZ) and ustekinumab (UST). However, in the decision problem the comparators are restricted to the biological treatments VDZ and UST. The company justifies the removal of TNF-alpha inhibitors (IFX and ADA) on the basis that the population is defined as one where TNF-alpha inhibitors are deemed unsuitable or where biological treatment is not tolerated or ineffective.

However, this rationale does not hold, because the company's definition of the population permits inclusion of people who have merely failed or not tolerated one biological treatment (BF population), which need not be an TNF-alpha inhibitor. Importantly, the use of the conjunction 'or' in the population definition means that these people need not also be those for whom TNF-alpha inhibitors are deemed unsuitable. Therefore, the population definition appears to include people for whom TNF-alpha inhibitors are suitable.

a) **Please clarify the rationale for omitting TNF-alpha inhibitors as a comparator given that the population definition appears to permit them.**

b) **Please clarify how in clinical practice it would be determined that TNF-alpha inhibitors are unsuitable?**

c) **If the BF population is distinct from the people for whom TNF-alpha inhibitors are deemed unsuitable then please include all comparators in the scope including IFX and ADA in all analyses (clinical effectiveness and cost effectiveness).**

Company response

TNF-alpha inhibitors are not relevant comparators in the BF population and were excluded from the analyses because, following their use in first-line, clinicians typically prefer to switch to a different treatment class. This approach is also consistent with the treatment paradigm presented in previous appraisals within CD i.e., vedolizumab (TA456) (8) and ustekinumab (TA352) (5).

To elaborate, as also described in the company response to A.3, TNF-alpha inhibitors are typically given as first-line biologic therapy in UK clinical practice, aligning with NICE guidance which recommends starting biologic therapy with the least expensive option (2). Following failure of a biologic (including TNF-alpha inhibitors), clinicians typically prefer to switch to a different drug class, meaning that a patient who has received a first-line TNF-alpha inhibitor is unlikely to receive a TNF-alpha inhibitor as second-line treatment. Instead, they would receive ustekinumab (IL-12/23 inhibitor) or vedolizumab (α4β7 integrin inhibitor). Therefore, TNF-alpha inhibitors are not relevant comparators in the BF population and were excluded from the analyses.

In clinical practice, suitability for TNF-alpha inhibitors is determined by a range of factors, including certain comorbidities and infection risk; for example, people with psoriasis receive ustekinumab instead of TNF-alpha inhibitors, and TNF-alpha inhibitors are not used for patients who are not suitable for immunomodulators (4).

The BF population and TNF-alpha contraindicated populations are not considered distinct for the purposes of this submission given the above rationale and that the comparators for these two populations are the same (ustekinumab and vedolizumab).

A 6. Ustekinumab seems to be both a biologic treatment option as well as a treatment option where TNF-alpha treatment has failed. Please explain the exact proposed position of upadacitinib in the clinical pathway and indicate exactly which comparator is relevant for each (sub-) population of patients (i.e. those for whom treatment failed, were intolerant to or were contra-indicated for specific other treatments).

Company response

The currently available biologics for CD in the UK are TNF-alpha inhibitors (adalimumab and infliximab), ustekinumab, and vedolizumab.

The NICE recommendation for ustekinumab in CD is: *as an option for treating moderately to severely active Crohn's disease, that is, for adults who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-alpha inhibitor or have medical contraindications to such therapies* (5). Therefore, according to its NICE recommendation, ustekinumab can be used for (1) patients who have failed or are contraindicated to conventional care and (2) for patients who have failed or are contraindicated to biologic therapy (i.e., TNF-alpha inhibitors, which are biologics). However, in UK clinical practice, TNF-alpha inhibitors are typically administered as first-line biologic therapy ahead of ustekinumab, meaning that ustekinumab is generally used in a BF population (i.e., for patients who have already received a TNF-alpha inhibitor).

The positioning of upadacitinib is shown in Figure 1 in A.3 and aligns with the second recommendation for ustekinumab, i.e., patients who have failed or are contraindicated to biologic therapy. Now that ustekinumab is available in the same line as TNF-alpha inhibitors, the ‘BF’ population for upadacitinib includes people who have failed or are contraindicated to TNF-alpha inhibitors and/or ustekinumab (which is not a TNF-alpha inhibitor). In line with its proposed positioning in the BF population, the appropriate comparators for upadacitinib are ustekinumab and vedolizumab.

A 7. The company justifies the removal of the comparator 'best supportive care' from the decision problem on the basis that alternative biological therapies would always be given clinically in preference to best supportive care. However, this would not be possible if the population have '*failed or are contraindicated to all currently available biologic therapies (TNF-alpha inhibitors [ADA, IFX], UST and/or VDZ)*' [Document B, Table 1]. Please clarify the rationale for omitting best supportive care as a comparator given that the population definition appears to permit it.

Company response

Based on clinician feedback on the CS, best supportive care (BSC) was not deemed an appropriate comparator for people with moderately to severely active CD. If a patient was intolerant to or unsuitable for a certain biologic therapy, they would be considered for a different class of biologic rather than BSC (9). Furthermore, if a patient failed all available biologic therapies, they would return to treatment with the biologic that was most effective for them.

A 8. Mucosal healing is not included as an outcome in the decision problem despite being in the NICE scope. The company's rationale is that 'mucosal healing' does not have a 'set definition'. Instead, the outcome 'endoscopic outcomes' is used, which is supposed to include multiple outcomes indicative of mucosal healing. Notwithstanding the possible variations in definition of 'mucosal healing', the Evidence Assessment Group (EAG) does not agree that 'endoscopic outcomes' is a useful term to encompass the construct of 'mucosal healing', as it appears to be an overly non-specific term. Furthermore, multiple outcomes covering a single construct are not ideal for decision-making as they may increase the risk of type I errors. Please explain more fully the rationale for this change in outcome definition.

Company response

No NMAs were performed for mucosal healing/endoscopic outcomes in the CS due to differences in definitions making comparability between active treatments challenging. Therefore, mucosal healing data between upadacitinib and comparators is unlikely to have a major influence on decision-making.

For the purposes of this submission, mucosal healing was determined by endoscopic response, as described in Section B.3.11.2.4 of the CS. This approach was taken as 'mucosal healing' is a non-specific term that may be considered the absence of ulceration or any improvement in ulceration. In addition to the improvement in endoscopic response rates with upadacitinib versus placebo, data from U-ENDURE showed that upadacitinib 30 mg and 15 mg were associated with significantly higher rates of ulcer-free endoscopy versus placebo at Week 52 [redacted].

As clinical trials move towards the inclusion of more objective measures, as seen most recently in the ustekinumab trials (e.g., UNITI) and associated NICE submission (5), endoscopic outcomes (usually measured using the SES-CD) are becoming the norm. However, as previously mentioned, definitions can still vary and comparability between trials is limited.

A 9. 'Surgery' is not included as an outcome in the decision problem despite being in the NICE scope. The company's rationale is that 'surgery' is liable to have a low event rate. Whilst this may be true, 'surgery' is a clinically relevant outcome for this population and should be not be excluded because of limitations in the sample sizes and the length of follow up in the company's evidence base. The data should be presented in order to inform the decision-making of the committee. Please provide data on the outcome of 'surgery', if available.

Company response

No data on surgery are available from the upadacitinib clinical trials.

Systematic review

A 10. The original systematic literature review (SLR) was based upon a pre-defined protocol (Table 2 in Appendix D.1.2, Appendices). However, it was unclear at what stage the additional protocol (Table 3, in Appendix D.1.2, Appendices) designed to narrow the SLR scope for the Network Meta-analysis (NMA) was formulated.

a) Please state if this latter protocol was designed before data have been initially searched and evaluated.

b) If this was not a *pre-hoc* protocol, please give the detailed methodology of how the protocol criteria were decided, and the rationale.

Company response

The additional NMA protocol was a pre-hoc protocol.

Clinical effectiveness evidence

A 11. Only participants achieving a clinical response in U-EXCEL and U-EXCEED were eligible for inclusion in U-ENDURE. Because the U-ENDURE sample predominantly comprised responders to upadacitinib rather than placebo (Table 3.8, Document B), the E-ENDURE analysis might be expected to yield an inflated effect compared to placebo. This would be non-representative of the target population in this submission, who are not people who have previously responded to the study drug. Please explain how the results of U-ENDURE are relevant to this submission.

Company response

U-ENDURE is included because it provides data on maintenance therapy with upadacitinib, a key part of management of a chronic inflammatory condition like CD. In inflammatory bowel disease (IBD), treatment is divided into induction and maintenance phases. The purpose of induction therapy is to induce remission (i.e., control inflammation) while the aim of maintenance therapy is to maintain remission and prevent relapse. As the key source of maintenance data for upadacitinib in CD, U-ENDURE reflects the anticipated UK label (10) and aligns with regulatory body

requirements (e.g., MHRA, EMA), as well as with the published literature and previous NICE appraisals of CD therapies (11, 12).

The re-randomisation design of U-ENDURE means that a proportion of subjects receiving placebo as maintenance therapy have previously had a response to induction therapy with upadacitinib. As described in Section B.3.11.2.6 of the CS, this re-randomisation design has also been used in maintenance trials of other advanced therapies for CD and was accepted as appropriate by NICE in previous appraisals, including those for ustekinumab and vedolizumab (11, 12). The chronic nature of CD and duration of therapy in the trials means that it would be unethical for subjects who did not respond to 12 weeks of induction treatment (or 24 weeks if they received extended induction) to subsequently receive 52 weeks of maintenance therapy to which they are also unlikely to respond. Moderately to severely active CD requires active treatment to improve symptoms and avoid disease progression and potentially irreversible bowel damage. This damage may include the development of scar tissue, which can cause bowel obstruction and the development of strictures, abscesses, and/or fistulas (abnormal connections between the inflamed intestine and other areas) (13-15).

This is a common challenge in trials of IBD and the EMA recommends the following approach to CD trials: ‘trials combining induction and maintenance treatment should preferably only enter patients that have achieved remission with either the trial drug or the comparator. Here, re-randomisation should be done’ (11, 12). Additional EMA guidance on the design of CD trials states: ‘maintenance of efficacy should be demonstrated in long-term studies, either as an extension study of the previously mentioned short term [induction] studies (treat-through design) or as a re-randomisation of responders in the previously mentioned [induction] studies to either placebo or test drug (randomised withdrawal study)…the treat-through design is ethically problematic as it would subject patients to a total of 12 months of placebo’ (16).

The trial design described above also reflects clinical practice, as patients who respond to induction treatment would proceed with maintenance treatment. Non-responders would stop the medication, switch to another drug, or have an extended induction.

A 12. For applicability, it is important that the overall upadacitinib trial population (in particular, the 80% included in the NMA) have similar characteristics to the UK target population.

a) Please provide the characteristics of the UK target population in terms of the criteria in Table 15, Document B.

b) Please also provide the number and characteristics (in terms of the criteria in Table 15, Document B) of the UK participants from the three trials.

Company response

Table 1 shows the number of UK subjects who were enrolled in the upadacitinib clinical trial programme. In total, [redacted] UK subjects participated in the induction studies (U-EXCEL and U-EXCEED) and [redacted] participated in the maintenance study (U-ENDURE). Given these low numbers, no meaningful analyses of UK subjects could be performed (17). However, it is important to note that UK clinicians (n=3) considered the characteristics of subjects in the upadacitinib clinical trials to be broadly representative of the UK population with moderately to severely active CD (18).

Table 1: Number of UK patients in upadacitinib clinical trials

	U-EXCEL	U-EXCEED	U-ENDURE
UPA 45 mg	[redacted]	[redacted]	[redacted]
UPA 30 mg	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Abbreviations: NA, not applicable; PBO, placebo; UK, United Kingdom; UPA, upadacitinib.

A 13. There are considerable differences in some population characteristics across U-EXCEED and U-EXCEL. For example, U-EXCEED has a much larger proportion of participants on CD-related medication prior to baseline than U-EXCEL. There are also a larger proportion of draining fistulas in U-EXCEED than U-EXCEL. Furthermore, U-EXCEL contains participants who failed on previous biological and non-biological treatment, whereas U-EXCEED is restricted to those failing on previous biological treatment. These differences have an implication for applicability. If these two studies represent different populations it is difficult to see how the synthesis of these results [which would be an important direct estimate in the NMA] could bear any applicability to a real-world population, such as the target population in England. Please justify synthesising the results of these studies.

Company response

The subjects in the upadacitinib clinical trials are well-matched, both across the three different studies and between the treatment and placebo arms of each study. Any differences in subject characteristics between the studies are the result of different inclusion criteria (e.g., Bio-IR and non-Bio-IR subjects versus Bio-IR subjects only). This approach is widely used in trials of CD therapies and its purpose is to include different patient populations that are relevant to clinical practice.

As described in Section B.3.3.1 of the CS, there are two different subpopulations considered in the trials, Bio-IR and non-Bio-IR, which are defined below.

- **Bio-IR population (considered equivalent to BF population[1]):** included subjects with a documented inadequate response or intolerance to one or more prior ***biologic*** therapies for CD (infliximab, adalimumab, certolizumab, natalizumab, vedolizumab, and/or ustekinumab)
- **Non-Bio-IR population (considered equivalent to CCF population[1])**: included subjects with a documented inadequate response or intolerance to one or more prior ***conventional*** therapies for CD, defined as oral locally acting steroids (budesonide, beclomethasone); IV or oral corticosteroids (prednisone or equivalent); and/or immunosuppressants (azathioprine, mercaptopurine, methotrexate, tacrolimus). The non-Bio-IR population included subjects who may

[1] This assumption was validated with clinicians (4).

have received a prior biologic therapy for up to 1 year but discontinued for reasons other than intolerance or inadequate response, e.g., a change in insurance or achieving well-controlled disease.

As noted by the EAG, U-EXCEL enrolled Bio-IR and non-Bio-IR subjects, while U-EXCEED only enrolled non-Bio-IR subjects. These populations are considered distinct and the approach aligns with that used and accepted by NICE in previous submissions for CD therapies, including ustekinumab and vedolizumab (11, 12). The NMAs were performed separately for BF and CCF populations, which are considered analogous with the Bio-IR and non-Bio-IR populations (for example, U-EXCEED was excluded from the CCF NMA, as shown in Table 44 of the CS). Therefore, the evidence synthesis does not aim to draw comparisons between the efficacy of upadacitinib and comparators in an overall population (i.e., a combined Bio-IR and non-Bio-IR population). As with the population distinction in the clinical trials, this NMA approach has been used in previous submissions for CD therapies and has been accepted by NICE (11, 12).

Many of the differences in disease characteristics, e.g., proportion of subjects with draining fistulas, arise due to the fact that U-EXCEED only enrolled Bio-IR subjects. Subjects who have already tried one or more biologics generally have more severe disease. Furthermore, the difference in the proportions of subjects with draining fistulas was [redacted] across the induction studies ([redacted] and [redacted] in U-EXCEL versus [redacted] and [redacted] in U-EXCEED). Therefore, differences in baseline characteristics across upadacitinib trials are not evidence that enrolled patients are not representative of real-world patients in England; rather, they show that the BF and CCF groups are distinguishable.

A 14. The company's rationale for using the 3 main sub-grouping strategies ['Bio-IR / non-Bio-IR', '1 prior TNF-alpha inhibitor failure / >1 failure' and '< 1 / >1 failed biologic'], which appear to overlap in terms of construct, is unclear. Please provide a detailed rationale for the choice of these sub-grouping strategies.

Company response

The main subgrouping strategy of relevance to the submission is Bio-IR (BF) versus non-Bio-IR (CCF) to support the target positioning of upadacitinib in the BF population. As described in the response to A.4, the CCF/BF subgrouping is a widely used approach for therapies in CD and has been used in previous NICE submissions, including ustekinumab and vedolizumab (11, 12).

The other two subgroups (1 vs >1 prior TNF-alpha inhibitor failure; (≤)1 vs >1 prior biologics failed) are further subanalyses within the Bio-IR population. As reported in the CS, these results have no bearing on the decision problem and were provided for transparency only.

A 15. For the '1 prior TNF-alpha inhibitor failure / >1 failure' strategy, categories only exist for 1 previous failure and >1 previous failure and there is no group for 'no previous failures. This means that the data are incomplete. For example, in the clinical remission outcome for U-EXCEL, only 157/350 of the participants in the upadacitinib group are accounted for, and only 75/176 of the participants in the placebo group are accounted for. Please provide data for the 'no failure' group as well.

Company response

The subgroup analysis of 1 vs >1 prior TNF-alpha inhibitor failure is a further subanalysis of the Bio-IR population. As reported in the CS, these results have no bearing on the decision problem and were provided for transparency only. Additional analyses of subjects without TNF-alpha inhibitor failure are presented in Appendix A:.

A 16. The ‘1 prior TNF-alpha inhibitor failure / >1 failure’ strategy was correctly applied to all three studies. The ‘Bio-IR / non-Bio-IR’ strategy was applied for U-EXCEL and U-ENDURE, and it did not need to be applied to U-EXCEED as all participants were in the ‘Bio-IR’ population in that study. However, the ‘≤ 1 / >1 failed biologic’ strategy was only applied to U-EXCEED, and the reasons for this are unclear.

a) Please clarify the reasons for this.

b) If possible, apply sub-grouping using the ‘≤ 1 / >1 failed biologic’ strategy to the other two study results.

Company response

The subgroup analysis of ≤1 vs >1 prior biologic failure is a further subanalysis of the Bio-IR population for U-EXCEED. As reported in the CS, these results have no bearing on the decision problem and were provided for transparency only. Further explanation of the subgroup analysis and additional data from U-EXCEL and U-ENDURE are presented below and in Appendix B:.

As noted by the EAG, U-EXCEED enrolled only Bio-IR subjects while U-EXCEL and U-ENDURE enrolled both Bio-IR and non-Bio-IR subjects.

The subgrouping of U-EXCEED into ≤1 versus >1 failed biologic is due to the eligibility criteria for trial enrolment. U-EXCEED included patients who had an inadequate response or intolerance to biologic therapy, with the eligibility criteria stating that demonstration of intolerance required no minimum dose or duration of use. Therefore, a small proportion of the U-EXCEED trial population (1 patient in the placebo arm) failed <1 prior biologic.

In U-EXCEL and U-ENDURE, the main subgrouping applied was for Bio-IR versus non-Bio-IR to compare the BF and CCF populations, respectively (please see response to A.14 for an explanation of the subgrouping hierarchy). In these trials, any patients receiving <1 prior biologic is included in the CCF population and therefore the ≤1 or >1 failed biologic subgroup analysis is not feasible. However, it is possible to analyse data within the Bio-IR populations of U-EXCEL and U-ENDURE according to the number of prior biologics failed (1 or >1). Subgroup analyses of the co-primary efficacy endpoints by number of prior biologics failed (1 or >1) for U-EXCEL and U-

ENDURE are presented in Table 38 (CDAI clinical remission, U-EXCEL), Table 39 (endoscopic response, U-EXCEL), Table 40 (CDAI clinical remission, U-ENDURE), and Table 41 (endoscopic response, U-ENDURE) (all Appendix B:).

A 17. The '1 prior TNF-alpha inhibitor failure / >1 failure' sub-grouping strategy was only applied to a) Crohn's Disease Activity Index (CDAI) clinical remission and b) endoscopic response, which were deemed the primary outcomes by the company. Please apply this sub-grouping strategy to the other outcomes in the decision problem.

Company response

Additional analyses by TNF-alpha inhibitor failure are presented in Appendix A:

A 18. The '< 1 / >1 failed biologic' sub-grouping strategy was only applied to a) CDAI clinical remission and b) endoscopic response, which were deemed the primary outcomes by the company. Please apply this sub-grouping strategy to the other outcomes in the decision problem.

Company response

Additional analyses by number of prior biologic failed are presented in Appendix B:.

A 19. The 'Bio-IR / non-Bio-IR' strategy was applied to all decision problem outcomes except quality of life for U-EXCEL, and applied to only a) CDAI clinical remission and b) endoscopic response for U-ENDURE. Please also sub-group U-EXCEL for quality of life, and U-ENDURE for CDAI response, endoscopic remission, hospitalisation and quality of life.

Company response

Additional analyses of the Bio-IR and non-Bio-IR populations of U-EXCEL and U-EXCEED are presented in Appendix C:

A 20. The EAG does not agree that low subject numbers would make sub-group analysis by location of CD untenable. The numbers appear adequate in all three studies (see Table 3.13 in section 3.2.3). The fact that the study sample size was not powered for the separate CD location sub-group analyses is likely to be an issue with the other sub-grouping strategies used, and so this appears to represent a weak reason to not attempt sub-grouping for CD location. Although clinical opinion deems CD location not clinically relevant, this is not the opinion of NICE (in the NICE scope) who stipulated that CD location should be a sub-grouping strategy.

a) Please justify more fully, with references, why CD location would not affect outcome.

b) If the above is not possible, please provide sub-grouping by CD location for each study.

Company response

The company validated the impact of an analysis by location of CD with UK clinical experts (n=6; gastroenterologists), who advised that disease location does not drive treatment choice for individuals with moderately to severely active CD. One gastroenterologist stated that 'In clinical practice location of disease is not a clinically relevant distinction and patients are not stratified by this subgroup for developing treatment plans.' The only distinction that is seen as clinically relevant in adjusting treatment choice is penetrating perianal disease, which is not relevant to the decision problem.

The company included the proportion of subjects with colonic, ileal, or ileal-colonic disease in Table 15, Section B.3.3.4 of the CS, highlighting the low subject numbers with isolated ileal disease. Gastroenterologists stated that there is limited ability to draw inferences from an exploratory analysis on CD by location (18). The CS also comprised the full clinical study reports (CSRs) with the requested subgroup outcomes.

In addition to the low subject numbers by subgroup location in the upadacitinib clinical trials, there was a lack of reporting of outcomes by disease location across all relevant comparator studies identified in the SLR. Consequently, a comparison of the relative

efficacy of upadacitinib versus relevant comparator therapies in a NMA by subgroup location was not feasible and CD location may not be a factor that can be fruitfully explored further in the context of this appraisal.

Nevertheless, in light of the EAG's request, a summary of results from each trial by disease location at baseline for co-primary efficacy outcomes is presented in Appendix D:.

A 21. Absolute risk difference (RD) is used as the measure of effects rather than a ratio measure of effect, although the latter would tend to be the more established measure to use. Risk differences tend to give slightly higher Z values (and therefore lower P values) than Odds Ratios (ORs) or Risk Ratios (RRs), and thus might provide the impression of a more positive benefit for upadacitinib. The company has stated that a 'risk-difference approach was selected to minimise the impact of different placebo rates which were observed across the included trials and because of the intuitive presentation of results when generated on the risk-difference scale'. Please provide a more detailed rationale for this decision, explaining how a risk-difference reduces the impact of different placebo rates.

Company response

The risk-difference (RD) approach was selected to minimise the impact of different placebo rates which were observed across the included trials and because of the intuitive presentation of results when generated on the risk-difference scale. A summary of the justification for this approach is provided in Section B.3.9.3.1 of the CS and further details are provided below.

Rather than calculating relative effects on the log-odds scale, which may inflate or deflate relative effects in treatments with particularly high or low associated placebo efficacy, RD NMAs are conducted on the RD scale, and absolute probabilities of treatment response are subtracted across interventions. RD NMAs yield estimates of the treatment effect as the linear difference in absolute rate to a reference treatment.

NMAs conducted on the RD scale form the base case of the NMA analysis for several reasons. Theoretically, the RD scale NMAs can yield valid estimates while mitigating differences in placebo efficacy across studies. Warn et al. (2002) extend a fully

Bayesian NMA using Gibbs sampling to perform analyses on the absolute risk scale and demonstrate how underlying risk can be incorporated (19). Binary outcome data from 46 trials of the effect of single-dose ibuprofen on post-operative pain are analysed, and the results are contrasted with those derived from classical and Bayesian summary statistic methods. Warn et al. show that the clinical interpretation of the RD NMA absolute risk scale is more intuitive, and that the RD NMA yields valid analysis compared to the log odds based NMA (19).

Like baseline risk adjustment, RD NMA is also recognised as valid framework by NICE (DSU TSD2, Section 3.7) (20). It has been used in publications and prior submissions to NICE (21-23). Cameron et al. (2018) found that use of an NMA on the RD scale represents a viable alternative approach to account for the presence of cross-study differences in placebo response rate (21). As per Dias et al. (2013; 2018), RD NMA could be used as an alternative method to log odds NMA when there are imbalances in the number of studies with low placebo response rates across pairwise contrasts in the network (24, 25). The RD model code used was adapted from Dias et al. (2018) (25) itself based on modelling frameworks by Warn et al. (2002) (19). In TA521, RD was used to adjust for cross-trial differences (22). Rather than calculating relative effects as ratios (such as odds ratios produced by traditional logit-link NMA frameworks), absolute probabilities of treatment response are subtracted across interventions in RD models minimising potential impacts of overly low or high placebo efficacy. This may help minimise bias when there are imbalances in the number of studies with low placebo response rates across pairwise contrasts in the network. TA521 concluded that baseline-risk adjusted models and risk difference NMAs should yield less biased estimates of effect than the unadjusted NMA analyses on the relative scale (22). Due to the general paucity of data in the relevant CD evidence networks leading to poor performance of baseline-risk adjusted logit-link NMAs, RD NMAs provide an attractive option to minimise impacts of placebo heterogeneity on NMA-produced treatment effect estimates.

Criticism of RD models stems from potential model instability leading to lack of convergence and sensitivity to starting values (26). In the NMAs examining advanced therapy CD trials, the RD models converge and have appropriate fit. Appropriate

vague prior distributions are used which correspond to the RD scale. Starting values are used which are dispersed across the probability space.

In other words, the RD models address, or at least reduce, placebo rate variation of the sort observed in advanced therapy CD trials, yield reasonable estimates, pass diagnostic tests based on their convergence and fit, are accepted by NICE, have been used in prior submissions, and have appeared in the published academic literature.

A 22. Please explain whether there is a maximum treatment duration for the intervention and its comparators.

Company response

NICE guidance for the use of advanced therapies (i.e., biologics in the current treatment pathway) in moderately to severely active CD indicates that evidence of treatment benefit should be re-evaluated at least every 12 months (2), which means that there is no official maximum treatment duration.

The anticipated label for upadacitinib states that treatment should be discontinued for patients who have no evidence of therapeutic benefit after 24 weeks of treatment (i.e., with standard induction plus extended induction) (10). The ustekinumab SPC states that consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit 16 weeks after the IV induction dose or 16 weeks after switching to the 8-weekly maintenance dose (27). According to the SPC for vedolizumab IV, treatment should be discontinued if no evidence of therapeutic benefit is observed by Week 14 (28).

A 23. If available, please provide data from comparators for this indication or intervention and comparators for other indications about the percentage of patients continuing treatment past the first year?

Company response

No data are available on the percentage of patients continuing upadacitinib treatment past the first year and, to the company's knowledge, no data are readily available for comparators.

A 24. The maintenance strategy states the following: “A dose of 30 mg once daily may be appropriate for patients with high disease burden or those who do not show adequate therapeutic benefit with 15 mg once daily.”

a) Why is the maintenance dose (30mg or 15 mg once daily) after the initiation period lower than the initiation phase (45 mg once daily) even for patients who did not have an adequate response?

b) What would be the time frame in which one can conclude that the patient has not shown an adequate therapeutic benefit?

c) Please explain how a high disease burden is defined. Additionally, please explain if this assessment of high disease burden is made at a current dose of 15mg once daily or based on the disease burden shown in the initiation phase?

Company response

The maintenance dose of upadacitinib (30 mg or 15 mg QD) aligns with the anticipated UK label (10). The reason for the lower dose following the 12-week induction period (even for patients without an adequate response) is to balance the benefit/risk associated with upadacitinib treatment. This aligns with the approach for currently available biologic treatments (e.g., ustekinumab and vedolizumab) used in CD, i.e., a high dose is administered as induction therapy to establish control of inflammation (remission) and a lower dose is used to maintain remission. However, according to clinicians, most patients who do not have an adequate response to standard induction will switch to another treatment instead of receiving extended induction with upadacitinib (4).

The time frame in which a patient is deemed to have not shown adequate therapeutic benefit with maintenance upadacitinib (i.e., 15 mg and therefore potentially requiring dose escalation to 30 mg) is based on clinical judgement.

The level of disease burden is based on the judgment of the treating clinician, with treatment decisions based on the risk/benefit for each patient.

A 25. The target population is a group that did not respond to TNF-alpha inhibitors or where biological treatment is not tolerated or not working well enough.

a) What is known about the period in which these TNF-alpha inhibitors are still active in the body?

b) What do we know about the period in which the other biological treatment options are still active?

c) What is known about the group that does not respond to TNF-alpha inhibitors and the potential effect of upadacitinib?

Company response

With regard to the period of activity in the body, the half-life of both adalimumab and infliximab is estimated to be 3 weeks (29, 30). Ustekinumab also has an estimated half-life of 3 weeks in people with CD (31) and the half-life of vedolizumab is estimated to be 25.5 days (32).

TNF-alpha inhibitors and other biologic therapies are large, complex protein structures and can be recognised as 'foreign' by the host immune system, resulting in immunogenicity and anti-drug antibody (ADA) development (33). As described in Section B.1.3.5 of the CS, the development of ADAs to TNF-alpha inhibitors can lead to loss of clinical efficacy (34, 35). The rates of ADA development with TNF-alpha inhibitors are high; ADA rates of 28.5% and 62.8% have been reported for adalimumab and infliximab, respectively (36). It has also been suggested that patients who have developed ADA to one biologic therapy may be more likely to develop ADA to subsequent biologic therapies (37), which may make them less effective and make treatment switching challenging.

Unlike biologic therapies, upadacitinib is a small molecule (non-protein) JAK inhibitor; JAK inhibitors do not cause immunogenicity or ADA development (38-40). This has two key implications: (1) patients are unlikely to develop ADA to upadacitinib in the first instance and (2) if patients have developed ADA to a prior biologic therapy, it should not impact their response to upadacitinib when switching treatment.

Data on the efficacy of upadacitinib in subjects who failed 1 or >1 TNF-alpha inhibitor is available from the upadacitinib clinical trials and is presented in Appendix E (Section E.1) of the CS.

A 26. Certain issues around treatment adherence are unclear.

a) Please explain any assumptions that were made regarding treatment adherence and justify the plausibility of these assumptions.

b) Please explain whether the differences in terms of frequency and route of upadacitinib administration have a possible impact on treatment adherence.

c) Please explain the potential impact of suboptimal treatment adherence on treatment effectiveness.

d) Please incorporate the impact of adherence on costs into the Excel model.

Company response

There are adherence risks and benefits associated with all modes of administration. Patients may be more adherent to oral therapies than alternative treatments as a result of poor technique when self-administering monthly injections. Additionally, patients may prefer oral therapies due to mobility problems, reducing their ability to attend injection appointments or self-administer therapies. Further, patients who self-administer may not administer injections at home at a similar rate to patients taking oral tablets.

In the absence of robust evidence on treatment adherence for upadacitinib and its comparators, all treatments were assumed to be equal as they are all likely to be associated with some level of non-adherence.

It is not possible to draw definitive conclusions on the impact of treatment adherence with upadacitinib as there is a lack of real-world evidence for upadacitinib in CD and treatment adherence in clinical trials is usually higher than in the real world. However, upadacitinib is the first oral advanced therapy for CD and there is potential for this to increase adherence amongst some patients due to convenience in contrast to comparators, which are subcutaneous (SC) and IV.

Treatment adherence of randomised subjects from the SA1 populations of the upadacitinib RCTs is shown in Table 2.

Table 2: Mean (SD) treatment compliance (%) in SA1 populations of upadacitinib clinical trials

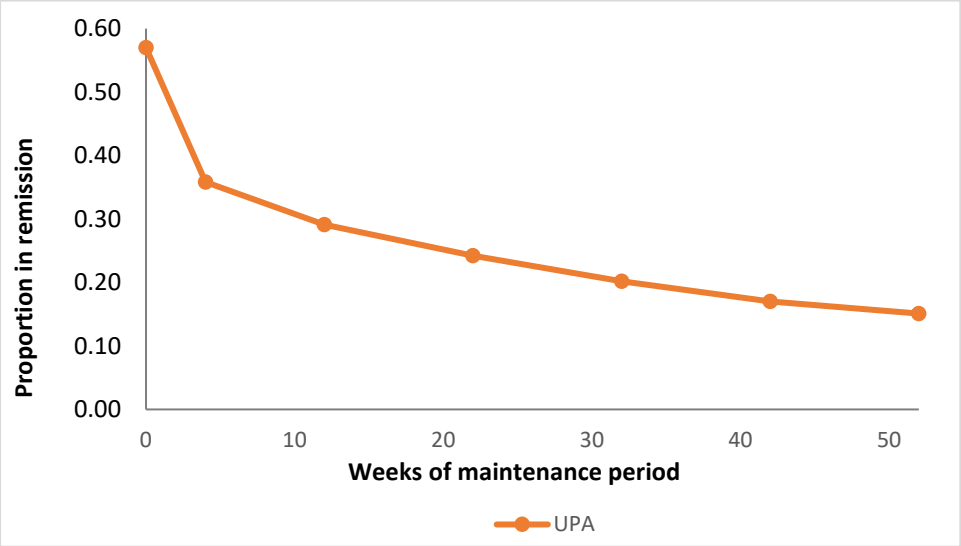
	U-EXCEL	U-EXCEED	U-ENDURE
UPA 45 mg	[redacted]	[redacted]	[redacted]
UPA 30 mg	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Abbreviations: NA, not applicable; PBO, placebo; SA, safety analysis; SD, standard deviation; UPA, upadacitinib.
Note: Compliance is calculated as the number of tablets actually taken by the subject divided by the number of tablets planned to be taken by the subject *100%.

Nevertheless, suboptimal upadacitinib treatment adherence is likely to have an impact on treatment effectiveness, as is the case for all medications. It is possible to make an assumption regarding the impact of upadacitinib non-adherence using data from the clinical trials. Figure 2 shows CDAI clinical remission rates among upadacitinib subjects who received active treatment in the induction period of the respective clinical trials and then received placebo in the maintenance period. When upadacitinib treatment stops, the remission rate declines but remains above the placebo rate for several weeks, showing that it may take several weeks of not taking therapy for the patient to return to placebo levels of response. This implies that upadacitinib has a residual benefit even after treatment has been stopped.

Furthermore, as upadacitinib is administered once daily, a patient would have to be non-adherent for a significant period of time for there to be an impact on clinical effectiveness. The availability of an oral mode of administration in a disease with limited alternatives outweighs the potential risks of non-adherence and provides an opportunity for CD patients to optimise their treatment adherence according to their preferences. In summary, based on the lack of data available for upadacitinib and comparators (as described above), treatment adherence was not considered in the cost-comparison model.

Figure 2: Proportion of PBO patients in CDAI clinical remission during the maintenance phase



A 27. On p. 11 of the CS it is noted that "Individuals with CD typically suffer from recurrent relapses, with acute exacerbations interspersed with periods of remission". On p. 13 it is also explained that relapses are associated with higher costs for treatment, adverse events and complications.

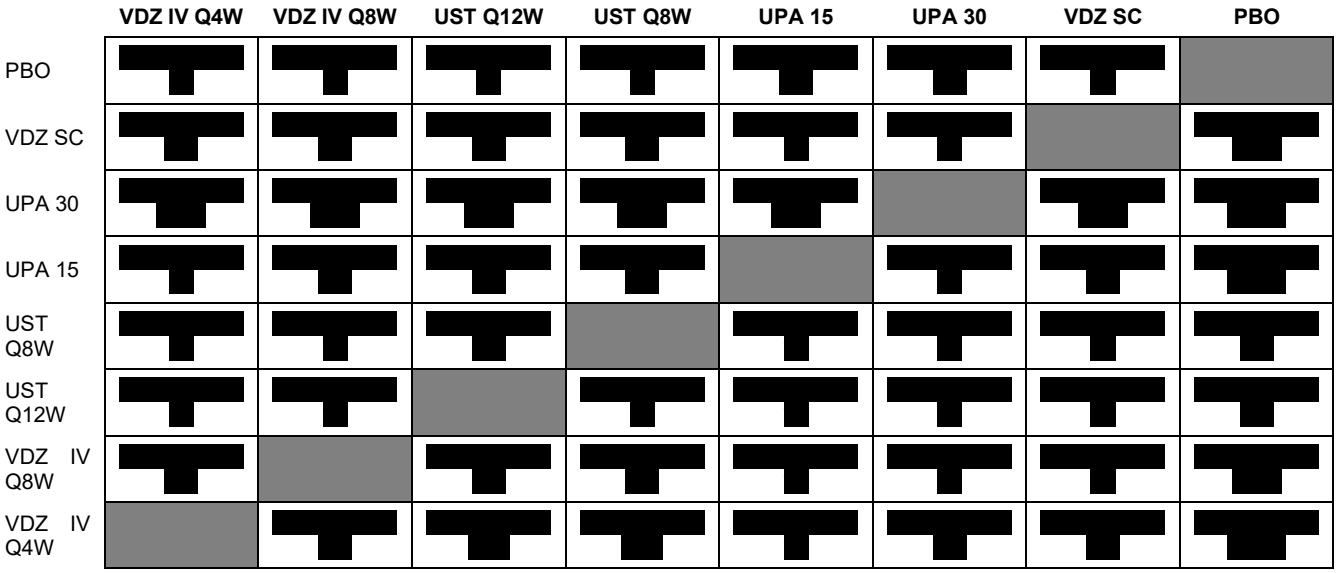
a) Please explain whether any data are available on the number of relapses during the treatment period for the intervention and comparators.

b) If so, please provide these data and incorporate them (and the resulting costs) in the Excel model.

Company response

As per discussions with NICE/EAG, relapse data cannot be included in the cost-comparison model. However, Table 3 shows results of the CDAI clinical remission NMA for the maintenance period (also presented in Table 51, Section B.3.9.2.3 of the CS), which shows that remission rates were comparable between upadacitinib and active comparators. Therefore, if relapse is defined as loss of remission, upadacitinib has comparable relapse rates to its active comparators.

Table 3: Results for CDAI clinical remission in BF maintenance NMA (FE model)



Abbreviations: BF, biologic failure; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; QxW, every x weeks; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

A 28. A concern about the current (biological) treatment options is the development of anti-drug antibodies.

a) Please explain whether anti-drug antibodies could develop that could lead to a loss of clinical efficacy of the intervention and the comparators and provide any data on this, if available.

b) What is known about the presence of anti-drug antibodies against one of the alternative treatments the effect this may have on the treatment effect when switching to another treatment?

Company response

As described in the response to A.25, biologic therapies are large, complex protein structures and can be recognised as 'foreign' by the host immune system, resulting in immunogenicity and anti-drug antibody (ADA) development (33). Although TNF-alpha inhibitors are not comparators for this submission, they can be used to illustrate how the development of ADA to biologics can lead to loss of clinical efficacy (34, 35). The rates of ADA development with TNF-alpha inhibitors are high; ADA rates of 28.5% and 62.8% have been reported for adalimumab and infliximab, respectively (36). ADAs can also develop with other biologic therapies, including ustekinumab and vedolizumab. A

loss of response rate of approximately 30% at 52 weeks has been reported for vedolizumab (integrin α4β7 inhibitor) and ustekinumab (IL-12/23 inhibitor) (37, 41). It has also been suggested that patients who have developed ADA to one biologic therapy may be more likely to develop ADA to subsequent biologic therapies (37), which may make them less effective and make treatment switching challenging.

As described in the response to A.25, upadacitinib is not a biologic therapy; it is a small molecule (non-protein) JAK inhibitor. JAK inhibitors do not cause immunogenicity or ADA development (38-40). This has two key implications: (1) patients are unlikely to develop ADA to upadacitinib in the first instance and (2) if patients have developed ADA to a prior biologic therapy, it should not impact their response to upadacitinib when switching treatment.

A 29. The trial data does not appear to include the results from extended induction. Please explain why these data were not used in the overall analyses.

Company response

Clinical data on extended induction are presented in Appendix J (Section J.7) of the CS. Safety data on extended induction are presented in B.3.10.1 of the CS. The focus of the clinical efficacy section was on standard induction because some clinicians may switch patients to another therapy rather than giving extended induction (although it should be noted that [redacted] of subjects receiving extended induction upadacitinib achieved clinical response by Week 24) (4).

Indirect treatment comparison (ITC)

A 30. Quality of life was not included as an outcome in the NMA, despite this outcome being important for the health economic analysis. Please explain the rationale for not including a quality-of-life outcome in the NMA, and provide the relevant NMA if possible.

Company response

As upadacitinib showed equal efficacy and safety to comparators, a HRQoL systematic review (and NMA) was not required (as HRQoL is driven by the health state that a patient is in).

HRQoL data from the upadacitinib clinical trials are presented in the CS; EQ-5D-5L data are provided in Section B.3.6, while FACIT-F and IBDQ data are presented in Appendix J (Section J.6).

Although not required for this appraisal, the company conducted an internal systematic literature review (SLR) to assess the HRQoL in patients with moderately to severely active CD. Searches for English-language publications were conducted on July 14 2022. For transparency, the report of this SLR has been included in the reference pack.

There are two main reasons why an NMA was not conducted following this SLR.

First, there was not sufficient data identified by the SLRs to conduct a robust HRQoL NMA for the comparators of interest (i.e., ustekinumab and vedolizumab). Based upon the records identified and extracted within the HRQoL/utility studies SLR ("AbbVie CD utility SLR_EXCEL report (v1.0) 06SEP2022.xlsx"); vedolizumab's VISIBLE 2 appears to be the only Phase 3 RCT captured which reports HRQoL data. Furthermore, these data do not appear to be available by subpopulation (i.e., by CCF and BF, which are important treatment effect modifiers). Thus, there is a paucity of necessary HRQoL data to conduct a robust NMA to the standards of NICE.

Second, there is no prior precedent for conducting HRQoL NMAs in previous NICE submissions of advanced therapies for moderately to severely active CD. Neither TA456 (ustekinumab) (42) nor TA352 (vedolizumab) (6) contain HRQoL NMAs conducted by the manufacturer or the EAG (referred to as the ERG at the time of TA456 and TA352). Thus, the EAG's request for a HRQoL NMA for the upadacitinib submission is not an equitable standard to previous submissions.

A 31. A fixed effect (FE) model is used for the base case, on the principal basis that the 'small number of trials eligible for inclusion in each network leading to implausible estimates of the between-study standard deviation when RE models were used'. This is a weak rationale. If there is high inconsistency between the populations in different comparisons then using a random effects (RE) model will lead to the background inconsistency being appropriately accounted for, and a by-product of this will be high levels of imprecision in the estimates. Failure to use a random effects model in this case will avoid the high imprecision, but this will fail to account for the inconsistency that exists, and therefore produce implausibly high precision that does not reflect reality. In addition, decisions on the use of FE or RE models should be made on an outcome-by-outcome basis, as a result of specific consideration of the clinical and statistical heterogeneity across comparisons for each separate outcome, and therefore it appears odd that all the outcomes should be analysed using an FE model. This wholescale use of an FE model has made a large difference to interpretation – the FE NMA results suggest a clear benefit for upadacitinib over VDZ and UST, whereas the RE results suggest that there are no clear differences.

a) Please provide a full rationale for the use of an FE model.

b) Please give a detailed description of the methodological procedures underlying the decision to use an FE or RE model for each outcome.

Company response

As set out in CS Section B.3.9.1.5, model selection was made after comparing model fit statistics, leverage plots, and density plots of posterior SDs for each set of two risk difference models (FE and RE). Additionally, FE models were selected on the basis of parsimony; this means that FE and RE models offered a similar fit to the data, suggesting the increased complexity of the RE model did not translate to improved fit and thus the simpler FE model was preferred (see Table 4 and Table 5 for fit statistics in the BF and CCF populations, respectively, and Table 6 for fit statistics for the safety NMAs).

Table 4: Fit statistics FE and RE NMA – BF population

Fit statistic	Induction – clinical response		Induction – clinical remission		Maintenance – clinical remission	
	FE	RE	FE	RE	FE	RE
Converged	Yes (<1.05)	Yes (<1.05)	Yes (<1.05)	Yes (<1.05)	Yes (<1.05)	Yes (<1.05)
Data points	12	12	12	12	13	13
Dbar	78.53	72.02	68.39	65.74	66.25	66.16
pD	8.86	12.46	8.83	11.82	11.54	12.51
DIC	87.39	84.48	77.23	77.56	77.79	78.68
Max-Gelman	1.0000	1.0018	1.0001	1.0013	1.0001	1.0002

Abbreviations: BF, biologic failure; DIC, deviance information criterion; FE, fixed effects; NMA, network meta-analysis; RE, random effects.

Table 5: Fit statistics FE and RE NMA – CCF population

Fit statistic	Induction – clinical response		Induction – clinical remission		Maintenance – clinical remission	
	FE	RE	FE	RE	FE	RE
Converged	Yes (<1.05)	Yes (<1.05)	Yes (<1.05)	Yes (<1.05)	Yes (<1.05)	Yes (<1.05)
Data points	18	18	18	18	19	19
Dbar	91.24	87.45	88.23	87.45	99.68	99.93
pD	13.21	15.03	13.58	15.03	17.02	17.22
DIC	104.46	102.48	101.80	102.48	116.70	117.15
Max-Gelman	1.0003	1.0013	1.0001	1.0013	1.0002	1.0036

Abbreviations: CCF, conventional care failure; DIC, deviance information criterion; FE, fixed effects; NMA, network meta-analysis; RE, random effects.

Table 6: Fit statistics FE and RE NMA - safety

Fit statistic	Induction – serious AEs		Induction – discontinuation due to AEs		Maintenance – serious AEs		Maintenance – discontinuation due to AEs	
	FE	RE	FE	RE	FE	RE	FE	RE
Converged	Yes (<1.05)	Yes (<1.05)	Yes (<1.05)	Yes (<1.05)	Yes (<1.05)	Yes (<1.05)	Yes (<1.05)	Yes (<1.05)
Data points	14	14	14	14	13	13	13	13
Dbar	74.37	73.87	67.61	67	70.24	69.92	62.47	62.48
pD	9.87	11.36	10.27	12.35	11.85	12.47	11.96	12.50
DIC	84.24	85.23	77.88	79.35	82.08	82.39	74.43	74.98
Max-Gelman	1.0004	1.0042	1.0002	1.0024	1.0002	1.0010	1.0005	1.0007

Abbreviations: AE, adverse event; DIC, deviance information criterion; FE, fixed effects; NMA, network meta-analysis; RE, random effects.

Further justification of the choice of FE versus RE NMA can be provided by comparing the results of the two NMAs with the clinical trial data. Table 7 shows the pairwise

comparisons from the NMAs that were informed by a single trial (for example maintenance upadacitinib 30 mg versus placebo was informed only by U-ENDURE). Robust NMA data should have credible intervals that align closely with the confidence intervals of the clinical trials. As shown in the table, the credible intervals for the FE NMAs align closely with the trial data while those for the RE NMAs are considerably wider. This suggests that the RE model results are not sufficiently robust and the FE model is more appropriate.

Table 7: Pairwise comparisons from NMAs and clinical trials

Outcome, comparator (trial)	Difference with intervention vs PBO from clinical trials (95% CI)	RD vs PBO from FE NMA (95% CrI)	RD vs PBO from RE NMA (95% CrI)
Induction CDAI clinical remission			
UST (UNITI-1)	8.6% (3.0, 14.2)	[redacted]	[redacted]
Induction CDAI clinical response			
UST (UNITI-1)	13.2% (5.5, 21.0)	[redacted]	[redacted]
Maintenance CDAI clinical remission			
UPA 30 (U-ENDURE)	[redacted]	[redacted]	[redacted]
UPA 15 (U-ENDURE)	[redacted]	[redacted]	[redacted]
UST Q12W (IM-UNITI)	12.4% (–4.41, 29.15)	[redacted]	[redacted]
UST Q8W (IM-UNITI)	14.8% (–2.13, 31.81)	[redacted]	[redacted]
VDZ IV Q4W (GEMINI 2)	14.5% (2.0, 26.9)	[redacted]	[redacted]
VDZ SC (VISIBLE 2)	17.6% (3.8, 31.4)	[redacted]	[redacted]

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence internal; CrI, credible interval; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; QxW, every x weeks; RD, risk difference; RE, random effects; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

The company provided the RE results in the CS as sensitivity analysis, which showed that upadacitinib was similar in efficacy (clinical response and remission) and safety (serious AEs and discontinuation due to AEs) to its relevant comparators in the BF population.

For a cost-comparison methodology the treatment being assessed must be similar or better across clinical efficacy and safety outcomes compared with the existing relevant comparator therapies. Regardless of the FE or RE NMA results, upadacitinib meets this criterion.

A 32. About 20% of patients were excluded from the U-EXCEL and U-EXCEED trials to enable them to be more consistent with comparator treatments in terms of the CDAI scores. This was done to improve consistency in the NMA.

a) Please explain how this procedure was performed without a reduction in internal and external validity of the upadacitinib trial data used in the NMA.

b) Please provide a full rationale for this approach, providing references.

c) Please provide details of the characteristics of upadacitinib trial participants remaining in the NMA (according to the criteria in Table 15, CS), so that the applicability of the upadacitinib NMA data to the UK target population can be evaluated.

Company response

A key criterion of NMA is the assumption of a sufficiently similar and thus comparable population across trials. All trials included in the presented NMAs institute a similar CDAI-level patient inclusion criterion, except for the upadacitinib CD trials. Upadacitinib CD trials did not include a CDAI inclusion criterion but rather opted to use the two key CD symptoms (i.e., abdominal pain and stool frequency, both of which components of the CDAI) along with other criteria to align with advice from regulatory agencies and reflect a more relevant real-world population. To align with the inclusion criteria of CDAI level (i.e., 220-450) observed in other CD trials in NMA, post-hoc analyses were conducted to obtain upadacitinib trial efficacy results utilising a CDAI-level inclusion criterion of between 220 and 450 (inclusive). After applying the post-hoc inclusion analysis, approximately 80% of patients were retained in each arm of the respective upadacitinib trials. Applying this exclusion to the upadacitinib trial populations improved validity as it made the included upadacitinib trial populations more akin to that of the comparators.

The details of the baseline characteristics for both the full upadacitinib CD trial populations and the baseline CDAI-restricted populations were presented in the CS Document B Appendices (Tables 17 and 18 for induction, Tables 19 and 20 for maintenance). For transparency we have provided these in Table 8 and Table 9 below, for induction and maintenance, respectively.

In general, baseline patient characteristics are similar between the whole trial population and the post-hoc CDAI 220–450 restricted population. Furthermore, efficacy across treatment arms in the upadacitinib CD trials does not vary meaningfully, with and without the CDAI inclusion criteria in U-EXCEL and U-EXCEED. In addition, baseline CDAI value in either the whole population or the post-hoc CDAI 220-450 restricted population of U-EXCEL and U-EXCEED are comparable to the values observed in other CD trials. Therefore, data from the CDAI 220–450 restricted population from upadacitinib programs were utilised in order to maximise the potential comparability of trial populations.

For completeness, the company has provided the results of the clinical efficacy and safety NMAs performed without the post-hoc CDAI restriction in Appendix E:. FE and RE NMA results are presented.

Table 8: Patient baseline characteristics for upadacitinib CD trial arms and populations (induction)

Study	Study arm	N	Males	Age, years	Weight, kg	Disease duration, years	CDAI score	IBDQ score	Concomitant treatment, n (%)	
			N (%)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	GS	IMM
U-EXCEL (restricted BF†)	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-EXCEL (restricted BF†)	UPA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-EXCEL (BF)	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-EXCEL (BF)	UPA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-EXCEED (restricted BF†)	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-EXCEED (restricted BF†)	UPA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-EXCEED (BF)	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-EXCEED (BF)	UPA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study	Study arm	N	Males	CRP, mg/L	FC, mg/kg	Draining fistulae	GI area(s) involved, n (%)		
			N (%)	Mean (SE)	Mean (SE)	N (%)	ileum	colon	both
U-EXCEL (restricted BF†)	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-EXCEL (restricted BF†)	UPA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-EXCEL (BF)	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-EXCEL (BF)	UPA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-EXCEED (restricted BF†)	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-EXCEED (restricted BF†)	UPA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-EXCEED (BF)	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-EXCEED (BF)	UPA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BF, biologic failure; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; FC, faecal calprotectin; GI, gastrointestinal; GS, glucocorticosteroids; IBDQ, Inflammatory Bowel Disease Questionnaire; IMM, immunomodulator; NMA, network meta-analysis; PBO, placebo; SE, standard error; UPA, upadacitinib. † Restricted population to patients with CDAI-score between 220 and 450 at baseline. Notes: Mean and SE values were imputed.

Table 9: Patient baseline characteristics for upadacitinib CD trial arms and populations (maintenance)

Study	Study arm	N	Males	Age, years	Weight, kg	Disease duration, years	CDAI score	IBDQ score	Concomitant treatment, n (%)	
			N (%)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	GS	IMM
U-ENDURE (restricted Overall†)	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-ENDURE (restricted Overall†)	UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-ENDURE (restricted Overall†)	UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-ENDURE (Overall)	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-ENDURE (Overall)	UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-ENDURE (Overall)	UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study	Study arm	N	Males	CRP, mg/L	FC, mg/kg	Draining fistulae	GI area(s) involved, n (%)		
			N (%)	Mean (SE)	Mean (SE)	N (%)	ileum	colon	both
U-ENDURE (restricted Overall†)	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-ENDURE (restricted Overall†)	UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-ENDURE (restricted Overall†)	UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-ENDURE (Overall)	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-ENDURE (Overall)	UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
U-ENDURE (Overall)	UPA 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CRP, C-reactive protein; CDAI, Crohn's Disease Activity Index; FC, faecal calprotectin; GI, gastrointestinal; GS, glucocorticosteroids; IBDQ, Inflammatory Bowel Disease Questionnaire; IMM, immunomodulator; NMA, network meta-analysis NR, not reported; PBO, placebo; SE, standard error; UPA, upadacitinib.
† Restricted population to patients with CDAI-score between 220 and 450 at baseline.
Notes: Mean and SE values were imputed.

A 33. The base case has provided NMA results for the BF stratum, and the results for the Conventional Care Failure (CCF) stratum are only presented in the appendices. Results for the CCF stratum are notably different from those in the BF stratum, with the CCF stratum failing to show any advantage of upadacitinib over the comparators, and, for some outcomes, demonstrating point estimates suggesting less benefit for upadacitinib. The NICE scope did not request stratification of the overall population, but the company's stratification appears to have led to beneficial results for one stratum.

a) Please state if the stratification was performed pre-hoc or post-hoc.

b) If this was a pre-hoc decision, please provide a full clinical rationale for the focus of the decision problem on the BF group.

Company response

The subpopulation analyses were predefined for the upadacitinib clinical trials (where applicable – U-EXCEL and U-ENDURE enrolled CCF and BF subjects while U-EXCEED enrolled BF subjects only).

As set out in Question A 4. the CS positions upadacitinib for use in the BF population. As stated in CS Section B.1.1, this represents a subpopulation to that specified in the NICE pre-invitation scope and licensed indication for upadacitinib. Upadacitinib is positioned for use in the BF population because in UK clinical practice most CCF subjects receive TNF-alpha inhibitors as first-line biologic therapy; this aligns with NICE guidance which recommends that biologic therapy begins with the least expensive option (2).

The division of the moderately to severely active CD population into the CCF and BF subpopulations is an established approach to analyses in this disease area and has been used for previous CD submissions to NICE, including ustekinumab and vedolizumab (11, 12).

A 34. The maintenance NMA analyses failed to show the benefits for upadacitinib over comparators that had been observed in the FE BF induction NMA analyses, despite the maintenance analyses involving an enriched group of upadacitinib responders. Please state possible reasons for this observation

Company response

The maintenance NMA showed that upadacitinib 15 mg was similar in efficacy and safety to its relevant comparators in the BF population, which is a minimum requirement for the cost-comparison route. Additionally, the 30 mg upadacitinib dose showed significantly higher clinical remission rates (CrIs not crossing zero) compared with all other treatments in the maintenance NMA.

The ‘enriched group of responders’ that the EAG calls out for upadacitinib also applies to the data sets used for ustekinumab and vedolizumab because re-randomisation for the maintenance part of the trials (i.e., allowing responders to continue onto maintenance treatment) was the trial design for all three treatments, and is reflective of clinical practice. Patients who do not respond to induction therapy will not carry on with the treatment into a maintenance phase.

A 35. The results of the NMA depend on the comparators used. Two TNF-alpha inhibitor drugs in the NICE scope – IFX and ADA – were requested as comparators, but these were excluded by the company on the basis that the anticipated target population would be one where '*TNF-alpha inhibitors are deemed unsuitable; or where biological treatment is not tolerated or not working well enough*'. However, as previously suggested in question A5, this rationale does not hold, because the company's definition of the population permits inclusion of people who have merely failed or not tolerated one biological treatment, which need not be an TNF-alpha inhibitor. Importantly, the use of the conjunction 'or' in the population definition means that these people need not also be those for whom TNF-alpha inhibitors are deemed unsuitable. Therefore, the company's rationale for the exclusion of IFX and ADA appears weak. In turn this suggests that the NMA analyses should have included these drugs. Please perform new NMAs using IFX and ADA as additional comparators

Company response

As described in the company response to A.3, TNF-alpha inhibitors are typically given as first-line biologic therapy in UK clinical practice. Following failure of a biologic (including TNF-alpha inhibitors), clinicians prefer to switch to a different drug class, meaning that a patient who has received a first-line TNF-alpha inhibitor is unlikely to receive a TNF-alpha inhibitor as second-line treatment. Instead, they would receive ustekinumab (IL-12/23 inhibitor) or vedolizumab (α4β7 integrin inhibitor). Therefore, TNF-alpha inhibitors are not relevant comparators in the BF population and were excluded from the analyses, which is consistent with the approach accepted by NICE in the submissions for ustekinumab and vedolizumab (11, 12).

Adverse events

A 36. Based on the NMA results the company concludes that adverse event (AE) rates are similar across intervention and comparators, and therefore excluded AEs from the analysis.

a) Please explain to what extent it can be assumed that the sample sizes and follow-up lengths of each trial included in the NMA are sufficient to detect meaningful differences in AE rates between treatments.

b) Please justify the assumption that AE rates remain similar across intervention and comparators, beyond treatment durations of one year and, if available, provide data that supports this assumption.

Company response

As indicated in CS (Table 16), upadacitinib trials were powered based upon detecting differences in efficacy outcomes and not safety outcomes. A similar trial design is likely for the comparator trials included in the NMA.

However, as indicated in Section B.3.10 of the CS, the AE outcomes used in the safety NMA (serious AEs and discontinuation due to AEs) were generally comparable between upadacitinib and placebo in both the induction and maintenance trials. Results from the upadacitinib trials were proportionally lower for treatment relative to placebo for all included NMA safety outcomes, except discontinuation due to AEs in the maintenance phase. Results from U-ENDURE show that there is no statistically significant difference between either of the upadacitinib doses and placebo for discontinuation due to AEs at Week 52, which is consistent with the safety NMA results.

Follow-up durations and timing of safety outcome measurements were chosen for consistency between all therapies. The assessment of safety outcomes in induction studies ranged from Week 4 to Week 12 (Week 12 in U-EXCEL and U-EXCEED). In maintenance studies, safety outcomes were assessed ranging from Week 44 to Week 60 (Week 52 for U-ENDURE). Any potential AEs that would require a longer treatment duration to be captured would be rare and therefore would have a very low cost per course of treatment associated with them. Therefore, the impact on the results of the cost-comparison analysis would not be substantial.

A 37. If available, please provide any (e.g. real-world, post-marketing, pharmacovigilance) long-term data on the incidence of AEs from the use of upadacitinib for the treatment of indications other than Crohn's disease.

Company response

Longer term safety data for upadacitinib is available in other therapy areas, such as rheumatoid arthritis (SELECT-COMPARE study) (43). However, an European Crohn's and Colitis Organisation (ECCO) statement noted that the extrapolation of JAK inhibitor safety data from other therapy areas to IBD may not be appropriate for several reasons, including differences in patient demographics and disease pathogenesis (44).

A 38. The clinical study report for U-EXCEL provides overviews of treatment-emergent severe adverse events, with a rate of serious infections that is [redacted] for patients treated with upadacitinib.

a) Please explain whether the risk of serious infections increases over time with increasing treatment durations.

b) Please explain the impact of serious infections on health-related quality of life, health care cost and mortality.

c) Please justify the plausibility of the assumption that rates of serious infections are the same across comparators, including with increasing treatment durations.

d) If it is not fully certain that serious infection rates are the same across comparators, regardless of treatment durations, then please provide a detailed explanation of this and address the impact of this uncertainty on the cost-effectiveness results in a model using a lifetime horizon.

e) For any severe adverse events other than serious infections for which there is uncertainty regarding their incidence over time with increasing treatment durations, please provide a detailed explanation of this uncertainty, whether it is the same across

comparators and its impact on cost-effectiveness (i.e., the same steps as described in question sub-parts a) to d) for serious infections).

Company response

As reported in the CS, the results of the upadacitinib CD trials did not identify any new safety risks (including in the occurrence of serious infections) compared with the known safety profile of upadacitinib, which has been established across six other indications with 19 Phase 3 trials and more than 5,000 patients.

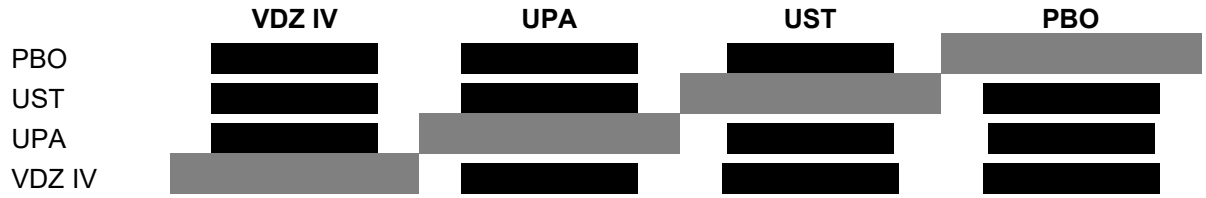
Furthermore, indirect comparison of upadacitinib with its comparators shows that the rate of serious infections with upadacitinib is not significantly different from that of active comparators or placebo. This applies in both the induction (Table 10) and maintenance (Table 11) periods. In the induction period, there were no significant differences in the rate of serious infections between any of the treatments; the RD for serious infections with upadacitinib was [redacted] versus ustekinumab and [redacted] versus vedolizumab.

In the maintenance period, the only significant difference was the RD for ustekinumab Q12W versus vedolizumab SC (RD 6.2% [0.2, 13.0]) (Table 11). The RDs for upadacitinib 30 mg versus comparators ranged from [redacted] but none reached statistical significance. Similarly, the RDs for upadacitinib 15 mg versus comparators ranged from [redacted] to [redacted] but none were significant (Table 11).

The results of the NMAs suggest that the rates of serious infections with upadacitinib are comparable to those of active comparators and placebo. Therefore, while serious infections may have an impact on HRQoL, healthcare cost and mortality, the impact is likely to be similar across upadacitinib and comparators, meaning that a cost-comparison approach is appropriate, as presented in Section B.4 of the CS.

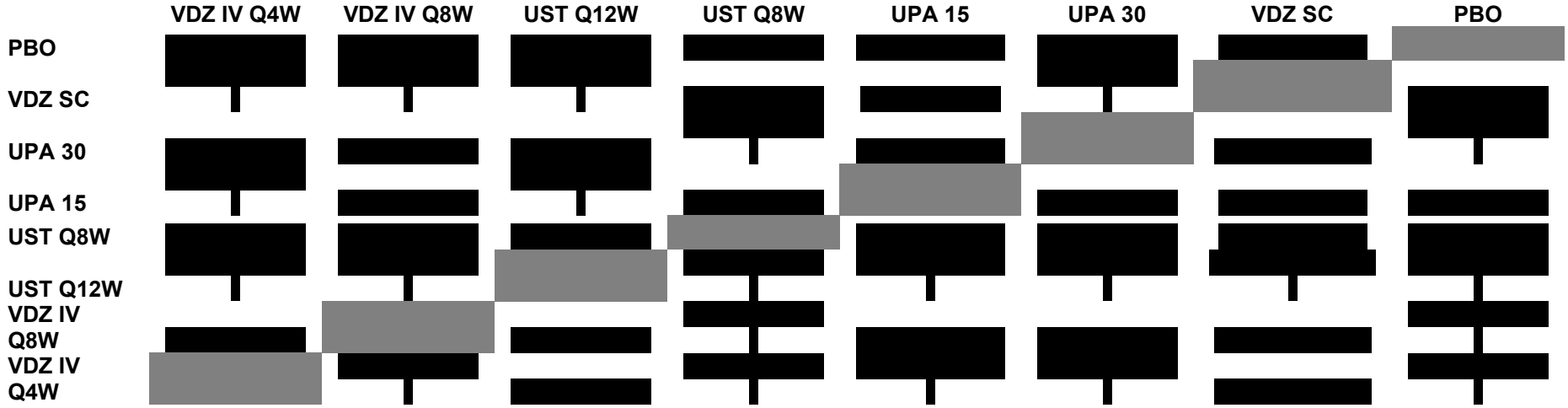
With regard to question e and as per discussions with NICE/EAG, this question is beyond the scope of the cost-comparison approach used in the submission.

Table 10: Results for serious infections induction NMA (FE model)



Abbreviations: FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered ‘significant’.

Table 11: Results for serious infection maintenance NMA (FE model)



Abbreviations: FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered ‘significant’.

Section B: Clarification on cost-effectiveness data

B 1. Priority Question. The economic analysis is restricted to a comparison of drug acquisition and administration costs, in contrast to a cost-effectiveness analysis using a model in which patients can transition to various health states and taking into account clinical effectiveness, health-related quality of life and health care resource use costs. This deviates from the usual approach to an STA and no explicit justification is provided for its appropriateness. Please provide a justification for submitting an economic analysis that is restricted to a comparison of drug acquisition and administration costs.

Company response

The company have provided a cost-comparison analysis to demonstrate the cost savings associated with the introduction of upadacitinib into UK clinical practice. A cost-comparison approach was chosen because upadacitinib was shown to have at least equivalent efficacy and safety to comparators (ustekinumab and vedolizumab) in NMAs. The results of the NMAs are presented in Section B.3.9.2 of the CS.

B 2. Priority Question. A cost comparison approach is used if it can be assumed that the intervention has equivalent or improved levels of benefit and harm to the comparators.

a) Please provide a precise definition of what is considered equivalent levels of benefit and harm between any two treatments

b) Please show how the clinical effectiveness evidence including the NMA results demonstrate that this has been achieved.

c) It is also possible that there could be differential rates of discontinuation between treatments such that switching to the next line of therapy, which is likely to be less effective than the previous one, occurs earlier for upadacitinib. Please provide a formal analysis of discontinuation rate and/or the underlying reasons for discontinuation such as duration of response adverse events.

Company response

Across the three pivotal trials (U-EXCEL and U-EXCEED for induction, U-ENDURE for maintenance), upadacitinib met all co-primary endpoints of clinical remission (defined either by CDAI or patient-reported outcomes [PROs]) and endoscopic response. Upadacitinib was superior to placebo for these outcomes across the overall trial populations and in the Bio-IR population.

In NMA, induction upadacitinib was found to have superior efficacy to ustekinumab, vedolizumab, and placebo for CDAI clinical remission and clinical response; the difference was significant for all comparisons with upadacitinib. As maintenance therapy, upadacitinib was also superior to its comparators for CDAI clinical remission (the only efficacy outcome assessed in the maintenance period), with significant results versus all comparators for the 30 mg dose. Upadacitinib 15 mg was significantly different from placebo but not significantly different from other comparators. Safety outcomes (serious AEs and discontinuation due to AEs) were comparable between upadacitinib and the comparators, including placebo. As shown in the additional NMAs presented in the response to A.38, rates of serious infection were also comparable between upadacitinib and comparators.

With regard to discontinuation rates, the company conducted NMAs for discontinuation due to AEs with upadacitinib versus comparators and the results are presented in Section B.3.9.2 of the CS.

B 3. Priority Question. The cost comparison analysis does not allow the exploration of the impact of any uncertainties regarding (potential) differences in costs or outcomes between the technologies being compared, other than its input parameters for drug acquisition costs, drug administration costs and drug dosing.

a) Please justify the assumption that there is no relevant uncertainty in terms of differences in clinical effectiveness, health-related quality of life, incidence rates of adverse events (including serious infections and malignancies) and their stability over time, and mortality.

b) Please highlight any uncertainties in terms of the aspects mentioned under 'a)', and provide a detailed explanation of their nature and impact on the cost-effectiveness results.

c) Please demonstrate the impact of any uncertainties in terms of the aspects mentioned under 'a)' using a cost-effectiveness model with a long enough time horizon.

Company response

The company have provided a cost-comparison analysis because NMAs showed at least equivalent efficacy and safety with upadacitinib versus comparators (ustekinumab and vedolizumab). The company has extensively explored differences in efficacy and safety across comparators and the results of the NMAs are presented in Section B.3.9.2 of the CS. This has allowed the company to conclude that upadacitinib is at least equivalent to its comparator treatments in the outcomes relevant to this appraisal.

The cost-comparison model does not allow for incorporation of any uncertainties in potential differences in costs or outcomes associated with the interventions.

B 4. Priority question: The time horizon for the base-case cost comparison is restricted to one year, and a sensitivity analysis is performed to demonstrate the costs of treatment beyond the first year. However, the 'Guide to the methods of technology appraisal 2022' by NICE stipulates that "The time horizon for estimating clinical effectiveness and value for money should be long enough to reflect all important differences in costs or outcomes between the technologies being compared".

a) Please justify that a one-year time horizon is sufficient to reflect all important differences in costs or outcomes.

Company response

Considering all clinical effectiveness and safety outcomes equal across upadacitinib and relevant comparators (ustekinumab and vedolizumab) in the BF population, the important differences between these technologies are limited to acquisition costs and administration costs. As these costs would vary between a maintenance year versus an induction year, the company presented both in their submission (CS Section B.4.3 [base case], CS Section B.4.4). In addition, NICE guidance states that patients should be re-assessed at least every 12 months to determine whether continuing with biologic treatment is appropriate.

Due to both the duration of the clinical trials in CD for upadacitinib and its relevant comparators, as well as NICE guidance, the company chose to show the induction year as the base case. However, irrespective of the duration of treatment, upadacitinib was shown to be cost saving compared with ustekinumab and vedolizumab (IV and SC options), therefore reflecting all important differences set out in the NICE reference case.

b) Please highlight any uncertainties surrounding the assumption of equal clinical effectiveness between the treatments under comparison with treatment durations beyond one year, considering that the maximum follow-up time was restricted to one year.

Company response

Clinical trials in CD for all comparators (and upadacitinib) are ~1 year (i.e., maintenance trials assessed clinical outcomes for up to 52 weeks). Any data beyond 1 year of biologic treatment would require assumptions regarding clinical effectiveness as there are no trial data or real-world evidence available beyond this timepoint for upadacitinib. Similarly, there are no trial data available for the biologic comparators. Although there may be real-world clinical data available for the biologic comparators, these evidence sources are of lower quality compared with RCTs. Available evidence supports the assumption of equivalent or superior efficacy and safety for upadacitinib compared with relevant comparators (ustekinumab and vedolizumab [IV and SC options]) and results from the cost comparison model confirm that upadacitinib is associated with lower costs than ustekinumab and vedolizumab (IV and SC options) in both the induction and maintenance years, irrespective of the duration of treatment.

c) Please explain whether any uncertainties surrounding the assumption of equal clinical effectiveness translate into uncertainties regarding mortality, health-related quality of life and costs, and, if so, address these uncertainties using a model with a long enough time horizon.

Company response

As the NMAs for clinical effectiveness outcomes (clinical response and remission) have demonstrated, upadacitinib is similar or superior to its relevant comparators (ustekinumab and vedolizumab) in the BF population. Sensitivity analysis using a RE model showed similar results. Therefore, upadacitinib meets the criteria set out for a cost-comparison route and as highlighted in Question B4a; the duration of treatment is irrelevant to the cost-comparison analysis as upadacitinib is shown to be cost-saving when compared with ustekinumab and vedolizumab (IV and SC options) in both the induction year and the maintenance year.

B 5. In the economic model it is assumed that extended induction for upadacitinib is always done using the 30 mg dose. The economic model can only be used to calculate results for either the standard induction or the extended induction, not a combination of the two. The proportions of patients receiving the standard or high dose for maintenance treatment is assumed the same for those with a standard induction period as those with an extended induction.

a) Please confirm that it is not possible for an extended induction to be done using the 45 mg dose, or adjust the model to accommodate this.

Company response

The anticipated label for upadacitinib with regards to the extended induction dose is upadacitinib [redacted]. Therefore, it is not enabled, nor should it be applied in the model, to use a 45 mg dose as an extended induction.

b) Please incorporate in the model the option to calculate results for a combination of standard and extended induction periods and justify the proportions of patients that are assumed to receive each type of induction. If available, please provide data on the proportions of patients receiving standard and extended induction for the intervention and the comparators and incorporate these in the model.

Company response

As the CS model is a CCM, results are expressed as cost per patient per year (on each treatment) and the difference between treatments. This is the reason the model allows for either the extended induction period to be considered or not to be considered, which also reflects the use of extended induction in clinical practice. Gastroenterologists advised that extended induction is not always used for patients with moderately to severely active CD on biologic treatment. If a patient has achieved no benefit at the end of the induction period, they are likely to be switched onto another biologic instead. Extended induction would be used if a patient had shown some evidence of clinical benefit during the initial induction phase or if a patient had failed all other available treatments and has no other alternative options (4). Although there are no real-world data available on the proportion of patients who would receive extended induction with upadacitinib in CD, it is important to note that [redacted] of patients with an inadequate response to standard 12-week induction with upadacitinib

achieved clinical response by Week 24 (i.e., with extended induction) of the upadacitinib clinical trials.

c) Please justify the assumption that the proportions of patients receiving the standard or high dose for maintenance treatment is the same for those with a standard induction period as those with an extended induction.

Company response

The assumption that the dose escalation patterns remain the same regardless of the addition of extended induction is a simplifying one. There is no clear evidence to suggest specific dose escalation rates after an extended induction across all relevant treatments. An assumption that there would be a difference may be a valid one, but it would apply across all comparators (aside from VDZ SC, as this has no licenced dose escalation).

Nonetheless, the company has provided an additional scenario in which it is assumed that if a patient needs extended induction they will start (and remain) on the high dose during the maintenance period. A summary of these results (CS assumptions on dose escalation and the new scenario) is presented in Table 12.

Table 12: Cost for 1 year of treatment with extended induction

	Induction year costs	
Treatment	**CS dose escalation assumption**	**All high dose assumption**
Upadacitinib	[redacted]	[redacted]
Ustekinumab	£21,527	£21,849
Vedolizumab IV	£24,581	£32,774
Vedolizumab SC †	£19,146	£19,146

Abbreviations: CS, Company submission; IV, intravenous; SC, subcutaneous.
† Vedolizumab SC does not have a licenced dose escalation option.
Note: Upadacitinib PAS and comparator list prices used.

B 6. The annual costs presented as base case results are based on the assumption that treatments are continued for the full 52 weeks.

a) Please explain whether the treatments continue for patients who are in remission.

Company response

NICE guidelines state that patients should be re-assessed at least every 12 months to determine whether continuing with biologic treatment is appropriate, meaning that some patients, i.e., those who will benefit from continued treatment, will be on advanced therapies for longer than 52 weeks. The costs associated with treatment beyond Year 1 (i.e., Year 2+) are presented as a scenario analysis in Section B.4.4 (Table 70) of the CS.

b) Please explain whether there is data available on time-to-remission for the intervention and the comparators and, if so, incorporate these in the economic analysis.

Company response

As the company submitted a cost-comparison and deems this the most appropriate model for this submission, time to remission data for upadacitinib and comparators is not considered relevant. Costs for induction and maintenance doses are irrelevant to the time to remission; additionally, when patients respond to treatment (but are not yet in remission) the same treatment will be continued.

B 7. Please explain why a ‘vial sharing’ option is included in the model, given that patients per definition only receive whole vials of ustekinumab.

Company response

As ustekinumab induction (IV) dosing is weight based, the company added a vial sharing option for completeness. This option is not used in the results presented in the CS and can be ignored.

B 8. Clinical experts were consulted to inform the proportions of patients receiving a low maintenance dose for each comparator. The results are provided in Figure 1 and Table 1 of the HTA advisory board report. [redacted]

a) Please justify the model inputs for the proportions of patients receiving a low maintenance dose and explain how input from clinical experts was used to inform these.

b) Please adjust the proportion of patients receiving a low maintenance dose for vedolizumab to more accurately reflect clinical expert opinion.

c) Please report the results of sensitivity analyses for the proportions receiving the low maintenance dose for vedolizumab (i.e. similar to those for upadacitinib and ustekinumab).

Company response

The original advisory board provided the results as referenced in the CS. Further interviews with clinical experts (gastroenterologists; n=3) in the UK supported the already identified dose escalation pattern of ustekinumab and an average of approximately 30% of patients who received vedolizumab IV to need dose escalation during the maintenance phase. The model is flexible and allows the user to adjust the percentage for the low dose.

As expert opinion on vedolizumab dose escalation ranges from 22–30%, the company has presented the results for both 22% and 30% dose escalated vedolizumab IV in Table 13.

Table 13: Sensitivity analyses dose escalation

	Induction year costs	
Treatment	**Base case (VDZ 30% dose escalated) – CS**	**VDZ 22% dose escalated**
Upadacitinib	[redacted]	[redacted]
Ustekinumab	£21,527	£21,527
Vedolizumab IV	£24,581	£23,644
Vedolizumab SC	£19,146	£19,146

Abbreviations: CS, company submission; IV, intravenous; SC, subcutaneous; VDZ, vedolizumab.
Note: Upadacitinib PAS and comparator list prices used.

B 9. Please explain whether the weight characteristics, as reported in Table 62 of the CS, are the same across the various subpopulations and, if not the same, please provide the option in the model to use the corresponding weight characteristics for each relevant subpopulation / comparison.

Company response

The weight characteristics that are used in the model are based on the baseline characteristics of the BF populations from the upadacitinib CD induction trials (U-EXCEL and U-EXCEED, CDAI restricted ITT-1). As the CS is specific to the BF population, this is the most appropriate and only population data to use in the model.

B 10. The sum of the proportions of patients in each weight category amounts to 100.10%. Please make sure the sum amount to 100%.

Company response

The company has adjusted the percentage as presented in Table 14 (as per the original reference). Please note that this does not impact on the results due to ustekinumab IV induction (the only included treatment that is weight based) as it leads to the same number of vials required.

Table 14: Weight distributions used in the model

Mean weight (kg)	Proportion
<55kg	23%
55–85kg	56%
>85kg	21%

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Appendix A: Analysis by prior TNF-alpha inhibitor failure (in response to A15 and A17)

A.1 U-EXCEL (overall population)

A.1.1 CDAI clinical remission at Week 12

Table 15: CDAI clinical remission at Week 12 in subjects with no prior TNF-alpha inhibitor failure (U-EXCEL ITT1 overall population)

Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI[†]	Missing due to COVID-19, n	Diff.	Adj. diff. (%)[‡]	95% CI[§]	P value
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: Data on file (45). Note: CDAI clinical remission defined as CDAI score <150. [†]95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. [§]95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

A.1.2 Endoscopic response at Week 12

Table 16: Endoscopic response at Week 12 in subjects with no prior TNF-alpha inhibitor failure (U-EXCEL ITT1 overall population)

Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI[†]	Missing due to COVID-19, n	Diff.	Adj. diff. (%)[‡]	95% CI[§]	P value
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; SES-CD, Simple Endoscopic Score – Crohn's Disease; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: Data on file (45). Note: endoscopic response defined as decrease in SES-CD of >50% from baseline of the induction study. [†]95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. [§]95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

A.1.3 CDAI clinical response (CR-100) at Week 12

Table 17: CDAI clinical response (CR-100) at Week 12 in subjects with no prior TNF-alpha inhibitor failure (U-EXCEL ITT1 overall population)

Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: Data on file (45). Note: CR-100 defined as decrease of ≥100 points in CDAI from baseline. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

A.1.4 Endoscopic remission at Week 12

Table 18: Endoscopic remission at Week 12 in subjects with no prior TNF-alpha inhibitor failure (U-EXCEL ITT1 overall population)

Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: Data on file (45). Note: endoscopic remission defined as SES-CD ≤4 and ≥2-point reduction from baseline and no subscore >1 in any individual variable, as scored by central reviewer. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

A.1.5 CD-related hospitalisation

Table 19: Occurrence of hospitalisations due to CD during the 12-week induction period by prior TNF-alpha inhibitor failure (AO, U-EXCEL ITT1 overall population)

Population Treatment	Responder (AO)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
Prior TNF-alpha inhibitor failure: 0								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]					
Prior TNF-alpha inhibitor failure: 1								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]					
Prior TNF-alpha inhibitor failure: >1								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]					

Abbreviations: AO, as observed; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; non-Bio-IR, conventional therapy inadequate response/intolerance; NR, not reported; PBO, placebo; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: Data on file (45). Note: For all subjects in the ITT1 population, occurrence of hospitalisation due to CD was a binary variable. The value was 'yes' for subjects who had at least one hospitalisation due to CD during the 12-week induction period and 'no' for subjects who did not have any hospitalisation during the 12-week induction period. †95% CI for response rate is based on the normal approximation to the binomial distribution. ‡Risk difference = UPA – PBO. §95% CI for treatment difference was based on normal approximation of the binomial proportions. P-value was calculated according to the Chi-squared test or Fisher's exact test if more than 20% of the cells have expected counts of less than 5.

A.1.6 Change from baseline in EQ-5D-5L at Week 4 and Week 12

Table 20: Change from baseline in EQ-5D-5L index value at Week 4 at Week 12 (MMRM; U-EXCEL ITT1 overall population)

Subgroup Timepoint Treatment	Within group change from baseline					Between group difference vs PBO		
	N	Baseline mean	Visit mean	LS mean	95% CI	LS mean	95% CI	SE
Prior TNF-alpha inhibitor failure: 0								
Week 4								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Week 12								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Prior TNF-alpha inhibitor failure: 1								
Week 4								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Week 12								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Prior TNF-alpha inhibitor failure: >1								
Week 4								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Week 12								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			

Abbreviations: CI, confidence interval; CSR, clinical study report; EQ-5D-5L, EuroQol-5 Dimensions 5-level; LS, least squares; MMRM, mixed effect model repeat measurement; PBO, placebo, SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: Data on file (45). MMRM was the mixed effect model repeat measurement with baseline value, stratification factors (baseline corticosteroid use [yes or no], endoscopic disease severity [SES-CD <15 or ≥15], and number of prior biologics failed [0, 1, or >1]), treatment visit, treatment-by-visit interaction included in the model. An unstructured covariance matrix was used.

Table 21: Change from baseline in EQ-5D-5L VAS at Week 4 at Week 12 (MMRM; U-EXCEL ITT1 overall population)

Subgroup Timepoint Treatment	Within group change from baseline					Between group difference vs PBO		
	N	Baseline mean	Visit mean	LS mean	95% CI	LS mean	95% CI	SE
Prior TNF-alpha inhibitor failure: 0								
Week 4								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Week 12								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Prior TNF-alpha inhibitor failure: 1								
Week 4								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Week 12								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Prior TNF-alpha inhibitor failure: >1								
Week 4								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Week 12								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			

Abbreviations: CI, confidence interval; CSR, clinical study report; EQ-5D-5L, EuroQol-5 Dimensions 5-level; LS, least squares; MMRM, mixed effect model repeat measurement; PBO, placebo; SE, standard error; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumour necrosis factor; UPA, upadacitinib; VAS, visual analogue scale.

Source: Data on file (45). MMRM was the mixed effect model repeat measurement with baseline value, stratification factors (baseline corticosteroid use [yes or no], endoscopic disease severity [SES-CD <15 or ≥15], and number of prior biologics failed [0, 1, or >1]), treatment visit, treatment-by-visit interaction included in the model. An unstructured covariance matrix was used.

A.1.7 Safety: overview of TEAEs and deaths

Table 22: Overview of TEAEs and deaths in U-EXCEL by prior TNF-alpha inhibitor failure (SA1 population)

Event, n (%)	UPA 45 mg	PBO
Prior TNF-alpha inhibitor failure: 0		
Any TEAE	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
TEAE related to study drug (assessed by investigator)	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]
TEAE leading to withdrawal of study treatment	[redacted]	[redacted]
TEAE resulting in death	[redacted]	[redacted]
Any death	[redacted]	[redacted]
Deaths occurring ≤30 days after last dose of study drug	[redacted]	[redacted]
Deaths occurring >30 days after last dose of study drug	[redacted]	[redacted]
Deaths due to COVID-19	[redacted]	[redacted]
Prior TNF-alpha inhibitor failure: 1		
Any TEAE	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
TEAE related to study drug (assessed by investigator)	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]
TEAE leading to withdrawal of study treatment	[redacted]	[redacted]
TEAE resulting in death	[redacted]	[redacted]
Any death	[redacted]	[redacted]
Deaths occurring ≤30 days after last dose of study drug	[redacted]	[redacted]
Deaths occurring >30 days after last dose of study drug	[redacted]	[redacted]
Deaths due to COVID-19	[redacted]	[redacted]
Prior TNF-alpha inhibitor failure: >1		
Any TEAE	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
TEAE related to study drug (assessed by investigator)	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]
TEAE leading to withdrawal of study treatment	[redacted]	[redacted]
TEAE resulting in death	[redacted]	[redacted]
Any death	[redacted]	[redacted]
Deaths occurring ≤30 days after last dose of study drug	[redacted]	[redacted]
Deaths occurring >30 days after last dose of study drug	[redacted]	[redacted]
Deaths due to COVID-19	[redacted]	[redacted]

Abbreviations: COVID-19, Coronavirus Disease 2019; PBO, placebo; SA, safety analysis; TNF, tumour necrosis factor; TEAE, treatment-emergent adverse event; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: Data on file (45). Note: In U-EXCEL, TEAEs in the induction period (Part 1) were defined as events that begin either on or after the first dose of the study drug in Part 1 and until (i) the first dose of study drug in U-ENDURE (if applicable), or (ii) until the first dose of study drug in Part 2 (if applicable), or (iii) within 30 days after the last dose administration of the study drug in Part 1, whichever is earlier.

A.1.8 Safety: AESI

Table 23: AESI in U-EXCEL by prior TNF-alpha inhibitor failure (SA1 population)

Event, n (%)	UPA 45 mg	PBO
Prior TNF-alpha inhibitor failure: 0		
Serious infections	[redacted]	[redacted]
Opportunistic infections excluding TB and herpes zoster	[redacted]	[redacted]
Active TB	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]
Adjudicated GI perforations	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
CPK elevations	[redacted]	[redacted]
Hepatic disorders	[redacted]	[redacted]
Renal dysfunction	[redacted]	[redacted]
Malignancies (all types)	[redacted]	[redacted]
Malignancies excluding NMSC	[redacted]	[redacted]
NMSC	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]
Adjudicated cardiovascular events	[redacted]	[redacted]
Adjudicated thrombotic events	[redacted]	[redacted]
Prior TNF-alpha inhibitor failure: 1		
Serious infections	[redacted]	[redacted]
Opportunistic infections excluding TB and herpes zoster	[redacted]	[redacted]
Active TB	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]
Adjudicated GI perforations	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
CPK elevations	[redacted]	[redacted]
Hepatic disorders	[redacted]	[redacted]
Renal dysfunction	[redacted]	[redacted]
Malignancies (all types)	[redacted]	[redacted]
Malignancies excluding NMSC	[redacted]	[redacted]
NMSC	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]
Adjudicated cardiovascular events	[redacted]	[redacted]
Adjudicated thrombotic events	[redacted]	[redacted]
Prior TNF-alpha inhibitor failure: >1		
Serious infections	[redacted]	[redacted]
Opportunistic infections excluding TB and herpes zoster	[redacted]	[redacted]
Active TB	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]

Event, n (%)	UPA 45 mg	PBO
Adjudicated GI perforations	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
CPK elevations	[redacted]	[redacted]
Hepatic disorders	[redacted]	[redacted]
Renal dysfunction	[redacted]	[redacted]
Malignancies (all types)	[redacted]	[redacted]
Malignancies excluding NMSC	[redacted]	[redacted]
NMSC	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]
Adjudicated cardiovascular events	[redacted]	[redacted]
Adjudicated thrombotic events	[redacted]	[redacted]

Abbreviations: AESI, adverse event of special interest; CPK, creatine phosphokinase; GI, gastrointestinal; NMSC, non-melanoma skin cancer; PBO, placebo; TB, tuberculosis; TNF, tumour necrosis factor UPA, upadacitinib; VTE, venous thromboembolic event.
Source: Data on file (45). Note: TEAEs were defined as events that began either on or after the first dose of study drug in the maintenance phase and until (i) the first dose of study drug in the long-term extension phase (if applicable), or (ii) the first dose of open-label upadacitinib 30 mg QD rescue therapy (if applicable), or (iii) within 30 days after the last dose administration of the double-blinded drug in the maintenance phase, whichever is earlier.

A.2 U-EXCEED (overall population)

A.2.1 CDAI clinical remission at Week 12

Table 24: CDAI clinical remission at Week 12 by prior TNF-alpha inhibitor failure (NRI-C, U-EXCEED ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
Prior TNF-alpha inhibitor failure: 0								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
Prior TNF-alpha inhibitor failure: ≥1								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: U-EXCEED subgroup analyses (data on file) (46). Note: CDAI clinical remission defined as CDAI score <150. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

A.2.2 Endoscopic response at Week 12

Table 25: Endoscopic response at Week 12 by prior TNF-alpha inhibitor failure (NRI-C, U-EXCEED ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
Prior TNF-alpha inhibitor failure: 0								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
Prior TNF-alpha inhibitor failure: ≥1								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; SES-CD, Simple Endoscopic Score – Crohn's Disease; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: U-EXCEED subgroup analyses (data on file) (46). Note: endoscopic response defined as decrease in SES-CD of >50% from baseline of the induction study. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

A.2.3 CDAI clinical remission at Week 4

Table 26: CDAI clinical remission at Week 4 by prior TNF-alpha inhibitor failure (NRI-C, U-EXCEED ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
Prior TNF-alpha inhibitor failure: 0								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
Prior TNF-alpha inhibitor failure: ≥1								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; TNF, tumour necrosis factor; UPA, upadacitinib. Source: U-EXCEED subgroup analyses (data on file) (46). Note: CDAI clinical remission defined as CDAI score <150. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

A.2.4 CDAI clinical response (CR-100) at Week 2 and Week 12

Table 27: CDAI clinical response (CR-100) at Week 2 by prior TNF-alpha inhibitor failure (NRI-C, U-EXCEED ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
Prior TNF-alpha inhibitor failure: 0								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
Prior TNF-alpha inhibitor failure: ≥1								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: U-EXCEED subgroup analyses (data on file) (46). Note: CR-100 defined as decrease of ≥100 points in CDAI from baseline. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

Table 28: CDAI clinical response (CR-100) at Week 12 by prior TNF-alpha inhibitor failure (NRI-C, U-EXCEED ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
Prior TNF-alpha inhibitor failure: 0								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
Prior TNF-alpha inhibitor failure: ≥1								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: U-EXCEED subgroup analyses (data on file) (46). Note: CR-100 defined as decrease of ≥100 points in CDAI from baseline. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors.

A.2.5 Endoscopic remission at Week 12

Table 29: Endoscopic remission at Week 12 by prior TNF-alpha inhibitor failure (NRI-C, U-EXCEED ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
Prior TNF-alpha inhibitor failure: 0								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
Prior TNF-alpha inhibitor failure: ≥1								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: U-EXCEED subgroup analyses (data on file) (46). Note: endoscopic remission defined as SES-CD ≤4 and ≥2-point reduction from baseline and no subscore >1 in any individual variable, as scored by central reviewer. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

A.3 U-ENDURE (overall population)

A.3.1 CDAI clinical remission at Week 52

Table 30: CDAI clinical remission at Week 52 in subjects with no prior TNF-alpha inhibitor failure (U-ENDURE ITT1 overall population)

Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NA, not applicable; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: Data on file (45). Note: CDAI clinical remission defined as CDAI score <150. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

A.3.2 Endoscopic response at Week 52

Table 31: Endoscopic response at Week 52 in subjects with no prior TNF-alpha inhibitor failure (U-ENDURE ITT1 overall population)

Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI[†]	Missing due to COVID-19, n	Diff.	Adj. diff. (%)[‡]	95% CI[§]	P value
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NA, not applicable; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: Data on file (45). Note: endoscopic response defined as decrease in SES-CD of >50% from baseline of the induction study or for subjects with an SES-CD of 4 at baseline, ≥2-point reduction from baseline, as scored by central reviewer. [†]95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. [§]95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

A.3.3 CDAI clinical response (CR-100) at Week 52

Table 32: CDAI clinical response (CR-100) at Week 52 in subjects with no prior TNF-alpha inhibitor failure (U-ENDURE ITT1 overall population)

Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI[†]	Missing due to COVID-19, n	Diff.	Adj. diff. (%)[‡]	95% CI[§]	P value
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CR, clinical response; CSR, clinical study report; ITT, intention to treat; NA, not applicable; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: Data on file (45). Note: CR-100 defined as decrease of ≥100 points in CDAI from baseline. [†]95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. [§]95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

A.3.4 Endoscopic remission at Week 52

Table 33: Endoscopic remission at Week 52 in subjects with no prior TNF-alpha inhibitor failure (U-ENDURE ITT1 overall population)

Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI[†]	Missing due to COVID-19, n	Diff.	Adj. diff. (%)[‡]	95% CI[§]	P value
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CR, clinical response; CSR, clinical study report; ITT, intention to treat; NA, not applicable; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: Data on file (45). Note: endoscopic remission defined as SES-CD ≤4 and ≥2-point reduction from baseline and no subscore >1 in any individual variable, as scored by central reviewer. [†]95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. [§]95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

A.3.5 CD-related hospitalisation

Table 34: Occurrence of CD-related hospitalisation during the 52-week double-blind maintenance period by prior TNF-alpha inhibitor failure (AO, U-ENDURE ITT1 overall population)

Population Treatment	Responder					Incidence rate difference vs PBO			
	N	N with CD-related hosp.	Time at risk (PY)	Incidence rate (n/100PY)	95% CI†	Diff.	Adj. diff. (%)‡	95% CI§	P value
Prior TNF-alpha inhibitor failure: 0									
UPA 30 mg	[redacted]								
UPA 15 mg	[redacted]								
PBO	[redacted]								
Prior TNF-alpha inhibitor failure: 1									
UPA 30 mg	[redacted]								
UPA 15 mg	[redacted]								
PBO	[redacted]								
Prior TNF-alpha inhibitor failure: >1									
UPA 30 mg	[redacted]								
UPA 15 mg	[redacted]								
PBO	[redacted]								

Abbreviations: AO, as observed; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CR, clinical response; CSR, clinical study report; ITT, intention to treat; NA, not applicable; NR, not reported; PBO, placebo; PY, patient-years; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: Data on file (45). †95% CI for incidence rate is based on the normal approximation to binomial distribution. ‡Incidence rate difference = UPA – PBO. §95% CI for incidence rate difference and p value are based on the normal approximation to Poisson distribution.

A.3.6 Change from baseline in EQ-5D-5L at Week 52

Table 35: Change from induction baseline to Week 52 in EQ-5D-5L index value and VAS (MMRM, U-ENDURE ITT1 overall population)

Subgroup Measure Treatment	Within group change from baseline					Between group difference vs PBO		
	N	Baseline mean	Visit mean	LS mean	95% CI	LS mean	95% CI	SE
Prior TNF-alpha inhibitor failure: 0								
Index value								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							
VAS								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							
Prior TNF-alpha inhibitor failure: 1								
Index value								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							
VAS								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							
Prior TNF-alpha inhibitor failure: >1								
Index value								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							
VAS								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CI, confidence interval; CSR, clinical study report; DB, double-blind; EQ-5D-5lL, EuroQol-5 dimensions-5 Levels; LS, least squares; MMRM, mixed effect model repeat measurement; non-Bio-IR, conventional therapy inadequate response/intolerance; OL, open-label; PBO, placebo, PRO, patient-reported outcome; TNF, tumour necrosis factor; UPA, upadacitinib; VAS, visual analogue scale.

Source: Data on file (45). Note: MMRM is the mixed effect model repeat measurement with induction baseline value, Week 0 value, stratification factors (prior induction population [non-Bio-IR, DB bio-IR, OL bio-IR), PRO clinical remission [yes/no], and endoscopic response status [yes/no]), treatment visit, visit, treatment-by-visit interaction included in the model. Induction baseline was defined as the last non-missing observation prior to the first dose of study drug in U-EXCEL/U-EXCEED. An unstructured covariance matrix was used.

A.3.7 Safety: overview of TEAEs and deaths

Table 36: Overview of TEAEs and death in in 52-week maintenance period by prior TNF-alpha inhibitor failure (U-ENDURE SA1 population)

Event, n (%)	UPA 30 mg	UPA 15 mg	PBO
Prior TNF-alpha inhibitor failure: 0			
Any TEAE	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
TEAE related to study drug (assessed by investigator)	[redacted]	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]
TEAE leading to withdrawal of study treatment	[redacted]	[redacted]	[redacted]
TEAE resulting in death	[redacted]	[redacted]	[redacted]
Any death	[redacted]	[redacted]	[redacted]
Deaths occurring ≤30 days after last dose of study drug	[redacted]	[redacted]	[redacted]
Deaths occurring >30 days after last dose of study drug	[redacted]	[redacted]	[redacted]
Deaths due to COVID-19	[redacted]	[redacted]	[redacted]
Prior TNF-alpha inhibitor failure: 1			
Any TEAE	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
TEAE related to study drug (assessed by investigator)	[redacted]	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]
TEAE leading to withdrawal of study treatment	[redacted]	[redacted]	[redacted]
TEAE resulting in death	[redacted]	[redacted]	[redacted]
Any death	[redacted]	[redacted]	[redacted]
Deaths occurring ≤30 days after last dose of study drug	[redacted]	[redacted]	[redacted]
Deaths occurring >30 days after last dose of study drug	[redacted]	[redacted]	[redacted]
Deaths due to COVID-19	[redacted]	[redacted]	[redacted]
Prior TNF-alpha inhibitor failure: >1			
Any TEAE	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
TEAE related to study drug (assessed by investigator)	[redacted]	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]
TEAE leading to withdrawal of study treatment	[redacted]	[redacted]	[redacted]
TEAE resulting in death	[redacted]	[redacted]	[redacted]
Any death	[redacted]	[redacted]	[redacted]

Event, n (%)	UPA 30 mg	UPA 15 mg	PBO
Deaths occurring ≤30 days after last dose of study drug	[redacted]	[redacted]	[redacted]
Deaths occurring >30 days after last dose of study drug	[redacted]	[redacted]	[redacted]
Deaths due to COVID-19	[redacted]	[redacted]	[redacted]

Abbreviations: COVID-19, Coronavirus Disease 2019; PBO, placebo; SA, safety analysis; TNF, tumour necrosis factor; TEAE, treatment-emergent adverse event; TNF, tumour necrosis factor; UPA, upadacitinib.
Source: Data on file (45). Note: TEAEs were defined as events that began either on or after the first dose of study drug in the maintenance phase and until (i) the first dose of study drug in the long-term extension phase (if applicable), or (ii) the first dose of open-label upadacitinib 30 mg QD rescue therapy (if applicable), or (iii) within 30 days after the last dose administration of the double-blinded drug in the maintenance phase, whichever is earlier.

A.3.8 Safety: AESI

Table 37: AESI in 52-week maintenance period by prior TNF-alpha inhibitor failure (U-ENDURE SA1 population)

Event, n (%)	UPA 30 mg	UPA 15 mg	PBO
Prior TNF-alpha inhibitor failure: 0			
Serious infections	[redacted]	[redacted]	[redacted]
Opportunistic infections excluding TB and herpes zoster	[redacted]	[redacted]	[redacted]
Active TB	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]
Adjudicated GI perforations	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]
CPK elevations	[redacted]	[redacted]	[redacted]
Hepatic disorders	[redacted]	[redacted]	[redacted]
Renal dysfunction	[redacted]	[redacted]	[redacted]
Malignancies (all types)	[redacted]	[redacted]	[redacted]
Malignancies excluding NMSC	[redacted]	[redacted]	[redacted]
NMSC	[redacted]	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]	[redacted]
Adjudicated cardiovascular events	[redacted]	[redacted]	[redacted]
Adjudicated thrombotic events	[redacted]	[redacted]	[redacted]
Prior TNF-alpha inhibitor failure: 1			
Serious infections	[redacted]	[redacted]	[redacted]
Opportunistic infections excluding TB and herpes zoster	[redacted]	[redacted]	[redacted]
Active TB	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]
Adjudicated GI perforations	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]
CPK elevations	[redacted]	[redacted]	[redacted]
Hepatic disorders	[redacted]	[redacted]	[redacted]
Renal dysfunction	[redacted]	[redacted]	[redacted]
Malignancies (all types)	[redacted]	[redacted]	[redacted]
Malignancies excluding NMSC	[redacted]	[redacted]	[redacted]
NMSC	[redacted]	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]	[redacted]
Adjudicated cardiovascular events	[redacted]	[redacted]	[redacted]
Adjudicated thrombotic events	[redacted]	[redacted]	[redacted]

Event, n (%)	UPA 30 mg	UPA 15 mg	PBO
Prior TNF-alpha inhibitor failure: >1			
Serious infections	[redacted]	[redacted]	[redacted]
Opportunistic infections excluding TB and herpes zoster	[redacted]	[redacted]	[redacted]
Active TB	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]
Adjudicated GI perforations	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]
CPK elevations	[redacted]	[redacted]	[redacted]
Hepatic disorders	[redacted]	[redacted]	[redacted]
Renal dysfunction	[redacted]	[redacted]	[redacted]
Malignancies (all types)	[redacted]	[redacted]	[redacted]
Malignancies excluding NMSC	[redacted]	[redacted]	[redacted]
NMSC	[redacted]	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]	[redacted]
Adjudicated cardiovascular events	[redacted]	[redacted]	[redacted]
Adjudicated thrombotic events	[redacted]	[redacted]	[redacted]

Abbreviations: AESI, adverse event of special interest; CPK, creatine phosphokinase; GI, gastrointestinal; NMSC, non-melanoma skin cancer; PBO, placebo; TB, tuberculosis; TNF, tumour necrosis factor UPA, upadacitinib; VTE, venous thromboembolic event.
Source: Data on file (45). Note: TEAEs were defined as events that began either on or after the first dose of study drug in the maintenance phase and until (i) the first dose of study drug in the long-term extension phase (if applicable), or (ii) the first dose of open-label upadacitinib 30 mg QD rescue therapy (if applicable), or (iii) within 30 days after the last dose administration of the double-blinded drug in the maintenance phase, whichever is earlier.

Appendix B: Analysis by number of prior biologics failed (response to A16 and A18)

B.1 U-EXCEL

B.1.1 CDAI clinical remission at Week 12

Table 38: CDAI clinical remission at Week 12 (NRI-C) – by number of prior biologics failed (U-EXCEL ITT1 Bio-IR population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
1 prior biologic failed								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
>1 prior biologic failed								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.
Source: U-EXCEL CSR (47). Note: CDAI clinical remission defined as CDAI score <150. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.1.2 Endoscopic response at Week 12

Table 39: Endoscopic response at Week 12 (NRI-C) – by number of prior biologics failed (U-EXCEL ITT1 Bio-IR population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
1 prior biologic failed								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
>1 prior biologic failed								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not

reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; SES-CD, Simple Endoscopic Score – Crohn's Disease; UPA, upadacitinib.
Source: U-EXCEL CSR (47). Note: endoscopic response defined as decrease in SES-CD of >50% from baseline of the induction study or for subjects with an SES-CD of 4 at baseline, ≥2-point reduction from baseline, as scored by central reviewer. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.2 U-ENDURE

B.2.1 CDAI clinical remission at Week 52

Table 40: CDAI clinical remission at Week 52 (NRI-C) – by number of prior biologics failed (U-ENDURE Bio-IR ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
1 prior biologic failed								
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>1 prior biologic failed								
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NA, not applicable; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.
Source: U-ENDURE CSR (48). Note: CDAI clinical remission defined as CDAI score <150. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

B.2.2 Endoscopic response at Week 52

Table 41: Endoscopic response at Week 52 (NRI-C) – by number of prior biologics failed (U-ENDURE Bio-IR ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
1 prior biologic failed								
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>1 prior biologic failed								
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NA, not applicable; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.
Source: U-ENDURE CSR (48). Note: endoscopic response defined as decrease in SES-CD of >50% from baseline of the induction study or for subjects with an SES-CD of 4 at baseline, ≥2-point reduction from baseline, as scored by central reviewer. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

Appendix C: Analysis of non-Bio-IR versus Bio-IR (response to A19)

C.1 U-EXCEL

C.1.1 Change from baseline in EQ-5D-5L at Week 4 and Week 12

Table 42: Change from baseline to Week 4 and Week 12 n EQ-5D-5L index value by Bio-IR status (MMRM, U-EXCEL ITT1 population)

Subgroup Timepoint Treatment	Within group change from baseline					Between group difference vs PBO		
	N	Baseline mean	Visit mean	LS mean	95% CI	LS mean	95% CI	SE
Bio-IR								
Week 4								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Week 12								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Non-Bio-IR								
Week 4								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Week 12								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			

Abbreviations: Bio-IR, biologic therapy inadequate response/intolerance; CI, confidence interval; CSR, clinical study report; EQ-5D-5L, EuroQol-5 Dimensions 5-level; LS, least squares; MMRM, mixed effect model repeat measurement; non-Bio-IR, conventional therapy inadequate response/intolerance; PBO, placebo, SES-CD, Simple Endoscopic Score for Crohn's Disease; UPA, upadacitinib; VAS, visual analogue scale.
Source: Data on file (45). MMRM was the mixed effect model repeat measurement with baseline value, stratification factors (baseline corticosteroid use [yes or no], endoscopic disease severity [SES-CD <15 or ≥15], and number of prior biologics failed [0, 1, or >1]), treatment visit, treatment-by-visit interaction included in the model. An unstructured covariance matrix was used.

Table 43: Change from baseline to Week 4 and Week 12 in EQ-5D-5L VAS by Bio-IR status (MMRM, U-EXCEL ITT1 population)

Subgroup Timepoint Treatment	Within group change from baseline					Between group difference vs PBO		
	N	Baseline mean	Visit mean	LS mean	95% CI	LS mean	95% CI	SE
Bio-IR								
Week 4								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Week 12								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Non-Bio-IR								
Week 4								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Week 12								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			

Abbreviations: Bio-IR, biologic therapy inadequate response/intolerance; CI, confidence interval; CSR, clinical study report; EQ-5D-5L, EuroQol-5 Dimensions 5-level; LS, least squares; MMRM, mixed effect model repeat measurement; non-Bio-IR, conventional therapy inadequate response/intolerance; PBO, placebo, SES-CD, Simple Endoscopic Score for Crohn's Disease; UPA, upadacitinib; VAS, visual analogue scale.
Source: Data on file (45). MMRM was the mixed effect model repeat measurement with baseline value, stratification factors (baseline corticosteroid use [yes or no], endoscopic disease severity [SES-CD <15 or ≥15], and number of prior biologics failed [0, 1, or >1]), treatment visit, treatment-by-visit interaction included in the model. An unstructured covariance matrix was used.

C.1.2 Safety: overview of TEAEs and deaths

Table 44: Overview of TEAEs and deaths by Bio-IR status (U-EXCEL SA1 population)

Event, n (%)	UPA 45 mg	PBO
Bio-IR		
Any TEAE	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
TEAE related to study drug (assessed by investigator)	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]
TEAE leading to withdrawal of study treatment	[redacted]	[redacted]
TEAE resulting in death	[redacted]	[redacted]
Any death	[redacted]	[redacted]
Deaths occurring ≤30 days after last dose of study drug	[redacted]	[redacted]
Deaths occurring >30 days after last dose of study drug	[redacted]	[redacted]
Deaths due to COVID-19	[redacted]	[redacted]
Non-Bio-IR		
Any TEAE	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
TEAE related to study drug (assessed by investigator)	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]
TEAE leading to withdrawal of study treatment	[redacted]	[redacted]
TEAE resulting in death	[redacted]	[redacted]
Any death	[redacted]	[redacted]
Deaths occurring ≤30 days after last dose of study drug	[redacted]	[redacted]
Deaths occurring >30 days after last dose of study drug	[redacted]	[redacted]
Deaths due to COVID-19	[redacted]	[redacted]

Abbreviations: Bio-IR, biologic therapy inadequate response/intolerance; COVID-19, Coronavirus Disease 2019; non-Bio-IR, conventional therapy inadequate response/intolerance; PBO, placebo; SA, safety analysis; TEAE, treatment-emergent adverse event; UPA, upadacitinib.
Source: Data on file (45). Note: In U-EXCEL, TEAEs in the induction period (Part 1) were defined as events that begin either on or after the first dose of the study drug in Part 1 and until (i) the first dose of study drug in U-ENDURE (if applicable), or (ii) until the first dose of study drug in Part 2 (if applicable), or (iii) within 30 days after the last dose administration of the study drug in Part 1, whichever is earlier.

C.1.3 Safety: AESI

Table 45: AESI by Bio-IR status (U-EXCEL SA1 population)

Event, n (%)	UPA 45 mg	PBO
Bio-IR		
Anaemia	[redacted]	[redacted]
CPK elevations	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]
Hepatic disorders	[redacted]	[redacted]
Serious infections	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Adjudicated cardiovascular events	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Opportunistic infections excluding TB and herpes zoster	[redacted]	[redacted]
Active TB	[redacted]	[redacted]
Adjudicated GI perforations	[redacted]	[redacted]
Renal dysfunction	[redacted]	[redacted]
Malignancies (all types)	[redacted]	[redacted]
Malignancies excluding NMSC	[redacted]	[redacted]
NMSC	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]
Adjudicated thrombotic events	[redacted]	[redacted]
Non-Bio-IR		
Anaemia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Hepatic disorders	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]
CPK elevations	[redacted]	[redacted]
Serious infections	[redacted]	[redacted]
Opportunistic infections excluding TB and herpes zoster	[redacted]	[redacted]
Active TB	[redacted]	[redacted]
Adjudicated GI perforations	[redacted]	[redacted]
Renal dysfunction	[redacted]	[redacted]
Malignancies (all types)	[redacted]	[redacted]
Malignancies excluding NMSC	[redacted]	[redacted]
NMSC	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]
Adjudicated cardiovascular events	[redacted]	[redacted]
Adjudicated thrombotic events	[redacted]	[redacted]

Abbreviations: AESI, adverse events of special interest; Bio-IR, biologic therapy inadequate response/intolerance; CPK, creatine phosphokinase; CSR, clinical study report; DB, double-blind; GI, gastrointestinal; NMSC, non-

melanoma skin cancer; non-Bio-IR, conventional therapy inadequate response/intolerance; OL, open-label; PBO, placebo; SA, safety analysis; TB, tuberculosis; UPA, upadacitinib.
Source: data on file (45). Note: In U-EXCEL, TEAEs in the induction period (Part 1) were defined as events that begin either on or after the first dose of the study drug in Part 1 and until (i) the first dose of study drug in U-ENDURE (if applicable), or (ii) until the first dose of study drug in Part 2 (if applicable), or (iii) within 30 days after the last dose administration of the study drug in Part 1, whichever is earlier. TEAEs for Part 2 were defined as events that began either on or after the first dose of study drug in Part 2 and until (i) first dose of study drug in U-ENDURE (if applicable) or (ii) within 30 days after the last dose of study drug in Part 2, whichever is earlier.

C.2 U-ENDURE

C.2.1 Endoscopic remission at Week 52

Table 46: Endoscopic remission at Week 52 by Bio-IR status (NRI-C, U-ENDURE ITT1 population)

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
Bio-IR								
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Non-Bio-IR								
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: Bio-IR, biologic therapy inadequate response/intolerance; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CR, clinical response; CSR, clinical study report; ITT, intention to treat; NA, not applicable; non-Bio-IR, conventional therapy inadequate response/intolerance; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; SES-CD, Simple Endoscopic Score for Crohn's Disease; UPA, upadacitinib.
Source: Data on file (45). Note: endoscopic remission defined as SES-CD ≤4 and ≥2-point reduction from baseline and no subscore >1 in any individual variable, as scored by central reviewer. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

C.2.2 CD-related hospitalisation during 52-week maintenance period

Table 47: Occurrence of CD-related hospitalisation by Bio-IR status (AO, U-ENDURE ITT1 population)

Treatment	Responder					Incidence rate diff. vs PBO		
	N	N with CD hosp.	Time at risk (PY)	Incidence rate (n/100PY)	95% CI†	Diff.‡	95% CI§	P value
Bio-IR								
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-Bio-IR								
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AO, as observed; Bio-IR, biologic therapy inadequate response/intolerance; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CR, clinical response; ITT, intention to treat; NA, not applicable; non-Bio-IR, conventional therapy inadequate response/intolerance; NR, not reported; PBO, placebo; PY, patient-years; UPA, upadacitinib.
Source: Data on file (45). †95% CI for incidence rate is based on the normal approximation to binomial distribution. ‡Incidence rate difference = UPA – PBO. §95% CI for incidence rate difference and p value are based on the normal approximation to Poisson distribution.

C.2.3 Change from induction baseline in EQ-5D-5L at Week 52

Table 48: Change from induction baseline in EQ-5D-5L index value and VAS at Week 52 (MMRM, U-ENDURE ITT1 population)

Subgroup / Measure / Treatment	Within group change from baseline					Between group difference vs PBO		
	N	Baseline mean	Visit mean	LS mean	95% CI	LS mean	95% CI	SE
Prior TNF-alpha inhibitor failure: 0								
Index value								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							
VAS								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							
Non-Bio-IR								
Index value								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							
VAS								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							

Abbreviations: Bio-IR, biologic therapy inadequate response/intolerance; CI, confidence interval; CSR, clinical study report; EQ-5D-5L, EuroQol-5 Dimensions 5-level; LS, least squares; MMRM, mixed effect model repeat measurement; non-Bio-IR, conventional therapy inadequate response/intolerance; PBO, placebo, SES-CD, Simple Endoscopic Score for Crohn's Disease; UPA, upadacitinib; VAS, visual analogue scale.
Source: Data on file (45). MMRM was the mixed effect model repeat measurement with baseline value, stratification factors (baseline corticosteroid use [yes or no], endoscopic disease severity [SES-CD <15 or ≥15], and number of prior biologics failed [0, 1, or >1]), treatment visit, treatment-by-visit interaction included in the model. An unstructured covariance matrix was used.

C.2.4 Safety: overview of TEAEs and deaths

Table 49: Overview of TEAEs and deaths in 52-week maintenance period by Bio-IR status (U-ENDURE SA1 population)

Event, n (%)	UPA 30 mg	UPA 15 mg	PBO
Bio-IR			
Any TEAE	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
TEAE related to study drug (assessed by investigator)	[redacted]	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]
TEAE leading to withdrawal of study treatment	[redacted]	[redacted]	[redacted]
TEAE resulting in death	[redacted]	[redacted]	[redacted]
Any death	[redacted]	[redacted]	[redacted]
Deaths occurring ≤30 days after last dose of study drug	[redacted]	[redacted]	[redacted]
Deaths occurring >30 days after last dose of study drug	[redacted]	[redacted]	[redacted]
Deaths due to COVID-19	[redacted]	[redacted]	[redacted]
Non-Bio-IR			
Any TEAE	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]
TEAE related to study drug (assessed by investigator)	[redacted]	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]
TEAE leading to withdrawal of study treatment	[redacted]	[redacted]	[redacted]
TEAE resulting in death	[redacted]	[redacted]	[redacted]
Any death	[redacted]	[redacted]	[redacted]
Deaths occurring ≤30 days after last dose of study drug	[redacted]	[redacted]	[redacted]
Deaths occurring >30 days after last dose of study drug	[redacted]	[redacted]	[redacted]
Deaths due to COVID-19	[redacted]	[redacted]	[redacted]

Abbreviations: Bio-IR, biologic therapy inadequate response/intolerance; COVID-19, Coronavirus Disease 2019; non-Bio-IR, conventional therapy inadequate response/intolerance; PBO, placebo; SA, safety analysis; TEAE, treatment-emergent adverse event; UPA, upadacitinib.
Source: Data on file (45). Note: TEAEs were defined as events that began either on or after the first dose of study drug in the maintenance phase and until (i) the first dose of study drug in the long-term extension phase (if applicable), or (ii) the first dose of open-label upadacitinib 30 mg QD rescue therapy (if applicable), or (iii) within 30 days after the last dose administration of the double-blinded drug in the maintenance phase, whichever is earlier.

C.2.5 Safety: AESI

Table 50: AESI in 52-week maintenance period by Bio-IR status (U-ENDURE SA1 population)

Event, n (%)	UPA 30 mg	UPA 15 mg	PBO
Bio-IR			
Anaemia	[redacted]	[redacted]	[redacted]
CPK elevations	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]
Hepatic disorders	[redacted]	[redacted]	[redacted]
Serious infections	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]
Adjudicated cardiovascular events	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Opportunistic infections excluding TB and herpes zoster	[redacted]	[redacted]	[redacted]
Active TB	[redacted]	[redacted]	[redacted]
Adjudicated GI perforations	[redacted]	[redacted]	[redacted]
Renal dysfunction	[redacted]	[redacted]	[redacted]
Malignancies (all types)	[redacted]	[redacted]	[redacted]
Malignancies excluding NMSC	[redacted]	[redacted]	[redacted]
NMSC	[redacted]	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]	[redacted]
Adjudicated thrombotic events	[redacted]	[redacted]	[redacted]
Non-Bio-IR			
Anaemia	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Hepatic disorders	[redacted]	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]	[redacted]
CPK elevations	[redacted]	[redacted]	[redacted]
Serious infections	[redacted]	[redacted]	[redacted]
Opportunistic infections excluding TB and herpes zoster	[redacted]	[redacted]	[redacted]
Active TB	[redacted]	[redacted]	[redacted]
Adjudicated GI perforations	[redacted]	[redacted]	[redacted]
Renal dysfunction	[redacted]	[redacted]	[redacted]
Malignancies (all types)	[redacted]	[redacted]	[redacted]
Malignancies excluding NMSC	[redacted]	[redacted]	[redacted]
NMSC	[redacted]	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]	[redacted]
Adjudicated cardiovascular events	[redacted]	[redacted]	[redacted]
Adjudicated thrombotic events	[redacted]	[redacted]	[redacted]

Abbreviations: AESI, adverse event of special interest; CPK, creatine phosphokinase; GI, gastrointestinal; NMSC, non-melanoma skin cancer; PBO, placebo; TB, tuberculosis; UPA, upadacitinib; VTE, venous thromboembolic event.
Source: Data on file (45). Note: TEAEs were defined as events that began either on or after the first dose of study drug in the maintenance phase and until (i) the first dose of study drug in the long-term extension phase (if applicable), or (ii) the first dose of open-label upadacitinib 30 mg QD rescue therapy (if applicable), or (iii) within 30 days after the last dose administration of the double-blinded drug in the maintenance phase, whichever is earlier.

Appendix D: Analysis by CD location (response to A20)

Table 51: CDAI clinical remission at Week 12 by CD location at baseline (NRI-C) – U-EXCEL ITT1 population

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
Colonic only								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
Ileal only								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
Ileal-colonic								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib. Source: U-EXCEL CSR (47). Note: CDAI clinical remission defined as CDAI score <150. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

Table 52: Endoscopic response at Week 12 by CD location at baseline (NRI-C) - U-EXCEL ITT1 population

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
Colonic only								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
Ileal only								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				
Ileal-colonic								
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]				

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; SES-CD, Simple Endoscopic Score – Crohn's Disease; UPA, upadacitinib. Source: U-EXCEL CSR (47). Note: endoscopic response defined as decrease in SES-CD of >50% from baseline of the induction study or for subjects with an SES-CD of 4 at baseline, ≥2-point reduction from baseline, as scored by central reviewer. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH

test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

Table 53: CDAI clinical remission at Week 12 by CD location at baseline (NRI-C) – U-EXCEED ITT1 population

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
Colonic only								
UPA 45 mg	[redacted]							
PBO								
Ileal only								
UPA 45 mg								
PBO								
Ileal-colonic								
UPA 45 mg								
PBO								

Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib. Source: U-EXCEED CSR (49). Note: CDAI clinical remission defined as CDAI score <150. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

Table 54: Endoscopic response at Week 12 by CD location at baseline (NRI-C) – U-EXCEED ITT1 population

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
Colonic only								
UPA 45 mg	[redacted]							
PBO								
Ileal only								
UPA 45 mg								
PBO								
Ileal-colonic								
UPA 45 mg								
PBO								

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; SES-CD, Simple Endoscopic Score – Crohn's Disease; UPA, upadacitinib.

Source: U-EXCEED CSR (49). Note: endoscopic response defined as decrease in SES-CD of >50% from baseline of the induction study or for subjects with an SES-CD of 4 at baseline, ≥2-point reduction from baseline, as scored by central reviewer. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

Table 55: CDAI clinical remission at Week 52 by CD location at baseline (NRI-C) – U-ENDURE ITT1 population

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI†	Missing due to COVID-19, n	Diff.	Adj. diff. (%)‡	95% CI§	P value
Colonic only								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							
Ileal only								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							
Ileal-colonic								
UPA 30 mg	[redacted]							
UPA 15 mg	[redacted]							
PBO	[redacted]							

Abbreviations: Bio-IR, biologic inadequate response/intolerance; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NA, not applicable; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.
Source: U-ENDURE CSR (48). Note: CDAI clinical remission defined as CDAI score <150. †95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. §95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

Table 56: Endoscopic response at Week 52 by CD location at baseline (NRI-C) – U-ENDURE ITT1 population

Population Treatment	Responder (NRI-C)				Response rate difference vs PBO			
	N	n (%)	95% CI[†]	Missing due to COVID-19, n	Diff.	Adj. diff. (%)[‡]	95% CI[§]	P value
Colonic only								
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
Ileal only								
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
Ileal-colonic								
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, Coronavirus Disease 2019; CSR, clinical study report; ITT, intention to treat; NA, not applicable; NR, not reported; NRI-C, non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.

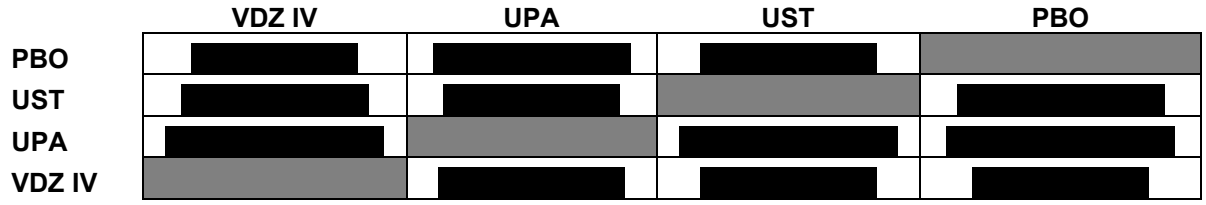
Source: U-ENDURE CSR (48). Note: endoscopic response defined as decrease in SES-CD of >50% from baseline of the induction study or for subjects with an SES-CD of 4 at baseline, ≥2-point reduction from baseline, as scored by central reviewer. [†]95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. ‡Risk difference = (UPA – PBO). Adjusted risk difference is calculated based on the CMH test adjusting for stratification factors. [§]95% CI for adjusted difference and p-value are calculated according to the CMH test adjusted for stratification factors. The calculations are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation only if there are no missing data due to COVID-19.

Appendix E: NMA results in unrestricted CDAI population (response to A25)

E.1 Clinical efficacy NMAs

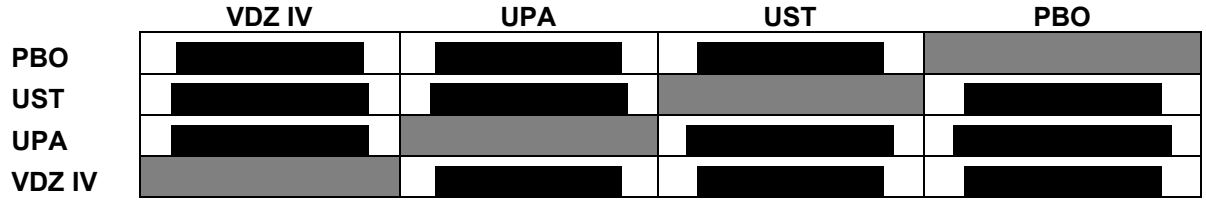
E.1.1 Induction – CDAI clinical remission

Table 57: Results for CDAI clinical remission in BF induction NMA (FE model, unrestricted CDAI population)



Abbreviations: BF, biologic failure; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

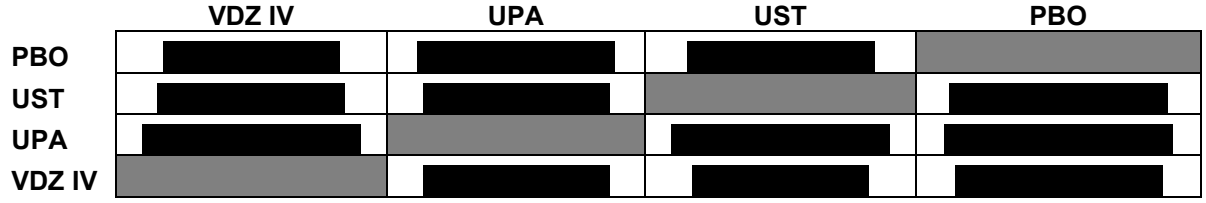
Table 58: Results for CDAI clinical remission in BF induction NMA (RE model, unrestricted CDAI population)



Abbreviations: BF, biologic failure; CDAI, Crohn's Disease Activity Index; IV, intravenous; NMA, network meta-analysis; PBO, placebo; RE, random effects; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

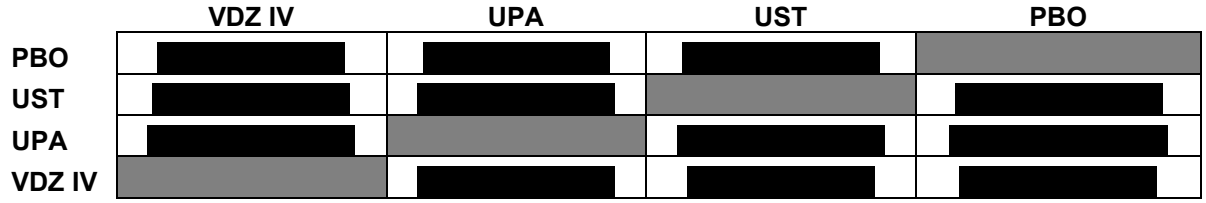
E.1.2 Induction – CDAI clinical response

Table 59: Results for CDAI clinical response in BF induction NMA (FE model, unrestricted CDAI population)



Abbreviations: BF, biologic failure; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

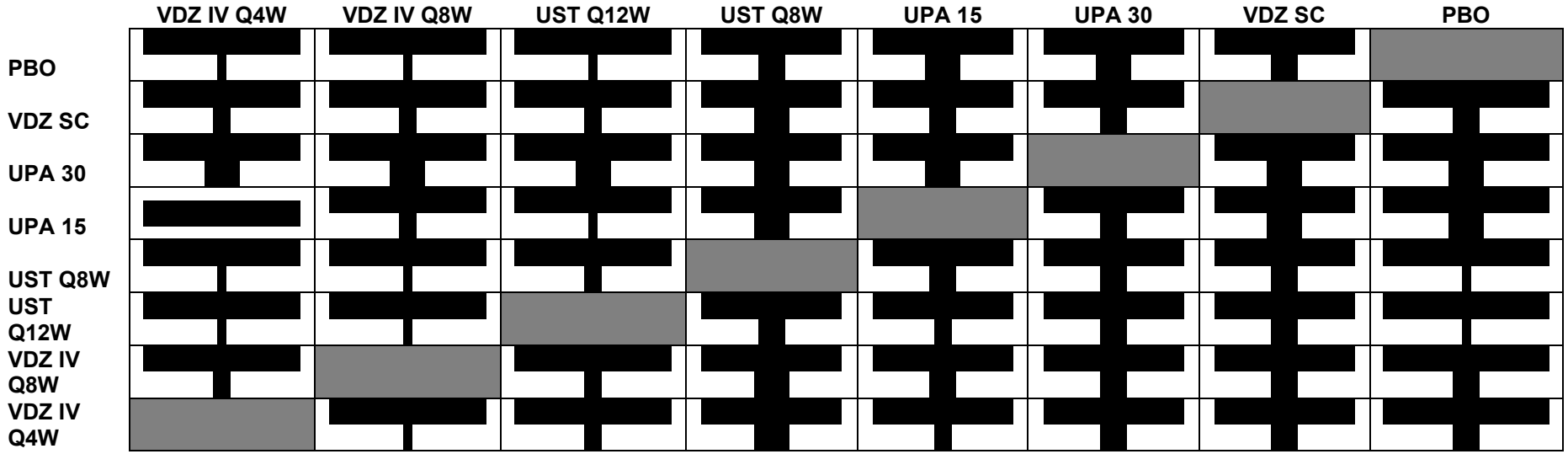
Table 60: Results for CDAI clinical response in BF induction NMA (RE model, unrestricted CDAI population)



Abbreviations: BF, biologic failure; CDAI, Crohn's Disease Activity Index; IV, intravenous; NMA, network meta-analysis; PBO, placebo; RE, random effects; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

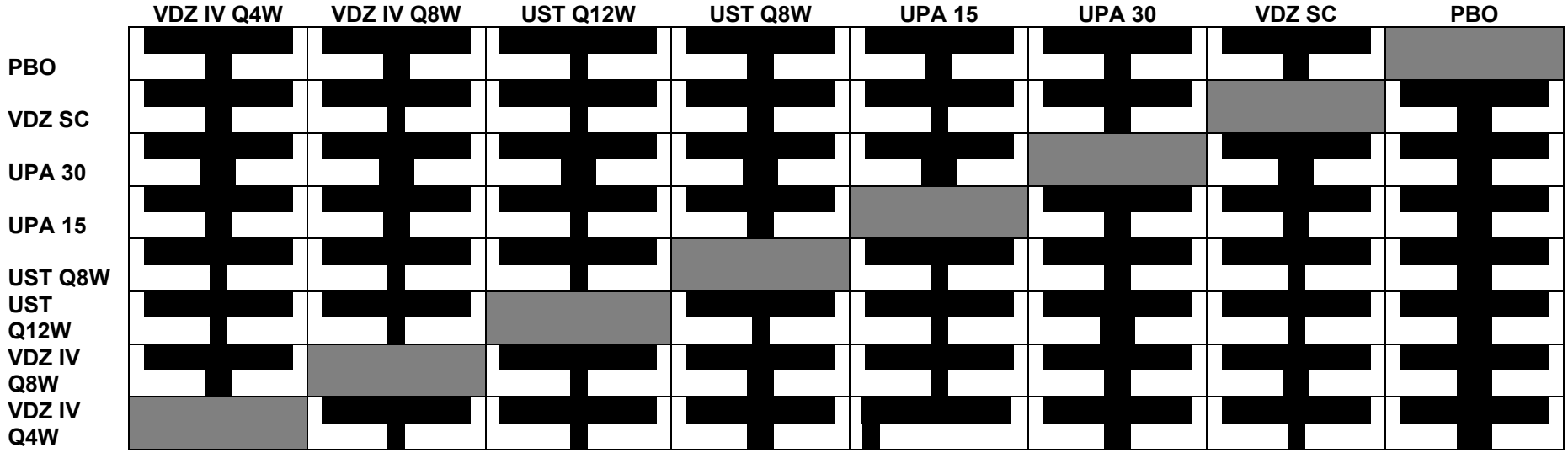
E.1.3 Maintenance – CDAI clinical remission

Table 61: Results for CDAI clinical remission in BF maintenance NMA (FE model, unrestricted CDAI population)



Abbreviations: BF, biologic failure; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

Table 62: Results for CDAI clinical remission in BF maintenance NMA (RE model, unrestricted CDAI population)

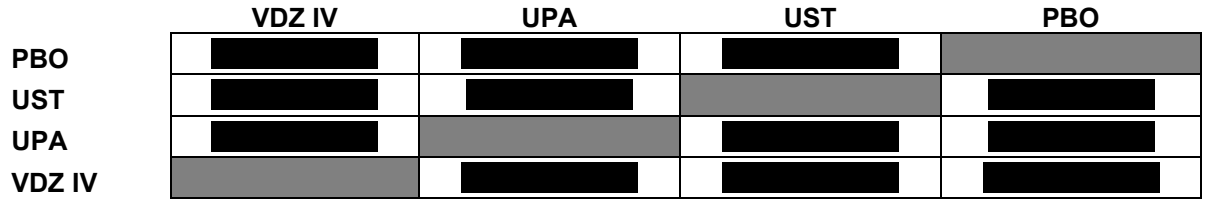


Abbreviations: BF, biologic failure; CDAI, Crohn's Disease Activity Index; IV, intravenous; NMA, network meta-analysis; PBO, placebo; SC, subcutaneous; RE, random effects; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

E.2 Safety NMAs

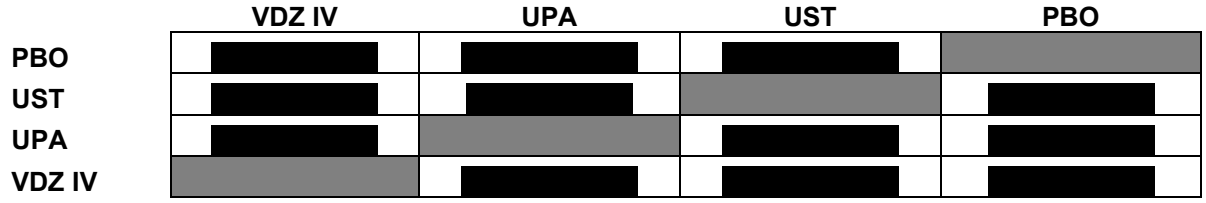
E.2.1 Induction – serious AEs

Table 63: Results for serious AEs induction NMA in overall population (FE model, unrestricted CDAI population)



Abbreviations: AE, adverse event; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

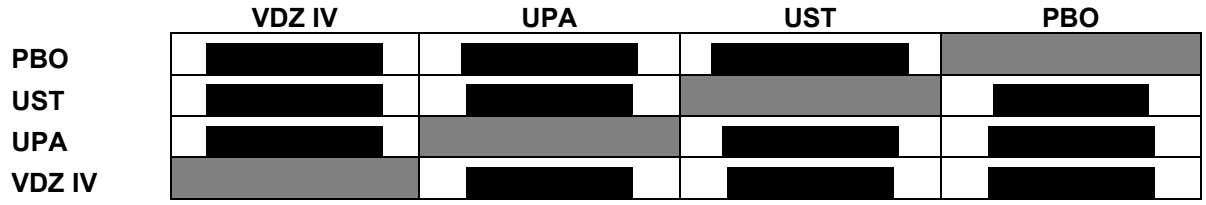
Table 64: Results for serious AEs induction NMA in overall population (RE model, unrestricted CDAI population)



Abbreviations: AE, adverse event; CDAI, Crohn's Disease Activity Index; IV, intravenous; NMA, network meta-analysis; PBO, placebo; RE, relative effects; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

E.2.2 Induction – discontinuation due to AEs

Table 65: Results for discontinuation due to AEs induction NMA in overall population (FE model, unrestricted CDAI population)



Abbreviations: AE, adverse event; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

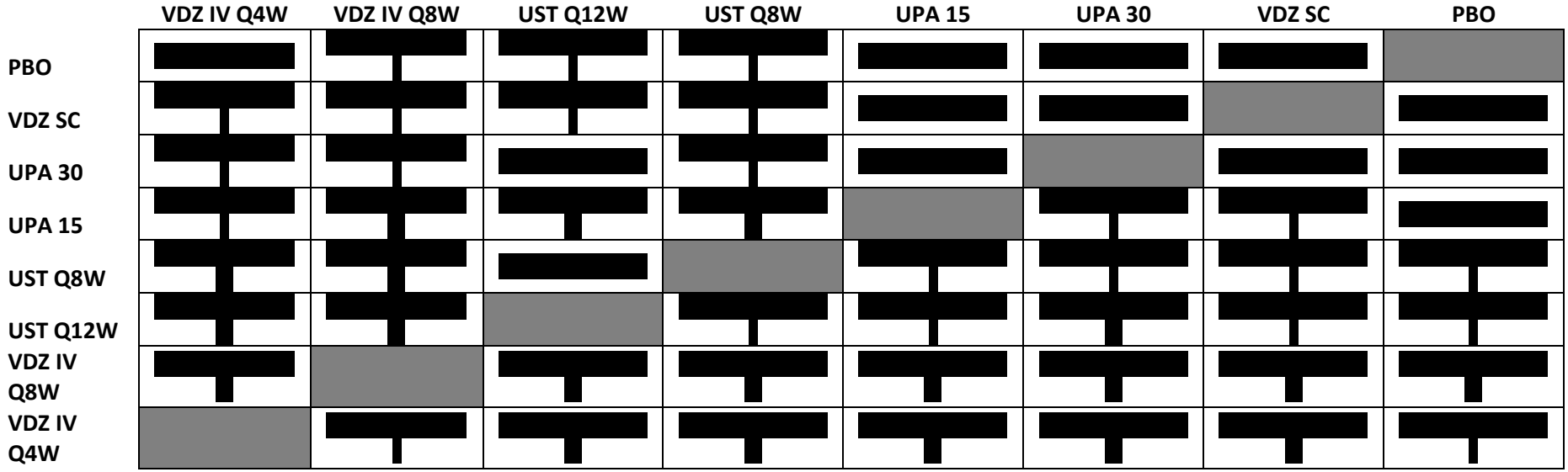
Table 66: Results for discontinuation due to AEs induction NMA in overall population (RE model, unrestricted CDAI population)

	VDZ IV	UPA	UST	PBO
PBO	[redacted]	[redacted]	[redacted]	
UST	[redacted]	[redacted]		[redacted]
UPA	[redacted]		[redacted]	[redacted]
VDZ IV		[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; CDAI, Crohn's Disease Activity Index; IV, intravenous; NMA, network meta-analysis; PBO, placebo; RE, relative effects; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

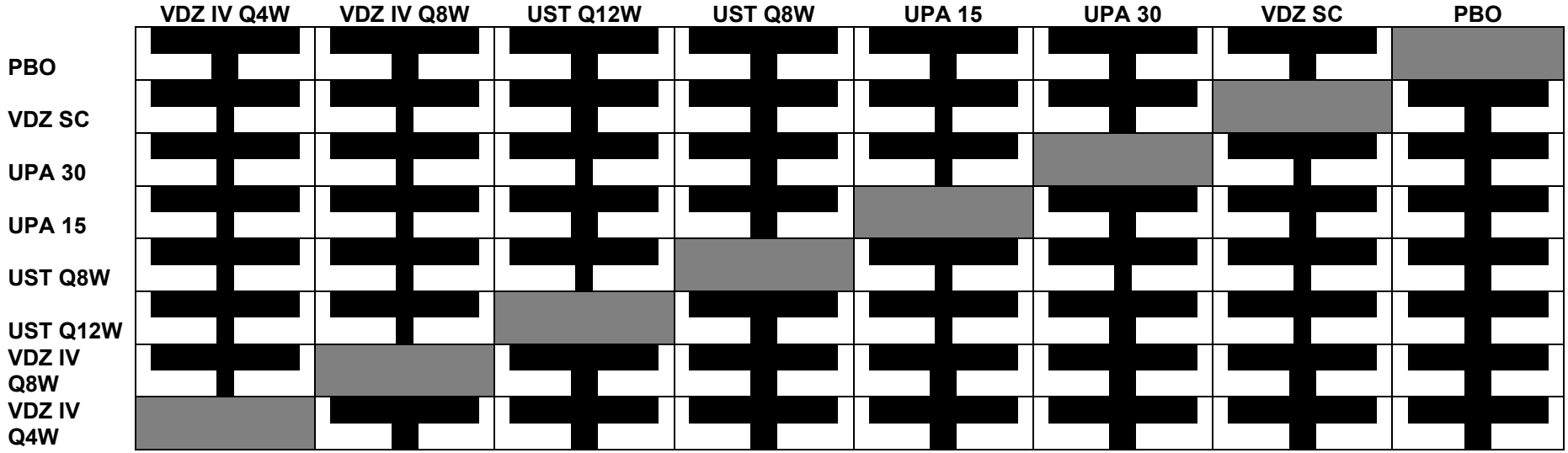
E.2.3 Maintenance – serious AEs

Table 67: Results for serious AEs maintenance NMA in overall population (FE model, unrestricted CDAI population)



Abbreviations: AE, adverse event; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

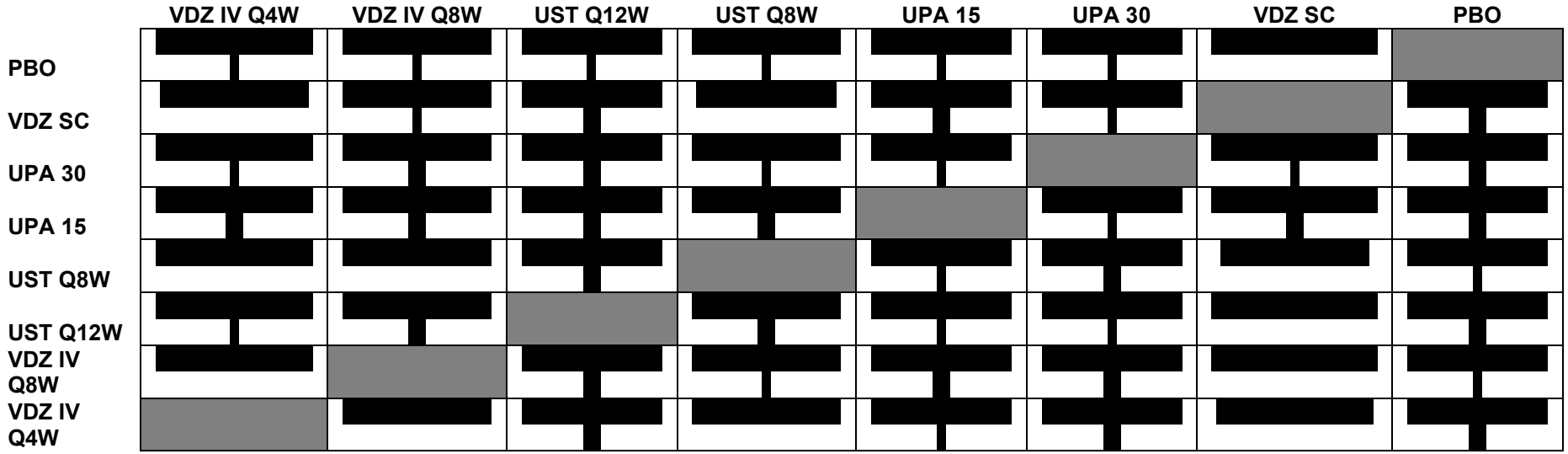
Table 68: Results for serious AEs maintenance NMA in overall population (RE model, unrestricted CDAI population)



Abbreviations: AE, adverse event; CDAI, Crohn's Disease Activity Index; IV, intravenous; NMA, network meta-analysis; PBO, placebo; RE, random effects; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

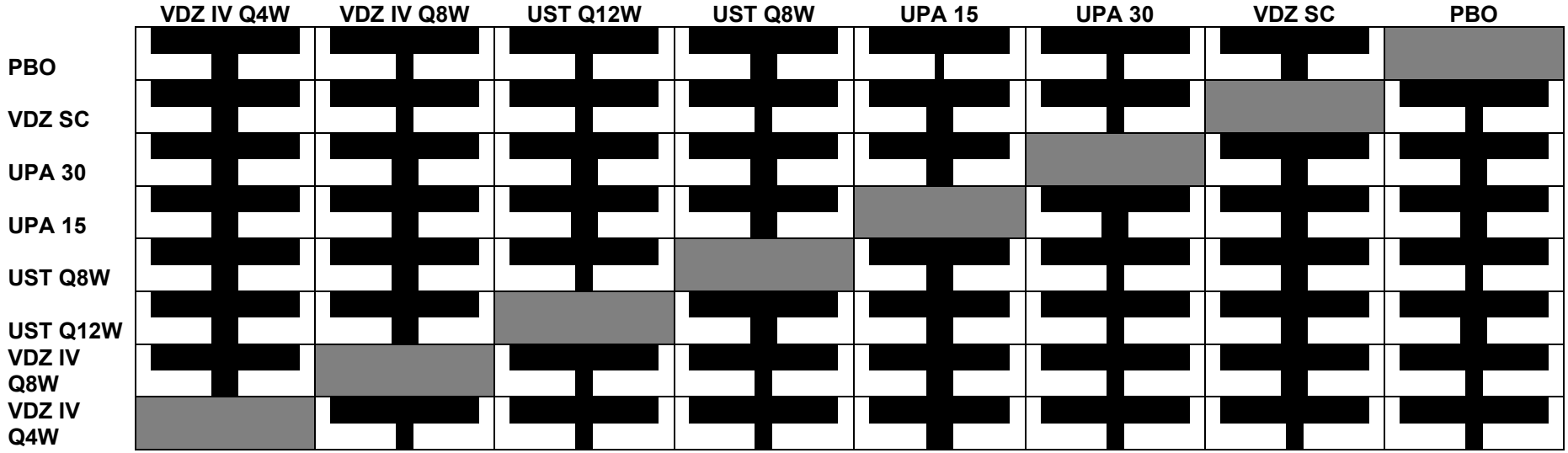
E.2.4 Maintenance – discontinuation due to AEs

Table 69: Results for discontinuation due to AEs maintenance NMA in overall population (FE model, unrestricted CDAI population)



Abbreviations: AE, adverse event; CDAI, Crohn's Disease Activity Index; FE, fixed effects; IV, intravenous; NMA, network meta-analysis; PBO, placebo; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

Table 70: Results for discontinuation due to AEs maintenance NMA (RE model, unrestricted CDAI population)



Abbreviations: AE, adverse event; CDAI, Crohn's Disease Activity Index; IV, intravenous; NMA, network meta-analysis; PBO, placebo; RE, random effects; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.
Asterisks indicate risk difference scale credible intervals do not cross zero, which may be considered 'significant'.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Upadacitinib for previously treated moderately to severely active Crohn's disease [ID4027]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Crohn's & Colitis UK
3. Job title or position	Policy Lead
4a. Brief description of the organisation (including who funds it). How many members does it have?	Crohn's & Colitis UK is the UK's leading charity for everyone affected by Crohn's and Colitis. We're working to improve diagnosis and treatment, and to fund research into a cure; to raise awareness and to give people hope, comfort, and confidence to live freer, fuller lives. We want: • To drive world-class research that improves lives today and brings us closer to a world free from Crohn's and Colitis tomorrow • Everyone to understand Crohn's and Colitis • To support and empower everyone to manage their conditions • To drive high-quality and sustainable clinical care • Early and accurate diagnosis for all. Founded as a patients' association in 1979, we now have over 47,000 members across the UK. Our members include people living with the conditions, their families and friends, health professionals and others who support our work. We have 50 Local Networks which arrange educational meetings, generate publicity and organise fundraising. Funding is through membership subscriptions and a wide range of fundraising activities, including

	events, grants, legacies and corporate partnerships. Full details are available in our annual accounts Crohn's & Colitis UK's annual reports and accounts (crohnsandColitis.org.uk)
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We gather information about the experience of patients, carers and families through: • the Crohn's & Colitis UK helpline • local networks • calls for evidence via our website and social media • one to one discussion with people with IBD, clinicians, and the wider IBD community; and • research - our own and that of external organisations.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The symptoms of Crohn's Disease, and their unpredictable nature, can have a profound and devastating impact on all aspects of a person's life. Frequent diarrhoea, blood or mucus in stools, abdominal pain and fatigue, extra-intestinal manifestations such as joint, skin and eye problems, and the side effects of medications, all affect an individual's ability to work, study, socialise, participate in leisure activities or have intimate relationships.[1] [2] The inflammation in Crohn's Disease may lead to strictures (narrowing) of the bowel resulting in abdominal pain caused by partial blockage. Severe cases may lead to life-threatening complications such as complete blockage or perforation of the bowel. At least 50% of people with Crohn's Disease may require surgery within ten years of diagnosis and 70-80% during their lifetime. Due to the nature of Crohn's Disease and the fact that it can occur anywhere in the gastrointestinal tract, having surgery once does not preclude the potential need to have surgery again. For patients with moderate to severe Crohn's Disease, the condition is more challenging, frequently overwhelming and detrimentally life-altering. This cohort is likely to experience more severe flares, weight loss, fever and constitutional symptoms. **Comorbidities** Patients with Crohn's Disease are at a higher risk of mortality and more likely to experience several comorbidities including diabetes, hypertension, atrial fibrillation, angina, stroke, rheumatoid arthritis, asthma, chronic obstructive pulmonary disorder and chronic liver disease.[3] **Mortality** Research suggests that people with Crohn's Disease are at a higher risk of mortality particularly from intestinal cancer, intestinal failure, perioperative complication and amyloidosis.[4]

[1] Crohn's & Colitis UK (2018) Quality of Life Survey https://ibduk.org/ibd-standards.
[2] IBD UK (2019) IBD Standards.
[3] Irving, P., Barrett, K., Nijher, M., & de Lusignan, S. (2021). Prevalence of depression and anxiety in people with inflammatory bowel disease and associated healthcare use: population-based cohort study. *Evidence-based mental health*, **24**(3), 102–109. Advance online publication. https://doi.org/10.1136/ebmental-2020-300223.
[4] Yasukawa, S., Matsui, T., Yano, Y. *et al.,* (2019). Crohn's disease-specific mortality: a 30-year cohort study at a tertiary referral center in Japan. *Journal of gastroenterology*, **54**(1), 42–52. https://doi.org/10.1007/s00535-018-1482-y.

	Quality of Life Education, employment, personal relationships, social and family life may all be disrupted by the unpredictable occurrence of Crohn's Disease flare-ups. The frequent and urgent need for the toilet, together with loss of sleep and the invisible symptoms of pain and continual or profound fatigue, can severely affect self-esteem and social functioning, particularly among the young and newly-diagnosed. Emotional wellbeing can be significantly affected by difficulty in coping with personal lives and feelings of embarrassment, frustration, sadness and fears of needing surgery or developing cancer.[5] Stigma and lack of wider understanding of the condition exacerbates the impact. Anxiety, depressive episodes and depressive disorders are higher in people with Crohn's Disease, at least in part as a consequence of the condition itself and its medical treatment (e.g. corticosteroid therapy).[6] Additionally, much research has shown that stress can be involved in triggering flares.[7] Social functioning can be impaired leading to an inability to work, attend school, participate in leisure activities, or have intimate relationships. In fact, 45% of respondents in our Quality of Life survey reported that IBD had stopped them reaching their full potential in life in general.[8] Research shows that young people aged 16-25 with Crohn's Disease who have not yet entered full-time employment often feel that their condition has compromised their education and significantly limited their career aspirations. Over half (56%) of young people responding to our survey said they ruled out career options due to the impact of their condition.[9] The experience of caring for someone with Crohn's Disease can be especially difficult given that it is an invisible condition, the unpredictable nature of the symptoms, which many also find extremely uncomfortable to talk about, and the effects of treatment. For parents of young people, there are challenges around providing support, while enabling independence and seeing lives and aspiration affected by their child's condition.

[5] Cosnes J, et al., (2011). Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology*, **140** (6), 1785-94.
[6] Irving, P., Barrett, K., Nijher, M., & de Lusignan, S. (2021). Prevalence of depression and anxiety in people with inflammatory bowel disease and associated healthcare use: population-based cohort study. *Evidence-based mental health*, **24**(3), 102–109. Advance online publication. https://doi.org/10.1136/ebmental-2020-300223.
[7] Sun, Y., Li, L., Xie, R., et al., (2019). Stress Triggers Flare of Inflammatory Bowel Disease in Children and Adults. *Frontiers in pediatrics*, **7**, 432. https://doi.org/10.3389/fped.2019.00432
[8] Crohn's & Colitis UK (2018) Quality of Life Survey https://ibduk.org/ibd-standards.
[9] Crohn's & Colitis UK (2013). IBD in young people, the impact on education and employment.

Patient organisation submission

	Here are a selection of quotes that highlight what living with Crohn's disease is like: *"Crohn's Disease blights my life. I am an experienced teacher and a trustee of a local charity but my ability to work and contribute to my community, is limited by the impact of the disease. It forces me to work part-time when I would otherwise work full-time and I have regular episodes of sick-leave, roughly every 12-18 months. The latest period of sick-leave will last six weeks, which is a burden on my employers. The impact on my family and social life is huge."* **Quote from a person living with with Crohn's Disease** *"I'm an active divorced 60 year old woman now who feels the impact of my symptoms have precluded me from having a regular social life and finding a partner. On the surface I'm a confident outgoing woman but emotionally I'm crying inside and feel completely isolated. This terrible disease has robbed me of my life in many ways and at times I have felt living on into my even older age is pointless. Nobody truly understands what it's like to have Crohn's unless they themselves are patients. My friends can't comprehend why a 'woman like me never remarried'. It's easy, I'm too embarrassed to even contemplate sharing a house with a man. The psychological effects keep me in like a hermit crab at the weekends."* **Quote from a person living with with Crohn's Disease** *"I am 23 years old and I have had to leave my university place studying Mental Health Nursing three times due to my Crohn's Disease. My life has been on hold for years due to this illness and I have lost 3 years of income, which has been a great burden."* **Quote from a person living with with Crohn's Disease** *"My wife states that I have changed since being diagnosed, I never thought I had, but looking back, she is right. We are battling this illness together ... it's not just me it affects, It's everyone, my wife, work and family".* **Quote from a person living with Crohn's Disease** *"Crohn's disease is a challenging condition that severely affects my life. I have been hospitalised on numerous occasions following severe flares, and even when in 'remission' the illness continues to affect me. The fatigue in particular is a major issue. It also causes me anxiety, particularly when travelling".* **Quote from a person living with Crohn's Disease**

7. What do patients or carers think of current treatments and care available on the NHS?	The IBD UK national repot revealed that 28% of patients with IBD rated the quality of their care as fair or poor.[10] Patients express dissatisfaction with many of the current treatment options. The effects of steroids are extremely unpleasant and long-term safety profile of other treatments, including biologics, are of some concern. **Steroids** Corticosteroids are commonly used a first line treatment. However, there are significant short and long-term side effects with these, including opportunistic infections, steroid-induced psychosis, steroid dependence, diabetes and osteoporosis.[11] Therefore they do not represent a therapeutic option as a maintenance treatment. The BSG guidelines set out clear stipulations on the best practice of prescribing steroid therapies given their diminishing returns, harsh side effects and risk of dependency.[12] *"My 'moon face' from the constant use of prednisolone was depressing and because of my ill health my hair became really thin. Prednisolone also affected my mood. I was so angry and unhappy. This also kept me awake at night, so I took sleeping pills."* **Quote from a person living with IBD** **Surgery** For many patients with Crohn's Disease, the prospect of surgery is one they face with considerable anxiety, and it can bring with it a range of potential complications, which may require further treatment and ongoing management. There can also be an associated profound psychological and social impact, for example, in terms of body image and self-esteem. For those who are facing this at an age when they have just begun to form relationships and do not yet have a family, this can be especially difficult, as it can for those of some religious faiths and cultures. Clinical outcomes after pouch surgery remain variable and fertility in women can be significantly affected by any pelvic surgery. *"Surgery would have been a massive emotional and psychological barrier for our son at this stage in his life*." **Quote from a person living with IBD**

[10] IBD UK (2021). *Crohn's and Colitis Care in the UK: The Hidden Cost and a Vision for Change*. CROJ8096-IBD-National-Report-WEB-210427-2.pdf
[11] Blackwell J, Selinger C, Raine T, *et al* (2021). Steroid use and misuse: a key performance indicator in the management of IBD. *Frontline Gastroenterology* , **12**, p.207-213.
[12] BSG (2019) British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. https://www.bsg.org.uk/resource/bsg-consensus-guidelines-ibd-in-adults.html

	"Personally I'm not prepared for the drastic surgery of having my colon removed." **Quote from a person living with IBD** *"I'd had enough of being ill and hospital admissions and blood transfusions and requested surgery to remove my colon. The surgeon said it disintegrated as he was taking it out it was in such a bad state. I now have a j-pouch and while life is a lot better it isn't the cure that was promised and it impacts on my life considerably."* **Quote from a person living with IBD**

8. Is there an unmet need for patients with this condition?	There is currently no medical or surgical cure for Crohn's Disease. Current available treatments are aimed at inducing and maintaining remission and improving quality of life. The range of options available for treating Crohn's Disease remain far from optimal for patients, a substantial number of whom experience lack of response (primary or secondary) and/or adverse reactions to biologic as well as conventional therapies. **Immunosuppressants** Up to one third of patients with IBD are intolerant to thiopurines and a further 10% are unresponsive to them.[13] [14] In the majority of patients who do respond, the benefits take three to six months to appear. Significant risks of thiopurines including non-Hodgkin's lymphoma (as high as 4-5-fold compared with unexposed IBD patients and further increased when used in combination with anti-TNFs). Other side effects include early hypersensitivity reactions such as fever and pancreatitis, bone marrow suppression and hepatotoxicity requiring frequent lab monitoring during treatment. [15] [16] **Anti-TNFs** These are increasingly being used earlier in the treatment pathway and can have a significant and positive effect on quality of life for patients. However, up to 40% of patients treated with anti-TNF therapy do not respond to induction therapy.[17] In the approximately one-third of patients who do achieve remission with anti-TNF therapy, between 10%-50% lose response over time.[18] Overall, there is a pressing need for additional treatment options which offer a different mode of action and the potential for people with Crohn's Disease to resume their lives and restore their quality of life. *"I am well aware that these drugs have a very significant cost but without them, the last 12 years would have been very different for me. Even with them I have had to have 2 lots of surgery to remove scarred bowel but without them I think I would have had to have more extensive surgery and possibly not even be here to send this email. I am also well aware that I am on my last chance here with current available drugs having taken everything the NHS has to offer; if the vedo stops working then I have nowhere else to go with medication. New*

[13] Fraser, A.G, Orchard, T.R, Jewell, D.P. (2002). The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut*, **50**: 485–9.
[14] Candy, S, Wright, J, Gerber, M, *et al.,* (1995) A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut*, **37**: 674–8.
[15] Siegel, C.A, Marden, S.M, Persing, S.M, *et al.,* (2009). Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol*, **7**:874–881
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Patient organisation submission

	drugs and options for medication will be vital for my health going forward." **Quote from a person living with IBD, in which drug treatments have not been effective.**

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	One of the key advantages is that Upadacitinib is an oral therapy and would give patients a treatment option to be taken at home, which will allow people to be treated at home. Furthermore the value of an additional treatment option, which has a different mode of action, reduced likelihood of loss of response, and a convenient delivery method would result in an associated reduction in NHS costs due to reduced infusions. Patients most likely to benefit from this drug are those for whom currently available therapies are ineffective, contraindicative or they develop an intolerance. In this group, it is likely that individuals, without further choice, will return to treatment/s which have already been established to be inadequate. This may include highly undesirable long-term steroid use or unproven unconventional therapy. It is also likely that patients in this group who exhaust all other treatment options would be forced to have a colectomy, either elective or as an emergency. *"I am well aware that these drugs have a very significant cost but without them, the last 12 years would have been very different for me. Even with them I have had to have 2 lots of surgery to remove scarred bowel but without them I think I would have had to have more extensive surgery and possibly not even be here to send this email. I am also well aware that I am on my last chance here with current available drugs having taken everything the NHS has to offer; if the vedo stops working then I have nowhere else to go with medication. New drugs and options for medication will be vital for my health going forward."* **Person with IBD, in which drug treatments have not been effective.**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Prescription costs faced people living with long-term and chronic conditions, including Crohn's Disease, in England, are shown to contribute to economic disadvantage, which can impact adherence and lead to complications and increased cancer risks and cost to the NHS.[19] However, the disadvantage is not specific to Upadacitinib, and the value of an additional treatment option may will remain beneficial as it will reduce the risk of loss of response.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who have had little or no success with currently available medical treatment options, and wish to avoid or delay surgery, are likely to benefit. This would include young people wishing to complete studies and those for whom surgery would be considered unacceptable due to cultural or religious factors. As Crohn's Disease is often more severe when presenting in childhood, with major consequences for lifelong morbidity, there may be particular benefits for younger people of this treatment.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	For certain religious groups, the impact of active disease and the effects of surgery may interfere with religious practices and cause distress, which could be alleviated by an additional medical therapeutic option. Although not specific to Upadacitinib, prescription costs may also be a factor associated with lower income.

Other issues

13. Are there any other issues that you would like the committee to consider?	None

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• The symptoms of Crohn's Disease, and their unpredictable nature, together with the side effects of medications, can have a profound and devastating impact on all aspects of a person's life. • There is significant unmet need within the moderate to severe cohort. Current treatments remain far from optimal for patients, a substantial number of whom experience a lack of response (primary or secondary) and/or adverse reactions to medical treatments and may face the prospect of surgery with considerable anxiety. • Upadacitinib offers a novel and effective treatment option and increases choice for both clinicians and patients (in the context of shared decision making). • Upadacitinib may delay or prevent surgery in UC patients. This is particularly important for patients who have exhausted all over treatment options and wish to avoid or delay surgery (e.g. to complete studies.

Thank you for your time.

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Single Technology Appraisal

Upadacitinib for previously treated moderately to severely active Crohn's disease [ID4027]

Clinical expert statement

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Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised

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data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

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Part 1: Treating Crohn's disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	James Lindsay
2. Name of organisation	Barts Health NHS Trust – nominated expert by Abbvie
3. Job title or position	Professor of Inflammatory Bowel Disease
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with Crohn's disease? ☐ A specialist in the clinical evidence base for Crohn's disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for Crohn's disease? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	1) Induce and maintain clinical and endoscopic remission 2) Prevent disease progression 3) Normalise patient QoL

9. What do you consider a clinically significant treatment response?	Improvement in clinical symptoms (CDAI response) Improvement in endoscopic disease activity (50% reduction in SES CD
10. In your view, is there an unmet need for patients and healthcare professionals in Crohn's disease?	There is a clear unmet need for new medications that reduce the burden of inflammation and associated symptoms particularly in patients refractory or who have lost response to currently available conventional / advanced therapies.
11a. How is Crohn's disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	National British Society of Gastroenterology guidelines and European Crohn's and Colitis organisation Grade Based evidence I feel the pathway is well defined with short term goals (improve symptoms) medium term goals (reduce objective markers of inflammation – CRP / FCP / Endoscopy; avoid steroid use) and longer term goals including reduction in requirement for surgery. The phase III clinical trials show exceptional benefit – more so than with other available approved therapies. They included a refractory as well as a naive population and mandated a steroid taper during the induction phase (which is not usual but very welcome). This is the first JAK inhibitor to be lisenced for crohn's disease and so it offers patients a new MOA and it is also a small molecule which will reduce requirement for infusions which have significant costs associated.
11b. The company has positioned upadacitinib as a treatment option for people with moderately to severely active Crohn's disease in whom tumour necrosis factor (TNF)-alpha inhibitors are deemed unsuitable, or where biological treatment is not tolerated or not working well enough (second-line advanced treatment). **For this population, are ustekinumab and vedolizumab the most appropriate comparators (i.e. would you expect upadacitinib to displace the use of**	This seems appropriate (although they could also be considered in bionaive patients). As stated the most appropriate comparators are ustekinumab and vedolizumab. Yes it is possible that upadacitinib would replace ustekinumab / vedolizumab in all patients who fall within the EMEA PRAC approved population (under 65 with no RF etc). However, for patients over 65 and / or cardiovascular / thromboembolic risk factors it is likely that vedolizumab and ustekinumab would be used prior to upadacitinib

ustekinumab and vedolizumab in the above stated population in clinical practice)? **How common is use of ustekinumab as first-line advanced treatment following conventional treatment (in line with TA456)? If commonly used, would ustekinumab as first-line advanced treatment mean TNF-alpha inhibitors are commonly used as second-line advanced treatment (and therefore appropriate comparators for this appraisal)?**	As per current NICE guidelines, ustekinumab would only really be used first line if an anti TNF were deemed unsuitable as biosimilar anti TNF is significantly less expensive. I would think we start <10% patients on ustekinumkab first line. Anti TNF would then only really be used second line if a patient subsequently developed a perianal fistula (as the evidence for anti TNF is stronger here), or is there were no suitable alternatives in a patient with ongoing active disease and on balance the risk / benefit profile of anti TNF is more favourable than surgery.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	It will be used in line with other advanced therapies for Crohn's disease and in the same way that it is currently used in ulcerative colitis It will remain secondary care use only It is licenced and NICE approved for UC so no additional facilities / training should be required
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	There is no data to suggest that it would improve life expectancy Given the strongly positive results in the setting for which this approval is being sought, I would anticipate that it would have a markedly greater impact on improving HRQoL than current care.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	In line with the EMEA article 20 PRAC analysis, upadacitinib should be used with caution and after other available appropriate alternatives in patients over 65 years old or with relevant co-morbidity.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	It has a significant advantage in being the only advanced therapy for Crohn's disease that is a tablet. All other are either infusions or SC injection that require nurse time for training / administering with associated infusion space. It is sued as a monotherapy
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There will be no additional testing over and above that required for currently available and approved advanced therapies.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	1) Reduced reliance on steroids with associated reduction in side effects 2) No need for concomitant imuunosupression 3) Documented impact in improving fatigue which has significant impact on patients QoL
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This is the first small molecule oral advanced therapy for Crohn's disease. The clinical trials results are definitely at the upper range in terms of clinical / endoscopic outcomes as compared to comparitors

• Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	It will provide a much needed therapy for patients refractory to current treatment who either face life changing surgery or ongoing active disease and significanty impaired QoL
19a. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life? **19b. How does the adverse event profile of upadacitinib compare with that of ustekinumab and vedolizumab?**	Please note EMEA PRAC article 20 advice. Risk of herpes zoster can be mitigated with Shingrix vaccination No comparative safety trials, however its MOA would make it likely that the risk of specific (herpes zoster) and serious infections would be greater than with ustekinumab or vedolizumab although these are very rare in published data
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • Are the populations in maintenance trials (including U-ENDURE) generalisable to clinical practice given only people who have achieved a clinical response during induction are enrolled? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes – the first trials in crohn's disease to include a forced steroid taper in induction which mirrors UK practice. Also the first to have both clinical and endoscopic primary endpoints Yes – given the MOA and speed of onset of the therapy, one would not continue a patient on treatment if they had not responded to the first 12 weeks of induction dosing Clinical remission and endoscopic response, speed of onset, impact on PROs including pain and fatigue No additional adverse events
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA456 and TA352]?	No

23. How do data on real-world experience compare with the trial data?	Limitted data on real world experience in Crohn's disease
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	No

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Clinical expert statement

Upadacitinib for previously treated moderately to severely active Crohn’s disease [ID4027]

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Excellent clinical trial data of a new therapy for Crohn's disease

First advanced therapy in Crohn's disease that is a small molecule and therefore taken orally

Significant impact in refractory patients on both clinical and endoscopic disease activity

Fast onet of action as early as 2-3 days in some patients

Improvement in patient reported outcomes such as fatigue

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Single Technology Appraisal

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Part 1: Treating Crohn's disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Ruth Rudling
2. Name of organisation	UK Clinical Pharmacy Association (UKCPA)
3. Job title or position	Advanced Clinical Pharmacist – Specialty Medicine
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with Crohn's disease? ☐ A specialist in the clinical evidence base for Crohn's disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
8. What is the main aim of treatment for Crohn's disease? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The aims of treatment in Crohn's disease are to induce and maintain remission including: Clinical remission Endoscopic remission

	Corticosteroid free remission
9. What do you consider a clinically significant treatment response?	A Harvey Bradshaw Index score ≤4 would suggest clinical remission. Reduction in Faecal Calprotectin, reduction in patients stool frequency and abdominal pain would be considered clinically significant to the patients.
10. In your view, is there an unmet need for patients and healthcare professionals in Crohn's disease?	Yes
11a. How is Crohn's disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	*NICE guideline [NG129]* and the *BSG consensus guidelines on the management of Inflammatory Bowel Disease in adults* are used as reference guides for Crohn's disease management. Current management of Crohn's disease: Conventional therapies: Corticosteroids +/- thiopurine/ methotrexate Exclusive enteral nutrition Biologics: First line would be infliximab or adalimumab followed by vedolizumab or ustekinumab. Surgery Best supportive care Choice is largely based on the age of the patient, the area affected by Crohn's disease and the complexity of the disease e.g., stricturing, fistulating

	This technology would impact choice for second line treatments following an anti TNF. Upadacitinib is an oral agent so patients may prefer this to an infusion or self-administered subcutaneous injection. Especially useful for patients who are needle phobic or needle exhausted. Anti TNF would be chosen first line due cost difference. If upadacitinib was competitive in price to adalimumab then it may be consider first line following conventional therapies.
11b. The company has positioned upadacitinib as a treatment option for people with moderately to severely active Crohn's disease in whom tumour necrosis factor (TNF)-alpha inhibitors are deemed unsuitable, or where biological treatment is not tolerated or not working well enough (second-line advanced treatment). **For this population, are ustekinumab and vedolizumab the most appropriate comparators (i.e. would you expect upadacitinib to displace the use of ustekinumab and vedolizumab in the above stated population in clinical practice)?** **How common is use of ustekinumab as first-line advanced treatment following conventional treatment (in line with TA456)? If commonly used, would ustekinumab as first-line advanced treatment mean TNF-alpha inhibitors are commonly used as second-line advanced treatment (and therefore appropriate comparators for this appraisal)?**	Ustekinumab and vedolizumab would be the most appropriate comparators Due to the cost implications between anti-TNF therapy and vedolizuab & ustekinumab in my experience very few patients receive vedolizumab or ustekinumab as a first line agents. If vedolizumab or ustekinumab were to be used first line anti TNF could be considered as a second line option.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	With upadacitinib being an oral agent, this technology will differ to current licenced/NICE approved options as it will not require nurse training on administration. The patient will not need to come to day units for infusions (loading dose or regular infusions) which is of benefit to the patient and the hospital day units. Homecare could still be a preferred method of supply for multiple reasons including, medication being delivered to the patient at a convenient time and convenient place as well as prescription management assistance for the clinical teams. Patients will still require regular blood tests and will therefore need access to appointments at a suitable venue and these will need to be reviewed before repeat prescriptions are issued. I would see this technology being used in secondary care.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	As a first in class option for patients with Crohn's disease I would say this could be of significant benefit to patients with Crohn's disease. It gives them more medical options prior to surgery or best supportive care. Being an oral option, this may improve patients perceived quality of life as they do not have to attend the hospital for infusions or inject themselves as with the other treatment options. Upadacitinib also does not have any special storage requirements – the other options need to be stored in a fridge- which is beneficial to the patient.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Need to consider risk/benefit of treatment. Recent EMA review of JAK inhibitors and their risks of serious adverse effects including cardiovascular events, blood clots and cancers. However, the U-ENDURE clinical trial did not report any major adverse cardiovascular event (MACE) in either treatment arms. No adjudicated thrombotic events were reported in the upadacitinib 15 mg however there was one in the 30mg group. Malignancy rates were also higher in the treatment arms in comparison to placebo so patients will need to be informed of these risks. No specific data available on the use of upadacitinib in patients with fistulating disease.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Patients may prefer this option with it being an oral agent. Blood monitoring would be similar to alternative options so should not cause significant problems. Need to make patients aware of the risks associated with JAK inhibitors which may require extra counselling time than other available options
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients will only be started on treatment if they do not have significant risk factors such as history or family history of cardiac events/blood clots. Treatment will be stopped if patient requires multiple courses of steroids, if they experience symptoms and have a raised FCP.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	Upadacitinib is an oral agent that is administered once a day. This will make it easier for the patient to administer and they will not need to schedule/remember when their next dose is due. Patients who are needle phobic/needle exhausted may experience stress and anxiety in the run up to their next dose for the alternative options which would not happen with upadacitinib.

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Patients do not have to attend the hospital to receive doses as they do with intravenous vedolizumab. This is of benefit to them as they do not have to be exposed to potential infections as well as the stress that is involved with attending a hospital unit; arranging transport, parking, waiting for treatment to be administered and potentially missing work.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Treatment options for Crohn's disease are limited and patients can cycle through options quickly leading them to require surgeries which can lead to long term issues such as short bowel syndrome. This is a first in class oral treatment option for patients with Crohn's disease therefore I would class this as having a significant impact on the management of patients with Crohn's disease.
19a. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life? **19b. How does the adverse event profile of upadacitinib compare with that of ustekinumab and vedolizumab?**	19a Upadacitinib has more significant adverse effects associated with it including cardiovascular events, blood clots and cancer risk. Therefore, patients will need to be extra vigilant regarding signs and symptoms of adverse events. Upadacitinib has multiple adverse effects that may result in the patient requiring more frequent blood tests and breaks in treatment due to advice from the manufacturer. Upadacitinib may cause; neutropaenia, leucopaenia, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia and hypertriglyceridaemia. Requiring more frequent blood tests and having breaks in treatment may impact on the patient's quality of life. Not to mention the risks associated with neutropenia and leucopaenia e.g. risk of infections. 19b Upadacitinib has similar adverse effects to vedolizumab and ustekinumab overall. Upadacitinib has increased risks as per paragraphs above. As

	upadacitinib is an oral agent it does not have injection site reactions as with vedolizumab and ustekinumab.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • Are the populations in maintenance trials (including U-ENDURE) generalisable to clinical practice given only people who have achieved a clinical response during induction are enrolled? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trial was multi centred including centres within the UK so will reflect our patient cohort. The trial did exclude patients with complications of Crohn's disease such as strictures, abscess, and fistula therefore results cannot be generalised to these more complex patients. I feel that the maintenance trials are generalisable to current patients as if the patient does not respond to the induction/extended induction treatment would be ceased anyway. The most important outcomes are – clinical remission, endoscopic remission and steroid-free remission which were all measured. I am not aware of any new reported adverse effects post clinical trial.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No I am not aware of any relevant evidence that would not be found by a systematic review.
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA456 and TA352]?	I am not aware of any new evidence.
23. How do data on real-world experience compare with the trial data?	I do not personally have experience of using upadacitinib to treat patients with Crohn's disease within the trust that I work in.

	However small case reports have reported similar results to those found in the clinical trials.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	Some commissioners do not fund beyond four biologics so this needs to be kept in mind when positioning this treatment option.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Upadacitinib for previously treated moderately to severely active Crohn’s disease [ID4027]

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

First in class to be licenced for Crohn's disease so novel mode of action in comparison to current available options

Oral agent which has significant advantages to patients

Serious adverse effects linked to JAK inhibitors appears to be less with upadacitinib

Could be more cost effective than vedolizumab and ustekinumab based on known PAS price for upadacitinib in regards to alternative indications

Click or tap here to enter text.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Upadacitinib for previously treated moderately to severely active Crohn's disease [ID4027]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with Crohn's disease or caring for someone with Crohn's disease. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 17 February 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Part 1: Living with this condition or caring for a patient with Crohn's disease

Table 1 About you, Crohn's disease, current treatments and equality

1. Your name	PROF DEREK FRASER
2. Are you (please tick all that apply)	☒ A patient with Crohn's disease? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with Crohn's disease? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	CROHNS AND COLITIS UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with Crohn's disease? **If you are a carer (for someone with Crohn's disease) please share your experience of caring for them**	Diagnosed with Crohn's in 2018 and initially treated with Pentasa. Then on self-administered ADALIMUBAB. Now on nurse injected USTEKINUMAB. The disease is debilitating and restricts social life, particularly because of its unpredictable symptoms
7a. What do you think of the current treatments and care available for Crohn's disease on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	a) I have been well treated by IBD clinic in Leeds and am content with the treatments available b) No knowledge of anyone else
8. If there are disadvantages for patients of current NHS treatments for Crohn's disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I suffered very badly when on Adalimubab. I know that "post hoc, ergo propter hoc" does not always apply, but my treatment with this injection was accompanied by severe weight loss, stomach cramps, fatigue and worsening stools. No adverse side effects with Ustekinumab.
9a. If there are advantages of upadacitinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does upadacitinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	I am not on this treatment but the main advantage would appear to be that it is oral in tablet form. The other treatments appear to be by various forms of injection so the oral alternative is a positive advantage.

10. If there are disadvantages of upadacitinib over current treatments on the NHS please describe these. For example, are there any risks with upadacitinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	No knowledge
11. Are there any groups of patients who might benefit more from upadacitinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Again the oral aspect would be helpful for most patients
12. Are there any potential equality issues that should be taken into account when considering Crohn's disease and upadacitinib? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	No knowledge

13. Are there any other issues that you would like the committee to consider?	none

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The disease is debilitating and has a profound effect on social life.
- The effect on individual patients will vary and my experience suggests that one biologic is much better than another. But this only emerged after treatment.
- An oral treatment in tablet form would be a major advantage for all patients but its effectiveness in treating the disease would have to be monitored before it could be rolled out.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Upadacitinib for previously treated moderately to severely active Crohn's disease [ID4027]

Clinical expert statement

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised

data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for your response is **5pm** on **Friday 17 February 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Part 1: Treating Crohn's disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Peter Irving
2. Name of organisation	Guy's and St Thomas' NHS Foundation Trust
3. Job title or position	Consultant Gastroenterologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with Crohn's disease? ☐ A specialist in the clinical evidence base for Crohn's disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for Crohn's disease? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The aim of treating Crohn's disease is multifaceted. Overall, it is to restore quality of life and prevent complications from Crohn's disease. Ideally this will encompass steroid-free symptomatic remission and resolution of inflammation (as measured by biomarkers, radiology and endoscopy). Of course, this is not

	always achievable. Long term remission using a drug (or drugs) with an acceptable side effect profile is also of importance.
9. What do you consider a clinically significant treatment response?	Improvement in clinical symptoms which for most patients with Crohn's disease includes diarrhoea and abdominal pain. The magnitude of that improvement that could be regarded as significant depends on the clinical situation and varies from patient to patient.
10. In your view, is there an unmet need for patients and healthcare professionals in Crohn's disease?	Yes - definitely
11a. How is Crohn's disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Treatment is becoming more aggressive using a rapid step-up or top down approach in order to prevent disease progression. Understanding of treatment targets and the avoidance of misuse of steroids is also starting to drive care. Guidelines issued by the British Society of Gastroenterology and the European Crohn's and Colitis Organisation are the most influential. Guidelines are, however, hampered by a fast moving field in terms of drug therapy and treatment strategy. Upadacitinib would enhance our ability to induce and maintain clinical remission and decrease bowel inflammation. The data are encouraging and I think it would be used widely in the post anti-TNF cohort. It is the only JAK inhibitor licensed in Crohn's (and will remain so for some time). As such, it represents a significant addition to the available therapies. It is, of course, also an oral option which is important for some patients.
11b. The company has positioned upadacitinib as a treatment option for people with moderately to severely active Crohn's disease in whom tumour necrosis factor (TNF)-alpha inhibitors are deemed unsuitable, or where biological treatment is not tolerated or not working well enough (second-line advanced treatment). **For this population, are ustekinumab and vedolizumab the most appropriate comparators (i.e. would you**	Yes – these are entirely appropriate comparators. Ustekinumab is only rarely used as a first line treatment because of cost. Biosimilar anti-TNF represents the majority of the first line market. Where ustekinumab or vedolizumab are used first line it is normally in an attempt to avoid anti-TNF because of safety concerns. Accordingly, the second line drug would normally be the other 'safer' biologic in this situation ie vedolizumab if ustekinumab was used first line and vice versa.

expect upadacitinib to displace the use of ustekinumab and vedolizumab in the above stated population in clinical practice)? **How common is use of ustekinumab as first-line advanced treatment following conventional treatment (in line with TA456)? If commonly used, would ustekinumab as first-line advanced treatment mean TNF-alpha inhibitors are commonly used as second-line advanced treatment (and therefore appropriate comparators for this appraisal)?**	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	I am afraid I don't really understand the question. It will be used in a similar way to toerh drugs that are used to treat moderately to severealy active Crohn's disease. It should be used in secondary or tertiary care. No additional investment is needed to introduce the technology
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes – although given that length of life is only rarely shortened in Crohn's disease, I would expect no change in this. I believe it will improve HRQoL by being an additional option to current options and, if the clinical trial data bear out in the real world setting, I would be optimistic that upadacitinib may result in better outcomes than current options

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No difference in efficacy. As per license, it is less appropriate for some groups of patients but this is no different to any drug we use; we are used to weighing up risk and benefit for all the available options in the context of each patient
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Easier for some patients as it is oral. In addition, it may decrease pressure on infusion services
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment will be discontinued if it is ineffective – normally after 8-16 weeks. In general, our practice is to review patients responding to drugs on a yearly basis to consider the appropriateness of continuing medication
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	As per the example cited – this is an oral medication. I am not sure if there could be any other benefits not measured in QALY assessment
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. This is a different mechanism of action to available alternatives which is likely to be effective in a proportion of patients who do not respond to other therapies. It is indeed a step change and meets a significant unmet need

• Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19a. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life? **19b. How does the adverse event profile of upadacitinib compare with that of ustekinumab and vedolizumab?**	The adverse effect profile of upadacitinib is acceptable and the majority of patients do not get significant side effects. Indeed, the side effects of active Crohn's disease are significantly worse than any potential side effects of upadacitinib (eg thromboembolism – which has not been shown to occur with upadacitinib) The side effect profile of vedolizumab and ustekinumab are very good (and possibly lightly better than upadacitinib) although serious side effects can occur with these drugs too.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • Are the populations in maintenance trials (including U-ENDURE) generalisable to clinical practice given only people who have achieved a clinical response during induction are enrolled? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes – the trials reflect UK practice We would not continue a drug into maintenance if a patient had not responded to induction so I believe the trial design is relevant The important outcomes are symptomatic response and remission and mucosal response. These were measured Mucosal response is probably the best predictor of long term outcome that we have No new side effects of which I am aware
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA456 and TA352]?	No
23. How do data on real-world experience compare with the trial data?	Very limited so far – but anecdotally very well
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	No obvious equality issues are apparent as long as the drug is used in its licensed indications.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

This is a new mechanism of action

It is the first oral advance therapy for Crohn's disease

The trial data show efficacy at least as good as available options and possibly better

It has an acceptable side effect profile

This is an important addition to our available treatments which have significant limitations

Thank you for your time.

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

External Assessment Group Report

Upadacitinib for previously treated moderately to severely active Crohn's Disease [ID4027]

Produced by	Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
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Rider on responsibility for report

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

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Contributions of authors

Mark Perry acted as a systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Nigel Armstrong acted as project lead and health economist/review manager on this assessment, critiqued the clinical effectiveness methods and evidence and contributing to the writing of the report. Maiwenn Al acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Pim Wetzelaer and Eline Krijkamp acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Robert Wolff critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

1. Summary of the EAG's view of the company's cost-comparison case

The Evidence Assessment Group (EAG) does not think that the company has demonstrated that upadacitinib (UPA) is equivalent to other technologies in the treatment of Crohn's Disease (CD), and therefore a cost-comparison case is not appropriate.

Upadacitinib is targeted as a second-line treatment in the advanced therapy stage, and therefore needs to be compared to other treatments that are targeted as second-line advanced therapy (Figure 1 of the company response to the request for clarification[1] shows the proposed treatment pathway, and is helpful to understand the issues discussed below).

The main problem is that not all appropriate second-line comparators have been included in the network meta-analyses (NMA), and so it is unknown if UPA is equivalent to all relevant second-line advanced therapy comparators. The comparators listed in the National Institute for Health and Care Excellence (NICE) final scope are the tumour necrosis factor alpha (TNF-alpha) inhibitors infliximab (IFX) and adalimumab (ADA), the biologics vedolizumab (VDZ) and ustekinumab (UST) and best supportive care. However, in the decision problem the comparators are restricted to the biologics VDZ and UST. The company justification for the exclusion of best supportive care as a comparator is strong: even if all biologics fail, the least ineffective of these will be used in the next line, making best supportive care a highly unlikely subsequent approach. In contrast, the rationale for the removal of TNF-alpha inhibitors is less robust. The company justifies the removal of TNF-alpha inhibitors (IFX and ADA) as comparators on the basis that the target population would not use TNF-alpha inhibitors for second-line advanced therapy. The company explains that this is because TNF-alpha inhibitors would have already been used for first-line advanced therapy, and that if a TNF-alpha inhibitor has failed it is not used again for second-line advanced therapy. The EAG does not accept this argument, because it is not true to say that first-line advanced therapy drugs will always be a TNF-alpha inhibitor. As shown in the company's response to clarification (Figure 1, company response to clarification[1]) UST is not a TNF-alpha inhibitor and yet it is used as a NICE-recommended first-line advanced therapy (as well as second-line advanced therapy) drug. This means that some patients will not receive TNF-alpha inhibitors for first-line advanced therapy, and so TNF-alpha-inhibitors can be regarded as appropriate second-line advanced therapy comparators for these patients. Failure to include all appropriate comparators recommended in the NICE scope means that it is unknown if UPA was comparable to all the appropriate comparators.

It could be argued that if UPA is shown to be comparable to UST, which has been shown to be cost-effective in this population, then this confirms that UPA is also cost-effective, and there is no need to involve other comparators. However, this ignores the fact that the TNF-alpha inhibitors, which are a different class of drug, may be more cost-effective than UPA, and therefore more appropriate for use in

this population. Therefore, excluding the TNF-alpha inhibitors from the comparators means that there is a risk that the non-optimal technology could be recommended.

Over and above the fact that not all the appropriate comparators are included in the NMA, additional issues remain for the NMA analyses concerning UPA and the two included comparators. Two principal issues are described below, which call into question the company's conclusion that equivalence exists between UPA and those particular comparators:

- Firstly, there was some doubt that clinical harm was equivalent between UPA and the two comparators. Although the outcome of serious adverse events demonstrated comparability between UPA and the two comparators, the NMA for discontinuation due to adverse events yielded point estimates that favoured the comparators. The credible intervals straddled the null line but demonstrated greater probability of a population effect denoting benefit for the comparators, rather than UPA.

- Secondly, heath-related quality of life (HRQoL) was not included as an outcome in the NMA, despite this being a highly relevant clinical effectiveness outcome for patients. The company's argument that there is no prior precedent from previous Single Technology Assessments (STAs) for including HRQoL is not relevant, because previous STAs are not necessarily reference standards of good practice and might reflect some discussions relevant to the respective intervention of interest (which might not apply to this submission). There is a strong methodological rationale for utilising HRQoL, because it is the most patient-focussed effectiveness outcome. The company also argues that HRQoL data were sparse in the included trials. This may be true, but the company should have used all available data, in order to allow the committee to interpret it. In addition, the NICE scope outcomes of mucosal healing, surgery, and hospitalisation rates were not subjected to NMA analysis. The failure to evaluate all the NICE scope outcomes is a serious limitation because it means that comparability cannot be assured; true comparability between treatments can only be confirmed if all relevant health outcomes are considered, particularly those that are patient-related such as HRQoL, surgery or hospitalisation.

2. Critique of the decision problem in the company's submission

In terms of population, the decision problem focuses only on a stratum of those previously treated – those who have previously failed on biologics or for whom TNF-alpha inhibitors were deemed unsuitable - even though the NICE scope makes no distinction between previous failure on biologics (BF) or conventional care failure (CCF) in its definition of the population. This narrowing of the scope was planned pre-hoc, and so it cannot be regarded as a biased response to initial results on an unstratified population. Nevertheless, because of the very different efficacy in the two strata, with the NMAs demonstrating inferior efficacy for the CCF stratum, it is vital not to base recommendations for both strata on the data from the BF stratum.

Only participants achieving a clinical response in U-EXCEL and U-EXCEED were eligible for inclusion in U-ENDURE. This would be non-representative of the target population in this submission, who are not people who have previously responded to the study drug. The EAG understands that it might be considered unethical for patients who did not respond, to continue to be followed up on the arm to which they were originally randomised. It might also be of interest to understand whether there is benefit to maintenance treatment (as opposed to curtailment of treatment) on achieving induction. However, the fact remains that the population are not relevant to the decision problem. In addition, the populations in the various maintenance trial comparisons are intrinsically different in terms of the drug to which they have responded. This level of clinical heterogeneity across comparisons may make an NMA approach inappropriate, and therefore makes any results derived from an NMA potentially invalid. The EAG therefore thinks that maintenance data should not be considered in this submission.

As argued in the previous Section, the inappropriate exclusion of appropriate comparators in the decision problem means that the NMA results cannot demonstrate that UPA is equivalent to all relevant comparators.

In terms of outcomes, mucosal healing is not included as an outcome in the decision problem despite being in the NICE scope. Instead, the outcome 'endoscopic outcomes' is used, which is supposed to include multiple outcomes indicative of mucosal healing. The EAG does not agree that 'endoscopic outcomes' is a useful term to encompass the construct of 'mucosal healing', as it appears to be an overly non-specific term. Similarly, 'surgery' is not included as an outcome in the decision problem despite being in the NICE scope. No surgery data were available in the UPA trials. This is a limitation in the submission because the need for surgery is a highly relevant clinical outcome. Its omission means that a full evaluation of UPA and its comparators is not possible.

The NICE scope suggested that stratification for CD location should be carried out. However, the company did not include stratification for CD location in the decision problem. This was partially because the studies were not powered for such an analysis. However, other sub-grouping analyses were

carried out without the study being powered for them either and so underpowering appears to represent a weak rationale. The company also referenced expert clinical opinion deeming CD location not clinically relevant, but this is not the opinion of NICE who stipulated that CD location should be a sub-grouping criterion. The company provided a sub-group analysis for CD location in response to clarification questions. This analysis did not reflect expert opinion, showing that location of CD was a potential outcome modifier, with ileal CD responding less well to UPA (relative to placebo) than other locations. No NMA was carried out for this but given the available evidence suggesting no benefit over placebo, it appears that UPA is not effective in this region. It is important that this is considered when making recommendations.

3. Summary of the EAG's critique of clinical effectiveness evidence submitted

The company does not detect any evidence of risk of bias in the three UPA trials, nor the seven trials involving the two comparators. The EAG has looked at the clinical study report (CSR) for each of the three studies[2-4] and agrees that the risk of bias is likely to be low. However, there is a lack of clarity around allocation concealment, because it is not made clear that those recruiting participants were unaware of the randomisation sequence, even though this is implied by the randomisation schedule being generated by the statistics department at AbbVie.

The evidence synthesis conducted by the company was of a good standard. Identified studies were assessed by two blinded, independent researchers in parallel using the pre-defined inclusion/exclusion criteria. Any discrepancies were resolved by a third party. Data from included studies were extracted into a pre-defined Excel-based template by a single analyst and all results were checked for accuracy by a senior reviewer.

Network meta-analyses were only conducted for clinical remission, clinical response, serious adverse events and discontinuation due to adverse events. The NICE scope outcomes of mucosal healing, surgery, hospitalisation rates and HRQoL were not subjected to NMA analysis. The failure to evaluate all the NICE scope outcomes is a serious limitation because it means that comparability cannot be assured; true comparability can only be confirmed if all relevant health outcomes are considered, particularly those that are patient-related such as HRQoL, surgery or hospitalisation.

The induction NMAs conducted for clinical remission, clinical response, serious adverse events and discontinuation due to adverse events demonstrated varying results.

- For clinical remission, there was fairly clear evidence of superiority of UPA over the two included comparators, but this was only observed in the BF stratum. This was conducted with a fixed effect (FE) NMA analysis, which was appropriate given the similarity of Deviance Information Criteria (DIC) values in the FE and random effects (RE) models.

- For clinical response, an FE NMA also demonstrated evidence of an advantage to UPA versus the two included comparators, although again this was only seen in the BF stratum. However, an RE NMA approach may have been more appropriate for the outcome of clinical response because of clinical heterogeneity between comparisons, combined with a DIC value that was 2.91 lower for the RE model than the FE model. Spiegelhalter et al. 2002[5] state that lower DIC values are preferred and typically differences of at least 3 points are considered meaningful. As the DIC difference is very close to 3, and the difference in Dbar is also over 6 points, the EAG would question the decision to use an FE model for this outcome. Use of the RE approach no longer demonstrated a clear benefit of UPA over the comparators for clinical response, but did show evidence of comparability, with a

point estimate favouring UPA, and most of the credible interval lying in the zone in favour of UPA. Therefore, it could be argued that if a FE model is believed to be more appropriate for this outcome, then the company have been conservative for this outcome in the NMA in assuming equivalence. If the RE model is believed to be appropriate for this outcome, then the result would still be consistent with equivalence, although only for this particular outcome.

- Both the induction safety outcomes were appropriately analysed with an FE model. For the outcome of serious adverse events, comparability was evident.

- However, for discontinuation due to adverse events, the point estimates in both the RE and FE NMAs favoured the comparators, and the credible intervals were consistent with a higher probability that the true population effect would favour the comparators.

- Maintenance NMAs were similar, but because the population for these was outside the decision problem (as argued previously) the results from these are not regarded by the EAG as relevant.

About 20% of patients were excluded from the U-EXCEL and U-EXCEED trials in the NMA. This restriction was aimed at increasing coherence between comparisons in terms of Crohn's Disease Activity Index (CDAI) score. However, this methodology may also have had the potential to affect the external validity of the NMA results. For the restriction of participants to adversely affect external validity two conditions would need to be fulfilled:

- Firstly, the restricted cohort would need to be shown to be different to the United Kingdom (UK) target population. It is conceivable that the unrestricted cohort could be closer to the UK target population in terms of CDAI score than the restricted population, on the simple grounds that the UK target population are also unrestricted. However, no data are available on the CDAI scores of the UK target population, and so this assumption cannot be confirmed.

- Secondly, a clear difference in results between restricted and unrestricted analyses would be needed. This would demonstrate that if the UK target population were more akin to the unrestricted population, then results derived from a restricted population would be less applicable to them. There was a trend for the efficacy results to be more beneficial towards UPA in the restricted analysis than the unrestricted analysis, but this effect was not large and did not change interpretations: in both restricted and unrestricted efficacy analyses there was either clear evidence of superiority for UPA over comparators, or a demonstration of equivalence. Therefore, the EAG concludes that it is unlikely that the exclusion of participants will have affected external validity to any great extent, and so the benefits accrued from improved coherence between comparisons in the NMA are unlikely to be significantly affected.

4. Summary of the EAG's critique of cost evidence submitted

4.1 Decision problem for cost comparison

As outlined in Section 2, the current analysis only considers one of the two sub-populations that were defined in the NICE scope, and in that regard, the current cost comparison can be considered as incomplete.

The analysis compares UPA with UST and VDZ. As stated in Section 1 above, first-line biologic failure does not necessarily involve a TNF-alpha-inhibitors, as UST may be used as first-line biologic as well. Hence, the TNF-alpha inhibitors IFX and ADA can also be regarded as appropriate comparators second-line. This means that the current cost comparison is incomplete.

4.2 Cost comparison model

The Excel model that was developed for the cost comparison has a time horizon of 1 year, with the option to also include the costs in each year of treatment beyond year 1. It is important to note though, that no clinical effectiveness data are available to inform the relative effectiveness and safety in the second year of treatment.

The model calculates the induction and maintenance costs for patients receiving UPA, UST, or VDZ. In this calculation the patient is assumed to have responded to induction treatment and proceed to receive maintenance treatment. The base case includes induction and maintenance treatment, and reflects the cost of the patient's first year on treatment, while the Year 2+ scenario reflects the cost of additional years on maintenance treatment only (these maintenance costs are assumed to be the same in all years after year 1)).

Alternative pathways, such as patients not responding to induction treatment or patients discontinuing treatment due to adverse events, relapse, or death are not incorporated in the model. This is in contrast to some previous appraisals – TA521, TA596, TA723 and TA803 - where a cost comparison was considered.[7, 8, 9, 10]

Presumably this modelling choice is based on the assumption that UPA, UST and VDZ can be considered equivalent in terms of efficacy and safety. However, by only including the pathway of patients successfully treated over the time horizon, the differences in costs will appear larger than when also less successful pathways are included (assuming costs of a potential next treatment are the same for all three treatments being compared).[1] When interpreting the magnitude of the result of the cost comparison it is important to keep this in mind.

[1] For example, assume the costs of full treatment (induction and maintenance) are £500 for treatment X and £1,000 for treatment Y. If we assume 70% of patients follow this pathway, whereas 30% does not respond to induction (at costs of £300 and £500 for X and Y, respectively), then the total average costs for treating patients with X are £440 and with Y £850.

Not only does the focus on successfully treated patients lead to estimated savings that cannot be extrapolated to all patients starting treatment with UPA, UST and VDZ, it also disregards the issue of treatment sequencing and thus the downstream costs. Due to the various mechanisms of action of the three drugs considered here, it is unclear what treatment would be given as the third-line option and how this would impact the cost comparison.

4.3 Model parameters

The parameter values used in the company's cost-comparison analysis are presented in the CS,[6] Tables 62-65. A summary of the key model parameters is presented in Table 67 of the CS. The main model assumptions are summarised in Table 68 of the CS.

i. *Weight*

For patients receiving UST, the IV dosage depends on the weight of the patient. Thus, the company did a post-hoc analysis of BF patients in U-EXEL and U-EXCEED to find the distribution of patients in the ≤55 kg, >55 kg and ≤85 kg, >85 kg weight bands (see Table 62, CS[6]).

ii. *Distribution high and low dose maintenance*

For UPA, UST, and IV VDZ patients may receive a low or a high dose during the maintenance phase of the treatment, and the distribution varies by treatment. For the cost comparison, the company has sought expert opinion regarding the distribution of patients between low and high dose (see Table 63, CS[6]). According to the experts on the Health Technology Assessment (HTA) Advisory Board for Risankizumab (RZB),[11] UST is mostly given in a high dose, 92.5%, whereas for UPA a high dose is given to 30% of the patients, for VDZ intravenous (IV) a high dose to 22% of the patients. For VDZ subcutaneous (SC) this is 0%. This is in line with the company submission, where only a fixed dose for SC VDZ is applied.

It should be noted that in later expert interviews, it was suggested that for VDZ IV high dose maintenance would be given to 30% of the patients. The company has used the latter value for the base-case analysis but has provided a scenario analysis using 22% in their response to the clarification letter (Question B8).

iii. *Acquisition costs*

Upadacitinib is administered orally, during induction (12 weeks) at 45 mg per day and during maintenance at 15 mg or 30 mg per day.

Thus, when only looking at successful patients a savings of £500 would be anticipated, but based on the mixture of more and less successfully treated patients, a savings of £410 would be achieved.

For the price of UPA a simple Patient Access Scheme (PAS) was agreed with National Health Service (NHS) England leading to the following prices: 45 mg = [redacted]; 30 mg = [redacted]; 15 mg = [redacted].

Ustekinumab is administered by IV during induction, with a single dose of, on average, 3*130 mg. During maintenance (starting at week 8, patients receive 90 mg SC either once per 12 weeks or once per 8 weeks. The list prices are: 130 mg (IV) = £2,147; 90 mg (SC) = £2,147.

Vedolizumab is given by IV during induction, as a dosage of 300 mg in weeks 0, 2 and 6. During maintenance (starting in week 14), it may be given by IV at a dose of 300 mg either once per 8 weeks or once per 4 weeks, or it can be administered via SC injections at a dose of 108 mg once every 2 weeks. The list prices are: 300 mg = £2,050 and 108 mg = £512.50.

Note that the confidential prices for the comparators are presented in the confidential appendix.

In the dosing schedules presented above the standard induction period has been used. Depending on the level of response to the induction treatment, the induction period may be extended. However, the company expects this to concern a minority of patients based on the clinical response rate in the first 12-week induction period in the UPA trials.[2, 3] Furthermore, clinical experts indicated that patients with an inadequate response would be more likely to switch to a different advanced therapy/biologic than receive extended induction.[11] Thus, the company excluded the extended induction from the base-case and instead included it in a scenario analysis.

For UPA, extended induction is 30 mg administered once daily for an additional 12 weeks (i.e., to Week 24) following inadequate response to standard induction therapy. The VDZ extended induction includes an additional 300 mg IV dose at week 10. The extended induction dose of UST is 90 mg and is administered at week 8. Since the maintenance dose of UST of 90 mg is also administered at week 8, the company has assumed in the model that any patients requiring extended induction of UST effectively receive a double dose (twice 90 mg) at week 8.

It is not clear to the EAG that this approach to extending induction with UST by giving a double dose at week 8 is indeed used in clinical practice, as the CS did not provide any references nor did the EAG find any confirmation that this dosing schedule may be used to extend induction.

iv. Administration costs

It was assumed that oral therapy is not associated with any administration costs. For IV treatment, the company assumed that the HRG code FD02H Inflammatory Bowel Disease without Interventions, with CC Score 0 would apply, at £291 per administration.[12]

For SC costs it was assumed that costs would only be incurred at the first administration, since patients will self-administer the subsequent injections. These initial administration costs were estimated at £44.

The EAG concurs with the assumption that SC administration will only incur costs the first time. For the costs of IV administration, the EAG compared the current approach with that used in previous STAs. For example, in TA633 (UST for treating moderately to severely active ulcerative colitis)[13] the tariff for an outpatient visit was used, which amounted to £142.

Recently a paper was published looking into the costs of IV and SC administration of biologics.[14] In that paper it was pointed out how various studies use different tariffs for the IV administration of biologics, as no specific tariff code is available for this procedure. It was put forward that most often tariffs for IV chemotherapy administration are used, with tariffs ranging from £142 to £426, with the latter value for 'Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance'.

Based on interviews with various stakeholders, a micro-costing approach was used to estimate the IV administration costs, which amounted to £414 if only in-tariff costs were included.

From the above, it is clear that the estimates for administration costs for IV biologics can differ between studies and no clear unique tariff is currently being used. If the cost estimate from the (expert opinion based) micro-costing study is used, the 1-year administration costs for UST and VDZ, will be higher than estimated in the current model. In an EAG scenario, we will explore how the costs change when the lower value of £142 is used.

4.4 EAG model check

The EAG conducted a range of checks on the company's cost-comparison model. This included a verification that the dosing scheme of the treatments in Excel matched the described scheme in the CS[6] and verification that the costs are in line with the costs described in the CS[6] (see CS, Table 64). We also performed an inspection of the formulae used in Excel.

Main observations:

- The model does not have any input parameters related to efficacy and safety that are informed by data from the trials.
- The calculated dosing scheme for UPA is in line with what is stated in the CS[6] (page 10, CS[6]).
- The dosing scheme for the comparators is described in less detail in the CS[6] (page 16, CS[6]). Although the CS[6] states that patients on a low dose can switch during treatment to a high dose this is not modelled. In the model it is assumed that those that end up with a high dose in the maintenance phase will do so since the start of the maintenance phase.

Other observation:

- In the CS[6] it is stated that for patients over 65 years UPA should only receive the 15 mg dose in the maintenance phase. As age is not part of the model this dose recommendation is not explicitly taken into account. The EAG acknowledges that it is possible that this dose limitation has implicitly been taken into account in the applied distribution between 15 mg (70%) and 30 mg (30%) during maintenance treatment.

Minor model errors, none of which affected the results:

- There is a hardcoding error in the calculation of the number of subsequent administrations for doses of VDZ SC. However, since only the first SC administration incurs costs, this error has no effect on the results.

- There is a reference error in the formula to estimate the number of dosages for UPA for standard and extended induction, in order to estimate the administration costs. However, the administration costs per dose are 0, because UPA is an oral drug. In addition, despite using the wrong cell reference, the value that is return is still correct, so the results are not affected.

4.5 Company's model results

The company base-case cost comparison results compare the 1-year results for UPA, UST, and VDZ both IV and SC. For UPA the PAS price was used whilst list prices were used for UST and VDZ (see CS,[6] Table 69). Results using discounted prices for UST and VDZ as well can be found in the confidential appendix.

Uncertainty over model assumptions was assessed with a range of scenario analyses (CS, Tables 70-76, response to clarification letter Tables 12 and 13). No subgroup analyses were performed.

The results of the company's base-case analysis indicated that UPA is a cost saving strategy compared to UST and both versions of VDZ (IV and SC) (see CS,[6] Table 69). The estimated base-case costs by the company are [redacted] for UPA, £19,336 for UST, £22,942 VDZ IV and £16,805 VDZ SC.

The conclusion that UPA is a cost saving strategy compared to UST and VDZ (IV and SC) applies also to all the sensitivity analyses performed by the company (see CS,[6] Tables 70–75). A complete overview of all results is presented in Table 1 below.

Table 1: Company base-case and scenario results

	Costs UPA (PAS price)	Costs UST (list price)	Costs VDZ IV (list price)	Costs VDZ SC (list price)
Company base-case	[redacted]	£19,336	£22,942	£16,805
Scenario results from CS				
Scenario 1: Year 2+ costs	[redacted]	£13,607	£19,781	£13,325
Scenario 2a: 100% on low dose maintenance of UPA 15 mg	[redacted]	£19,336	£22,942	£16,805
Scenario 2b: 0% on low dose maintenance of UPA 15 mg	[redacted]	£19,336	£22,942	£16,805
Scenario 3a: 0% on UST standard maintenance dose	[redacted]	£19,658	£22,942	£16,805
Scenario 3b: 20% on UST standard maintenance dose	[redacted]	£18,799	£22,942	£16,805
Scenario 3c: 30% on UST standard maintenance dose	[redacted]	£18,370	£22,942	£16,805
Scenario 4: Extended induction	[redacted]	£21,527	£24,581	£19,146
Additional scenario results from clarification response				
Scenario CR1: Extended induction with 100% on high maintenance dose	[redacted]	£21,849	£32,774	£19,146
Scenario CR2: 22% on VDZ IV high maintenance dose[a]	[redacted]	£19,336	£21,818	£16,805

	Costs UPA (PAS price)	Costs UST (list price)	Costs VDZ IV (list price)	Costs VDZ SC (list price)
EAG scenario results				
Scenario EAG1a: 100% on low dose maintenance of VDZ IV	[redacted]	£19,336	£18,728	£16,805
Scenario EAG1b: 0% on low dose maintenance of VDZ IV	[redacted]	£19,336	£32,774	£16,805
Scenario EAG2: Cost IV administration £142	[redacted]	£19,187	£21,482	£16,358

CR = clarification response; CS = company submission; EAG = External Assessment Group; IV = intravenous; mg = milligram; PAS = Patient Access Scheme; SC = subcutaneous; UPA = upadacitinib; UST = ustekinumab; VDZ = vedolizumab

[a]These results were corrected by the EAG, because the results as reported by the company in their clarification results were erroneously based on the "Extended induction" setting.

4.6 EAG exploratory analysis

The EAG undertook three additional exploratory analysis using the company's original submitted Excel model. The analysis presented in this Section reflects the PAS discount price for UPA whilst list prices were used for UST and VDZ. Results using discounted prices for UST and VDZ as well can be found in the separate confidential appendix.

Since the company only changed the percentage of patients receiving VDZ high dose maintenance to 22%, and not the more extreme limits of 100% and 0% as was done in Scenarios 2a and 2b for UPA, the EAG explored the impact of these more extreme values.

In addition, the model was amended to assess the impact of using a lower estimate of IV administration costs, £142, on the results.

For all these scenarios UPA remains cost-saving.

4.7 EAG conclusion

The EAG considers the current cost comparison incomplete as the the TNF-alpha inhibitors IFX and ADA can also be regarded as appropriate comparators in the second-line for the BF population.

In addition, compared to the NICE scope the cost comparison may be regarded as incomplete as only the BF population is regarded. However, the only input estimated from the trials is the weight

distribution of the patients, so the impact of limiting the population on the overall conclusions reading costs will be minimal.

In the current model, only the pathway of patients successfully treated over the time horizon is included, alternative pathways, such as patients not responding to induction treatment or patients discontinuing due to adverse events, relapse, or death are not incorporated in the model. Even if all treatments can be considered equivalent in terms of efficacy and safety, by only including the pathway of patients successfully treated over the time horizon, the differences in costs will appear larger than when also less successful pathways are included (assuming costs of a potential next treatment are the same for all three treatments being compared). When interpreting the magnitude of the cost difference resulting from the cost comparison it is important to keep this in mind.

With list prices for all treatments, UPA is estimated to be cost saving compared to the comparators UST and VDZ. This applies for the company's base-case analysis and for all company and EAG scenario analyses. Results with discounted prices for all treatments are shown in a confidential appendix to this report.

5. EAG commentary on the robustness of evidence submitted by the company

The company's evidence is not robust enough to confirm comparability of efficacy and safety between UPA and all appropriate comparators. To summarise points made previously:

- Not all the appropriate comparators have been included. The company's justification for not including TNF-alpha inhibitors as second-line comparators (because TNF-alpha inhibitor comparators would be used first-line, and so would not be able to be used second-line) was insufficient because it ignored the fact that TNF-alpha inhibitors are not the only biologics given first-line. Without all appropriate comparators included it is impossible to know if UPA is comparable to all such comparators.

- Network meta-analyses were not conducted for all the relevant outcomes. In particular HRQoL should have been included as it is the key clinical effectiveness outcome. Justification for the omission of relevant outcomes was weak. Without inclusion of all appropriate outcomes, it is impossible to ascertain true comparability between UPA and its comparators.

- The NMAs that were carried out were not all conducted optimally. The NMA for induction clinical response used an FE model when an RE model would have been more appropriate.

- The results from the NMA for discontinuation due to adverse events did not suggest comparability.

- Results for the maintenance data are not relevant to the decision problem population, as they comprised responder data only. Though such data were inevitable for ethical and pragmatic reasons, the use of responder data does mean that the data are not applicable to the decision problem in this submission.

6. References

[1] AbbVie. Upadacitinib for previously treated moderately to severely active Crohn's disease [ID4027]: Response to request for clarification from the ERG: AbbVie, 2022. 105p.

[2] AbbVie. A multicenter, randomized, double-blind, placebo controlled induction study of the efficacy and safety of upadacitinib (ABT-494) in subjects with moderately to severely active Crohn's disease who have inadequately responded to or are intolerant to conventional and/or biologic therapies (U-EXCEL [M14-433]). Clinical study report, 2022

[3] AbbVie. A multicenter, randomized, double-blind, placebo-controlled induction study of the efficacy and safety of upadactinib (ABT-494) in subjects with moderately to severely active Crohn's disease who have inadequately responded to or are intolerant to biologic therapy (U-EXCEED [M14-431]). Clinical study report, 2022

[4] AbbVie. A multicenter, randomized, double-blind, placebo-controlled maintenance and long-term extension study of the efficacy and safety of upadacitinib (ABT-494) in subjects with Crohn's disease who completed the studies M14-431 or M14-433 (U-ENDURE [M14-430]). Clinical study report, 2022

[5] Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A. Bayesian measures of model complexity and fit. J R Stat Soc Series B Stat Methodol 2002;64:583-639.

[6] AbbVie. Upadacitinib for previously treated moderately to severely active Crohn's disease [ID4027]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Document B - Company evidence submission: AbbVie, 2022. 125p.

[7] National Institute for Health and Care Excellence. Guselkumab for treating moderate to severe plaque psoriasis [TA521]. London: NICE, 2018 Available from: https://www.nice.org.uk/guidance/ta521

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[11] AbbVie. Crohn's disease HTA advisory board report (MAP ID: 2021-GB-MNP-00091) [Data on file], 2021

[12] NHS England. National tariff payment system [Internet]. Available from: https://www.england.nhs.uk/pay-syst/national-tariff/national-tariff-payment-system/

[13] National Institute for Health and Care Excellence. Ustekinumab for treating moderately to severely active ulcerative colitis [TA633]. London: NICE, 2020 Available from: https://www.nice.org.uk/guidance/ta633

[14] Heald A, Bramham-Jones S, Davies M. Comparing cost of intravenous infusion and subcutaneous biologics in COVID-19 pandemic care pathways for rheumatoid arthritis and inflammatory bowel disease: a brief UK stakeholder survey. Int J Clin Pract 2021;75(9):e14341.

Cost-comparison evaluation

Upadacitinib for previously treated moderately to severely active Crohn's disease [ID4027]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 6 January 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Decision problem, population needs further clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG comments
The EAG report states 'the decision problem focuses only on a stratum of those previously treated – those who have previously failed on biologics' (Section 2, page 5).	The Company suggest that the EAG amend this to (changes in bold): 'the decision problem focuses only on a stratum of those previously treated – those who have previously failed biologic therapy **or for whom TNF-alpha inhibitors were deemed unsuitable**.'	To clarify that the target population includes patients who are TNF-alpha contraindicated and may not have previously failed a biologic (but have failed conventional care), as well as those who have experienced biologic failure.	This has been amended in the report
The report states 'Nevertheless, because of the very different efficacy in the two strata, with the NMAs demonstrating inferior efficacy for the CCF stratum, it is vital not to base recommendations for both strata on the data from the BF stratum' (Section 2, page 5).	The Company suggest that the EAG remove this statement.	To clarify that the target population is the BF population only and no recommendation was sought for the CCF population.	Not a factual inaccuracy
The report states 'Similarly, 'surgery' is not included as an outcome in the decision	The Company suggest that 'No surgery data were available in the UPA trials' is rephrased to state **'No**	This statement is incorrect. Occurrence of CD-related surgeries is reported in Table	Not a factual inaccuracy – surgery was not

Description of problem	Description of proposed amendment	Justification for amendment	EAG comments
problem despite being in the NICE scope. No surgery data were available in the UPA trials. This is a limitation in the submission because the need for surgery is a highly relevant clinical outcome' (Section 2, page 5).	**surgery data were reported in the CS due to low numbers'**	14.2_4.7 of the U-EXCEL, U-EXCEED and U-ENDURE CSRs. However, due to low numbers, these were not reported in the submission.	included as an outcome in the decision problem.
The report states 'The company eventually provided a sub-group analysis for CD location in response to clarification questions' (Section 2, page 6).	The Company suggest that the EAG amend the wording to ''The company provided a sub-group analysis for CD location in response to clarification questions'	To clarify that the Company provided the sub-group analysis for CD location as part of the original submission within the data pack and respective CSRs. As such, the term 'eventually' is misleading.	The term 'eventually' has been removed
The EAG report states 'Only participants achieving a clinical response in U-EXCEL and U-EXCEED were eligible for inclusion in U-ENDURE. This would be non-representative of the target population in this submission, who are not people who have previously responded to the	The Company would prefer the removal of the statements in which the maintenance data for UPA and comparators are discounted by the EAG	Discounting maintenance treatment does not reflect how patients with CD (or other chronic inflammatory conditions) are treated in clinical practice. In clinical practice, patients receive induction therapy to gain control of their disease and then move on to a	Not a factual inaccuracy – the responder data is not relevant to the decision problem

Description of problem	Description of proposed amendment	Justification for amendment	EAG comments
study drug….. It might also be of interest to understand whether there is benefit to maintenance treatment (as opposed to curtailment of treatment) on achieving induction. However, the fact remains that the population are not relevant to the decision problem' (Section 2, page 5) The report also states 'Results for the maintenance data are not relevant to the decision problem population, as they comprised responder data only. Though such data were inevitable for ethical and pragmatic reasons, the use of responder data does mean that the data are not applicable to the decision problem in this submission' (Section 5, page 17)		maintenance dose to retain disease control; treatment naïve patients would not be initiated on a maintenance dose. Clinical guidelines from NICE and the British Society for Gastroenterology also divide CD therapy into induction and maintenance of remission (1, 2). UPA as maintenance therapy is included in the anticipated UK label (3) and aligns with regulatory body requirements (e.g., MHRA, EMA). Furthermore, all previous advanced therapies for CD that have been recommended by NICE have been approved on the basis of data from similarly designed induction and maintenance trials (4-6).	

Issue 2 Model parameters, statement ambiguity

Description of problem	Description of proposed amendment	Justification for amendment	EAG comments
The EAG report states: (a) 'costs are assumed to be the same in all years after year 1' (Section 4.2, page 9) and that; (b) 'the patient is assumed to have responded to induction treatment and receive maintenance treatment for at least 1 year (base case) or at least 2 years (scenario).' (Section 4.2, page 9)	The company suggest the text in (a) is removed and that in the text denoted (b) the following changes are made (changes in bold) 'The patient is assumed to have responded to induction treatment and **proceed to** receive maintenance treatment. **The base case includes induction and reflects the cost of the patient's first year on treatment, while the Year 2+ scenario reflects the cost of additional years on maintenance treatment only**.'	The parameters of the cost-comparison model are not accurately described and it is unclear that year 2+ costs do not duplicate induction costs. Year 1 base case costs reflect the cost of a total of 1 year, which includes induction and maintenance. The Year 2+ scenario reflects the cost of one year on maintenance treatment.	The EAG agrees that the rephrasing for point (b) as suggested by the company is a better description of the process. The slightly adjusted version of the suggestion is implemented in the text. We have moved the section in part (a) to make clear that these maintenance costs in additional years are the same each year. It now reads:" In this calculation the patient is assumed to have responded to induction treatment and proceed to receive maintenance treatment. The base case includes induction and maintenance treatment, and reflects the cost of

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			the patient's first year on treatment, while the Year 2+ scenario reflects the cost of additional years on maintenance treatment only (these maintenance costs are assumed to be the same in all years after year 1)"
The EAG report states 'For patients receiving UST, the dosage depends on the weight of the patient' (Section 4.3 [i], page 10)	The Company suggest that this is amended to (changes in bold): 'For patients receiving UST, the **IV** dosage depends on the weight of the patient.'	To clarify that only the IV dose (not the SC dose) of UST is weight dependent.	The EAG agrees with the rephrasing and implemented this suggestion in the report
The report states 'For all three treatments patients may receive a low or a high dose during the maintenance phase of the treatment, and the distribution varies by treatment' (Section 4.3 [ii], page 10).	The Company suggest that this is amended to (changes in bold): 'For **UPA, UST, and IV VDZ,** patients may receive a low or a high dose during the maintenance phase of the treatment…' To align with the above suggestion, the Company also suggest removing the final phrase from this paragraph, '…and for VDZ subcutaneous (SC) to 0%.'	To distinguish the possibility of dose escalation with VDZ IV from the fixed dose of VDZ SC.	The EAG understands the desire from the company to specify this and implemented the distinguishing between the treatments. The EAG did not remove the final phrase, but rather rephrased it to make clear that there is

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			just one fixed dose for VDZ SC and that this is in line with the recommendations. The text reads now:' For, and for VDZ subcutaneous (SC) this is 0%. This is in line with the company submission, where only a fixed dose for SC VDZ is applied."
The report states 'For UPA extended induction means that in another 12 weeks 30 mg per day is administered' (Section 4.3 [iii], page 10).	The Company would prefer this to read 'For UPA, extended induction is 30 mg administered once daily for 12 weeks (i.e., to Week 24) following inadequate response to standard induction therapy.'	To clarify when the extended UPA induction period starts and ends.	The EAG agrees with these clarifications and implemented this suggestion with a small change in **bold.** 'For UPA, extended induction is 30 mg administered once daily for **an additional** 12 weeks (i.e., to Week 24) following inadequate response to standard induction therapy.'

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The report states 'For SC costs it was assumed that costs would only be incurred at the first administration, since patients will self-administer the subsequent injections. These administration costs were estimated at £44' (Section 4.2 [iv], page 12).	The Company suggest that the text is amended as follows (changes in bold): 'For SC costs it was assumed that costs would only be incurred at the first administration, since patients will self-administer the subsequent injections. These **initial** administration costs were estimated at £44.'	To further clarify that the £44 only applies to the first SC administration.	The EAG implemented this suggestion to further clarify the one-time administration of this cost

Issue 3 NMAs

Description of problem	Description of proposed amendment	Justification for amendment	EAG comments
The EAG report states that 'the NMA for discontinuation due to adverse events yielded point estimates that favoured the comparators.' and 'credible intervals straddled the null line but demonstrated greater probability of a population effect denoting benefit for the comparators' (page 4 and 8)	Removal of the statement that the discontinuation due to AEs NMA shows benefit for comparators and that this is consistent with a higher probability that the true population effect would favour the comparators.	The EAG is referring to the following results: [redacted] Credible intervals mean that there is 95% probability of the true population estimate lying within the interval. Given the wide intervals around 0, one cannot conclude that this favours the comparators. The report makes a conclusion on the comparative likelihood of discontinuing treatment for CD based on a non-statistically significant point estimate.	Not a factual inaccuracy – the EAG indicated the balance of probabilities, which is important for interpretation.
The EAG report states 'Secondly, heath-related quality of life (HRQoL) was not included as an outcome	The Company would prefer the removal of 'despite this being the most relevant clinical effectiveness outcome for patients.'	HRQoL is an important outcome for patients, but a wide range of outcomes are relevant to patients with CD,	The statement has been amended to 'Secondly, heath-related quality of life (HRQoL) was not

Description of problem	Description of proposed amendment	Justification for amendment	EAG comments
in the NMA, despite this being the most relevant clinical effectiveness outcome for patients' (Section 1, page 4).		including the symptomatic improvements indicated by the CDAI score, commonly a primary endpoint in CD trials. One of the NICE criteria for cost comparison submissions is 'the technology is likely to provide similar or greater overall health benefits to patients than technologies recommended by NICE for the same indication, measured by relevant outcomes.' No ranking of the relevance of clinical outcomes is stated.	included as an outcome in the NMA, despite this being a highly relevant clinical effectiveness outcome for patients'
The EAG states 'In addition, the populations in the various maintenance trial comparisons are intrinsically different in terms of the drug to which they have responded. This level of clinical heterogeneity across comparisons may make an NMA approach	The Company would prefer that this statement is removed.	As maintenance treatment reflects the continuation of care that patients would receive following induction therapy (i.e., they would remain on the same treatment and not be switched to another therapy), it is inaccurate to conclude	Not a factual inaccuracy.

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inappropriate, and therefore makes any results derived from an NMA potentially invalid' (Section 2, page 5)		that this is a relevant heterogeneity issue. As described in Issue 1, previous advanced therapies for CD that have been recommended by NICE have been approved on the basis of data from similarly designed induction and maintenance trials. Previous submissions have included NMAs to assess relative efficacy of relevant treatments using data from both induction and maintenance trials (7, 8).	
The EAG report states 'The results from the NMA for discontinuation due to adverse events did not suggest comparability' (Section 5, page 17)	Removal of text	As stated above, this statement is inaccurate as there was no evidence of statistically significant differences in discontinuation due to AEs between UPA, UST and VDZ in the NMAs due to wide credible intervals that crossed 0.	Not a factual inaccuracy – the results did not suggest comparability. If the company's reasoning is followed, then any 'non-significant' finding would be construed as indicating comparability. This would mean that under-

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			powered analyses would be frequently misinterpreted.

Issue 4 Other issues that could lead to misinterpretation/Company points for clarification

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Exclusion of TNF-alpha inhibitors from comparators: 'As shown in the company's response to clarification (Figure 1, company response to clarification1) UST is not a TNF-alpha inhibitor and yet it is used as a NICE-recommended first-line advanced therapy (as well as second-line advanced therapy) drug. This means that some patients will not receive TNF-alpha inhibitors for first-line advanced therapy, and so TNF-alpha-inhibitors can be regarded as appropriate second-line advanced therapy comparators for these patients' (Section 1, page 3; Section 4.1, page 9; Section 4.7, page 15; Section 5, page 17).	The Company suggest that the EAG acknowledge that patients are very unlikely to receive TNF-alpha inhibitors as second-line biologic therapy. This aligns with NICE guidance which recommends that biologic therapy is initiated with the least expensive treatment option (2) (i.e. TNF-alpha inhibitors), and therefore all patients eligible for TNF-alpha inhibitors would receive these as first-line treatment.	In UK clinical practice, TNF-alpha inhibitors are typically given as first-line biologic therapy in CD, aligning with NICE guidance which recommends starting biologic therapy with the least expensive option (2). As a therapy class switch is usually preferred when switching to second-line biologics, a patient who received a TNF-alpha inhibitor as first-line therapy would not typically switch to another TNF-alpha inhibitor as second-line therapy. Patients who are contraindicated to TNF-alpha inhibitors receive UST as first-line biologic therapy, with VDZ as their only current option for second-line biologic therapy. Therefore, the vast majority of patients in the target population receive either UST or VDZ as second-	Not a factual inaccuracy – the EAG statements reflect the reality that some patients will not have TNF-inhibitors at first line advanced therapy.

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		line biologic therapy and TNF-alpha inhibitors would not usually be administered second-line.	
Comparison of CCF and BF NMA results: The report states 'Nevertheless, because of the very different efficacy in the two strata, with the NMAs demonstrating inferior efficacy for the CCF stratum, it is vital not to base recommendations for both strata on the data from the BF stratum' (Section 2, page 5).	The Company suggest that the EAG remove this statement as has also been suggested in Issue 1 above.	As presented in Appendix L of the Company submission, all credible intervals for UPA versus relevant comparators (UST and VDZ) across induction and maintenance NMAs for the outcome of CDAI remission cross 0, and there are therefore no statistically significant differences between treatments. Following the EAG interpretation on page 4 that 'the NMA for discontinuation due to adverse events yielded point estimates that favoured the comparators' and 'credible intervals straddled the null line but demonstrated greater probability of a population effect denoting benefit for the comparators', the maintenance	Not a factual inaccuracy

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		NMA for CDAI remission showed improved point estimates for UPA versus UST and VDZ. It would therefore be inaccurate to conclude that UPA has inferior efficacy in the CCF stratum.	
Disease location as an outcome modifier: 'location of CD was a potential outcome modifier, with ileal CD responding less well to UPA (relative to placebo) than other locations' (Section 2, page 6).	Remove text stating 'with ileal CD responding less well to UPA (relative to placebo) than other locations'	Clinical experts consulted during the submission advised that that disease location does not drive treatment choice for individuals with moderately to severely active. Furthermore, the clinical trials were not powered for the separate CD location sub-group analyses and it is therefore not possible to conclude that ileal CD responds less well to UPA than other locations.	Not a factual inaccuracy – the use of the qualifier 'potential' reflects the EAG's caution. As the sub-group analysis was probably underpowered (as the company acknowledges) then it is important to be vigilant for possible type II errors. This means it is important to consider the possibility that there may have been real differences in the efficacy of upadacitinib across bowel regions given the point estimate values, even if these differences are probably

Description of problem	Description of proposed amendment	Justification for amendment	EAG comments
			statistically non-significant. Importantly, the EAG statement is driven by data rather than opinion.
Relevance of model structure: 'The model does not align with those used in various previous appraisals where a cost comparison was considered. In the current model, only the pathway of patients successfully treated over the time horizon is included, alternative pathways, such as patients not responding to induction treatment or patients discontinuing due to adverse events, relapse, or death are not incorporated in the model. (Section 4.7, page 16)	Remove text stating 'The model does not align with those used in various previous appraisals where a cost comparison was considered'	A number of previous appraisals have been conducted using a cost-comparison model where aspects such as response to treatment and discontinuation were not considered including TA794 (9), TA735 (10) and TA671 (11). Furthermore, across the previous appraisals referenced by the EAG (TA521 (12), TA596 (13), TA723 (14) and TA803 (15)), response to treatment and discontinuation rates were considered equal, AEs were considered equal or were not included, and mortality was considered equal or not included.	We have made the suggested change.

Issue 5 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG comments
'For the restriction of participants to affect external validity two conditions would need to be fulfilled' (Section 3, page 8).	The company suggest that the text is amended to: 'For the restriction of participants to **not** affect external validity two conditions would need to be fulfilled'.	Correction of error	In contrast to what has been suggested by the company, the term 'adversely' has been added to clarify that the two conditions, if fulfilled, *would* adversely affect external validity
'…the first-line biologic failure does not necessarily involve a TNF-alpha-inhibitors' (Section 4.1, page 9).	The Company suggest that the text is amended as follows (changes in bold): '…~~**the**~~ first-line biologic failure does not necessarily involve **a** TNF-alpha-inhibitors.'	Correction of typographical error	Amended
'The model calculates the costs induction and maintenance costs for patients receiving UPA, UST, or VDZ' (Section 4.2, page 9).	The Company suggest that the text is amended as follows (changes in bold): 'The model calculates the ~~**costs**~~ induction and maintenance costs for patients receiving UPA, UST, or VDZ.'	Correction of typographical error	Amended
'Not only does the focus on successfully treated	The Company suggest that the text is amended as follows (changes in	Correction of typographical error	Amended

patients lead to an estimated savings that cannot be extrapolated…' (Section 4.2, page 10).	bold): 'Not only does the focus on successfully treated patients lead to ~~**an**~~ estimated savings that cannot be extrapolated…'		
'In the above presented dosing schedules the standard induction period has been used' (Section 4.2, page 11).	The Company suggest that the text is amended as follows (changes in bold): '**In the dosing schedules presented above,** the standard induction period has been used.'	Readability/clarification	Amended
The EAG report states that the IV administration costs used by the Company were £219 per administration (Section 4.3, [iv] page 11).	The Company suggest that the EAG amend the administration cost to **£291**, which was used by the Company in their analyses.	To correctly report the IV administration costs used by the Company in the economic model.	Amended
'The dosing scheme for the comparators is less detailed described in the CS' (Section 4.4, page 12).	The Company suggest that the text is amended to: 'The dosing scheme for the comparators **is described in less detail** in the CS'	Readability	Amended
'For UPA the PAS price was used whilst list prices for UST and VDZ (see CS, Table 69)' (Section 4.5, page 13).	The Company suggest that the text is amended as follows (changes in bold): 'For UPA the PAS price was used whilst list prices **were used** for UST and VDZ (see CS, Table 69).'	Amend incomplete sentence	Amended

Location of incorrect marking	Description of incorrect marking	Amended marking
None noted	NA	NA

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