ACESO

FULL PROTOCOL TITLE	ACESO trial: Upadacitinib Co-therapy with Corticosteroids in Early Acute Severe Ulcerative Colitis (A Phase III randomised placebo controlled double blinded trial)
SHORT TITLE	ACESO
PROTOCOL VERSION	V1.3 14.AUG.2025
SPONSOR NUMBER	R4126
REC NUMBER	24/WS/0123
IRAS	1010109
ISRCTN NUMBER	ISRCTN17100156
INVESTIGATIONAL PRODUCT	Upadacitinib
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TRIAL SPONSOR	Hull University Teaching Hospitals NHS Trust [HUTH], RDI Department, Second Floor Daisy Building, Castle Hill Hospital, Cottingham, UK, HU16 5JQ

Confidentiality Statement:

Information in this protocol should not be disclosed, other than to those involved in the execution or ethical review of the study, without written authorisation from the Sponsor.

Regulatory Statement:

All study procedures will be conducted within ICH GCP guidelines and regulatory requirements.

SPIRIT statement:

NOTE: The SPIRIT 2013 Statement provides evidence-based recommendations for the minimum content of a clinical trial protocol. "SPIRIT is intended to facilitate the drafting of protocols and improve their completeness. High-quality protocols can promote proper trial implementation, reduce avoidable protocol amendments, and facilitate full appraisal of the study's scientific and ethical considerations".

PROTOCOL SIGNATURE PAGE

Protocol Version 1.3 14.AUG.2025

The undersigned confirm that the following clinical trial protocol has been agreed and accepted and that the Principal Investigator (PI) agrees to conduct the trial in compliance with the approved clinical trial protocol and will adhere to the Clinical Trials Regulations and subsequent amendments, ICH GCP guidelines, the Sponsor's Standard Operating Procedures (SOPs), and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Funder and Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies regarding the study are explained.

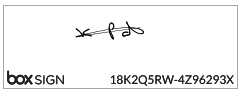
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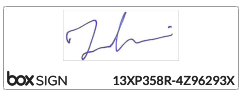
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PROTOCOL AMENDMENTS SINCE VERSION 1.0

State "none" if no amendments			
Version number	Date	Provide reason for the amendment	State which sections of the protocol were replaced, added or deleted
Version 1.1	19.09.2024	MHRA review	
Version 1.2	19.DEC.2024	Adding clarification and rectifying some minor errors.	• Minor changes on the protocol & intervention schedule tables due to some errors and adding further clarifications. • Collecting the body temperature instead of respiratory rate and adding collection of optional handgrip strength assessment. • Adding more clarifications on exploratory objectives for sub-studies, inclusion criteria number 4, rescue therapy & collection of Rectal biopsies & Faecal Calprotectin. • Adding more clarifications on collecting the endoscopy report & collecting the endoscopy images for internal validation. • Correction from Erythrocyte sedimentation rate (ESR) to C Reactive Protein (CRP) in the Modified Trulove Witts Index in Appendix B • Inclusion of Appendix D form for calculation of MTWI score • Inclusion of Appendix E form for calculation of Partial MAYO Score • Inclusion of Appendix F Travis criteria • Inclusion of Appendix G form for calculation of MAYO Endoscopy Score • Inclusion of Appendix H form for calculation of UCEIS Endoscopy score
Version 1.3	14.AUG.2025	Adding clarification and rectifying some minor errors.	• Per DMEC recommendation, eligibility has been expanded to include new molecules such as Risankizumab and Guselkumab. Amendments made in Section 5.1. • To align with the SmPC and EMEA approval the exclusion criteria 8, 9, 11, 13, 24 modified. • Clarification of timing of primary endpoint (10 days from start of IV steroids and not 10 days from the first dose of IMP). NB Clarification of sections of text only, in response to site feedback, no change in endpoint definition. • As recommended by DMEC, a clarification has been made regarding withdrawal from treatment in the trial summary and withdrawal criteria section. • Alteration of cut of values of ANC (from 1.5 to 1.0 x109 cells/L) and Lymphocyte count (from 1.0 to 0.5 x109 cells/L). Amendments made in exclusion criteria. • Removing the levels of AST and ALT for severe hepatic dysfunction as these are not markers of severe dysfunction in the trial summary and withdrawal criteria section. • The unblinding schedule has been changed from Day 10 (+/- 1) to Day 10 (+2) following administration of IV steroids. • A clarification has been added regarding Day 10 assessments. If participants are discharged before Day 10,

			provisions should be made to collect CRP, calprotectin, and complete Day 10 assessments (Section 4.2). • Minor clarifications have been made to the intervention schedule tables & flow chart based on comments from TMG, TSC, and site staff. The main body of the protocol has been amended to align with the revised tables. • Clarification has been added to indicate that participation in the sub-studies is optional and should be based on the clinical judgment of the treating physician and in line with local site prescribing practices and guidance (Section 1.4). • Clarification has been added regarding emergency unblinding and enrolment into sub-studies. Eligibility for entry into sub-studies for non-responders will be confirmed through the database to avoid unnecessary early unblinding (Section 3.5). • A clarification has been added to Section 3.12 regarding treatment options available after completion of IMP treatment. • Clarifications have been made to biobank sample collection timepoints based on site feedback. • Biobank stool buffer collection has been removed, as collection of stools in Omnibet and Omnigene tubes is considered sufficient (Section 8.3). • A urine pregnancy test will be conducted for WOCBP at baseline, week 4 and week 8 after the last dose of the IMP. The IMP has a short half-life (<6h) no cumulative or late effects are anticipated. For this reason, a further pregnancy test will not be performing a month after the last dose of the IMP (Section 8.4).

ABBREVIATIONS

APR	Annual Progress Report
ASUC	Acute Severe Ulcerative Colitis
AXR	Abdominal Xray
AE	Adverse Event
AR	Adverse Reaction
AESI	Adverse Events of Special Interest
ARR	Absolute Risk Reduction
BMI	Body Mass Index
BP	Blood Pressure
CI	Chief Investigator
CV	Curriculum Vitae
CI[1]	Confidence Interval
CTA	Clinical Trial Authorisation
C&C	Capacity and Capability
C.Diff	Clostridium Difficile
CRP	C-Reactive Protein
CMV	Cytomegalovirus

CRF	Case Report form
CTCAE	Common Terminology Criteria for Adverse Events
CACE	Complier Average Causal Effect
CTIMP	Clinical Trial of an Investigational Medicinal Product
DVT	Deep Vein Thrombosis
DPIA	Data Protection Impact Assessment
DMEC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
DISCUSS	Decision Conflict Scale & Decision Regret Scale
eCRF	Electronic Case Report Form
eTMF	Electronic Trial Master File
EDC	Electronic Data Capture
EMA	European Medicines Agency
EDTA	Ethylenediamine tetraacetic acid
eGFR	Estimated glomerular filtration rate
EU	European Union
EME	Efficacy and Mechanism Evaluation
FBC	Full Blood Count
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GDPR	General Data Protection Regulations
GLP	Good Laboratory Practice
GI	Gastrointestinal
GP	General Practitioner
HHTU	Hull Health Trials Unit
HRA	Health Regulatory Authority
HUTH	Hull University Teaching Hospital
HBV	Hepatitis B
HCV	Hepatitis C
HDPE	High-density polyethylene
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IBD	Inflammatory Bowel Disease
IV	Intravenous
IWRS	Interactive Web Response System
IUS	Intrauterine hormone-releasing system
IUD	Intrauterine device
ISF	Investigator Site File
ID	Identification
IDMC	Independent Data monitoring Committee
ICH	International Conference on Harmonisation
LFT	Liver Function Test
IRAS	Integrated Research Application System
medDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MC&S	Microscopy, culture, and sensitivity
MTWSI	Modified Truelove Witts Severity Index Form

NICE	National Institute for Health and Care Excellence
NHS	National Health Service
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Public Patient Involvement
PPIs	Proton Pump Inhibitors
PE	Pulmonary Embolism
PAX Gene	Paired box Gene
QP	Qualified Person
RDI	Research, Development and Innovation
R&D	Research and Development
RCC	REDCap Cloud
REC	Research Ethics Committee
RSI	Reference Safety Information
RR	Respiratory Rate
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SIV	Site Initiation Visit
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SOC	Standard of Care
TMG	Trial Management Group
TSC	Trial Steering Committee
TB IGRA	Tuberculosis Interferon Gamma Release Assay
TNFα	Tumor necrosis factor alpha
TMC	Toxic Megacolon
TB	Tuberculosis
UoH	University of Hull
U&E's	Urea and Electrolytes
UC	Ulcerative Colitis
UK	United Kingdom
VZV	Varicella Zoster Virus
VTE	Venous Thromboembolism
WoCBP	Women of Childbearing Potential

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TRIAL SUMMARY

Sponsor	Hull University Teaching Hospitals NHS Trust

Sponsor Reference	R4126
Title of Study	ACESO trial: Upadacitinib Co-therapy with Corticosteroids in Early Acute Severe Ulcerative Colitis (ASUC) (A Phase IIIb randomised placebo controlled double blinded trial)
Study Centres	Up to 30 United Kingdom (UK) National Health Service (NHS) Trusts across England, Scotland, Northern Ireland, and Wales
Trial Phase	Phase IIIb
Hypothesis	Early addition of the rapidly acting agent Upadacitinib to conventional therapy using IV corticosteroids may reduce the need for medical rescue therapy and/or rescue surgical therapy in patients with ASUC
Intervention	**IMP intervention:** Early Upadacitinib in addition to IV corticosteroids **Comparator intervention:** IV corticosteroids **Outcome of interest**: Percentage of patients who need medical or surgical rescue therapy **Time for measuring outcome:** 10 days from first dose of IV corticosteroids
Aims and Objectives	**Primary objective** The overall study objective is to evaluate the clinical efficacy of Upadacitinib as combined treatment with intravenous steroids in patients with ASUC **Secondary objectives** • To evaluate the impact of combination therapy (Upadacitinib + steroids) on the need for rescue medical or surgical therapy • Evaluate the safety of use of combination therapy (Upadacitinib + steroids) in the setting of ASUC • Evaluate the efficacy and safety of the combination (Upadacitinib + steroids) in a subgroup of patients with prior exposure to advanced therapies • Determine the impact of combination therapy (Upadacitinib + steroids) on a range of other indices of treatment response including duration of hospital stay, time to treatment response, quality of life using CUCQ-32, patient preference using DISCUSS tool and 2 Validated psychometric tools (Decision Conflict Scale & Decision Regret Scale) • Collect biobanking samples to develop and refine high risk immunophenotype in ASUC who will benefit from combination (Upadacitinib + steroids) therapy. • Health economic assessment of treatment in ASUC **Exploratory Objectives for Sub-studies** • Need for further surgical rescue therapy at index admission after starting medical rescue • Need for further surgical rescue therapy 8 weeks after starting medical rescue

Study Design	The study will be a pragmatic, Phase IIIb, two-arm, double-blind randomised (1:1) placebo-controlled trial of ASUC patients admitted to UK National Health Service (NHS) hospitals
Number/Type of Participants	The study will recruit 300 patients admitted to hospital with suspected ASUC over ~30 months across up to 30 UK sites
Summary of eligibility Criteria	**Inclusion criteria** 1. Patients aged 18–65 inclusive 2. Have given written informed consent to participate 3. Hospitalised patients with clinically confirmed or suspected ASUC 4. Modified Truelove and Witts severity index (MTWSI) score ≥ 11 at or immediately before first dose of IV steroids. 5. Requirement for treatment with IV corticosteroids in the judgement of the treating clinician and the possibility to receive the IMP within 36 hours of admission 6. Prior treatment with corticosteroids and mesalamine at entry is permitted. In addition, prior treatment with immunomodulators, anti-TNFs, anti-integrins, Ustekinumab, Mirikizumab, Risankizumab, Guselkumab, Ozanimod or Etrasimod is permitted but these will all be stopped at admission with ASUC. 7. Prior treatment with other JAK inhibitors (e.g. Tofacitinib and Filgotinib) is also permitted if patients have not taken these within 4 weeks of the time of ASUC admission. Patients who had prior failed treatment with Upadacitinib will not be eligible. **Exclusion criteria** 1. Patients with any absolute contraindication to Upadacitinib 2. Proven infective colitis within 4 weeks of baseline assessment (Stool Cultures or C Diff Toxin assay positive, Cytomegalovirus (CMV) on biopsies) 3. Pregnant patients or patients breast feeding 4. Patients with toxic megacolon (TMC) at baseline assessment prior to randomisation 5. Use of strong CYP3A4 inhibitor medications (azoles, clarithromycin) and co-administration of food and drink containing grapefruit 6. Use of strong CYP3A4 inducer medications (including Rifampicin and Phenytoin) 7. Recent history of incompletely treated malignancy within 12-months (patients with a solid organ malignancy that remains under active treatment or where oncologists have not confirmed complete eradication) 8. Neutropenia with baseline ANC < 1.0 x10^9 cells/L 9. Absolute Lymphocyte Count < 0.5 x 10^9 cells/L 10. Hb < 80 g/L

	11. Moderate or Severe renal impairment (estimated glomerular filtration rate [eGFR] <40ml/min/1.73m^2) 12. Severe hepatic impairment (Child-Pugh C) 13. Patients with personal history of confirmed Venous Thromboembolism (VTE)/Pulmonary Embolism (PE) who are not on effective anticoagulation (e.g. history of previous Deep Vein Thrombosis ((DVT) or PE but no longer requiring anticoagulation), history of previous DVT or PE requiring anticoagulation where anticoagulation was not tolerated or withdrawn because of side-effects) 14. Evidence (from blood cultures etc) of active, serious localised as well as systemic infection or clinical suspicion of systemic infection 15. Currently taking part in another Clinical Trial of an Investigational Medicinal Product [CTIMP] 16. Treatment with other Janus kinase (JAK) inhibitors (e.g. Tofacitinib or Filgotinib) within 4 weeks of the time of screening 17. Patients unwilling or unable to provide informed consent. 18. Patients previously exposed to Upadacitinib as per local label 19. Patients with significant risk factors for MACE/malignancy 20. A history of untreated pulmonary Tuberculosis (TB) infection 21. Any absolute contraindication to corticosteroid 22. Patients with administered live vaccines of replication potential within 30 days prior to screening 23. Patients with untreated active or latent HCV and HBV infection
Study Treatment(s)	**IMP:** Oral 45mg Upadacitinib or matching placebo tablet First dose of oral Upadacitinib/placebo 45mg within 36 hours of first dose of IV corticosteroids. Followed by oral Upadacitinib / placebo 45mg once daily [OD] **Non-IMP**: IV methylprednisolone or hydrocortisone administered as per local guidelines and ASUC standard care • Responders to IV steroids on Upadacitinib/placebo will continue to Day 10 when all participants will be unblinded • Responders to Upadacitinib 45mg continue OD for a total of 8 weeks • Non-responders to placebo will have the option to enrol in Sub study 1 or 2 • All other aspects of ASUC treatment will follow standard care
Study Endpoints and Statistical Methods	Randomisation at baseline (1:1) **Primary Outcome Measure:** • Need for medical or surgical rescue therapy within 10 days following commencement of IV corticosteroids therapy. **Secondary outcome measures:**

	• Percentage of patients who achieve clinical response by Day 10 from starting of the IV steroids (MTWSI reduction ≥3 points and MTWSI < 10) • Time to clinical response (MTWSI reduction ≥3 points + MTWSI <10) • Time to rescue therapy (medical or surgical) • Percentage of patients who meet Oxford Travis rescue criteria for rescue therapy on or beyond Day 3 of hospitalisation • Percentage of patients who achieve clinical remission by 10 days and 8 weeks (Mayo stool frequency sub-score of 0 or 1, and rectal bleeding sub-score of 0) • Percentage of patients who achieve biomarker remission by 10 days and 8 weeks (CRP ≤ 5mg/L and/or, calprotectin ≤ 250µg/g where available) • Percentage of patients who adhere to the protocolised steroid taper (without needing to escalate steroid dose within taper) and clinical remission at 8 weeks (stool frequency sub-score of 0 or 1, and rectal bleeding sub-score of 0) • Percentage of patients who achieve endoscopic remission at 8 weeks where data available (endoscopic Mayo sub-score 0-1) • Incidence of colectomy within 8 weeks following commencement of IV corticosteroid therapy • Incidence of Adverse Events (AE) and Serious Adverse Events (SAE) • Total duration of hospital stay
Safety Analyses	• The Data Monitoring and Ethics Committee (DMEC) will periodically review safety data during the study • Feasibility assessment after the 20th patient is recruited • An interim analysis will be conducted after 50% of patients have completed Day 10 assessments
Withdrawal criteria	• Withdrawal of consent for treatment administration (data on the outcomes of these participants at Week 8 and 12 months will still be routinely collected) • Development of new severe renal impairment (eGFR <40 mL/min/1.73 m^2) or new severe hepatic dysfunction • Development of neutropenia with ANC <1.0 x10^9 cells/L • Detection of significant GI pathogen in stool specimen, or CMV • SAEs necessitating termination of IMP treatment • Withdrawal of consent for any reason

TABLE 1: INTERVENTION SCHEDULE - Main Study [Responders To IMP / Placebo]

Assessment	Screening	Baseline Day 1 of IMP	Day 2 of IMP	Day 3-7 of IMP	Day 5-10 of IMP	Day 10 (+2 days) of IV steroids	Day 15 of IV steroids (+/- 1 day) - if still in hospital	Week 4/Day 30 of IV steroids (+ 4 days) [phone call]	Week 8/Day 56 of IV steroids (+2 weeks) [clinic visit]	12 months assessment (+4 weeks) [Clinic visit]	NHS England data collection [H]
	Can be done on the same day										
Eligibility assessment	X										
Informed consent	X										
Medical history, smoking history, socio-demographic data	X										
Prior immune suppressive, biologics, 5ASAs and steroids	X										
Vital signs [P, BP, T)	X	X	X	X	X						
Physical examination	X	X	X	X	X						
Optional handgrip strength assessment		X		X[M]					X[M]	X[M]	
Weight / Height / BMI	X										
Ensure IMP can be administered within 36 hrs of 1st IV steroid dose	X										
Review of standard of care blood results (FBC, U&Es, CRP, LFTs)	X	X	X	X	X	X[F]			X	X	
Serum CRP						X[O]					
Review of standard of care stool cultures (MC&S, C. Diff)	X[C]	X[C]		X	X[A]						
Stool - faecal calprotectin	X[N]					X[N]			X [N]	X[N]	
Review of endoscopy MAYO score (If available within 28 days & or during current admission from sigmoidoscopy/colonoscopy reports)	X[B]	X[C]		X[D]			X[D]	X[C]	X[C]	X[C]	
Review of standard of care AXR (if available)	X[C]	X[C]	X[C]	X[C]							
MTWSI assessment / review of standard care clinical MTWSI (Appendix D) X[L]	X[L]	X[L]	X[L]	X[L]	X[L]	X[L]	X[L]				
Concomitant medications (full list)	X		X	X	X			X	X	X	
Urine β-HCG (WOCBP only) must be done before randomisation		X						X	X		
Randomisation (IWRS)		X									
Biobank research bloods (EDTA, SERUM, PAX Gene), Urine sample, Stool sample as close to days mentioned as possible & Rectal biopsies (if available)		X[I]		X[J]							
UCEIS score (only if available within 28 days & or during current admission from sigmoidoscopy or colonoscopy reports)	X[C]	X[C]		X[C]				X[C]	X [C]	X[C]	
Partial MAYO score assessment or Modified Partial MAYO score assessment (if endoscopy not available)	X	X		X				X	X	X	
Questionnaires: EQ5D-5L / VAS, CUCQ-32, HRUQ		X							X	X	
Decisional Conflict scale		X		X[K]	X[K]	X[K]					
Decisional Regret scale									X	X	
Tuberculosis Interferon Gamma Release Assay (TB IGRA), Hepatitis B (HBV) Hepatitis C (HCV), Varicella Zoster Virus (VZV), Lipids	X[A]										
Administration schedule											
IMP Upadacitinib 45mg / Placebo OD [Day 1 to Day 10]		X	X	X	X	X					
IV steroids [Day 1 to Day 10] Standard of care	X	X	X	X	X						
Clinical response/Rescue therapy (medical or surgical) assessment				X	X	X					
Unblinding at Day 10						X					
Instruction on continuation/ discontinuation of the IMP/placebo and oral steroids following unblinding						X[E]					
Continuation of Upadacitinib 45mg [Day 11 to Day 56]						X	X	X	X		
Oral tapering steroids -See protocol for regime [Day 11 to Day 56]						X	X	X	X		
Colectomy assessment [medical notes review]		X		X	X	X	X	X[F]	X[F]	X[F]	X
Review Participant Medication Diary		X	X	X	X	X		X	X		
Review of adverse events		X	X	X[G]	X[G]	X[G]	X	X	X		

Table 1 Key to [A] to [JN] definitions: X^{A} = if previously not available; X^{B} = if available within last month; X^{C} = if available; X^{D} = if done after baseline; X^{E} = Upadacitinib which is given as a full supply at randomisation will be continued following unblinding at Day 10 in responding patients; X^{F} = if in hospital/re admitted; X^{G} AEs will be collected DAILY from randomisation; X^{H} up to 5 years after last dose of IMP; X^{I} Baseline biobank research samples are collected prior to IMP or placebo administration where possible and rectal biopsies taken if sigmoidoscopy is done after consent; X^{J} Second collection of research samples is done between Day 3 and Day 7 and rectal biopsies can be taken if sigmoidoscopy is done after baseline, eligibility will access respectively at the screening visit; X^{K} in non-responders undergoing rescue therapy or surgery Decisional Conflict scale should be completed on the day of rescue therapy or surgery; X^{L} the MTWI score should be calculated daily from the first dose of corticosteroids; X^{M} if optional handgrip strength done at baseline, then repeat this at discharge, 2 months and at 12 months; X^{N}: calprotectin sample as close to the days mentioned as possible; X^{O} If the participants are discharged before day 10 provision should be made to collect the CRP, calprotectin and for completion of day 10 assessments.

TABLE 2: INTERVENTION SCHEDULE – Sub-study 1 [Non-Responders to Placebo (Infliximab Naïve)]

Assessment		Between Day 3-7 Response decision	Day 10 (+ 2 days) of IV steroids	Day 15 (+/- 1 day if still in hospital)	Day 30 (+4 days) [phone call]	Day 56 (+2 weeks) [Clinic visit]	12 months assessment (+4 weeks) [Clinic visit]
Eligibility assessment	Follow Main study intervention table 1 for visits before enrolment into Sub study 1	X					
Concomitant medications (changes since last assessment)		X	X	X	X	X	X
Verbal re-consent for sub study 1 before randomisation & Randomisation		X					
Vital signs [P, BP, T)		X					
Physical examination		X					
Optional handgrip strength assessment (to be done on day of discharge, 2 m and 12 m)		X				X	X
Biobank research bloods (EDTA, Serum, PAX Gene), Stool sample, Urine sample & Rectal biopsies (if available)		X[E]					
Randomisation [2:1] Upadacitinib or Infliximab		X					
Review of standard of care blood results (FBC, U&Es, CRP, LFTs)		X	X			X	X
Serum CRP			X[G]				
Review of standard of care stool cultures (MC&S, C.Diff)		X[E]	X[E]				
Review of standard of care Faecal Calprotectin [D]			X			X	X
Review of endoscopy [D] MAYO score		X		X		X	X
Review of standard of care AXR[D]		X					
MTWSI assessment / review of standard care clinical MTWSI (appendix D)		X	X	X			
Urine β-HCG [WOCBP only)					X	X	
UCEIS score (only if available from routine care sigmoidoscopy or colonoscopy reports)		X					X
Partial MAYO score assessment or Modified Partial MAYO score assessment (if endoscopy not available)		X				X	X
Oral steroid dose [standard of care protocol]			X	X	X	X	X
Review of Adverse Events		X	X	X	X	X	X
Rescue therapy (medical or surgical) assessment		X	X				
Colectomy assessment		X				X	X
Questionnaires: EQ5D-5L / VAS, CUCQ-32, HRUQ						X	X
Decisional Conflict scale X[F]		X[F]					
Decisional Regret scale						X	X
Administration schedule [A]							
Upadacitinib 45mg OD Open Label or Infliximab schedule Open Label [B]		X	X	X	X	X	
IV steroids [Day 3-10]		X	X				
Oral tapering steroids – see protocol for regime [Day 11 to Day 56] [C]			X	X	X	X	
Review Participant Medication Diary		X	X	X	X	X	

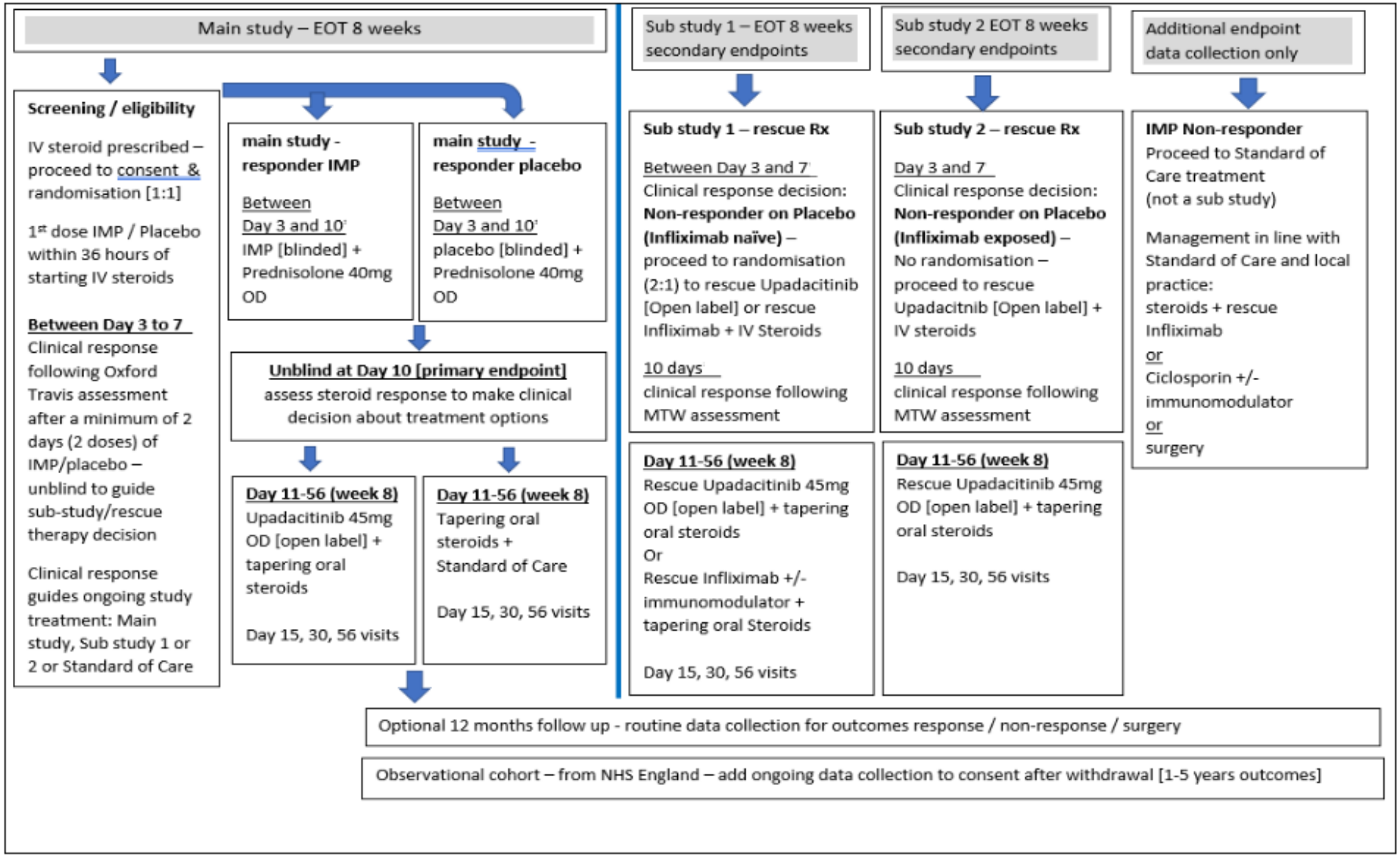
Table 2 Key to [A] to [F] definitions: X[A] = Sub study 1 medication sourced from routine stock and prescribed as per Trust protocols by direct care team - not considered an IMP; X[B] = Starts between Day 3 and 7 depending on day entered into sub study 1; X[C] = Timing of change to oral steroid is determined by direct care team; X[D] = if available; X[E] only if not taken on Day 3-7of main study, X[F] in non-responders undergoing rescue therapy or surgery Decisional Conflict scale should be completed on the day of rescue therapy or surgery; X[G] If the participants are discharged before day 10 provision should be made to collect the CRP, calprotectin and completion of day 10 assessments.

TABLE 3: INTERVENTION SCHEDULE - Sub-study 2 [Non-Responders to Placebo (Previous Infliximab Exposure)]

Assessment	Follow Main study intervention table 1 for visits before Day 3-7	Day 3-7 Response decision	Day 10 (+2 days) of IV steroids	Day 15 (+/- 1 day if still in hospital)	Day 30 (+4 days) [phone call]	Day 56 (+2 weeks) [Clinic visit]	12 months assessment (+4 weeks) [Clinic visit]
Eligibility assessment for sub-study 2		X					
Concomitant medications (changes since last assessment)		X	X	X	X	X	X
Verbal re-consent for Sub-Study 2		X					
Vital signs [P, BP, T)		X					
Physical examination		X					
Optional handgrip strength assessment (to be done on day of discharge, 2 m and 12 m)		X				X	X
Biobank research bloods (EDTA, Serum, PAX Gene), Stool sample, Urine sample & Rectal biopsies (if available)		X[E]					
Review of standard-care routine blood results (FBC, U and Es, CRP, LFTs)		X	X			X	X
Serum CRP			X[O]				
Review of standard-care stool cultures – (MC and S, C.Diff)		X[E]	X[E]				
Review of standard of care Faecal calprotectin			X			X	X
Review of endoscopy [D] MAYO score		X		X		X	X
Review of standard-care AXR [D]		X					
MTWSI assessment / review of standard care clinical MTWSI (appendix D)		X	X	X			
Urine β-HCG [WOCBP only)					X	X	
UCEIS score (only if available from routine care sigmoidoscopy or colonoscopy reports)		X					X
Partial MAYO score assessment or Modified Partial MAYO score assessment (if endoscopy not available)		X			X	X	X
Oral steroid dose [standard of care protocol]			X	X	X	X	X
Review of adverse events		X	X	X	X	X	X
Rescue therapy (medical or surgical) assessment		X	X				
Colectomy assessment		X				X	X
Questionnaires: EQ5D-5L / VAS, CUCQ-32, HRUQ						X	X
Decisional Conflict scale X[F]		X[F]					
Decisional Regret scale						X	X
Continuing Upadacitinib 45mg OL			X				
Administration schedule [A]							
IV steroids [Day 3-10] [B]		X	X				
Oral tapering steroids- see protocol for regime [Day 11 to Day 56] [C]			X	X	X	X	
Review Participant Medication Diary		X	X	X	X	X	

Table 3 Key to [A] to [F] definitions: X[A] = Sub study 2 medication sourced from routine stock and prescribed as per Trust protocols by direct care team - not considered an IMP; X[B] = Starts between Day 3 and 7 depending on day entered into sub study 1; X [C] = Timing of change to oral steroid is determined by direct care team; X[D] = if available; X[E] only if not taken on Day 3-7 of main study, X[F] in non-responders undergoing rescue therapy or surgery Decisional Conflict scale should be completed on the day of rescue therapy or surgery; X[G] If the participants are discharged before day 10 provision should be made to collect the CRP, calprotectin and completion of day 10 assessments.

FLOW CHART


Main study – EOT 8 weeks
Screening / eligibility
IV steroid prescribed – proceed to consent & randomisation [1:1]
1st dose IMP / Placebo within 36 hours of starting IV steroids
Between Day 3 to 7
Clinical response following Oxford Travis assessment after a minimum of 2 days (2 doses) of IMP/placebo – unblind to guide sub-study/rescue therapy decision
Clinical response guides ongoing study treatment: Main study, Sub study 1 or 2 or Standard of Care
main study - responder IMP
Between Day 3 and 10
IMP [blinded] + Prednisolone 40mg OD
main study - responder placebo
Between Day 3 and 10
placebo [blinded] + Prednisolone 40mg OD
Unblind at Day 10 [primary endpoint]
assess steroid response to make clinical decision about treatment options
Day 11-56 (week 8)
Upadacitinib 45mg OD [open label] + tapering oral steroids
Day 15, 30, 56 visits
Day 11-56 (week 8)
Tapering oral steroids + Standard of Care
Day 15, 30, 56 visits
Sub study 1 – EOT 8 weeks secondary endpoints
Sub study 2 EOT 8 weeks secondary endpoints
Additional endpoint data collection only
Sub study 1 – rescue Rx
Between Day 3 and 7
Clinical response decision:
Non-responder on Placebo (Infliximab naïve) – proceed to randomisation (2:1) to rescue Upadacitinib [Open label] or rescue Infliximab + IV Steroids
10 days
clinical response following MTW assessment
Sub study 2 – rescue Rx
Day 3 and 7
Clinical response decision:
Non-responder on Placebo (Infliximab exposed) – No randomisation – proceed to rescue Upadacitnib [Open label] + IV steroids
10 days
clinical response following MTW assessment
IMP Non-responder
Proceed to Standard of Care treatment (not a sub study)
Management in line with Standard of Care and local practice:
steroids + rescue Infliximab
or
Ciclosporin +/- immunomodulator
or
surgery
Day 11-56 (week 8)
Rescue Upadacitinib 45mg OD [open label] + tapering oral steroids
Or
Rescue Infliximab +/- immunomodulator + tapering oral Steroids
Day 15, 30, 56 visits
Day 11-56 (week 8)
Rescue Upadacitinib 45mg OD [open label] + tapering oral steroids
Day 15, 30, 56 visits
Optional 12 months follow up - routine data collection for outcomes response / non-response / surgery
Observational cohort – from NHS England – add ongoing data collection to consent after withdrawal [1-5 years outcomes]

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1.0 INTRODUCTION

1.1 Background

Ulcerative Colitis (UC) is a chronic debilitating disease with a prevalence that varies globally up to 0.5%. In about 10% of cases, UC presents as Acute Severe Ulcerative Colitis (ASUC) requiring inpatient admission. Patients meeting diagnostic criteria for ASUC are started on high dose intravenous (IV) corticosteroids.

However, about 35% are steroid resistant and these patients are often considered for colectomy or offered rescue therapy using Infliximab or Cyclosporine. The short and longer-term benefit of rescue therapy has been subject to two randomised controlled trials (RCTs) [1,2]. Ongoing uncertainty remains regarding dosing of Infliximab in ASUC [3] and there are subsequent problems associated with known loss of efficacy with Infliximab as maintenance therapy. Similarly, the toxicity profile of Cyclosporine and the practical aspects relating to administration has resulted in declining use of Cyclosporine as rescue therapy [4]. Furthermore, the increasing use of biologics in patients with UC means that patients admitted with ASUC increasingly may have a history of prior or current Infliximab exposure and/or failure, creating a need for approaches to management that do not depend upon use of Infliximab as a rescue therapy.

1.2 Clinical Data

There is emerging consensus that a key focus of work in ASUC should be earlier identification of "high risk patients" who may not respond to corticosteroids, as well as development of more efficacious "up-front" treatments in addition to corticosteroids.

The prospective UK study ELEVATE ASUC [5] aims to develop early predictors of the need for rescue therapy, and the UK IASO trial successfully tested the use of an anti-IL1 antagonist along with corticosteroids as initial therapy for ASUC [6]. An attractive potential approach is to use an additional mechanism of action upfront when patients present with ASUC. This is particularly important given that the initial care of patients with ASUC has changed little in over 60 years and still depends upon the use of high doses of corticosteroids.

Although steroids are appropriately embedded in the initial management of ASUC, the recognised failure rate of a "steroid only" strategy creates an opportunity for exploration of adjunctive therapies given alongside corticosteroids in the initial management of ASUC. Any adjunctive therapies to corticosteroids should have a rapid onset of action and relatively short half-life to reduce risks.

1.3 ASUC Study Challenges and Successes

Although RCTs of initial therapy in ASUC are perhaps the most challenging of trials to deliver in Inflammatory Bowel Disease (IBD), the IASO trial demonstrated that this sort of study can be delivered. Although the study was terminated early for futility, the study design provided practical lessons relating to conduct of interventional studies in ASUC, in particular around how to motivate

and maintain a network of investigators, how to optimise patient acceptability and how to manage practical challenges of running a study requiring rapid identification, recruitment, screening, and randomisation of inpatients admitted with a serious, acute pathology.
The IASO study recruited ahead of schedule despite the COVID-19 pandemic. Thus, although RCTs in patients with ASUC are rare and subject to unique challenges, both IASO and the earlier CONSTRUCT trial have demonstrated that this type of study can be implemented successfully and deliver on its aims and objectives to time and target.
Based on the study teams' experience of implementing the IASO and CONSTRUCT studies, we are confident that our teams can identify and approach potential participants who are admitted to hospital. We also know that there are high levels of proven patient acceptability. Over 80% of the participants approached for IASO were subsequently successfully consented, randomised, and dosed.

1.4. Study Rationale

Upadacitinib is a small molecule inhibitor that targets the Janus kinase (JAK) pathway, which is involved in many immune-mediated inflammatory diseases. Upadacitinib inhibits the JAK pathway with higher selectivity against JAK1 proteins than the other three subtypes [7]. The key registration data for Upadacitinib stem from two induction trials - U-ACHIEVE and U-ACCOMPLISH which [8] randomised patients to Upadacitinib 45 mg vs placebo and the U-ACHIEVE maintenance study. Recent clinical trial data and network meta-analyses have suggested that Upadacitinib is among the most effective agents for induction of clinical remission in outpatients with moderate to severe UC [9]. Upadacitinib has been approved by the Food and Drug Administration (FDA), European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA). The licensed indication by both the MHRA and EMA is for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent. The licensed indication by the FDA is adults with moderately to severely active who have had an inadequate response or intolerance to one or more Tumour necrosis factor (TNF) blockers. In the UK Upadacitinib is approved by National Institute of Clinical Excellence (NICE) [10] for use in moderate to severe UC in TNF inhibitor naïve and exposed patients with moderate to severe UC. Increasing real world experience of use in the UK, including easy access within both anti-TNF naïve and exposed populations further positions UK IBD services to evaluate the use of Upadacitinib in other areas of unmet need such as ASUC.

While Upadacitinib is provided as a sustained-release formulation, the majority of the drug is absorbed in the first 6 hours, and the serum levels after 6 hours are nearly the same as an immediate release formulation [11]. The proportion of patients who achieved clinical response at two weeks with Upadacitinib was significantly greater than with placebo in both U-ACHIEVE and in U-ACCOMPLISH (60% vs 27% and 63% vs 26%), which emphasises the rapid onset of action for Upadacitinib. Indeed, symptomatic improvement occurred as early as day 1 after Upadacitinib 45 mg induction [12] and this was maintained over 14 days. Biomarker response was also rapid. This rapidity of action combined with short half-life makes it an attractive proposition as a co-therapy

given not after steroid failure but alongside steroids in the setting of ASUC, including in those who have previously been exposed to biologics. However, this approach has not been tested in a RCT in a cohort of admitted patients with ASUC. In this study, we will conduct a randomised, double-blind, placebo-controlled trial using Upadacitinib co-therapy in patients admitted to hospital with ASUC receiving corticosteroids to impact on clinically important outcomes of colectomy or rescue therapy. Patients who require rescue therapy will have failed the primary endpoint. Further participation of these patients in smaller sub-studies, builds in an evaluation of Upadacitinib as a rescue treatment, in both Infliximab naïve and experienced ASUC patients who have not responded to Intravenous (IV) steroids, which are additional important clinical questions of interest. Therefore, we will also conduct two smaller exploratory sub-studies to analyse the utility of Upadacitinib as rescue treatment in both Infliximab naïve and experienced ASUC patients not responding to IV steroids. Participation in the sub-studies is optional and should be determined based on the clinical judgment of the treating physician and in alignment with local site prescribing practices and guidance.

2.0 AIMS AND OBJECTIVES

2.1 Study Hypothesis

Early addition of the rapidly acting agent Upadacitinib to conventional therapy using IV corticosteroids may reduce the need for medical rescue therapy and/or rescue surgical therapy in patients with ASUC.

2.2 Objectives and Outcome Measures

2.2.1 Primary Objective

To evaluate the clinical efficacy of Upadacitinib as a combined treatment with IV corticosteroids in patients with ASUC.

2.2.1.1 Primary Outcome Endpoint

Percentage of patients who need medical or surgical rescue therapy within 10 days following commencement of IV corticosteroid therapy. Need for rescue therapy reflects failure to respond to initial treatment is judged against clinical criteria between 3-7 days after commencement of IV corticosteroid therapy (see Clinical Response decision assessment Appendix A). In line with international guidelines, the initiation of rescue therapy should not be delayed in those with clinical need. A reduction in the need for rescue therapy will reflect evidence of beneficial effects of the intervention. Although rescue therapy may be initiated as early as 3 days following commencement of IV corticosteroids, some clinicians may choose to delay this decision to allow more time for a clinical response. The outcome measure will therefore be the proportion of participants in each group who have started rescue therapy within 10 days following the commencement of IV corticosteroids.

For the purposes of the primary endpoint analysis, the timepoint of the start of rescue therapy will be as follows:

- **Medical rescue therapy:** Date and time of first rescue treatment administration
- **Surgical rescue therapy:** Date and approximate time of start of surgery

2.2.2 Secondary objectives

- To evaluate the impact of combination therapy (Upadacitinib + steroids) on the need for rescue medical or surgical therapy
- Evaluate the safety of use of combination therapy (Upadacitinib + steroids) in patients with ASUC
- Evaluate the efficacy and safety of combination therapy (Upadacitinib + steroids) in a subgroup of patients with prior exposure to advanced therapies
- Determine the impact of combination therapy (Upadacitinib + steroids) on a range of other indices of treatment response including duration of hospital stay, time to treatment response, quality of life using CUCQ-32, EQ5D-5L and 2 Validated psychometric tools (Decision Conflict Scale & Decision Regret Scale)
- Collect biobanking samples to develop and refine high risk immunophenotype in ASUC who will benefit from combination (Upadacitinib + steroids) therapy

2.2.2.1 Secondary Outcome Endpoints*

- Percentage of patients who achieve clinical response by Day 10 from starting of the IV steroids (Modified Truelove Witts Severity Index Form (MTWSI) reduction ≥3 points and MTWSI < 10)
- Time to clinical response (MTWSI reduction 3 or more points and MTWSI <10)
- Time to rescue therapy (medical or surgical)
- Percentage of patients who meet Oxford Travis rescue criteria for rescue therapy on or beyond Day 3 of hospitalisation
- Percentage of patients who achieve clinical remission by Day 10 and Week 8 (Mayo stool frequency subscore of 0 or 1, and rectal bleeding subscore of 0)
- Percentage of patients who achieve biomarker remission by Day 10 and Week 8 (C-Reactive Protein (CRP) normal and /or, calprotectin ≤ 250µg/g where available).
- Percentage of patients who adhere to the protocolised steroid taper (without needing to escalate steroid dose within taper) and clinical remission at Week 8 (Mayo stool frequency subscore of 0 or 1, and rectal bleeding subscore of 0).
- Percentage of patients who achieve endoscopic improvement at Week 8 where data available (endoscopic Mayo subscore 0-1)
- Incidence of colectomy within 8 weeks following commencement of IV corticosteroid therapy
- Incidence of Adverse Events (AE) and Serious Adverse Events (SAE)
- Total duration of hospital stay

** Secondary Outcome Endpoints measured from 1st dose of IV corticosteroids*

2.2.3 Additional Endpoints*

- Percentage of patients who achieve clinical response by 7 days (MTWSI reduction 3 or more points and MTWSI < 10)
- Time to clinical response (MTWSI reduction 3 or more points and MTWSI < 10).
- Time to medical or surgical rescue therapy
- Percentage of patients who achieve clinical remission by 7 days (Mayo stool frequency of 0 or 1, and rectal bleeding of 0)
- Percentage of patients who achieve clinical remission within 8 weeks (Mayo stool frequency of 0 or 1, and rectal bleeding of 0)
- Percentage of patients who achieve biomarker remission by 7 days (CRP normal, calprotectin ≤ 250µg/g where available)
- Percentage of patients who achieve biomarker remission within 8 weeks (CRP normal, calprotectin ≤ 250µg/g
- Percentage of patients who adhere to the protocolised steroid taper (without needing to escalate steroid dose within taper) and clinical remission at 8 weeks (stool frequency sub score of 0 or 1, and rectal bleeding sub score of 0)

** Additional Endpoints measured from first dose of IV steroids for all patients*

2.2.4 Exploratory Outcome endpoints

- Incidence of colectomy at 1 year after the first dose of IV steroids
- Patient-reported quality of life (CUCQ-32) at baseline and Week 8 after 1st dose of IV steroids treatment
- Patient perspectives with administration of Decisional Conflict Scale administered at baseline and on one further occasion between day 3 up to day 10 if participants are in the hospital and a Decisional Regret Tool administered at 8 weeks and at 12 months after the first dose of IV steroids.
- Utilisation of hospital resources
- Patient borne costs; including number of days off work per year and travel costs for health care for 8 weeks after the first dose of IV steroids
- Re-admissions; including for non-UC specific causes
- Drug persistence rates at 12 months after the first dose of IV steroids
- Health Economic analysis

In addition to the above exploratory outcome endpoints, the study will also perform further exploratory analyses related to the identification of biomarkers and treatment response predictors from the biobank samples.

- Need for further surgical rescue therapy in patients who received medical rescue therapy (assessed by Day 10 from starting of IV steroids)
- Need for colectomy within 8 weeks after starting of IV steroids

2.3. Exploratory sub-studies [Non-responders]

Sub-study 1: The subset of non-responding patients who were randomised to placebo and who have not been exposed to prior Infliximab will be randomised in a 2:1 ratio to open label Upadacitinib 45mg daily or Infliximab.
Sub-study 2: The subset of non-responding patients who were randomised to placebo and who have previously failed primary non-response Infliximab will be allocated to Upadacitinib 45mg daily in an open-label observational cohort.

2.3.1 Exploratory Sub-study Outcome Measures

- Percentage of patients needing further surgical rescue therapy by Day 10 from starting of IV steroids
- Percentage of patients needing colectomy within 8 weeks from starting of IV steroids
- Percentage of patients who achieve clinical response by Day10 from starting of IV steroids (MTWSI reduction 3 or more points and MTWSI < 10)
- Time to clinical response (MTWSI reduction 3 or more points and MTWSI < 10)
- Time to surgical rescue therapy
- Percentage of patients who achieve clinical remission by day 10 from starting of IV steroids (Mayo stool frequency subscore of 0 or 1, and rectal bleeding subscore of 0)
- Percentage of patients who achieve clinical remission at 8 weeks from starting of IV steroids (Mayo stool frequency subscore of 0 or 1, and rectal bleeding subscore of 0)
- Percentage of patients who achieve biomarker remission by day 10 from starting of IV steroids (CRP normal, calprotectin ≤ 250µg/g where available)
- Percentage of patients who adhere to the protocolised steroid taper (without needing to escalate steroid dose within taper) and clinical remission at 8 weeks (Mayo stool frequency sub score of 0 or 1, and rectal bleeding sub score of 0)
- Percentage of patients who achieve endoscopic remission at 8 weeks from starting of IV steroids where data available (endoscopic Mayo subscore 0-1)
- Incidence of AEs and SAEs
- Total duration of hospital stay

3.0 STUDY DESIGN

This is a Phase 3b, pragmatic, multicentre, two-arm, double-blind, randomised placebo-controlled study of ASUC patients admitted to UK NHS secondary care hospitals, with a pre-specified feasibility assessment and interim analysis for evidence of harm or futility.

3.1 Study population

Adults admitted to hospital with ASUC.

3.2 Sample size

The study will recruit 300 participants to the main study with potential for enrolment into sub-study 1 or 2 depending on participant clinical response to IMP or placebo plus IV corticosteroids. Please refer to section 14.1 for details on sample size calculation.

3.3 Sites

Multicentre study in approximately 30 NHS secondary care sites (hospitals) across the UK.

3.4 Study Duration

Participant involvement in the study will depend on their response to IMP or placebo treatment. Screening, baseline assessment and randomisation will take place within 36 hours from the first dose of IV corticosteroids. The initial blinded IMP or placebo treatment period will be up to Day 10 at which point all participants will be unblinded. Clinical response or maintenance treatment will continue until the end of the 8-week maintenance treatment period. There is a 12-month routine clinical care visit for observational data collection. In addition, SAEs will be reported up to 30 days after the last dose of IMP of placebo. Data collection and analysis of participant outcomes following study participation may continue for up to 5 years using data linkage via NHS England, or devolved nation equivalent, without any additional burden to the participant.

3.5 Study Treatments

IMP: Oral Upadacitinib 45mg tablets
Placebo: Oral matching placebo tablets

300 participants will be randomised (1:1) at baseline to one of two arms: IMP or placebo. All participants will receive an initial dose of IMP or placebo within 36 hours of first dose of IV corticosteroids. This will be followed by IMP or placebo once daily (OD) based on response or the need for rescue therapy (see study flowchart page 20).
If not already unblinded for rescue treatment between Day 3 to 7, all participants will be unblinded at Day 10+2 of IV steroids. Emergency unblinding before Day 10 should only be performed for making appropriate medical or surgical rescue therapy decisions, or if a SAE affecting patient safety necessitates unblinding in the opinion of the PI/delegate in discussion with the Chief Investigator (CI). For patients not responding to IMP/Placebo and needing rescue therapies, the database will confirm eligibility on for either sub-study if relevant, upon entry by the investigator to confirm that the decision to initiate medical rescue therapy has been taken.
Further information on unblinding is provided in section 4.3.

Ongoing treatment will be allocated to one of the following options depending on response to IMP or placebo:

3.6. Responders to IMP or Placebo at Day 10+2 of first dose of IV steroids

- Responders randomised to IMP will continue open label Upadacitinib IMP until Week 8. Participants may continue 5-ASA therapy and will complete a steroid taper but should not be

offered any other immunosuppressive or biological therapy. After Week 8, further treatment will be at routine clinical care team discretion and according to local protocols, but the expectation remains that participants responding to IMP will receive open label Upadacitinib as maintenance therapy.

- Responders randomised to placebo will discontinue placebo at Day 10+2 of first dose of IV steroids and will be initiated on further treatment according to the judgement of the routine clinical care team.
- For all responders to IV corticosteroids receiving either IMP or placebo, a switch to oral steroids (Prednisolone 40mg) should be instituted within 5 – 10 days of the first dose of IV corticosteroids. A protocolized steroid wean is mandatory, (40mg daily for 1 week, then 30 mg daily for 1 week followed by reduction of 5 mg per week till zero), with the expectation that steroids stopped before the Week 8 visit.

3.7 Non-responders to IMP or Placebo

- Non-responders to placebo between Day 3 and Day 7 (if Infliximab naïve) will be randomised in a 2:1 ratio, to open label Upadacitinib 45mg OD or Infliximab (dose as per investigator discretion) **(sub-study 1)**
- Non-responders to placebo between Day 3 and Day 7 (if previously Infliximab exposed) will be offered enrolment into the open label Upadacitinib 45mg OD (**sub-study 2**)
- Non-responders randomised to IMP will be managed in accordance with standard of care (SOC) and local practice (steroids with rescue Infliximab or Ciclosporin or surgery – see decision tree – Appendix C for rescue therapy protocol).
- Non-responders randomised to Upadacitinib, or placebo will switch to alternative treatments as per routine clinical care team. The eligibility for entry into sub studies for non-responders will be confirmed through the database on between Day 3 and 7 before alternative treatment options are considered.
- The timing of rescue therapy and the decision to include patients into sub-studies will be at the discretion of local investigators.

3.8 Rescue Therapy

In accordance with routine clinical practice, within 3-7 days of starting IV corticosteroids, a clinical assessment for steroid response based on routine local practice implementing the Oxford Travis rescue criteria and MTWSI, Abdominal X-ray (AXR) assessment where required (to exclude toxic megacolon) will be carried out. At the point a clinical decision is made that the participant is not responding to IMP/placebo typically between Day 3 and Day 5 using Oxford Travis Index, medical or surgical rescue therapy will be considered. The decision for rescue therapy will remain with the treating clinicians.

The Oxford Travis rescue criteria will be assessed and recorded on study Case Report Forms (CRFS) daily from 3 completed days of treatment with IV steroids. Where a decision is made to offer rescue therapy despite these criteria not being met, or where these criteria are met but rescue

therapy is not offered, the clinical reasons should be recorded on the CRF. If medical or surgical rescue therapy is considered, participants should ideally stop Upadacitinib/placebo treatment for 12 hours prior to medical or surgical rescue therapy. If patients meet the criteria for rescue therapy, patients will proceed to one of the following options:

- Rescue medical therapy (corticosteroids with Infliximab or Cyclosporine at the doses routinely used locally)
- Surgical intervention
- The option to be enrolled in the sub-studies

There is a clear expectation that objective indices including the Oxford Travis rescue criteria will be considered for the above options.

3.9 Standard Treatment

Regardless of randomisation group at baseline or following clinical response decision made before Day 10, all participants will be treated in accordance with standard clinical care of admitted patients with ASUC. IV methylprednisolone or hydrocortisone will be administered to participants as per local guidelines and practice for ASUC standard care. Escalation to any other treatment required based on clinical judgement will not be withheld.

3.10 Concomitant Medications

Participants will continue to be treated with routine concomitant medications for other comorbidities as appropriate within their current clinical condition, with modifications (e.g., oral to intravenous switches), or temporary cessation as necessary. Appropriate supportive care may also be prescribed, including fluids, electrolyte correction, nutritional supplements, Venous Thromboembolism (VTE) prophylaxis and other medications as necessary. VTE prophylaxis should also continue in alignment with local practice. Steroid related Vitamin D/Calcium prophylaxis and Proton Pump Inhibitors (PPIs) should be prescribed in alignment with local practice. Introduction of strong CYP3A4 inhibitor (including azoles, clarithromycin) or CYP3A4 inducer (including Rifampicin and Phenytoin) will be prohibited during blinded trial period and those on Upadacitinib treatment during open label phase.

3.11 Routine Investigation

AXR assessment for colonic dilatation and endoscopic examination (with biopsies to exclude Cytomegalovirus (CMV) colitis) in accordance with routine practice should also be performed. Stool cultures and stool Clostridium Difficile (C. Diff) assay will be done as per standard guidelines. Dietetic referral if needed and surgical review should also be requested as considered appropriate.

3.12 End of treatment period

After 8 weeks participants will stop taking study medication and will continue standard care management of UC. For those participants who have received and responded to Upadacitinib

treatment, routine clinical care teams will be asked (but not mandated) to consider use of Upadacitinib as a maintenance therapy as per standard care dosing in accordance with licence and NHS NICE approval. However, the treating team is free to use other agents in line with local prescribing practice.

3.13 Follow Up at 12 Months

Observational data will be collected at the follow Up visit at 12 months for all participants (unless withdrawn) including but not limited to treatment persistence, readmissions and need for delayed colectomy.

4.0 SUMMARY OF STUDY VISITS

As participants will follow standard of care protocols for ASUC most data required for the study analysis will be collected from routine care sources such as medical notes and laboratory records. Depending on participant response to Investigational Medicinal Product (IMP) and/or rescue therapy there may some variation in the number and type of visits. A summary of the study visits is outlined below:

4.1 Screening and Baseline visit: All participants (inpatient hospital visit)

Note: the baseline visit can be done at the same time as the screening visit.

At screening, eligibility will be confirmed prior to informed consent. The IMP or placebo must be administered within 36 hours of the first dose of IV corticosteroids and will be confirmed during eligibility checks. Once informed consent has been obtained, randomisation should be done immediately. The remaining screening activity will be completed including demographics, smoking history, social and ethnicity, vital signs including blood pressure (BP), body temperature (T), pulse, weight, and height for Body Mass Index (BMI) (auto calculated in the study database), handgrip strength assessment (optional). If optional handgrip strength done at baseline, then should be repeated at discharge, 2 months and at 12 months visits. A physical examination by a study clinician listed on the delegation log or recorded from clinical care records as well as a detailed medical history (from birth) and medication history including previous biologic and immunomodulatory therapy will be collected. The data on MTWI (Appendix D) and CRP at or immediately prior to the first dose of corticosteroids will be collected including for determining the inclusion criteria MTWI score and daily thereafter. Given the tight timeline from first dose of IV steroids and administration of IMP/placebo the baseline and randomisation visits may be the same.

Data collection will also include a review of routine clinical care for ASUC including:

- Routine blood results: Full Blood Count (FBC), Urea and Electrolytes (U&Es), C-Reactive Protein (CRP), Liver Function Tests (LFTs)
- Routine screening blood results done as per standard care: Tuberculosis Interferon Gamma Release Assay (TB IGRA), Hepatitis B (HBV) Hepatitis C (HCV), Varicella Zoster Virus (VZV),

Lipids. If results are unavailable at baseline, randomisation will not be delayed, but results should be collected as soon after admission as possible. If results are available within the previous 24 months of the current hospital admission, repeat results are not necessary unless needed in the opinion of the PI.

- Stool cultures: Microscopy, Culture and Sensitivity (MC&S) and Clostridium Difficile (C.Diff). If results are unavailable at baseline, randomisation will not be delayed, but results should be collected as soon after admission as possible
- Modified Truelove and Witts Score (MTWS) (see Appendix D).
- Review of AEs
- A review of any change to concomitant medications since the screening visit (including previous biologic, and immunosuppressive therapy)
- Faecal Calprotectin should be collected during the admission if unable at later day should be collected
- Decisional Conflict, CUCQ-32 IBD Questionnaire, Health Resource Utilisation Questionnaire (HRUQ) and EQ5D-5L/VAS
- For Women of childbearing potential (WoCBP), confirmation of a negative urine pregnancy test as part of standard care ASUC treatment (serum test if unable to obtain urine samples)
- Collection of study specific biobank samples including urine, stool, rectal biopsy (only if available from standard of care endoscopy), and blood samples (EDTA, serum, PAX Gene). Biobank samples to be obtained prior to administration of first dose of IMP/Placebo where possible. If any biobank samples were not collected prior to the administration of the first dose of IMP/placebo, they can be collected later but as close as possible to the baseline visit (The samples should be collected before participants take more than one dose of IMP/placebo).
- Partial Mayo Score
- Endoscopy Mayo score and UCEIS score reports and Full Mayo score (only if available with routine care sigmoidoscopy or colonoscopy). De-identified endoscopy images and/or videos where available will be uploaded for central reading to ensure internal validation of endoscopic scoring by the sites.
- AXR reports (if not collected at screening and only if available from routine care)

Note: all routine blood results FBC, LFTs and U&Es must be reviewed by a study clinician listed on the delegation log as part of eligibility checks prior to consent.
If positive stool cultures for a pathogen of major Gastrointestinal (GI) significance become available after consent or randomisation the participant will be withdrawn from the study. Withdrawal for other abnormal screening results is not mandated and is on the discretion of the local PI.

Eligibility will be confirmed before randomisation. If eligible, participants will be randomised at a ratio of 1:1 to IMP or placebo. The first dose of blinded IMP or placebo will start on the day of the baseline visit which could also be the day of screening. The first dose of the IMP or placebo should

be administered within 36 hours of the receipt of the first dose of IV corticosteroids (i.e. any time between the time of first dose of IV corticosteroid and 36 hours). IV corticosteroids will continue as per standard of care.

4.2 Day 3 to Day 10 - Clinical Response Decision Visit [inpatient visit]

Between Day 3 and Day 7 participants will continue IMP or placebo and IV steroids. During this period of hospital admission, routine assessments of clinical response to study medication will be performed as per standard of care. Daily record of MTWI score (Appendix D) and CRP will be done. The site study team will review routine clinical assessments and will discuss with the clinical care team whether the participant requires rescue therapy during this period. Participants can be withdrawn from study medication at any time if deemed to be in the participants' best interest. For emergency unblinding, see section 7.2.2.

On Day 3 (or soon after when possible) after the first dose of IV corticosteroids, biobank samples will be collected including stool, urine, bloods (EDTA, serum). In addition, we will collect biopsies during sigmoidoscopy for research if sigmoidoscopy is done as part of routine care **on any day** after consent. See the study laboratory manual for further detail.
A review of routine clinical assessments will support the treatment decisions. See Appendix A.

Depending on the clinical response, ongoing study treatment options will be reviewed.

- IMP/placebo responders will continue in the main study – go to section 4.4
- If participants are not responding to IMP/placebo and medical rescue therapy is required, then the participants taking placebo can proceed to one of the two sub-studies:
  - sub-study 1 - Placebo non-responder (infliximab naive) – go to section 4.8.2
  - sub-study 2 - Placebo non-responder (infliximab exposed) – go to section 4.8.3
- If surgery is required, standard of care procedures are followed
- If not eligible for sub studies 1 or 2, the participant will be treated as per standard care (see section 4.9

Responders between Day 3 and Day 10 will continue IMP or placebo and steroids. There will be review of the Participant Medication Diary to evaluate IMP compliance. Participants who have responded to the IMP or placebo may have been discharged from hospital at the discretion of the routine clinical care team by or before Day 10. If the participant is to be discharged, they will be discharged with their original study medication (IMP or placebo) along with a mandated tapering dose of oral steroids. The mandated regime for tapering steroids is Prednisolone 40mg daily for 1 week, then 30mg daily for 1 week and then taper by 5mg per week till zero. They will continue to complete their participant medication diary to record compliance. If the participants are discharged before Day 10 provision should be made to collect the CRP, calprotectin and completion of Day 10 assessments with window of Day 10+2 of start of IV steroids.
Post randomisation patients will be managed by routine care team including over weekends. Weekend data will be collected on structured data collection forms by clinical care team for

collection and eCRF entry at earliest possible opportunity, e.g. Monday by research team or research teams will transcribe from ward entry to e-CRF by the research teams after weekend.

4.3 Day 10+2 of first dose of IV steroids – Unblinding

All participants (including those who have enrolled into the sub studies) will be unblinded at Day 10+2 of first dose of IV steroids. Unblinding will be done by the local investigator team.
Responders who were on placebo will stop taking the study placebo medication. Treatment will thereafter be in alignment with local standard of care. The participant will begin (if not already started due to discharge before Day 10) to taper oral steroids (regime for tapering steroids is Prednisolone 40mg daily for 1 week, then 30mg daily for 1 week and then taper by 5mg per week till zero). In addition, they may be started on additional maintenance therapy according to the judgement of the local treatment team. Responders to Upadacitinib will continue taking open label Upadacitinib 45mg OD and continue to taper oral steroids (regime for tapering steroids is Prednisolone 40mg daily for 1 week, then 30mg daily for 1 week and then taper by 5mg per week till zero) following local standard care schedules. They will continue to complete their Participant Medication Diary until Week 8.
Participants will have a Day 10 assessments including routine blood, MTWSI, Faecal Calprotectin and to record any AEs or changes to their medications. If the participant was discharged before Day 10, CRP & Faecal Calprotectin test should be performed at day 10+2. The study team may provide the participants an NHS labelled container to collect their stool sample and CRP and take it to their GP/local hospital. The MTWSI and any AEs or changes to the participants medications will be collected during a telephone visit.
If the participant was discharged before Day 10, the study team will inform the participant of their study medication allocation and ongoing treatment as above with a telephone visit on the day of unblinding. If the participants are discharged before day 10 provision should be made to collect the CRP, calprotectin and completion of day 10 assessments.

4.4 MAIN STUDY – Day 15+/- 1 day [only to be conducted if participant is still in hospital]

If the participant is still in hospital, the routine clinical care team will perform an assessment of clinical response to study medication as per standard of care. The site study team will review routine clinical assessments and will discuss with the clinical care team whether the participant requires rescue therapy during this period. Participants can be withdrawn from study medication at any time if deemed to be in the participants' best interest.

4.5 MAIN STUDY – RESPONDERS [Week 4 / Day 30+4 Days] Telephone visit

Responders will continue open label Upadacitinib 45mg OD or standard of care medications and continue to taper oral steroids (Prednisolone as per the mandated tapering regime mentioned on section 3.6) with a review of the Participant Medication Diary to review compliance. This may be

done on the telephone. A urine pregnancy test will also be done by WoCBP. A self-check pregnancy test kit will be provided to WoCBP before their discharge from the hospital.

4.6 MAIN STUDY – RESPONDERS [Week 8 / Day 56+2 Weeks] End of Treatment [clinic visit]

Responders will continue open label Upadacitinib 45mg OD up to this visit with a review of the Participant Medication Diary to review compliance. Tapering of oral steroids (Prednisolone as per the mandated tapering regime detailed in section 3.6) should have now been completed. A clinical response assessment will take place to review participant response to open label Upadacitinib (see Appendix A). The participants may continue taking dispensed upadacitinib until this clinical review.
Discussions regarding ongoing routine prescribing of Upadacitinib or other therapy after this visit will be undertaken by the routine clinical care team. A urine pregnancy test will be done by WoCBP.

4.7 MAIN STUDY – RESPONDERS [12 months+4 Weeks] Follow up clinic visit

At 12 months the participant will have a routine outpatient appointment with an optional study visit. Although this visit is optional, participants should be encouraged to attend if possible. At this visit, participants will complete four questionnaires and the study team will collect data from medical records as part of exploratory endpoints. These will include assessments of changes in medical therapy, steroid prescriptions, further hospitalisations, and incidence of colectomy. If this information is not available, a member of the study team may contact the participant for further information on the telephone. Participants may also have given permission to link their data using NHS number via NHS England (or devolved nation equivalents). This will enable long-term follow up of UC related outcomes (for example, colectomy rates, drug safety data, drug persistence rates and health economic analyses) for up to 5 years after the study medication end date.

4.8 SUB-STUDY 1 and 2

4.8.1 Sub-study enrolment

If the participant has not responded to the study medication between Day 3 and Day 7, rescue therapy options will be discussed. This clinical decision can be made at any time between Day 3 and Day 7. Non-responders taking placebo where medical rescue therapy is required in the opinion of the routine clinical care team, have the option to proceed to one of two sub-studies. Sub study eligibility checks will be conducted by a study clinician listed on the delegation log to confirm their suitability.

- Sub-study 1 Infliximab naïve interventions – see section 4.8.2.
- Sub-study 2 Infliximab exposure interventions – see section 4.8.3

4.8.2. SUB-STUDY 1 - Non-responder to Placebo (Infliximab naïve)

Participants in sub-study 1 will follow main study interventions up to the time when the clinical decision confirms that the participant has not responded to study medication.

4.8.2.1 SUB-STUDY 1 [Between Day 3 to Day 7] Randomisation [inpatient visit]

Once sub-study 1 eligibility has been confirmed the Interactive Web Response System (IWRS) will be available to randomise participants to open label Upadacitinib or Infliximab rescue treatment [ratio 2:1]:

- Open label Upadacitinib 45mg OD until end of study at Week 8 from 1st dose of IV steroid if responding.
- Infliximab infusion [weight dependent dose] at week 0, 2 and 6 (with the week 0 dose being given between Day 3 and 7 from admission). The dose given is at the discretion of the routine clinical care team as the week 2 dose may be given earlier or dose may be given at a higher dose than 5mg/kg Infliximab as per local protocol.
- Twice as many participants will be randomised to Upadacitinib than Infliximab.

These medications are not considered to be study IMP and will be prescribed by the routine clinical care team and dispensed from routine NHS stock. Sub-study 1 medication will commence at any time point between Day 3 and Day 7 and on the same day that the participant enrolled into sub-study 1.

There will be a review of SOC results (if available) including MC&S, C. Diff, Faecal Calprotectin, SOC endoscopy report with a Full or Partial MAYO score assessment, AXR and a review of SOC MTWSI assessments and Colectomy Assessment.

There should be a review of the current dose of IV corticosteroids in preparation to switch to a tapering oral steroid schedule according to regime mentioned in Section 3.6. Participants not responding to rescue therapy will follow standard care including consideration of colectomy.

Patients will be managed by routine care team including over weekends. Weekend data will be collected on structured data collection forms by clinical care team for collection and eCRF entry on Monday by research team or research teams will transcribe from ward entry to e-CRF by the research teams after weekend.

4.8.2.2 SUB-STUDY 1 [Day 10 from 1st dose of IV steroids]

The routine clinical care team will undertake standard care monitoring and clinical response assessments to determine to whether the participant will continue in Sub-study 1 or requires additional medical or surgical intervention. If the participant responds to the rescue treatment medication used in sub-study 1 and is discharged from hospital before Day 10 from 1st dose of IV steroids, they will conduct a telephone visit on Day 10 where a clinical assessment will support rescue therapy assessments to determine whether further medical or surgical interventions are required. If the participant is to be discharged before Day 10, open label Upadacitinib prescriptions will be dispensed from NHS stock prior to discharge and Infliximab infusion appointments will be arranged as per local routine schedule.

If responding, participants will continue open label Upadacitinib 45mg OD or Infliximab infusion regimen and begin tapering oral steroids (prednisolone according to regime detailed in Section 3.6).
Note: Open label Upadacitinib 45mg OD will be dispensed from routine NHS stock to commence between Day 3 and Day 7 depending on the day they enrolled into sub-study 1. The Infliximab infusions will be arranged by the routine clinical care team.

Note: Follow the Main study intervention guidance for the Day 15 visit.

4.8.2.3 SUB-STUDY 1 [Week 4 / Day 30] Telephone visit

The participant will continue open label Upadacitinib 45mg once daily or their Infliximab regime and tapering oral steroids according to the regime detailed in Section 3.6. The routine clinical care team will undertake standard care monitoring and determine whether the participant will continue in sub-study 1 or if the participant requires additional medical or surgical intervention. There will be a review of the Participant Medication Diary to evaluate compliance. This can be done on the telephone review.

4.8.2.4 SUB-STUDY 1 [Week 8 / Day 56] Clinic visit

Participants will continue open label Upadacitinib 45mg OD or Infliximab up to this visit with a review of the Participant Medication Diary to evaluate compliance. Tapering of oral steroids (Prednisolone) should have now been completed (or near completion). Sub-study 1 participants will have a week 8 review as per the main study schedule to assess response using MTWSI, partial Mayo score, CRP, Faecal Calprotectin and to record any AEs. Discussions regarding ongoing routine prescribing of Upadacitinib or Infliximab will be undertaken by the routine clinical care team.

Note: Follow the Main study intervention guidance for the 12 month follow up visit.

4.8.3 SUB-STUDY 2 - Non-responder to Placebo (Infliximab exposed)

Participants in sub-study 2 will follow main study interventions up to the time when the clinical decision confirms that the participant has not responded to study medication. This decision may be made at any point between Day 3 and Day 7.

4.8.3.1 SUB-STUDY 2: [Between Day 3 to Day 7] inpatient visit

This is for non-responders to placebo who are previously Infliximab exposed. Once sub-study 2 eligibility has been confirmed and informed consent has been obtained, the participant will be prescribed open label Upadacitinib 45mg OD by the routine clinical care team.
This medication is not considered to be a study IMP and will be prescribed by the routine clinical care team and dispensed from routine NHS stock. Sub-study 2 medication will commence at any time point between Day 3 and Day 7 and on the same day that the participant enrolled into sub-study 2.

There will be a review of standard of care results (if available) including MC&S, C. Diff, Faecal Calprotectin and a review of standard of care MTWSI. The routine clinical care team will do the standard care monitoring and a clinical response assessment will take place to determine to whether the participant will continue in Sub-study 2 or requires additional medical or surgical intervention. If responding, there will be a review of IV corticosteroids in preparation to switch to a tapering oral steroid schedule according to the regime detailed in Section 3.6 Participants not responding to rescue therapy with Upadacitinib in sub-study 2 will follow standard care including consideration of colectomy.
Patients will be managed by routine care team including over weekends. Weekend data will be collected on structured data collection forms by clinical care team for collection and eCRF entry on Monday by research team or research teams will transcribe from ward entry to e-CRF by the research teams after weekend.

4.8.3.2 SUB-STUDY 2 [Day 10 from 1st dose of IV steroid]

If the participant is discharged from hospital before Day 10, this visit can take place on telephone where a clinical assessment will be made to determine whether further medical or surgical interventions are required (see Appendix A).
If responding, participants will continue open label Upadacitinib 45mg OD and begin tapering oral steroids (prednisolone according to the regime detailed in Section 3.6).
Open label Upadacitinib 45mg will be dispensed from routine NHS stock to commence between Day 3 and Day 7 depending on the day they enrolled into sub-study 2.
If the participant is to be discharged before Day 10, open label Upadacitinib prescriptions will be dispensed from NHS stock prior to discharge.

Note: Follow the Main study intervention guidance for the Day 15 visit.

4.8.3.3 SUB-STUDY 2 [Week 4 / Day 30] Telephone visit

Participants will continue open label Upadacitinib 45mg OD and continue to taper oral steroids (prednisolone according to the regime detailed in Section 3.6) with a review of the Participant Medication Diary to evaluate compliance. A clinical response assessment will take place to determine how well the participant has responded to open label Upadacitinib and whether the participant will continue in the study. This can be done during the telephone review.

4.8.3.4 SUB-STUDY 2 [Week 8 / Day 56] Clinic visit

Participants will continue open label Upadacitinib 45mg OD up to this visit with a review of the Participant Medication Diary to evaluate compliance. Tapering of oral steroids (Prednisolone) should have now been completed (or near completion). A clinical response assessment will take place to determine to how well the participant responded to open label Upadacitinib.

Discussions regarding the ongoing routine prescribing of Upadacitinib or Infliximab will be undertaken by the routine clinical care team. Following this the continuation of Upadacitinib or initiating alternative therapies are at the discretion of routine clinical care team.

Follow the Main study intervention guidance for the 12 month follow up visit

4.9 Additional Endpoint Data Collection – IMP Non-responder

Non-responders to IMP Upadacitinib and IV corticosteroids before Day 7 of the main study, will have been switched to ASUC standard of care that may include one of the following treatments:

- IV steroids and rescue Infliximab
- IV steroids and rescue Ciclosporin
- Surgery

In this situation, following withdrawal from study treatment, no additional study visits are required. These participants will not follow the main study or sub-study intervention schedule tables. We will enter routinely collected data on the outcomes of these participants at Week 8 and 12 months.

At the time of informed consent, participants will have given permission for the study team to access their medical records to determine longer term outcomes as part of exploratory endpoints. These will include assessments of changes in medical therapy, steroid prescriptions, further hospitalisations, and incidence of colectomy. If this information is not available from routine care records, a member of the study team may contact the participant for further information. Participants may also have given permission to link their data using NHS number via NHS England, or devolved nation equivalent. This will enable long-term follow-up of UC-related outcomes (for example, colectomy rates, drug safety data, drug persistence rates and health economic analyses up to 5 years after the study medication end date.

5.0 RECRUITMENT PROCESS AND STUDY POPULATION

Participants will be recruited from up to 30 NHS Trust sites across England, Scotland, Wales, and Northern Ireland over a 30-month period.
Participants admitted to hospital for ASUC treatment will require rapid identification, approach, consent, screening, randomisation, and dosing in order to participate in the study.
The study is designed pragmatically to enable the recruitment of participants who have clear evidence of both active symptoms and active inflammation, without mandating an endoscopy or stool cultures, which would be a barrier to timely screening and randomisation of participants.
The inclusion and exclusion criteria listed below support safe identification of potential participants with confirmed or suspected ASUC.

5.1 Eligibility

Eligibility for study participation will be confirmed by the site PI or appropriately qualified clinician listed on the delegation log. Eligible participants who meet all inclusion and none of the exclusion criteria detailed below will be recruited. No eligibility protocol waivers permitted.

5.1.1 Inclusion Criteria

1. Patients aged 18–65 inclusive.
2. Have given written informed consent to participate.
3. Hospitalised patients with clinically confirmed or suspected ASUC with stool frequency ≥ 6 per day and at least one of:
   a. confirmation of Mayo 3 endoscopic sub-score beyond rectum obtained on endoscopy during present admission or at any point within 28 days prior to admission. [1]
   b. faecal calprotectin within 28 days of admission ≥ 250µg/g.
   c. CRP ≥ 12mg/L within 48h of screening.
4. Modified Truelove and Witts severity index (MTWSI) score ≥ 11 at or immediately before first dose of IV steroids.
5. Requirement for treatment with IV corticosteroids in the judgement of the treating clinician and the possibility to receive the IMP within 36 hours of admission.
6. Prior treatment with corticosteroids and mesalamine at entry is permitted. In addition, prior treatment with immunomodulators, anti-TNFs, anti-integrins, Ustekinumab, Mirikizumab, Guselkumab, Risankizumab Ozanimod or Etrasimod is permitted but these will all be stopped at admission with ASUC.
7. Prior treatment with other JAK inhibitors (e.g. Tofacitinib and Filgotinib) is also permitted if patients have not taken these within 4 weeks of the time of ASUC admission. Patients who had prior failed treatment with Upadacitinib will not be eligible.

[1] The study will collect routine SOC baseline sigmoidoscopy data only if available. Delivering RCTs in ASUC will require a number of practical considerations to facilitate rapid patient identification, consent, screening, randomisation and dosing. Findings should be generalisable to the context in which the intervention would be used in standard practice. As such, patient identification will be based upon similar criteria to those used when considering starting corticosteroids in clinical practice. We will use clinician diagnosis of ASUC and will not mandate endoscopic inclusion criteria that might be expected in other IBD trials.
Similarly, stool culture results will not typically be available at the point of starting steroids, so a full GI pathogen screen will not be mandated.
Baseline sigmoidoscopy data will be collected if available. Patients who are found to have positive stool pathogen culture results will immediately be withdrawn from the study.

5.1.2 Exclusion Criteria

1. Patients with any absolute contraindication to Upadacitinib.
2. Proven infective colitis within 4 weeks of baseline assessment (Stool Cultures or C Diff Toxin assay positive, CMV on biopsies); Where stool culture results are not available, and clinically suspected ASUC treatment has been instituted, this is not an exclusion to randomisation, however where results return positive, the individual will stop IMP, and be removed from the study and analysis. Stool results should be available within 3 days.[1]
3. Pregnant patients or patients breast feeding.[2]
4. Patients with toxic megacolon (TMC) at baseline assessment prior to randomisation.
5. Use of strong CYP3A4 inhibitor medications (azoles, clarithromycin) and co-administration of food and drink containing grapefruit.
6. Use of strong CYP3A4 inducer medications (including Rifampicin and Phenytoin).
7. Recent history of incompletely treated malignancy within 12-months (patients with a solid organ malignancy that remains under active treatment or where oncologists have not confirmed complete eradication).
8. Neutropenia with baseline ANC <1.0 $x10^9$ cells/L.
9. Absolute Lymphocyte Count <0.5$10^9$ cells/L.
10. Hb < 80 g/L.
11. Moderate or Severe renal impairment. (estimated glomerular filtration rate [eGFR] 40ml/min/1.73m^2).
12. Severe hepatic impairment (Child-Pugh C).
13. Patients with personal history of confirmed Venous Thromboembolism (VTE)/ Pulmonary Embolism (PE) who are not on effective anticoagulation (e.g. history of previous Deep vein Thrombosis ((DVT) or PE but no longer requiring anticoagulation), history of previous DVT or PE requiring anticoagulation where anticoagulation was not tolerated or withdrawn because of side-effects).
14. Evidence (from blood cultures etc) of active, serious localised as well as systemic infection or clinical suspicion of systemic infection (concurrent prescription of antibiotics to cover the possibility of GI infection whilst awaiting stool culture results, or the possibility of bacterial translocation relating to severe colitis) is not an exclusion criterion where the physician suspects UC is the most likely diagnosis.

15. Currently taking part in another Clinical Trial of an Investigational Medicinal Product (CTIMP)
16. Treatment with other JAK inhibitors (e.g. tofacitinib or Filgotinib) within 4 weeks of the time of screening.
17. Patients unwilling or unable to provide informed consent.
18. Patients previously exposed to Upadacitinib as per local label.
19. Patients with significant risk factors for major adverse cardiac events (MACE) or current active malignancy.
20. A history of untreated pulmonary Tuberculosis (TB) infection.
21. Any absolute contraindication to IV corticosteroid.

22. Patients with administered live vaccines of replication potential within 30 days prior to baseline.
23. Patients with a history of untreated active or latent HCV and HBV infection

[1] Participants who have positive stool pathogen culture results will be withdrawn immediately from the study.

[2] For WOCBP only - currently pregnant, breast feeding, or planned pregnancy during the study or not using acceptable contraception. Women of childbearing potential (WOCBP) participants are eligible to participate if they agree to use an effective method of contraception from point of signing the informed consent throughout the study. The following birth control methods are allowed during the study:

- Combined (oestrogen- and progestogen- containing) hormonal contraception (Oral, Intravaginal, Transdermal, or Injectable).
- Progestogen-only hormonal contraception (Oral or Injectable).
- Progestogen- only contraceptive implant.
- Intrauterine hormone-releasing system (IUS)
- Intrauterine device (IUD)
- Bilateral tubal occlusion
- Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Hormonal contraceptive methods are only considered highly effective if associated with inhibition of ovulation.

WOCBP are defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

5.2 Participant Identification and Screening

Identification of participants needs to occur as soon after admission as possible to recruit participants before standard treatment options over and above IV corticosteroids is decided.

Potential participants can be identified in two ways or a combination of both by the routine clinical care team or study research team.

a. The routine clinical care team will make the initial approach to the patient and ask if they are interested in taking part. If they are, the patient details will be shared with the site research team who will come and discuss the study in more detail.
b. The study team will check overnight ASUC hospital admissions and will make the initial approach to the patient on the ward and ask if they are interested in taking part. If the patient is interested the study team will provide a PIS and will liaise with the routine clinical care team.

The information in the PIS should answer any questions, but potential participants will be given adequate time to review the information and ask the study team any questions before consent. The site research team will assess patient understanding of the implications of study involvement prior to obtaining informed consent. The sites study team will provide the PIS and the consent forms in English. Translation of the PIS into other languages is not feasible given the time restriction for participants recruitment at this study. In addition, the questionnaires used cannot be translated to other languages as they will then need re-validation. However, where a non-English speaker is identified as eligible for the study and there is sufficient time, a local NHS Trust interpreter or NHS language line resources may be requested by the potential participant to attend study discussions and informed consent with the participant.
The tests required for screening all form part of standard clinical care. No additional tests will be performed other than a urine β-human chorionic gonadotropin test for females where there is a possibility of pregnancy. A serum pregnancy test will be requested if unable to provide a urine sample. Participants of childbearing potential will be made aware of the risks of getting pregnant whilst on the study. In the event of a pregnancy, this will be recorded. Participants are strongly advised to use appropriate use of contraception during the study and for 30 days after their last dose of Upadacitinib.

5.3 Informed Consent

Written informed consent will be obtained from all participants before any study specific procedures or interventions are performed and within 36 hours of the first dose of IV corticosteroids. Consent will be taken by the site PI or other appropriately trained clinician listed on the Delegation Log and in accordance with Good Clinical Practice (GCP).
The PI has overall responsibility for informed consent of participants and must ensure that anyone delegated responsibility to conduct informed consent is duly authorised, trained and competent to undertake consent according to the protocol, GCP and regulatory requirements. A General Practitioner (GP) letter will be sent after randomisation.
All informed consent forms will be stored in accordance with local requirements. A copy of the consent form will be given to the participant, a copy entered into the clinical record and the original signed copy will be filed in the Investigator Site File (ISF). In addition, a copy will be uploaded into the study database for central monitoring purposes.

5.4 Adult Participants Unable to Give Consent

Participants unable to provide informed consent will not be eligible to participate in this study. If a participant loses the ability to provide informed consent during the study, they will be withdrawn, and no further study assessments or procedures will be undertaken. No further data will be collected. All data collected prior to the participant withdrawal will be retained.

5.5 Withdrawal of Participants

Participants remain free to withdraw at any time from the study without giving reasons and without prejudicing any future treatment. If the participant is willing to provide a reason for the withdrawal, this should be recorded in the study database.
For all participants, a clinical judgement of failure to respond to treatment will normally prompt consideration of rescue therapy or a surgical referral. This will not constitute withdrawal from the study. These participants will remain in the study as an observational cohort as they continue their normal clinical care. At any time between randomisation and the end of treatment, the participant or routine clinical care team may discontinue or change the allocated treatment.

5.6 Treatment termination

Study treatment should stop according to clinical judgement and/or for the following criteria:

- Withdrawal of consent for treatment administration.
- Development of new severe renal impairment (eGFR <40 mL/min/1.73 m^2) or new severe hepatic impairment (Child-Pugh grade C).
- Development of neutropenia (neutrophil count <1.0×10^9/L).
- Detection of a significant GI pathogen in stool specimen, or CMV.
- The development of an SAE necessitating termination of IMP treatment.

Where possible, study assessments will continue following treatment termination unless the following arise leading to full study withdrawal with no further assessments being performed:

- Withdrawal of consent for further assessments and data collection.
- Death.

If a participant withdraws their consent after providing study biobank samples, the samples will be destroyed, if requested. If the samples have already been processed and are no longer identifiable i.e. cannot be attributed to a specific participant, the results cannot be removed from data analysis.
Data pertaining to safety will be collected at each study visit for regulatory reporting purposes and will be included in any safety analyses. If any significant new information becomes available regarding the study medication they have received, it may be necessary to contact participants in the future.

6.0 ENROLMENT AND RANDOMISATION

6.1 Enrolment

Eligibility details, including confirmation of written consent, will be entered into the study database by an authorised staff member at site to enrol the participant into the study. This will automatically generate a pseudonymised Participant Identification (ID) Number, which will be used on all participant study documentation for the remainder of the study, including sub study enrolment. Participant ID Numbers will be created according to the format ACE-01-XXX, where ACE refers to the study (ACESO), 01,02,03 etc is the site code number, and XXX is the sequential study number (e.g. ACE-01-001 for the first participant enrolled, ACE-03-002 for the second, etc).
The following minimum information is required for study enrolment:

- Participant details: initials, sex, date of birth.
- Name of trial research site and site code.
- Person conducting enrolment.
- Confirmation of eligibility.
- Confirmation of written informed consent and date.

Site study teams will update site Screening Log and Participant Register with the Participant ID Number and contact details. The Participant ID Number will be entered on all participant study documents and future correspondence from that point forward throughout the study. No other participant identifier will be used.
Once all enrolment details have been completed in the study database, the participant can then be randomised in the IWRS system.

6.2 Randomisation

Purpose-built, secure web-based randomisation systems will be used for randomisation to the main study and sub-study 1. Randomisation permissions will not be activated at the site until the Sponsor Green Light approval has been confirmed and Sponsor Green Light Letter has been issued.
Online randomisation systems will require an eligibility check by the site PI or delegated clinician listed on the delegation log before allowing randomisation to be completed.
Authorised study staff at site with delegated responsibility for randomising participants will follow instructions in the study User Manual filed in the ISF.

6.2.1 Baseline Randomisation

Each participant will be randomly allocated in a 1:1 ratio using IWRS web-based randomisation system to receive either: Upadacitinib (IMP) or matching placebo.
Baseline randomisation will be stratified for three variables:

1. Previous or current therapy with any of biologics (anti-TNF-α monoclonal antibodies, anti-adhesion molecule antibodies, other anti-cytokine antibodies) or oral JAK inhibitors /S1P receptor modulators.
2. Current or previous oral corticosteroid prescription(s) within 4 weeks prior to first dose of IV corticosteroids.
3. Baseline albumin of < 30 g/L (on the day of randomisation).

All participants will be randomised sequentially according to a randomisation schedule agreed and prepared by the HHTU statistician. Full details of the randomisation schedule will be provided in a separate restricted access document to avoid facilitating deciphering of the allocation sequence and undermining randomisation. HHTU will receive an alert with confirmation of a participant randomisation event. Immediate allocation of treatment will be performed, with documentation of the decision in a confirmatory email. The IWRS system will allocate the participant a treatment code which will relate uniquely to a supply of IMP or placebo (to cover the full 8 weeks of the main study) held at that study site. The IWRS system will not automatically generate a study prescription but will generate the kit numbers to be added to the site prescription. An automatic email will be sent at the time of randomisation to confirm the kit numbers and they will remain visible in the IWRS system for the duration of the study. Prescriptions will be completed by the PI or appropriately delegated study clinician as listed on the delegation log. The participant and site staff will be blind to treatment allocation.

6.2.2. Sub-study 1 randomisation

Following an eligibility check by the PI or delegated clinician listed on the delegation log sub-study 1 randomisation can be completed. HHTU will receive an alert with confirmation of a participant randomisation event. Immediate allocation of treatment will be performed, with documentation of the decision in a confirmatory email.
Sub-study 1 medications are sourced and dispensed from NHS stock and kit numbers will not be generated by the IWRS system.

7.0 STUDY IMP

The study IMP is licenced in the UK for use in the study population and is being used within its existing license. A summary of IMP management is provided below with further details and instructions provided on ordering, management, labelling and destruction in the ACESO Pharmacy Manual.

7.1 Trial Medication

Generic Name: Upadacitinib.
Dose: 45mg once daily [extended release].
Route of administration: Oral.

UK Trade Name: Rinvoq.

Full product information for Upadacitinib can be found in the latest MHRA-approved Summary of Product Characteristics (SmPC). The SmPC will be used as the study Reference Safety Information (RSI) document.
Commercial supplies of the medication (AbbVie) will be used for the study from baseline to week 8. Sub study medication will be sourced from routine stock.
Commercial stock will be imported from Germany and will be approved for use by the UK Importer Qualified Person (QP) who will also distribute IMP to participating sites. The IMP will be used as supplied and will not be repackaged or relabelled for the purpose of the study. The expiry date assigned by the manufacturer will be used.

7.1.2. Matching Placebo

Commercial supplies of placebo (AbbVie) will be used for the study. The placebo tablets will match the active coated tablets in size, shape, colour and marking of the Upadacitinib. The excipient used for the placebo tablets consists of a mixture of common pharmaceutical ingredients that meet compendial requirements. The manufacturing process consists of tableting and coating and there are no excipients of human or animal origin. The placebo tablets will be packaged with desiccant in sealed high-density polyethylene (HDPE) bottles with child resistant polypropylene caps.

7.2 Blinding

Study participants, site research and pharmacy teams will be blinded to the treatment group up to Day 10 when all participant allocations will be unblinded. Note that non-responders to IMP or placebo between Day 3 and Day 7 may have already been intentionally unblinded to determine rescue treatment decisions. The physical appearance of the placebo is matched to the IMP, and they will be presented in identical packaging. There will be no blinding for rescue treatments or sub-study treatments due to differences in routes of administration.

7.2.1 Intentional Unblinding

All responders will continue IMP or placebo until Day 10 when they will be intentionally unblinded to the central study team for analysis of the primary outcome.
For non-responders on placebo, the database will direct the participants to the sub-studies without formally unblinding the research team.
For non-responders who enrol into a sub-study, the site research team and routine clinical care team will know that the participant was taking placebo at baseline. It is important to note that at entry into a sub-study due to non-response, the primary endpoint will already have been reached and all participants will have been unblinded. However, local PIs will not be able to gain an overall

sense of study outcomes due to relatively small numbers of patients in each group at individual sites.

7.2.2 Emergency Unblinding

Whilst the safety of participants in the study must always take priority, maintenance of blinding is crucial to the integrity of this study. Investigators should only break the blind when information about participant study treatment is clearly necessary for the appropriate medical management of the participant and where stopping the blinded medication is not sufficient.
In the event of a valid medical or safety reason (e.g. in the case of a Serious Adverse Reaction (SAR) where it is necessary for the investigator or treating health care professional to know which treatment the participant is receiving before the participant can be treated), the responsibility to break the treatment code resides solely with the routine care clinician. The routine care clinician should contact the CI or the delegated study team physician to discuss the need for unblinding.
The online IWRS randomisation system will be used for emergency unblinding. Appropriately trained and delegated site staff will be given the necessary access rights and permissions to access this facility. The unblinder will enter the reason for unblinding and the name, email or telephone contact details of the person to receive the unblinded allocation information.
The unblinder will not be shown the treatment allocation on-screen. Instead, the allocation will be sent by text message or email directly to the person who requested the unblind. An email stating that an unblinding has taken place will be automatically sent to the coordination team for oversight purposes.

7.3 Reference Safety Information

The Upadacitinib SmPC will be used as the RSI. The current MHRA-approved version will be filed in the pharmacovigilance section of the ISF and Electronic Trial Master File (eTMF).
The Sponsor will assess the need to replace the RSI with updated versions as appropriate during the study period, with new versions being formally reviewed as part of an updated risk assessment and implemented after a substantial amendment has been approved by the MHRA.

7.4 IMP Storage and Supply

IMP and placebo will be acquired from AbbVie [Germany], labelled for study use, and stored according to requirements on the label. Site pharmacy will be responsible for maintaining adequate stock of the study medications within the site pharmacy.
Further details are provided in the Study Pharmacy Manual.

7.5 Product Complaints

The site pharmacy team will report any suspected quality defect in an AbbVie Product or its AbbVie-provided packaging, labelling, or medical device component (collectively, “Product

Complaint") to HHTU within 24 hours of becoming aware of the event. Site pharmacy teams will immediately place the item in quarantine until given AbbVie permission to dispense the product. HHTU will report all Product Complaints to AbbVie within 24 hours of becoming aware of the issue. Product Complaints that involve an AbbVie Product, whether AbbVie has supplied the AbbVie Product used in the study or not. Product Complaints may include, but are not limited to:

- Damaged or broken product or packaging issues
- Product appearance whose colour/markings do not match the labelling
- Missing component/product

For more detail on how to report a Product Complaint, see the Study Pharmacy Manual.

7.6 IMP Preparation, Dispensing and Labelling

Baseline IMP or placebo will be dispensed from participating site pharmacy units according to the study prescription following local study specific dispensing procedures, and in accordance with GCP. The study medication will be collected by a member of site research team. Further details are provided in the Study Pharmacy Manual.
Medications prescribed for sub-study or rescue treatments are not considered IMP medication and will be dispensed from local NHS stock according to local procedures.

7.7 IMP / Placebo Administration

7.7.1 Inpatient administration

Baseline IMP or placebo will be administered to the participant via their routine clinical care team during their acute admission to hospital according to the prescribed dosing schedule detailed on the prescription, medication chart and IMP or placebo label.

7.7.2 Maintenance Treatment After Discharge from Hospital

Responding participants will continue to take the IMP or placebo dispensed at baseline until Day 10. After unblinding at Day 10, responders on active Upadacitinib will continue taking their IMP Upadacitinib medication until the Week 8 study visit. Participants randomised to placebo will stop taking their study medication and ongoing treatment decisions including use of other therapies along with steroids will be at discretion of the routine clinical care team.

7.8 Drug Accountability

IMP or placebo will be supplied from AbbVie and will be held by the clinical trials pharmacy team at site. The site clinical trials pharmacy team will be delegated oversight of study medication. IMP or placebo must be stored in accordance with the manufacturer's instructions and must be kept in a locked area with access restricted to designated study personnel. The site clinical trials

pharmacy team will maintain accurate records of IMP or placebo management as detailed in the Study Pharmacy Manual. For sub-study medications (Upadacitinib, Infliximab), site hospital stock will be used.

7.9 IMP Destruction

An IMP or placebo destruction form will be completed by the site clinical trials pharmacy team and checked by HHTU, who will then request Sponsor IMP destruction. Under no circumstances can study medication be destroyed until Sponsor approval has been given. Documentation confirming destruction will be sent to HHTU.

At Week 8, any unused study medication and / or empty kit bottles will be brought to the Week 8 study visit (or earlier if withdrawn) by the participant and returned to clinical trials pharmacy for reconciliation and accountability.

8.0 STUDY PROCEDURES

8.1 Data Collection

Participant data will be recorded into CRFs or worksheets and entered into the study database by the site research team within 5 working days of each visit. From baseline till end of the inpatient stay the data should be entered daily into CRF preferably within 24 hours. Patients will be managed by routine care team including over weekends. Weekend data will be collected on structured data collection forms by clinical care team for collection and eCRF entry on Monday or research teams will transcribe from entry in clinical notes to e-CRF by the research teams after weekend.

8.1.1 Questionnaires

Participants will complete 4 paper questionnaires at each of the following study visit:

- Baseline visit (Decisional Conflict scale, CUCQ-32, HRUQ, EQ5D-VAS)
- Decisional Conflict scale also needs to be completed between days 3-7 preferably but up to Day 10 until the study doctors make a decision. In non-responders undergoing rescue therapy or surgery this should be completed on the day of rescue therapy or surgery.
- Week 8 visit (Decisional Regret scale, CUCQ-32, HRUQ, EQ5D-VAS)
- 12 month visit (Decisional Regret scale, CUCQ-32, HRUQ, EQ5D-VAS)

8.2 Routine Care Sample Collection

Blood, urine, and stool tests will be processed at participating site laboratories in accordance with local standard of care protocols for managing ASUC. Results will be made available to the site research team through the site hospital health record system. Similarly, sigmoidoscopy, rectal biopsies, and AXR results (if available) will be entered into the study database. All results and reports will be printed and signed by the PI, or delegate, with the signed copy filed in the participants' medical notes and ISF.

8.3 Biobank Samples

Only samples taken specifically for study purposes will be biobanked for use in future translational work including but not limited to biomarker prediction of treatment response and transcriptomic analysis. The blood sampling for genetic analysis is optional. We will ask participants to give consent for us to store their samples for Future Biomedical Research. Participation is optional and those who do not wish to consent to this element of the study may still participate in the main study.

A summary of biobank study sample management is provided below. For more detail, refer to the Study Laboratory Manual.

It is envisaged that some of the samples for biobank such as stool sample may not be available on specific days and hence biobank samples collection as close to the specified day is acceptable.

8.3.1 Blood samples [Baseline and Day 3]

- one EDTA (purple top), 5mls each time = total 10mls
- one serum tube (gold top), 5mls each time = total 10mls
- two PAX gene tubes, 3mls = total 6mls at enrolment only

A total of 26mls of blood will be collected (16mls at baseline and 10mls at Day 3) during the study and will be stored for future use.

Blood samples will be processed and stored frozen according to the Study Laboratory Manual.

8.3.2 Stool sample [Baseline and Day 3]

Stool samples will be collected in omnibet and omnigene tubes and stored frozen according to the Study Laboratory Manual.

8.3.3 Urine Sample [Baseline and Day 3]

Urine samples will be collected for metabolomics in containers, centrifuged and stored in a -80°C freezer as detailed in the Study Laboratory Manual

8.3.4 Rectal Biopsy sample [if and when available]

Biopsies for research will be collected during routine care sigmoidoscopy or if spare tissue is available at routine care sigmoidoscopy. This is optional and participants will have the choice to consent or decline the optional biopsies.

If patient undergoes sigmoidoscopy at any day during the index admission after consent to the study, four rectal biopsy samples and four sigmoid biopsy samples (if sigmoid was reached at sigmoidoscopy) will be collected and stored according to the Study Laboratory Manual. In addition we will seek to obtain spare paraffin embedded tissue from participating sites. If there is paraffin embedded tissue available which was obtained at routine sigmoidoscopies undertaken before consent or within the previous six months of admission, we will request this to be made available for research.

8.4 Urine pregnancy tests

A urine sample from WOCBP only will be collected for pregnancy testing at baseline to confirm eligibility. Pregnancy test will be conducted for WOCBP at week 4 and week 8 after the last dose of the IMP. Home testing would be acceptable. If a urine sample cannot be collected, a pregnancy test will be added to routine blood samples collection. Urine samples will be destroyed immediately after use.

8.5 Sample Shipment

HHTU will liaise with site research teams to coordinate batch shipment of samples to the biobank laboratory according to the Study Laboratory Manual. Documentation including the date of shipment, number of samples being shipped, and nature of the samples will be maintained and filed in the ISF. The samples will be analysed in study collaborator laboratories.

8.6 Sample Destruction

All routine blood samples will be destroyed after analysis according to local SOPs.
Study biobank samples will be stored at participating site laboratories until shipped at designated timepoints to the biobank for long term storage. Samples will be stored until used and then destroyed in line the protocol and Human Tissue Act (2004) and biobank laboratory SOPs.

8.7 End of Study

The study end point is defined as the point at which the study results have been analysed and reviewed by the CI and Sponsor team and an agreement is made that no further analysis is required. An End of Study Declaration Form will be submitted to the main Research Ethics Committee (REC), Health Regulatory Authority (HRA) and MHRA, and site Research Development and Innovation (RDI) within 90 days from the End of Study date or within 15 days if the study is discontinued prematurely. A final report (a summary of the study final report/publication) will be submitted to the REC, HRA and MHRA, and site Research and Development (R&D) within 12 months of the end of study date. Site RDI will be notified immediately of any reason to halt the study. The CI and Sponsor will decide if the study should be halted temporarily or early termination due to futility or on advice of the DMEC. The REC and site RDI will be notified within 15 days of a decision to temporarily halt the study by submitting a substantial amendment notification.

9.0 DATA MANAGEMENT

9.1 Source Data

International Conference on Harmonisation (ICH) E6 section 1.51 defines source data as "*All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies)".*
For this study, data will be sourced from:

9.1.1 Table 4: Source data

Assessment	Data Source	Completed by
Eligibility confirmation	Screening Form	Study Doctor
Informed Consent	Clinical record and informed consent form	Study Doctor
Demographics	Clinical record, Source Data worksheets	Study Nurse, Study Doctor, Study Research Assistant
Past Medical history	Clinical record, Source Data worksheets	Study Doctor or Study Nurse or research assistant
Medication history / concomitant medications	Clinical record, Source Data worksheets	Study Nurse, Study Doctor
Vital signs	Clinical record, Source Data worksheets	Study Nurse, Study Doctor, Study Research Assistant
Physical Exam & handgrip strength assessment	Clinical record, Source Data worksheets	Study Doctor for physical exam, Study Doctor or Study Nurse for hand-grip strength
Questionnaires	Questionnaires, Source Data worksheets	Study Nurse, Study Doctor, Study Research Assistant
Urine pregnancy test (WOCBP)	Clinical record, Source Data worksheets	Study Nurse, Study Doctor
Randomisation	IWRS email / REDCap Cloud database	Study Nurse, Study Doctor, Study Research Assistant
Sample collection	Clinical record, Source Data worksheets	Study Nurse, Study Doctor, Study Research Assistant
Endoscopy report	Clinical record, Source Data worksheets	Study Nurse, Study Doctor
Abdominal Xray report	Clinical record, Source Data worksheets	Study Nurse, Study Doctor
Drug accountability	Trial prescriptions, Pharmacy records	Study Doctor, Pharmacy team, Study Nurse
Adverse Event clinical assessments	Clinical record, Case Report Form	Study Doctor (assessment), Study Nurse (reporting)
Medication compliance	Participant medication diary	Participant
Long term follow up of UC related outcomes	NHS England platform	CI / delegated member of research team
Health economic analysis	Questionnaires / Database	Health Economist

A statement of permission to access source data by HHTU, regulatory agencies and Sponsor for monitoring, regulatory and audit purposes will be included within the participant informed consent form (ICF) with explicit explanation as part of the consent process and PIS.
The site PI and NHS Trust will permit monitoring, audits and MHRA review (as applicable) and provide direct access to source data and documents where required.

9.2 Record of study contact in clinical record

As a minimum, the following information will be recorded in participant clinical records for study visits or telephone contacts:

- Clearly written date of visit or contact, brief trial title, acronym and visit number.
- Date participant given PIS and which version was given.
- Date and version of ICF signed.
- Date of screening.
- Medical history, co-morbidities and medication, and any changes in co-morbidities and concomitant medications at subsequent visits.
- A clear description of any AE/SAEs with start and stop dates/times, severity and causality assessments as determined by a delegated research clinician, any significant test results.
- Anything which is relevant to the ongoing care of the participant.

9.3 Case Report Forms

Individual participant data required by the study protocol will be recorded by site research staff on study CRFs or worksheets provided, identified by the unique Participant ID Number. The design of the CRFs will:

- Enable adequate collection of data.
- Provide an audit trail to demonstrate the validity of the study (both during and after the study).
- Ensure that only the data required by the protocol are captured.

The site will retain a copy the CRF to ensure that the site can provide access to the source documents to a monitor, auditor, or regulatory agency when and if required.

9.4 Data Handling and Storage

A study specific Data Management Plan agreed by the CI, Co-Investigator leads, Sponsor, HHTU and study statistician will provide detailed guidance relevant to database development, data entry, validation, review, query generation and resolution, quality control processes involving data access, transfer of data to the Sponsor at the end of the study, and archiving. All information collected over the course of the study is confidential and will be held in accordance with General Data Protection Regulations (GDPR) 2018.

Data will be hosted and managed by HHTU using online data capture systems, Box Governance file storage system and e-signature platform. HHTU hold an NHS Digital Data Security and Protection Toolkit covering the various information systems.

Data will be collected and stored in an online Electronic Data Capture (EDC) system managed by HHTU (REDCap Cloud (RCC)). RCC is a cloud-based EDC system provided by nPhase. Data are stored on dedicated RCC hardware in European Union (EU) datacentres (including real-time backup) managed by Amazon Web Services to industry standards outlined in ISO 27001, PCI DSS, SOC 1-3, FISMA, CIS, CSA, NIST and UK Cloud Security Principles. Data are encrypted at rest and in transit. RCC delivers compliance to HIPAA, CFR Part 11 and EMEA Annex 11. Access to the EDC system is managed by the HHTU Data Management team who will create role-based user access on behalf of the study team. Users will be required to complete training and sign a terms of use document. All activity within RCC is subject to a full user audit, including timestamp.

HHTU use Box.com for collaborative cloud file storage. The HHTU Box instance is managed by HHTU with access limited to HHTU staff and authorised members of the research team and sponsor. Box uses EU data centres and complies with (and is independently audited against) the following standards:

- SOC 1, SOC 2 and SOC 3
- ISO27001/270018
- Department of Defence Cloud computing Security Requirements Guide
- FedRAMP Level 4
- FISMA
- FINRA/SEC 17a-4
- HIPAA/HITECH

Box acts as a data processor only for the purposes of storage of study data.
Further details on Box data security and GDPR compliance is available here: **https://www.box.com/n-gb/security.** The data protection risks of HHTU's use of Box have been formally evaluated via a data protection impact assessment.

DocuSign is a cloud-based eSignature provider that provides a full password linked eSignature along with an audit trail and is used by HHTU for tracking of approvals. The HHTU instance is managed solely by HHTU staff and is within scope of HHTU's Data Security and Protection Toolkit. DocuSign holds ISO27001, SOC1 and SOC2 reports, and has EU approval for their Binding Corporate Rules. Data are encrypted at rest and in transit using AES encryption and TLS1.2 with 256-bit keys and stored in EU datacentres. Under GDPR, DocuSign act as a data processor on behalf of the University of Hull (UoH), who is the data controller for HHTU projects. DocuSign uses user specific login, logically separating access to documents meaning only staff working on a project have access to the data.

Following data completion and resolution of queries, the database will be locked. Data will be exported from the trial database in the required formats for analysis, long-term storage and sharing. The study dataset will be exported from RCC for analysis and stored in HHTU Box Instance with restricted access. HHTU SOPs will be followed for the process of database lock and export including pseudo-anonymisation. HHTU will ensure no direct participant identifiers are present in any exported datasets. The site and sponsor will receive a copy of the locked dataset after database hard-lock. Access will be granted to the study statistician. Further details regarding data storage and transfer are given in the Study Data Management Plan.

The site research team will be expected to maintain a file of essential trial documentation (ISF) and keep copies of all completed study CRFs/worksheets. All study files will be stored in accordance with GCP guidelines and GDPR 2018 regulations. Study documents (paper and electronic) will be retained in a secure (locked when not in use) location during and when the study ends.

In line with the Data Protection Act (2018), access to fully identifiable information will be minimised. For the purposes of ongoing data management, once created as a participant on the RCC database, individual participants will only be identified by their unique Participant ID number on all subsequent forms and documents (electronic case report forms (eCRFs), etc.). Data is therefore pseudonymised and as such will still be treated as personal data.

The analysis dataset will contain only pseudonymised data (Participant ID number) but the team will have no access to the key. As such, the data will be classed as anonymous in context.

9.5 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits, and inspections.
HHTU Data Management Team will control access permissions to RCC, IWRS and the eTMF held on Box throughout the study and afterwards when the documents have been archived. Access permission will be granted based on delegated study role and level of access required, e.g. editor or read only. Access will be revoked when staff leave the study or at the end of the study after Data Lock.

9.6 Access to the final study dataset

The database will be 'locked' to obtain the final dataset after:

- Study completion (Last Participant Last Visit).
- Completion of coding and data entry.
- All data queries resolved, and the database updated; any SAE queries resolved, and the database updated.
- Study team notified of date of lock.

A copy of the final study dataset and notification of completion of the study participant visits will be sent to the Sponsor will be released by HHTU prior to the statistical analysis. A copy of the final study dataset will be sent to the site and will be archived by according to site SOPs. Participant consent forms held on the study database will not be exported by HHTU as part of the final study dataset.

9.7 Data Sharing

In principle, the anonymised data generated by the study will be suitable for sharing, e.g. for further research analysis and meta-analysis.

The study will be registered on ISRCTN prior to commencement of recruitment, and the study team will maintain the registry entry throughout the study lifetime, including uploading a copy of the study protocol within 12 months of the study starting. Final anonymised clinical study datasets and meta-data will be produced by HHTU data team and stored in an appropriate format to enable discoverability and sharing.

Requests for access to the dataset will be directly to the CI. If access to data is approved, a Data Sharing Agreement will be signed.

9.8 Study File Management

The study will use an eTMF and paper ISF. The eTMF will be held on Box managed by the HHTU Data Management Team. Access will be restricted to those delegated on the HHTU or participating site Delegation Log and will be granted based on role and level of access required.

9.9 Archiving

Archiving will be authorised by the Sponsor following submission of the End of Study Report. All essential study documents including source documents will be archived in accordance with the HHTU SOPs for a minimum period of 25 years after study completion. Destruction of essential documents will require authorisation from the Sponsor. Where permitted by the site NHS Trust, a notice stating the date after which the documents can be destroyed will be placed on the clinical record file. The archiving of study documents and data at site (including consent forms) will be done according to site policies and SOPs. HHTU will archive the study eTMF and datasets in line with HHTU SOPs. The study eTMF and datasets will be moved to a restricted access folder within Box, managed by HHTU on behalf of the Sponsor. Document retrieval from the archive documented will be fully auditable.

HHTU have backup procedures approved by auditors for disaster recovery. There will be a separate archive of electronic data performed at the end of the study to safeguard the data in accordance with regulatory requirements.

10.0 PHARMACOVIGILANCE

Upadacitinib is an MHRA licenced product used in for the patient population with the disease indication of UC being investigated in this study (MHRA Licence number MIA IMP 4102 V 6). Upadacitinib has a well-known safety profile and is used for treatment in the ASUC population in line with its licence. Given the short duration of treatment with IMP or placebo no unknown side effects or harms are likely. In addition, the IMP has a short half-life (<14 hours) and no cumulative or late effects are anticipated.

Study participants will be admitted patients under hospital care under specialists. The treatment processes will follow standard care which are well established following admission with ASUC. All participants will receive the standard care and will be monitored as per standard care thereby adding limited risk to participants. In addition, we have built in a feasibility as well as an interim analysis in the proposal adding to further safety.

In the event of an Adverse Reaction (AR) during working hours [Monday to Friday 09:00 – 17:00] participants will be advised to contact their hospital research team. In the event of an emergency, and/or outside these hours, participants will be advised to contact their GP, the ambulance service and/or attend the Emergency Department for urgent care following usual care pathways. The GP will be made aware of this guidance in the GP letter sent after informed consent has been taken.

The collection and reporting of data on AE and SAE will be in accordance with ICH GCP and the UK Policy Framework for Health and Social Care Research. Monitoring and reporting of pharmacovigilance aspects of the study will be performed in accordance with the HHTU Pharmacovigilance SOP and detailed in the Study Monitoring Plan.

10.1 Reference Safety Information (RSI)

A list of medical events that defines which reactions are expected for the IMP within a given study and thus determines which Serious Adverse Reactions (SARs) require expedited reporting. The RSI is the SmPC for Upadacitinib approved by the MHRA for use in this study.

10.1.1 Safety Reporting Definitions

Definitions of the safety reporting terms are detailed in Table 5.

Table 5: Adverse Event Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.
Unexpected adverse reaction	An adverse reaction, the nature, or severity of which is not consistent with the applicable RSI. When the outcome of the adverse reaction is not consistent with the applicable RSI this adverse reaction should be considered as unexpected.
Serious Adverse Event (SAE)	An SAE is any untoward medical occurrence that: • results in death. • is life-threatening. • requires inpatient hospitalisation or prolongation of existing hospitalisation. • results in persistent or significant disability/incapacity. • consists of a congenital anomaly or birth defect. • Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. **Note:** The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An AE that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the RSI:

	• in the case of a product with a marketing authorisation, in section 4.8 of the SmPC for that product. • in the case of any other IMP, in the IB relating to the trial in question.

The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on participant /event outcome or action criteria. To avoid confusion or misunderstanding of the differences between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above and relates to the consequence of the event.

10.1.2 Expected Adverse Events (non-serious) due to disease and comorbidities

A pre-existing condition (i.e. a disorder present at the baseline study visit and noted on the baseline medical history/physical examination form/medical notes), is not to be reported as an AE unless the condition worsens, or episodes increase in frequency during the AE-reporting period. Expected AEs (non-serious) will not be reported or entered in the CRF but will need to be recorded in the participant’s clinical record.

10.1.3 Expected Adverse Reactions/Serious Adverse Reactions (AR /SARs)

All expected ARs are listed in the latest MHRA approved version of the RSI. This must be used when assessing the expectedness of the AR. If the AR meets the criteria for seriousness this must be reported as per section 11.

10.1.4 Expected Serious Adverse Events

The following AEs, which may fall under the definition of SAEs as indicated in Table 5, are expected to occur commonly as a result of disease progression, rather than study participation. Signs and symptoms listed in table 6 are expected during disease progression necessitating rescue therapy (medical or surgical). As these events are common and expected outcomes, they will be exempt from SAE reporting, however details will be collected in the CRF. In addition, the decision to prescribe medical rescue therapy or perform emergency colectomy will not need SAE reporting. All instances of medical and surgical rescue therapy will still be collected via the study outcome data and provided to the Data Monitoring and Ethics Committee (DMEC) for review. The events will need to be recorded in the clinical record and a monthly return of number of expected events will be reported to HHTU. The number of expected SAEs exempt from SAE notification will still require reporting to the DMEC and annually on the Development Safety Update Report (DSUR).

Expected SAEs exempt from SAE notification are listed in Table 6.

Table 6 – Expected SAEs exempt from SAE notification

Diarrhoea/worsening diarrhoea
Abdominal pain/increased abdominal pain
Rectal pain/worsening rectal pain
Development of toxic megacolon
Development of hypoalbuminaemia
Decision to prescribe medical rescue therapy or perform emergency colectomy

10.1.5 Expected Upadacitinib related side-effects with consequences meeting criteria for seriousness (SARs)

Unlike the expected SAEs in Table 6, expected Upadacitinib related side-effects with consequences meeting ACESO protocol criteria for seriousness (SARs), will be reported but will only require reporting within 14 days and not the expedited report within 24 hours.
These will be recorded as part of the CRF and rated according to Common Terminology Criteria for Adverse Events (CTCAE) severity grading. If they meet ACESO protocol criteria for "seriousness", a SAE form will be completed.

10.1.6 Adverse Events of Special Interest (AESI)

In this study, there are some AEs of Special Interest. These include:

- Drug Induced Liver Injury (DILI)
- Infection
- Malignancy
- Myocardial Infarction, and cardiovascular death (MACE)
- Thromboembolic events (DVT, PE, any other venous thrombosis)
- GI perforation

10.2 Reference Safety Information

The RSI to be used for pharmacovigilance reporting will be section 4.8 of the latest MHRA-approved SmPCs for Upadacitinib.
If the SmPC is updated during the study, the CI and Sponsor will consider whether the risk-benefit ratio has been changed and whether any protocol mitigations are warranted. If there is a change, the updated SmPC will be sent to the MHRA, along with any other study document changes, via a substantial amendment. HHTU will perform regular checks for updates to the SmPC as detailed in the Study Monitoring Plan and in line with DSUR reporting.
However please note that a SAR whose nature and severity is not consistent with the applicable product information (MHRA approved SmPC) and where a report could add significant information on the specificity, increase of occurrence or severity of a known and already documented SAR, this is considered a SUSAR and will require completion of an SAE form within 24 hours of becoming aware of the event.

11.0 EVALUATION OF ADVERSE EVENTS

AEs will be recorded after Informed Consent regardless of whether the participant has received the study medication. A pre-existing condition must not be recorded as an AE or reported as an SAE unless the condition worsens during the study and meets the criteria for reporting or recording on the AE log. AE seriousness and causality will be evaluated and recorded in the medical records by the PI or appropriately delegated clinician listed on the site delegation log.

11.1 Assessment of Causality and Severity

Table 7 – Definitions of causality

Definitely	A causal relationship is clinically/biologically certain. This is therefore an Adverse Reaction
Probably	A causal relationship is clinically/biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal. This is therefore an Adverse Reaction.
Possibly	A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product. This is therefore an Adverse Reaction.
Unlikely	A causal relation is improbable, and another documented cause of the AE is most plausible. This is therefore an Adverse Event.
Unrelated	A causal relationship can be definitely excluded, and another documented cause of the AE is most plausible. This is therefore an Adverse Event.

Table 8 - Definitions of Severity

Mild	The participant is aware of the event or symptom, but the event or symptom is easily tolerated
Moderate	The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity
Severe	Significant impairment of functioning; the subject is unable to carry out usual activities and / or the participant's life is at risk from the event.

11.2 Recording of SAEs, SARs and SUSARs of adverse events

Participant health status will be checked at each study visit and the site team will record directly observed AEs and self-reported AEs. Participants will be given appropriate contact details and advised to contact the site research team if they experience any AEs within the reporting period.

The site research team will be responsible for collecting AE data and entering data into the study database. AEs and ARs will be recorded in the medical notes and appropriate section of the CRF.

11.3 SAE / SAR Reporting process

HHTU pharmacovigilance SOP and study specific instructions about the reporting process must be followed. This study will use an electronic safety reporting process embedded within the study database. Sites will receive training on pharmacovigilance reporting during site set-up, and copies of reporting guidance will be available in the ISF.

Each SAE will be identified by the Participant ID Number and sequential SAE number, e.g. ACE-01-001-SAE-001 and will be documented on the SAE Log held in the ISF. SAE events will be reported directly via the study RCC database, although there will be a corresponding paper form to be completed if the study database is not available, which will be scanned and email to HHTU (**hhtusafetyreporting@hyms.ac.uk**).

The site research team will report all SAEs within 24 hours of becoming aware of the event using the Initial SAE Report Form within the study database. HHTU will be responsible for processing safety reports for the site and will inform the CI and Sponsor via email within 24 hours after they become aware of the event. If the Initial SAE Report does not include a causality assessment, HHTU will request a Follow-Up SAE Report to be completed as soon as possible until causality has been determined. Several Follow-Up Forms may need to be completed until the outcome is determined. There will be no paper Follow-Up SAE Report Forms, as the data will be entered directly into the study database.

HHTU will receive automatic notification of all SAEs entered into the study database. The HHTU study management team will then release the form in sequence for the required assessments, first to the PI/delegated study doctor to assess severity, seriousness and causality, followed by CI/Sponsor assessment of expectedness. The CI and Sponsor will assess expectedness within 24 hours of receiving notification from HHTU using the MHRA approved version of the RSI. Events will be followed up until resolved or an outcome has been reached. The CI and Sponsor will sign to confirm their assessments in the study database.

For AE, AR, SAE, SARs and SUSARs, the following information will be collected:

- Full details in medical terms, case description and CTCAE grade
- Event duration (start and end dates, if applicable)
- Date of hospital admission and discharge (if applicable)
- Seriousness criteria
- Causality assessment (i.e. relatedness to trial drug/investigation), in the opinion of the investigator, in relation to:
    - Study procedure(s)
    - IMP/Placebo
    - Other assessments
    - Whether the event would be considered expected or unexpected

- Date AE met criteria for SAE
- Action taken
- Outcome
- Probable cause and date of death (if applicable)

SAEs determined suspected to be both related to IMP or placebo administration and unexpected, will be classified as SUSARs and will be subject to expedited reporting to the MHRA. The sponsor will inform the MHRA and REC of SUSARs within the required expected reporting timescales (no later than 7 days for fatal or life-threatening reactions or 15 days for all other SUSARs).

11.4 Safety Reporting period

The safety reporting period begins as soon as participants are consented to the study. However, if a participant provides informed consent but is subsequently found to be ineligible, then the reporting period will end when the participant screen fails.

The IMP has a short half-life (<6h). No cumulative or late effects are anticipated. For this reason, recording of AEs and reporting of SAEs will be actively monitored up to Day 10 (+3 days). Following the end of the active monitoring period, PI or delegated clinicians will continue to report SAEs, SARs or SUSARs of which they become aware until the 12 month follow up visit.

11.5 SAR/SUSAR reporting

SAR/SUSAR reporting will start after the first dose of IMP or placebo. SARs that are both unexpected and serious (SUSARs) are subject to expedited reporting. The MHRA and REC must be notified as soon as possible but no later than 7 calendar days after the study team and sponsor has become aware of the event. Where a participant withdraws consent for further processing of data, this does not preclude the reporting of SARs and SUSARs for regulatory purposes. All participants must be followed-up until SAR and SUSAR resolution in all instances.

11.5.1 Format of the SUSARs reports

Electronic reporting is the expected method for expedited reporting of SUSARs to the competent authority. The format and content as defined by the competent authority should be adhered to.

12.0 REPORTING OF SAFETY EVENTS TO ABBVIE

SAE information will be shared with the AbbVie Drug Safety Department. Safety data and timelines for reporting given in Table 9 will be reported to AbbVie by the sponsor or delegate.

Table 9 – Definition of Events to be reported to AbbVie

Event to be reported to ABBVIE	timeline
Serious events that are fatal / life-threatening	7 days
All other serious events (unless exempt)	15 days
Non-Serious – if there is local requirement to collect	30 days

Special situations (accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal), including pregnancy	15 days
Product complaint	1 day
Identified new safety signal (unknown AE or SAE)	15 days

Note: No identifiable personal details regarding the participants will be including within the ABBIVE reporting process.

The Sponsor or delegate will report any safety issue that may be necessary and relevant to AbbVie to investigate an event including:

- the submission to the MHRA of SUSARs or Urgent Safety Measures meeting the definition of an expedited safety report
- All pregnancies occurring up to the 12-month visit will be reported to AbbVie regardless of randomisation allocation. Participants receiving the study IMP (including those on sub-study) whose pregnancy has resulted in a negative outcome or untoward event during the course of pregnancy or upon delivery will be reported a SAE

The AbbVie contact for reporting serious adverse drug experiences, pregnancy experiences, and MHRA submissions for expedited safety reports is: **PPDINDPharmacovigilance@abbvie.com**

12.1 Reporting of urgent safety measures

If any urgent safety measures are taken, the CI or Sponsor shall immediately, and no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

12.2 Development Safety Update Reports [DSUR]

HHTU will be responsible for preparing DSUR reports with Sponsor and AbbVie input, which will be submitted to the MHRA and REC annually during the study and within 30 days (absolute deadline 60 days) of the anniversary of the MHRA Clinical Trial Authorisation (CTA).
The MHRA-approved SmPC will also be reviewed at the same time as the DSUR is completed. If the SmPC has been updated, the CI and Sponsor will risk assess the changes and decide if they have an impact on participant safety. If the decision is that the updated SmPC needs to be used as the new RSI, then this must be submitted to the MHRA as a substantial amendment. The updated SmPC can be used once approved by the MHRA.

12.3 Responsibilities for safety reporting

12.3.1 Chief Investigator (CI) / or delegate

- Clinical oversight of the safety of participants, including an ongoing review of the risk / benefit

- Use medical judgment in assigning seriousness, causality, and expectedness of SAEs (in line with the RSI) where it has not been possible to obtain local medical assessment
- Use medical judgement in assigning whether an event/reaction was anticipated or expectedness in line with the RSI
- Immediate review of all SUSARs
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan
- Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs
- Preparing the clinical sections and final sign off, of the DSUR

12.3.2 Principal Investigator (PI) / or delegate

- Check for AEs and ARs when participants attend for study visits
- Use medical judgment in assigning seriousness, causality and whether the event/reaction was anticipated using the RSI approved for the study
- Ensure all SAEs and SARs (including SUSARs) are recorded and reported to HHTU within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs and SARs (including SUSARs) are chased with HHTU if a record of receipt is not received within 2 working days of initial reporting
- Ensure that AEs and ARs are recorded and reported to HHTU in line with protocol requirements
- Ensuring at AEs and SAEs are recorded in the participants medical records with clear documentation regarding severity and causality as per GCP

12.3.3 Hull Health Trials Unit (HHTU)

- Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the study protocol onto a database
- Report safety information to the CI, delegate, or independent clinical reviewer for the ongoing assessment of the risk/benefit according to the Study Monitoring Plan
- Report safety information to the independent oversight committees (DMEC and Trial Steering Committee (TSC))
- Expedite reporting of SUSARs to the Sponsor within the required timelines
- Notify investigators of SUSARs that occur within the study
- Unblinding of a participant for the purposes of expedited SUSAR reporting
- Annual checks and notification to PIs of updates to the study RSI
- Prepare standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and main REC

12.3.4 Sponsor

- Maintain overall oversight of safety reporting and ongoing safety evaluation of the study IMP/Placebo

- Causality and expectedness of SAEs using the RSI approved for the study will be assessed by the HUTH RDI Director in the absence of the CI
- Expedite reporting of SUSARs to the MHRA and main REC within the required timelines if delegate not able to do so
- prompt reporting of all SAE findings to the MHRA if they could:
    - Adversely affect the health of participants.
    - Impact on the conduct of the study
    - Alter the risk to benefit ratio of the study
    - Alter the competent authority's authorisation to continue the study in accordance with Directive 2001/20/EC

12.4 Pregnancy report

All pregnancies occurring during study participation up to the 12-month visit should be reported to the CI and Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification and should be followed until outcome. Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets 'serious' criteria, this would be considered an SAE.

12.5 Notification of deaths

Any deaths occurring whilst a participant is enrolled on the study up to the 12-month visit will be reported to Sponsor as soon as site become aware of the event via the Notification of Death CRF.

13.0 STUDY MONITORING AND QUALITY ASSURANCE

13.1 Study Roles and Responsibilities

The study Sponsor is Hull University Teaching Hospitals NHS Trust (HUTH), who will hold overall responsibility for the study. The study will be managed by HHTU, on behalf of the CI, Prof Shaji Sebastian and the Co-Leads Dr Tim Raine and Dr Kamal Patel. The study sites will be monitored by HHTU in accordance with the Study Monitoring Plan, HHTU SOPs to ensure compliance with UK Clinical Trials Regulations as outlined below in Table 10.

Table 10 – Study Roles and Responsibilities

Chief Investigator	The CI will have overall responsibility for the design, set-up, conduct, coordination, and management of the study, and for IMP drug supply and pharmacovigilance. This includes study authorisation (responsibility for the protocol and obtaining approvals from the MHRA, REC and site RDI approvals; ensuring that the study is conducted according to the UK Clinical Trials Regulations, and to GCP, Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP); and assessment of SAEs and expedited reporting of any SUSARs to MHRA.
Co-lead investigators	Responsibilities of the CI in the absence of the CI.
Principal Investigator	The PI has overall responsibility for the conduct of the study at the participating site. In particular, the PI has responsibilities which include (but not limited to): • Ensuring the appropriate approvals are sought and obtained. • Continuing oversight of the study. • Ensuring the study is conducted according to the protocol. • Ensuring consent is received in accordance with the protocol and national requirements. • Ensuring that the ISF is accurately maintained. • Delegation of activities to appropriately trained staff (this must be documented on the Delegation of Authority Log). • Providing protocol or specialised training to new members of the study team and ensuring that if tasks are delegated, the member of staff is appropriately trained and qualified. • Appropriate attendance at the initiation meeting. • Ensuring appropriate attendance at the TSC/Independent Data monitoring Committee (IDMC) meetings if required and ensuring appropriate safety information is made available to the coordinating centre team in advance of the meetings. • Dissemination of important safety or study -related information to all stakeholders at the participating site. • Safety reporting within the timelines and assessment of causality and expectedness of all SAEs.
Study Sponsor	The Sponsor, HUTH, will hold responsibility for overall study oversight and will be responsible for study initiation management. Responsibilities delegated to HHTU, and other parties are detailed in the Task Allocation Matrix in the Sponsor Collaboration Agreement.
Lead Organisation	HHTU/UoH will have responsibility for overall study management including stakeholder management, study progression, financing, budget monitoring.

Clinical Trials Unit (HHTU)	Will have responsibility for study conduct as delegated by the Sponsor and PI in accordance with GCP standards. HHTU will conduct study set-up and monitoring in line with HHTU SOPs, partner SOPs and the UK Policy Framework for Health and Social Care Research, as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations, 2006. Responsibilities include study administration, protocol development, eCRF design, input into study design, main REC/MHRA/HRA regulatory submissions, data management, safety reporting, randomisation design and service, database development and provision, database administrative functions, source data verification, monitoring, HHTU and site training, study reports and results dissemination.
Trial Statistician	The study statistician will oversee the statistical aspects of the study, including drafting of the analysis plan, the conduct of analyses and the reporting of results.
Site study teams	Authorised study doctors are permitted to take consent, confirm eligibility and prescribe study IMP/Placebo. Study research nurses, practitioners and associates are responsible for the management of participant recruitment, support for the consent process and coordination of all aspects of data collection. Sites are specifically responsible for conducting the study in accordance with the protocol, SOPs, contract agreements, the UK Clinical Trial Regulations and GCP.
Trial Management Group (TMG)	The TMG will comprise of the PI, other lead investigators (clinical and non-clinical), members with a specific interest (e.g. nurses, patient representatives), and members of HHTU and a Sponsor representative. A Terms of Reference document will be developed and approved at the first meeting. The TMG will meet monthly and will be responsible for oversight of study set-up, study management, study data collection, data quality and analysis, and publishing study results.
Trial Steering Committee (TSC)	The TSC is comprised of an Independent Chair and at least one other independent member. The TSC will provide overall supervision of the study looking at progress, adherence to protocol, participant safety and consideration of new information. TMG members may attend the TSC meetings to present and report progress. The Committee will meet approximately three-monthly, but six-monthly as a minimum. The TSC will consider recommendations from a fully independent DMEC.
Data Monitoring Ethics Committee (DMEC)	DMEC members and their host institutions will not be involved in the running of the study. Meetings and running of the DMEC will be subject to a separate DMEC charter to be agreed by the DMEC chair

13.2 Study Monitoring Plan

The HHTU study team will oversee trial monitoring activities, ensuring the study is conducted in accordance with agreed SOPs (HHTU or Sponsor), to ensure compliance with the GCP under UK Clinical Trials Regulations and the UK Policy Framework for Health and Social Care Research. All study related documents will be made available upon request for monitoring by HHTU monitors and for inspection by the MHRA.

A risk-based approach to monitoring will be adapted for the study. Full details will be given in the Study Monitoring Plan, which will be developed and agreed by the Sponsor, CI, HHTU, TMG and TSC, based on the study risk assessment. Monitoring will be a combination of central, remote, and on-site monitoring, with appropriate risk adaptations considered during the risk assessment process. HHTU will coordinate and perform monitoring, submit reports to the site and Sponsor, and escalate findings as required.

Data will be monitored for quality and completeness by HHTU. Missing data will be chased until it is received or confirmed as unavailable. Missing data items will not be chased from participants. HHTU will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from HHTU. There will be ongoing central collection of consent forms.

13.3 Study Oversight Committees

13.3.1 Trial Management Group

The TMG is comprised of individuals closely involved in the running of the study. Including the CI, Co-leads, other lead investigators (clinical and non-clinical), members with a specific interest (e.g. nurses), Patient and Public Involvement (PPI), members of the HHTU team and a Sponsor representative. The TMG will be responsible for day-to-day running and management oversight of the study. The TMG will meet more frequently to ensure that all practical details of the study are progressing well in person or via teleconference.

13.3.2 Trial Steering Committee

The TSC will provide overall supervision for the study, in particular in relation to study progress, adherence to the protocol, participant safety and the consideration of any new relevant information. Overall supervision of the study will rest with the TSC.

The TSC will be constituted in accordance with Efficacy and Mechanism Evaluation (EME) guidance. In particular, 66% of the TSC members will be required in order to achieve quorum; 75% of members voting must be independent; the TSC chair will be independent. A patient representative will serve as a member of the TSC.

The TSC provides advice through its independent Chair and is responsible for making executive decisions about the continuation of the trial. In addition to the independent Chair, the TSC will

include an independent statistician, as well as other independent expert members with clinical or other expertise relevant to the project, and the CI as a non-voting member. In addition, observers from the TMG (e.g. trial manager, study statistician), Funder and Sponsor can be invited to attend at the discretion of the Chair. The TSC will meet regularly, as required in person or by teleconference approximately every 4 months with a minimum frequency of 3/year (more frequent meetings may be required at the discretion of the TSC chair) as fully detailed in the TSC Charter.
The TSC will consider recommendations from a fully independent DMEC.

13.3.3. DMEC

An independent DMEC will be constituted for DMEC members, and their host institutions will not be involved in the running of the study. Meetings and running of the DMEC will be subject to a separate DMEC charter to be agreed by the DMEC chair.
During the study, interim analyses of all SAEs will be provided regularly in strict confidence to the chair of the DMEC in accordance with the charter. In the light of these analyses and any other information considered relevant, the DMEC will advise the TSC if, in their view, the randomised comparisons in the study have provided both;

- "Proof beyond reasonable doubt" that for all, or some specific types of patients, use of the IMP Upadacitinib is clearly indicated or clearly contraindicated
- Evidence that might reasonably be expected to influence materially the patient management of many clinicians who are already aware of the results of other studies.

The TSC will then decide whether to modify the study, or to seek additional data. Unless this happens, the TSC, collaborators, participants, and all study staff (except those who provide the confidential analyses to the DMEC) will remain blind to the interim results on mortality and morbidity until the end of the study.

14.0 STATISTICAL ANALYSIS

14.1 Sample size calculations

We will recruit 300 patients (150 per group) to give 80% power to detect a 15% absolute risk reduction (ARR) in the primary endpoint from a rate in the control group of 35% testing at the 5% significance level. A statistical power of 80% is accepted as a high-enough for a RCT of this nature. Since the main study observation is brief and performed in an inpatient setting, we expect negligible loss-to-follow up. This sample size was calculated by the sample size and power calculation software, nQuery version 9.3.

We have based our estimate of the primary endpoint taking an approximate conservative mid-point realistic estimate for the need for rescue therapy from the CONSTRUCT trial, the IASO trial, a 2007 systematic review and meta-regression of 32 cohort studies and randomized controlled trials between 1974 and 2006 and real-world observation studies (PROTECT-ASUC). The need for

rescue intervention with either medical therapy or surgery ranges from 26% to 49% in controlled trials. Hence, a mid-point estimate of 35% was applied to the power calculation.

There is no estimate for the effect size of Upadacitinib in ASUC. We chose to power this study to detect an ARR of 15% based on realistic outcomes from registrational studies of Upadacitinib and other new advanced therapies for IBD. Expert consensus would also support an intervention reducing the need for rescue intervention to 20% or less would make a substantial difference to the patient population (based upon our previous interviews conducted with clinicians as part of study design for IASO).

14.2 Statistical methods

A statistical analysis plan (SAP) will be prepared before the final database lock and will be approved by the TSC. The primary and secondary analysis is based on the treatment arms according to baseline randomisation (Upadacitinib at baseline or matched placebo).

14.3 Primary analysis

We will report summary statistics on the primary and all secondary endpoints according to treatment group. The primary analysis will be conducted on modified intention to treat basis. An estimate, 95% confidence interval and p-value of the absolute risk difference of the incidence rates of the need for medical or surgical rescue therapy within 10 days following the first administration of IV corticosteroids (primary endpoint) between the two treatment arms (randomised to Upadacitinib at baseline or matched placebo at baseline) will be calculated from a logistic regression model [13] to adjust for important baseline covariates including baseline albumin, baseline CRP, Endoscopic severity (Mayo endoscopic score) exposure to oral steroids within 4 weeks preadmission, prior hospitalization, prior biologic treatment and transfer to absolute risk difference with 95% Confidence Interval (CI[1]).

Secondary endpoints will be compared in a similar regression model to estimate the treatment effect on an appropriate scale of comparison. This will include an assessment of the effects of treatment with Upadacitinib on the endpoints. Note that power calculations have not been performed for the secondary endpoints and therefore the analysis of these end points may not be conclusive and will be exploratory in nature.

Not all patients in ACESO will receive the same number of doses of Upadacitinib prior to a decision being made regarding rescue therapy. To assess whether the clinical effects of Upadacitinib in ASUC may differ according to the timing of first dose administration and/or the number of doses received, pre-specified subgroup analyses, in the form of estimating treatment-covariate interactions, will be performed according to characteristics including duration between 1st dose of IV corticosteroids to 1st dose of IMP and number of doses of IMP received (<24 hours of corticosteroids versus 24-36 hours). All subgroup analyses will be based on the primary endpoint under Full Analysis Population. Additionally, we will use Complier Average Causal Effect (CACE) analysis to assess the influence of the amount of treatment received, as distinct from treatment

assigned. A sub analysis will exclude participants whose eligibility was changed due to a positive stool pathogen result after randomisation and dosing of the IMP or placebo.

All continuous variables will be summarised using the following descriptive statistics: mean, median, maximum, minimum, and standard deviation. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for categorical variables. All summary tables will be structured with a column for each treatment in the order (placebo, Upadacitinib) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

14.4 Sub-study analysis

Infliximab naïve non-responders who received placebo have option for a randomised controlled sub-study (sub-study 1). We expect around 25 patients in total for this sub-study. Patients will be further randomised into Upadacitinib 45mg OD or Infliximab in 2:1 ratio. We will employ descriptive statistics to summarise clinical and treatment outcomes by treatment groups. We will also report the between group differences in key sub-study outcomes, together with their 95% CIs[1].

Infliximab exposed non-responders who received placebo have an option for participation in an open label sub-study (sub-study 2). We expect around 20 patients in total for this sub-study. Patients will be offered open label Upadacitinib 45mg OD. We will employ descriptive statistics to summarise clinical and treatment outcomes. We will also report key sub-study outcomes, together with their 95% CIs[1].

We will consider adding the historical patients who received Infliximab rescue therapy from CONSTRUCT study who will meet the same inclusion criteria as our study into the control group to increase the sub-study sample size. This historical group will be used to power the Infliximab rescue therapy arm. Prior to this data combination, baseline clinical and demographic characteristics of patients from control group and historical control group will be checked and compared. We will use propensity score matching approach to match the control and historical control group patients. In addition, we may use Bayesian approach.

14.5 Definition of populations

Populations to be analysed in the study are as follows: Full Analysis Population: All randomised participants who receive at least one dose of IMP. Randomised Population: All randomised participants, regardless of whether IMP was received. Safety Population: All consenting participants.

14.6 Feasibility analysis

After the first 20 participants have been recruited, and all completed a minimum of 10 days follow up (to the time of the primary endpoint), feasibility will be assessed. The study will be regarded as feasible only if all the following measures are met:

- ⩾25% of eligible participants are recruited
- Adherence to dosing as per protocol (⩾80% of participants received IMP within 36 hours of first dose of IV steroids)
- Rescue therapy started on or before the 7th day following initial IV corticosteroid administration in ⩾80% cases where required
- No serious safety concerns identified, especially about infections or SUSARs.

14.7 Interim analysis

After 50% of the participants (150 patients) have completed Day 10 assessments, futility, safety, and efficacy analysis will be performed by an unblinded statistician working on behalf of the DMEC, to check the reduction in absolute risk difference in the primary outcome against pre-specified thresholds. No formal hypothesis testing will be conducted and therefore, this approach will not affect the Type I error rate or required sample size for the main study analysis. The results of this analysis will be made available to the DMEC and will inform any recommendations made by the DMEC to the TSC (who will remain blinded).
When the sample size of evaluable patients in each group is 75 (i.e. n=150), a one-sided 95% confidence interval for absolute risk difference of 15% will extend 9.2% from the observed difference in proportions.
If the lower bound of its 1-sided 90% confidence interval is above 5% (i.e. the absolute risk difference is likely above 15%), the DMEC will recommend continuing the study.
If there is a strong positive signal for efficacy of the IMP, the DMEC may wish to advise the TSC regarding early termination to permit early reporting of the results.

If the lower bound of its 1-sided 90% confidence interval is below 5% but above 0% (i.e. the absolute risk difference is likely between 10-15%), the DMEC will check other clinical and safety data to determine their recommendation as to whether the study should stop early or continue.
If the lower bound of its 1-sided 90% confidence interval is below 0% (i.e., the absolute risk difference is likely below 10%), the DMEC will consider the recommendation for the study to stop early for futility.
A Statistical Analysis Plan (SAP) will be developed during the study recruitment period and will be available before the data analysis period begins.

15.0 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Regulatory Compliance

The study will be performed subject to REC favourable opinion, MHRA Clinical Trial Authorisation, HRA approval and Sponsor and NHS Trust site permissions. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant subsequent amendments; GCP, GMP, GLP guidelines and the UK Policy Framework for Health and Social Care Research.

Before a site can enrol participants into the study, a Capacity and Capability (C&C) assessment must be completed and confirmed by the site R&D department. For any amendment that will potentially affect site NHS permissions, HHTU will request confirmation of continuing C&C from the site RDI department prior to implementing the amendment at site.

15.2 Research Ethics Committee

Before the start of the study, approval will be sought from a REC. Substantial amendment that require review by the REC will not be implemented until the REC grants a favourable opinion for the study (note that substantial amendments may also need to be reviewed and accepted by MHRA and each site RDI departments before they can be implemented at site).
All correspondence with the REC will be retained in the eTMF/ISF.
An Annual Progress Report (APR) will be submitted to the REC within 30 days of the anniversary date on which favourable opinion was given, and annually until the study is ends. It is the CI or delegates responsibility to produce the APR. The CI or delegate will notify the REC of the end of the study. If the study is ended prematurely, the CI or delegate will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the CI or delegate will submit a final report with the results, including any publications/abstracts, to REC.

15.3 Amendments

The process for making and communicating amendments will be described in relevant HHTU SOPs. Under the Medicines for Human Use (Clinical Trials) Regulations 2004, the Sponsor may make a non-substantial amendment at any time during the study. There is no requirement for investigators to notify MHRA of non-substantial amendments, but REC and HRA must be notified. If the Sponsor wishes to make a substantial amendment, all amendments will be submitted via the Combined Integrated Research Application System (IRAS) Gateway. It is Sponsor responsibility to decide whether the amendment is substantial or non-substantial for the purposes of submission to the MHRA and/or REC. The MHRA and/or the REC will provide a response regarding the amendment within 35 days of receipt of the notice. Amendments need to be notified to the R&D department to review continuing C&C confirmation for that site.

15.4 Non-Compliance

Protocol and GCP non-compliances are defined as departures from the approved protocol and/or principles of GCP identified during study implementation, data management checks and/or monitoring visits. Such non-compliances are categorised according to table 11 below.

Table 11: Definitions of deviation

Deviation	a planned or unplanned departure from the protocol or the conditions or principles of GCP that does not increase risk or decrease benefit; or have a significant impact on participant rights, safety, or welfare, and/or on data integrity.

Violation	an unplanned departure from the protocol or the conditions or principles of GCP that does increased risk or decrease benefit; or may have an impact on participant rights, safety, or welfare, and/or on data integrity.
Serious breach	a breach of the protocol or of the conditions or principles of GCP which is likely to affect to a significant degree either the safety or physical or mental integrity of the participants of the study; or the scientific value of the trial.

Planned deviations may be permitted if they are in place to protect participant safety, rights, and welfare, but they should not become standard practice. If necessary, a protocol amendment could be considered. Planned deviations or waivers relating to eligibility criteria will not be permitted. Accidental protocol deviations can happen at any time. They will be adequately documented on the relevant forms and reported to the CI and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action (may trigger additional monitoring visits and refresher training sessions) and may be classified as a violation or serious breach. Prospective or planned violations or serious breaches will not be permitted under any circumstances.

15.5 Notifications of Serious Breaches to GCP and/or Protocol

Deviations from the protocol which are found to occur repeatedly will not be accepted and will require immediate action and could potentially be classified as a serious breach. Any potential/suspected serious breaches of GCP must be reported immediately to the Sponsor without any delay. Sites are required to promptly notify HHTU of a serious breach (as defined in Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments) as soon as they become aware of an event. The CI and HHTU are required to promptly notify the Sponsor of a potential serious breach.
In the event of a serious breach, the Sponsor will be notified immediately of any case where the above definition applies during the study conduct phase. The sponsor will notify the MHRA in writing of any serious breach of:

- The conditions and principles of GCP in connection with that study
- The protocol relating to that trial, as amended from time to time
- within 7 days of becoming aware of that breach

In the event of doubt or for further information on whether a protocol deviation should be classed as a serious breach, the PI should contact the Trial Manager at HHTU.

15.6 Ethical Considerations

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, 1996.

This is a CTIMP as defined by the EU Directive 2001/20/EC. Therefore, CTA is required before the trial can commence. An ISRCTN number will be automatically generated when submitted via IRAS for approval. This study protocol will form part of the CTA application for submission to the MHRA. As part of study set-up and before initiation of the study at any participating site, the protocol, ICF's and any material to be given to prospective participants will be submitted to a national REC for approval. Any subsequent amendments to these documents will be submitted for further approval. Each site will provide R&D C&C approval before the study can be given green light to start recruitment.

Written informed consent will be obtained from participants prior to study enrolment and randomisation. The right to decline study participation without giving a reason must be respected. The participant must remain free to withdraw at any time without giving a reason and without prejudicing their further treatment. The study will be submitted to and approved by a REC and the site R&D team for each participating site prior to entering participants into the study. HHTU will provide the main REC with a copy of the final protocol, participant information leaflets, consent forms and all other relevant study documentation.

SAEs are not anticipated for this study as the medications administered during this study are licenced in the UK for use in the participating patient population and have established safety profiles. However, SAE reporting process is in place to capture any events.

15.7 Patient and Public Involvement and Engagement

PPI representatives have reviewed patient facing study documents and have informed the study design and methods. PPI representatives will be involved in reviewing a plain-English summary of the research findings to support dissemination activities. PPI representatives will be supported by the CI, with appropriate training and access to systems/resources provided to enable them to fulfil their role.

15.8 Confidentiality

Full details will be available in the study specific Data Impact Assessment [DPIA] and Data Flows document. All information collected during the trial will be kept strictly confidential. Information will be held securely either on paper and/or electronically at HHTU. HHTU will comply with all aspects of GDPR 2018. Operationally, this will include:

- Consent from participants to record personal details: name, date of birth, address, telephone number, hospital number, NHS number, GP name and address
- Appropriate storage, restricted access, and disposal arrangements for participant personal and clinical details
- Consent from participants for access to their clinical record by responsible individuals from the research staff or from regulatory authorities, where it is relevant to study participation.
- Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research

- Fully identifiable information is logically separate from all study data
- Identifiable data is tagged as such during database development. Identifiable data is excluded from study database downloads by default. As such there is no change of accidental export of identifiable information

All HHTU systems used are within scope of the HHTU NHS Data Security and Protection Toolkit. These have been independently checked by the NHS Digital Information Security Team. See **https://www.dsptoolkit.nhs.uk/OrganisationSearch/EE133824-HHTU**

Where central monitoring of source documents by HHTU (or copies of source documents) is required, the participant's name must be redacted before sending. Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to HHTU. All site investigators and research staff must comply with the requirements of the General Data Protection Regulation 2018 with regards to the collection, storage, processing, and disclosure of personal information, and will uphold the Regulation's core principles.

HHTU and the Sponsor will maintain the confidentiality of all participants' data in accordance with GDPR 2018 and will not reproduce or disclose any information by which participants could be identified. Representatives of HHTU and the Sponsor will need access to participant clinical records for the purposes of monitoring and source data verification. Confidentiality will be always maintained. Representatives of regulatory authorities may require access to participant clinical records for regulatory purposes only. These points will be made clear in the PIS and ICF.

The PI (or delegated person) at each site will keep a participant identification list of Participant ID numbers, names, addresses and hospital numbers. The PI must ensure that participant confidentiality is maintained and that all trial documents (e.g. consent forms) are maintained in strict confidence.

15.9 Declaration of Helsinki and Good Clinical Practice

The study will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

15.10 GCP Training

All study staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this trial. This training should be updated every 3 years or in accordance with site policy.

16.0 INDEMNITY

16.1 Potential Legal Liability of the Sponsor or employer

This is an NHS-sponsored study and NHS indemnity covers sponsor potential legal liability for harm to participants arising from the design of the research. Protocol authors with a substantive university contract will also have indemnity cover from the employing university.

16.2 Potential Legal Liability of Investigators/Collaborators

If there is negligent harm during the clinical trial, the NHS body owes a duty of care to the person harmed. NHS indemnity covers NHS staff and medical academic staff with honorary contracts only when the study has received confirmation of capability and capacity from the Trust R&D department.

16.3 Arrangements in the Absence of Legal Liability

NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Protocol authors with a substantive university contract will also have indemnity cover from their employing university. The universities do not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.
The sponsor will provide 'no-fault' indemnity for harm arising due to study procedures carried out as part of the study. The sponsor will not provide payment for medical costs for medical complications caused by failure of participants to follow instructions given or if the medical complication was not related to the study agent or research study procedure. Study associated staff employed by NHS and university will also have personal indemnity from their employers.

17.0 QUALITY CONTROL

17.1 Training Procedures

The following training procedures will be conducted to ensure quality control:

Table 12 – Training procedures

Research Nurse	Blood sampling, processing and shipment, participant identification, approach, randomisation, data collection and entry, SAE reporting process
Site PI / delegated clinicians	Eligibility assessment, consent process, prescription, AE, SAE assessment and reporting process
Clinical Trials Pharmacist	Medication dispensing procedures, accountability, and IMP destruction

17.2 Site approval, start-up procedures and on-going support

HHTU will complete a site Greenlight checklist prior the requesting Sponsor permission to open the site to recruitment. Documentation requested will include, but is not limited to:

- A copy of the REC, MHRA and HRA approval and site R&D Capacity and Capability confirmation
- A copy of the signed Clinical Trial Agreement, including PI declaration
- Completed Delegation Log and contact details.
- IWRS and REDCap access permissions to the 'live' database
- ISF release and confirmation of receipt at site

- Curriculum Vitae (CV), including evidence of GCP training for named persons.
- Copies of honorary contracts
- Pharmacy Final Green Light Confirmation Ready to Dispense Checklist

Once these documents have been received by HHTU, confirmation that the site may commence recruitment will be sent to the site PI by the Sponsor (Site Green Light). The Sponsor will copy HHTU into the site greenlight email.
Prior to recruitment start, the research team, including the PI, will attend a Site Initiation Visit (SIV) with HHTU, either face-to-face or via telephone/video conference. Clinicians and research teams (including pharmacy) at site will be trained in the data collection, data entry, filing and study interventions to comply with GCP. Study and pharmacy procedures will be clarified, the protocol reviewed in detail, and a pharmacy and laboratory manual provided. A Site Initiation Report will be written, and a copy sent to the participating site.
Remote and on-site support will be provided to sites as per their requirements during the study, mainly by the HHTU Trial and Data Management team.

17.3 Monitoring, Audit & Inspection

Site monitoring frequency will be determined by an initial risk assessment performed prior to the start of the study. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the study. Throughout the course of the study, the risk assessment will be reviewed, and the monitoring frequency adjusted as necessary.
The investigator must make all study documentation and related records available should an MHRA Inspection occur. Should a monitoring visit or audit be requested, the CI must make study documentation and source data available to the Sponsor representative. All participant data must be handled and treated confidentially.

18.0 REFERENCES

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19.0 APPENDICES

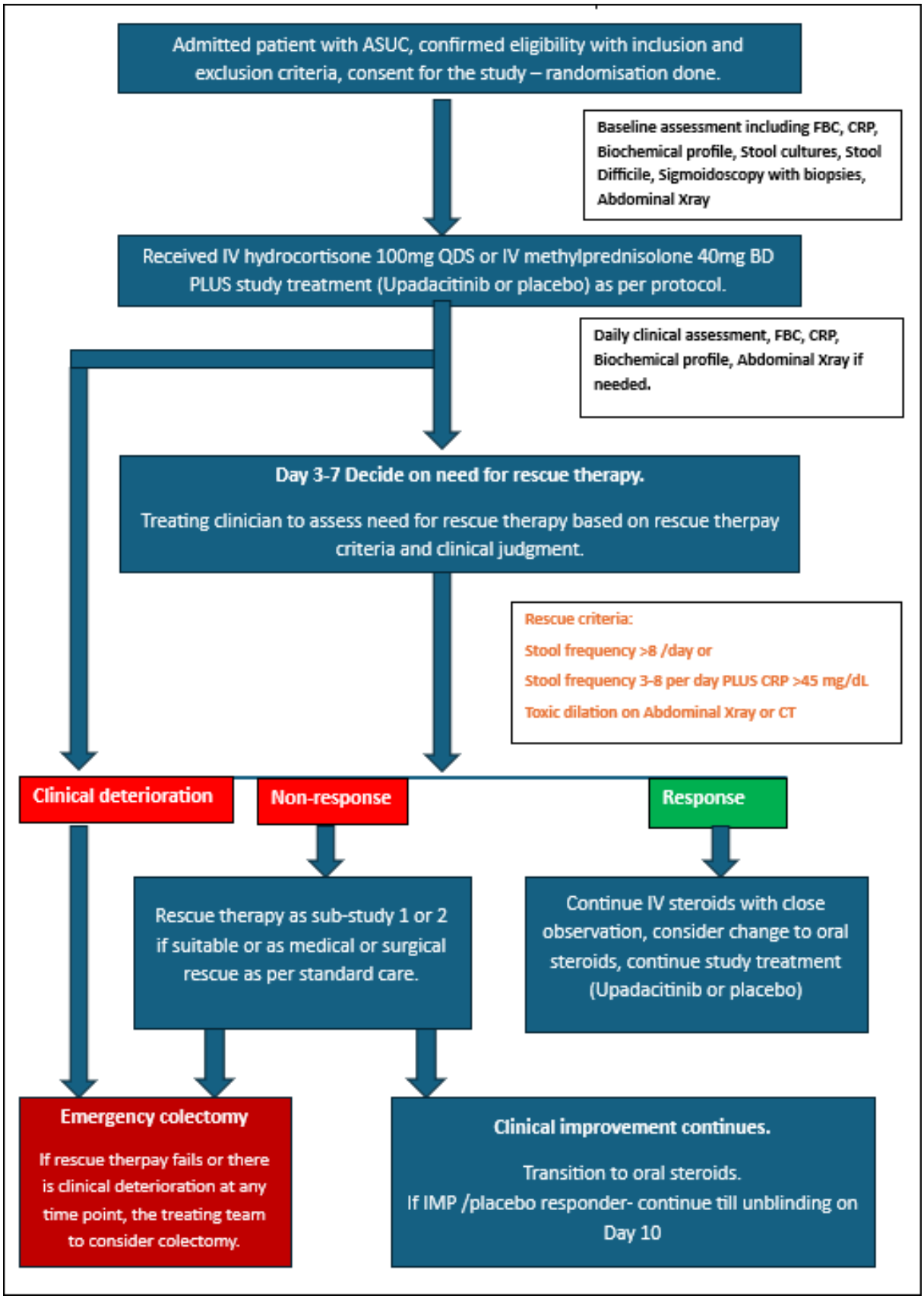
APPENDIX A: CLINICAL RESPONSE DECISION ASSESSMENTS

A Colectomy assessment
A review of adverse events
A physical examination by a delegated clinician
Recording of vital signs (BP, RR and T)
A review and update of concomitant medication (including previous biologic and immunosuppressants, Janus Kinase Inhibitors, SiP agonist therapy)
A review of SOC bloods (FBC, U&E's LFT's CRP) (if still an inpatient)
A review of SOC stool cultures (MC&S and C.Diff) (if not previously available)
The Truelove and Witts Severity Index (MTWSI) (see appendix B&D)

APPENDIX B: MODIFIED TRUELOVE AND WITTS SCALE INDEX

Criteria	Mild	Moderate	Severe
Bowel Movement (number a day)	Fewer than 4	4 - 6	6 or more plus at least 1 of the features of systemic upset (marked with * below)
Blood in stools	No more than small amounts of blood	Between mild and severe	Visible blood
Pyrexia (temperature greater than 37.8°C*	No	No	Yes
Pulse rate greater than 90 bpm*	No	No	Yes
Anaemia*	No	No	Yes
C Reactive Protein (CRP) in mg/L	30 or below	30 or below	Above 30

APPENDIX C: CLINICAL DECISION TREE



APPENDIX D: MODIFIED TRULOVE AND WITTS SCORE

Modified Truelove Witts Severity Index Form

Symptom Checklist (Circle the score that applies)

Category	Score
Diarrhoea (Number of daily stools)	
0–2	0
3–4	1
5–6	2
7–9	3
⩾10	4
Nocturnal diarrhoea	
No	0
Yes	1
Visible blood in stool (% of movements)	
0%	0
50%	1
⩾50%	2
100%	3
Faecal incontinence	
No	0
Yes	1
Abdominal pain or cramping	
None	0
Mild	1
Moderate	2
Severe	3
General well-being	
Perfect	0
Very good	1
Good	2
Average	3
Poor	4
Terrible	5
Abdominal tenderness	
None	0
Mild and localised	1
Mild to moderate & diffuse	2
Severe or rebound	3
Need for antidiarrheal drugs	
No	0
Yes	1

Total Score (Add all the circled scores together)

Total MTWSI score (between 0–21): ☐

APPENDIX E: PARTIAL MAYO SCORE

Category	Score
Stool frequency (per day)	
Normal number of stools	0
1-2 more than normal	1
3-4 more than normal	2
⩾ 5 more than normal	3
Rectal bleeding (indicate the most severe bleeding of the day)	
None	0
Streaks of blood with stool in less than half of the cases	1
Obvious blood with stools in most cases	2
Blood alone passes	3
Physician's global assessment	
Normal	0
Mild disease	1
Moderate disease	2
Severe disease	3

Total Score (Add all the circled scores together)

Total Partial MAYO Score (between 0–9): ☐

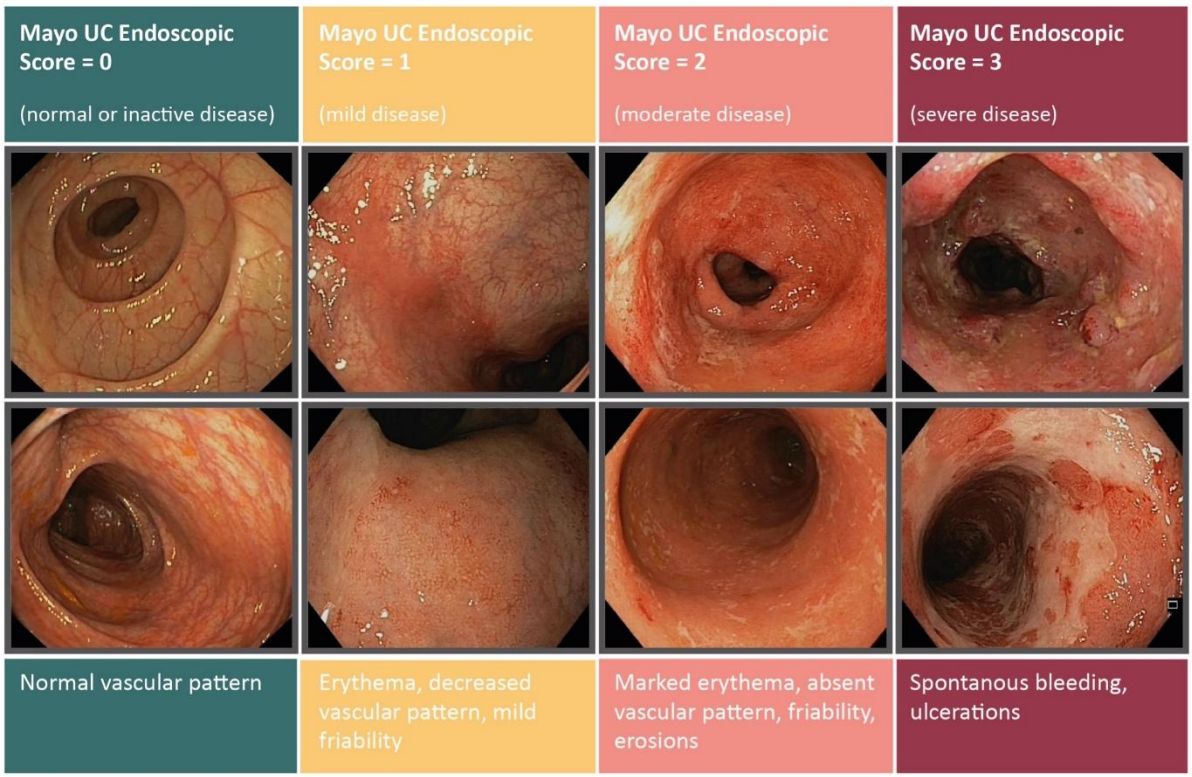
APPENDIX F: TRAVIS CRITERIA

Travis or Oxford criteria

More than 8 bowel movements on Day 3
OR
3 to 8 bowel movements and CRP > 45 mg/L

APPENDIX G: MAYO ENDOSCOPY SCORE

Score	Disease activity	Endoscopic features
0	Normal or inactive	None
1	Mild	Erythema, decreased vascular pattern, mild friability
2	Moderate	Marked erythema, absent vascular pattern, friability, erosions
3	Severe	Spontaneous bleeding, ulceration



APPENDIX H: UCEIS ENDOSCOPY SCORE

Vascular pattern	**Normal**	**0**
	Patchy obliteration	+1
	Obliterated	+2
Bleeding	**None**	**0**
	Mucosal	+1
	Luminal mild	+2
	Luminal moderate or severe	+3
Erosions and ulcers	**None**	**0**
	Erosions	+1
	Superficial ulcer	+2
	Deep ulcer	+3

