Statistical Analysis Plan

TRIAL FULL TITLE	A Phase II randomised placebo controlled double blinded trial of Interleukin 1 blockade in Acute Severe Colitis
EUDRACT NUMBER	2017-001389-10
SAP VERSION	1.0
ISRCTN NUMBER	43717130
SAP VERSION DATE	18/03/2022
TRIAL STATISTICIAN	Dr Wendi Qian
TRIAL CHIEF INVESTIGATOR	Professor Arthur Kaser / Dr Tim Raine
SAP AUTHOR	Simran Vaja

1 SAP Signatures

I give my approval for the attached SAP entitled IASO dated <18/03/2022>

Chief Investigator

Name: Timothy RAINE

Signature: 

Date: 23-March-2022

Statistician

Name: WENDI QIAN

Signature: W Q

Date: 23 March 2022

2 Table of Contents

3 Abbreviations and Definitions

AE	Adverse Event
AR	Adverse Reaction
ARR	Absolute Risk Reduction
ASUC	Acute Severe Ulcerative Colitis
BPM	Beats per minute
CRF	Case Report Form
CMV	Cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
CUCQ-32	Crohn's and Ulcerative Colitits Questionnaire
CTIMP	Clinical Trial of an Investigational Medicinal Product

DoB	Date of Birth
eGFR	Estimated Glomerular Filtration Rate
EQ-5D	EuroQol – 5 Dimension
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
GI	Gastro-Intestinal
g/dl	Grams per decilitre
HR	Heart Rate
IASO	Interleukin 1 blockade in Acute Sever Colitis
IBD	Inflammatory Bowel Disease
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iDMC	Independent Data Monitoring Committee
IL-1	Interleukin-1 (including A and B variants)
IL-6	Interleukin-6
IL-10	Interleukin-10
IL-1RA	IL-1 receptor antagonist
IMP	Investigational Medical Product
IV	Intravenous
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
Mm/h	Millimetres per hour
MTWSI	Modified Truelove Witts Severity Index
PI	Principle Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SC	Subcutaneous
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TNF- α	Tumour Necrosis Factor α
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UC	Ulcerative Colitis
VAS	Visual Analogue Scale
WBC	White Blood Cell

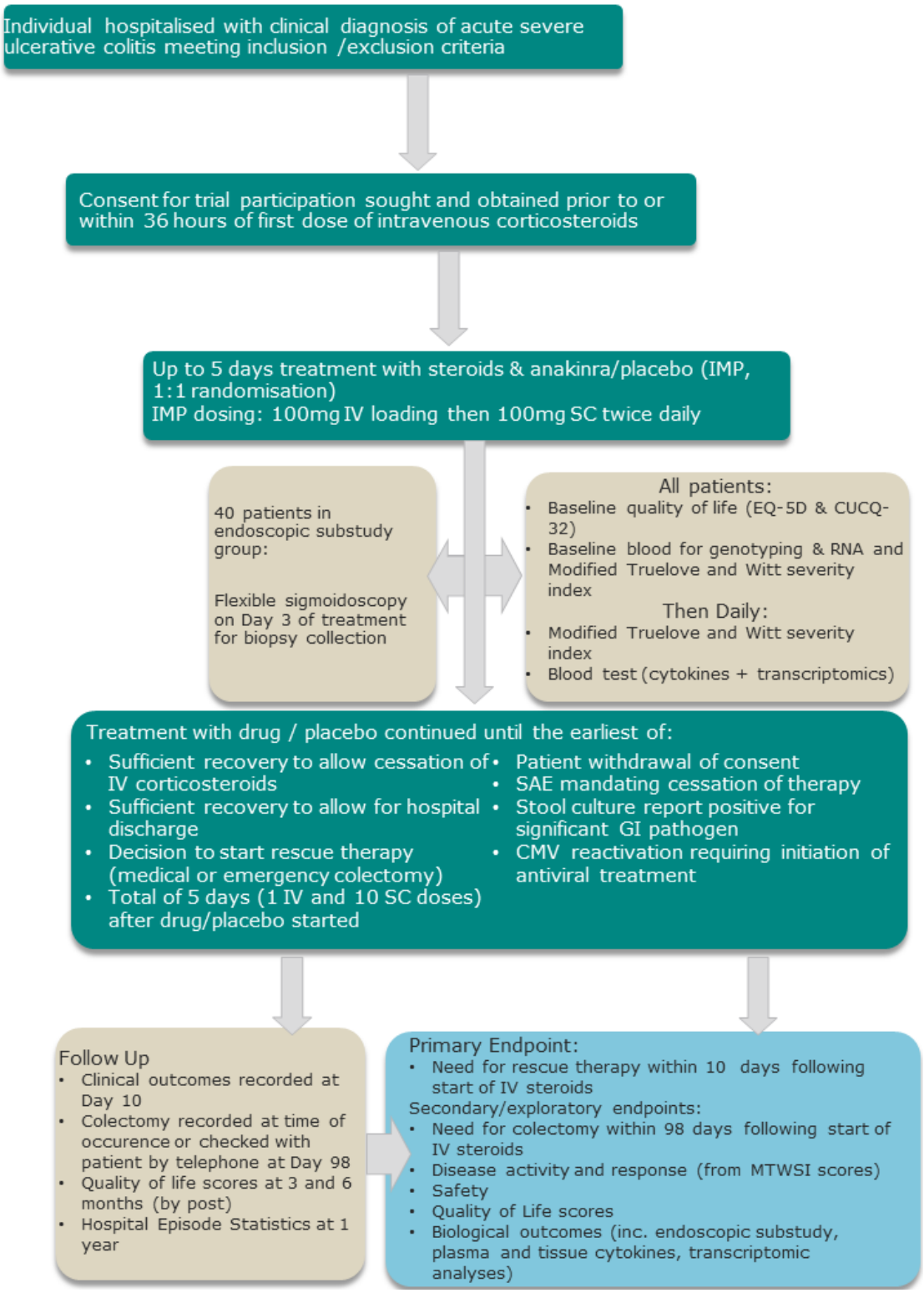
4 Introduction

This SAP is based on IASO protocol Version 3.0 date 30/10/2018 of the protocol and the annotated CRF Version 2.0 date 01/08/2018.

4.1 Summary of IASO trial

IASO is a randomised, two-arm, placebo-controlled, multi-centre, double-blinded study in patients with acute severe ulcerative colitis (ASUC). This trial is to test whether giving patients another medicine, called anakinra, in addition to the initial treatment with corticosteroids will increase the number of patients who get better without needing to go on to receive additional medical treatments or surgery. A feasibility and an interim futility analyses were planned.
The study flow chart can be found below.

IASO: Trial overview



4.2 Purpose of the analyses

The study was stopped early following the planned interim futility analyses (recommended by the Independent Data Monitoring Committee, and approved by the Trial Steering Committee on 17 March 2021). The end of study final statistical analyses with all patients recruited are to be performed when data are cleaned.

5 Study Objectives and Outcome Measures

5.1 Study Objectives

The primary aim of this trial is to compare the clinical effects (in terms of reduction in rescue therapy incidence) of anakinra with placebo when given in addition to current standard of care in patients with ASUC.

The secondary aims include assessing safety and need for colectomy.

5.2 Outcome Measures

5.2.1 Primary outcome measure

Incidence of medical or surgical rescue therapy within 10 days following the commencement of intravenous corticosteroid therapy.

Need for rescue therapy reflects failure to respond to initial treatment and is judged against clinical criteria between 3-5 days after commencement of IV corticosteroid therapy (see Appendix 4 in the protocol). 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 intravenous 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 intravenous corticosteroids (recorded in Day 10 CRF page 2 of 4).

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

- Medical rescue therapy: Date and approximate time of first treatment administration (recorded in the Rescue Therapy by Day 10 (+3) CRF page 1 of 2)
- Surgical rescue therapy: Date and approximate time of start of surgery (recorded in the Rescue Therapy by Day 10 (+3) CRF page 1 of 2)

5.2.2 Secondary outcome measures

1. Incidence of Colectomy within 98 days following commencement of IV corticosteroid therapy.
2. Burden of disease activity, measured by daily modified Truelove and Witts severity index (MTWSI) scores over Days 1-5 after initial IMP administration.
3. Time to clinical response (defined as 2nd consecutive day with MTWSI<10)
4. Time to medical or surgical rescue therapy, measured according to the time after the first dose of IV corticosteroids until the time that rescue therapy occurs (using definitions as set out in primary endpoint). Data will be captured up to the same time point as the primary endpoint
5. Incidence of AEs and SAEs, measured until Day 10 (+3) following commencement of IMP treatment.

5.2.3 Exploratory outcome measures (to be analysed separately in future)

1. Patient-reported quality of life (EQ-5D-5L and CUCQ-32[26]) at baseline (± 1 day) and at approximately 3 and 6 months following commencement of IMP treatment
2. Endoscopic response at Day 3 (± 1 day) (via standardised endoscopic scoring completed by a local and a central blinded assessor) following commencement of IMP treatment (endoscopic sub-study group only) (not relevant due to the study stopped early)
3. Histological disease progression prior to and during treatment based on immunohistochemistry and other histology staining techniques (not relevant due to the study stopped early)

6 Study Methods

6.1 Inclusion-Exclusion Criteria and General Study Population

6.1.1 Inclusion Criteria

To be included in the trial the participant must:

- Be aged 16-80 years inclusive
- Have given written informed consent to participate
- Be hospitalised with clinically confirmed or suspected ASUC and a MTWSI score ≥11
- Have a requirement for treatment with IV corticosteroids in the judgement of the treating clinician, with the possibility to receive a first dose of IMP within 36 hours of commencement of IV corticosteroids

6.1.2 Exclusion Criteria

The presence of any of the following will preclude participant inclusion:

- Pregnant or breast-feeding women
- Oral corticosteroid dosing for the treatment of UC and for a duration of 8 weeks or more immediately prior to commencement of IV corticosteroid dosing
- History of severe hepatic impairment (e.g. Child-Pugh = Grade C)
- Moderate or Severe renal impairment (estimated glomerular filtration rate [eGFR] <60ml/min/1.73m^2)
- Neutropenia (neutrophil count <1.5x10^9/l)
- Previous treatment with anakinra for any indication
- Documented hypersensitivity to the active substance or to any of the excipients or to E. coli derived proteins; latex allergy
- Evidence (from blood cultures etc) or clinical suspicion of systemic infection*
- Current or previous cytomegalovirus (CMV) infection requiring treatment with anti-viral agents
- Current treatment with anti-TNF-α/ciclosporin therapy or anti-TNF-α/ciclosporin discontinuation within previous 16 weeks
- A history of pulmonary TB infection
- Any absolute contraindication to IV corticosteroid
- History of malignancy (with the exception of non-melanoma skin cancer) or colonic dysplasia
- Rectal therapy in previous 14 days prior to admission (sub-study exclusion only)
- Receipt of another IMP as part of a CTIMP within the previous 16 weeks

**Concurrent prescription of antibiotics to cover for the possibility of GI infection whilst awaiting stool culture and/or PCR-based detection results, or the possibility of bacterial translocation relating to severe colitis, is not an exclusion criterion where the physician suspects ulcerative colitis is the most likely diagnosis.*

6.2 Randomisation and Blinding

6.2.1 Randomisation

Eligible participants were randomised (1:1) to anakinra:placebo using a web-based system (Sealed Envelope accessible via password-protected access). Stratified random block method is used with the following stratification factors:

- Yes/No: Previous or current therapy with any of: immunomodulators (azathioprine, 6-mercaptopurine, 6-thioguanine, methotrexate, ciclosporin) biologics (anti-TNF-α monoclonal antibodies, anti-adhesion molecule antibodies, other anti-cytokine antibodies) or oral janus kinase inhibitors
- Yes/No: Current or previous oral corticosteroid prescription(s) within 8 weeks prior to first dose of intravenous corticosteroids

The system will allocate the participant a treatment code which will relate uniquely to a supply of IMP (complete pack for up to 5 days of treatment) that is held at that trial site.

6.2.2 Blinding

Trial participants and research teams were blinded to the treatment group for the duration of the trial. Site pharmacies were also be blinded. The physical appearance of the IMPs is matched and the IMPs were presented in identical packaging. SC administration of the trial drug has been associated with injection site reactions. The incidence of reactions is reduced by pre-warming the pre-filled syringe prior to injection by holding the syringe in the hand, which will form part of the administration instructions. It is important to note that injection site reactions also occur with the placebo, since, in part, the reaction relates to the carrier buffer. This greatly reduces the risk of accidental unblinding.

Except in the case of a valid medical or safety reason, unblinding analyses were only be performed as part of an interim analysis by a designated unblinded statistician. The unblinded statistician will provide outcome data to the iDMC.

The web-based Sealed Envelope randomisation system will be used for emergency unblinding.

6.3 Study Variables

Table 1 shows the schedule of assessments.

Table 1. Schedule of assessments

Assessments	Screening/Baseline		Treatment phase		Follow up phase			
	Screening	Baseline	Day 0	Days 1 – 5 [1]	Day 10 (+3 days)	Day 98 (+ 14 days)	~3 Months	~6 Months
Informed consent	✓							
Eligibility assessments	✓							
Urine β-hCG[6]	✓							
Medical history review		✓						
Socio-demographic data		✓						
Questionnaires (EQ-5D-5L, CUCQ-32)		✓[9]					✓	✓
Review of standard-care blood parameters		✓		✓				
Collection of 3 research blood samples		✓[10]						
Collection of 2 research blood samples				✓				
Daily MTWSI assessment / review of standard care clinical MTWSI assessment domains		✓		✓[7]				
Stool Sample Collection		✓[8]		✓[2,7]				
Concomitant medications (full list)		✓						
Randomisation		✓						
Concomitant medications (changes since last assessment)			✓	✓				
Review of adverse events			✓	✓	✓			
Confirmation of continued eligibility to receive IMP and that IMP administration falls within 36 hour window			✓					
Rescue therapy (medical or surgical) assessment				✓	✓[5]			
Colectomy assessment				✓		✓[5]		
Sub-study-Only Assessments								
Informed consent	✓							
Flexible sigmoidoscopy and up to 12x pinch biopsy collection				✓[3]				
Administration Schedule								
IMP administration – 100 mg IV			✓					
IMP administration – 100 mg SC BD			✓	✓[4]				

[1]Treatment will continue until hospital discharge/treatment termination criteria have been met. Where possible after treatment termination, assessments and/or research sample collection will continue until hospital discharge/withdrawal/death. [2]Assessment Day 5 only ± 1 day. [3]Assessment Day 3 only ± 1 day. [4]Dosing at Day 5 (representing the 10th BD SC dose) will only occur in the event that a participant received their 1st overall SC dose in the latter part of Day 0. [5]If information not already collected. [6]for women of childbearing potential, [7]Not for participants that have undergone colectomy, [8]Stool sample collection will not be mandated in the event that waiting for a bowel movement would considerably increase the risk of missing the 36 hour window for the 1st administration of IMP. Collection is however still encouraged where possible up to 24h after the 1st IMP dose. [9]Baseline visit ± 1 day. [10]Baseline blood samples may be taken after randomisation but must be taken before the first administration of IMP

7 Sample Size

It was planned to recruit 214 patients (107 per group). This would give 85% power to detect a 20% absolute risk reduction (ARR) in the primary endpoint from a rate in the control group of 49% testing at the 5% significance level. Since the main trial observation is brief and performed in an inpatient setting, we expect negligible loss-to-follow up. The trial intervention is well tolerated and we expect low dropout rates.

Interim Analysis

The interim analysis was planned to investigate whether there would be evidence of harm or futility in the research arm based on the first 100 participants who had received at least one dose of protocol treatment and completed Day 10 assessments (primary endpoint).

The hypothesis that the absolute risk difference in the reduction of rescue therapy incidence is ≥10% using a 1-sided 2.5% significance test using logistic regression model.

8 General Considerations

8.1 Timing of Analyses

The final analysis will occur once the planned assessments for all randomised participants are completed and the data has been cleaned.

8.2 Analysis Populations

8.2.1 Full analysis population

All randomised participants who received at least one dose of IMP.

8.2.2 Randomised population

All randomised participants, regardless of whether IMP was received.

8.2.3 Safety Data Analysis Population

All randomised participants who received at least one dose of IMP. They will be analysed as treated.

8.3 Covariates and Subgroups

8.3.1 Covariates

The two stratification factors will be included in the primary analysis:

- Previous or current therapy with any of: immunomodulators (azathioprine, 6-mercaptopurine, 6-thioguanine, methotrexate, ciclosporin) biologics (anti-TNF-α monoclonal antibodies, anti-adhesion molecule antibodies, other anti-cytokine antibodies) or oral janus kinase inhibitors
- Current or previous oral corticosteroid prescription(s) within 8 weeks prior to first dose of intravenous corticosteroids

In addition the following baseline variables will be considered

- Prior diagnosis of IBD at the point of hospitalisation ('first presentation')
- Prior hospitalisation for ASUC
- Demographics

8.3.2 Subgroup analysis

To test the hypothesis that the clinical effects of anakinra in ASUC may differ between groups of patients with differing levels of prior inflammatory burden, pre-specified subgroup analyses, in the form of estimating treatment-covariate interactions, will be performed on the following baseline characteristics:

- Prior diagnosis of IBD at the point of hospitalisation ('first presentation') (mh_ibdyn)
- Prior hospitalisation for ASUC (mh_asucyn)
- Naïvety to any of: immunomodulators (azathioprine, 6-mercaptopurine, 6-thioguanine, methotrexate, ciclosporin) biologics (anti-TNF-α monoclonal antibodies, anti-adhesion molecule antibodies, other anti-cytokine antibodies) or oral janus kinase inhibitors at the point of hospitalisation. (randsv1)
- Receipt of oral corticosteroids within 8 weeks prior to first dose of intravenous corticosteroids (randsv2)
- Cases of suspected or confirmed ASUC without evidence of CMV reactivation requiring treatment with anti-viral agents or without evidence of a significant GI pathogen (withdrawal forms) (not performed as there is a total of 2 cases)
- Duration between 1st dose of IV corticosteroids to 1st dose of IMP.

The subgroup analyses will be based on the primary endpoint under Full Analysis Population.

8.4 Missing Data

Due to short and intensive period of follow up for the primary endpoint, we do not anticipate significant missing data. No imputation for the primary endpoint will be performed as there were few missing cases.

For the exploratory analyses of quality of life, which will require postal questionnaire responses some months after discharge, where we are unable to obtain missing data within 12 weeks of the 3- or 6-month time points, we will consider the standard approaches to management of missing quality of life data previously described in the CONSTRUCT trial.

For participants who withdraw consent to treatment, permission to continue to acquire data for outcome analysis will be sought. For those who do not consent to ongoing monitoring, including those who wish to withdraw entirely from the study, existing data acquired to the point of withdrawal will be included in the final study analysis, with missing data handled according to standard missing data methods, including missing-at-random (MAR) methods with sensitivity testing for deviation from MAR assumptions will be considered.

8.5 Interim Analyses and Data Monitoring

8.5.1 Adjustment of Confidence Intervals and p-values

One planned interim futility analyses only were performed. The final analysis will not be adjusted for the futility. Standard p-values and confidence intervals will be reported.

8.5.2 Documentation of Interim Analyses

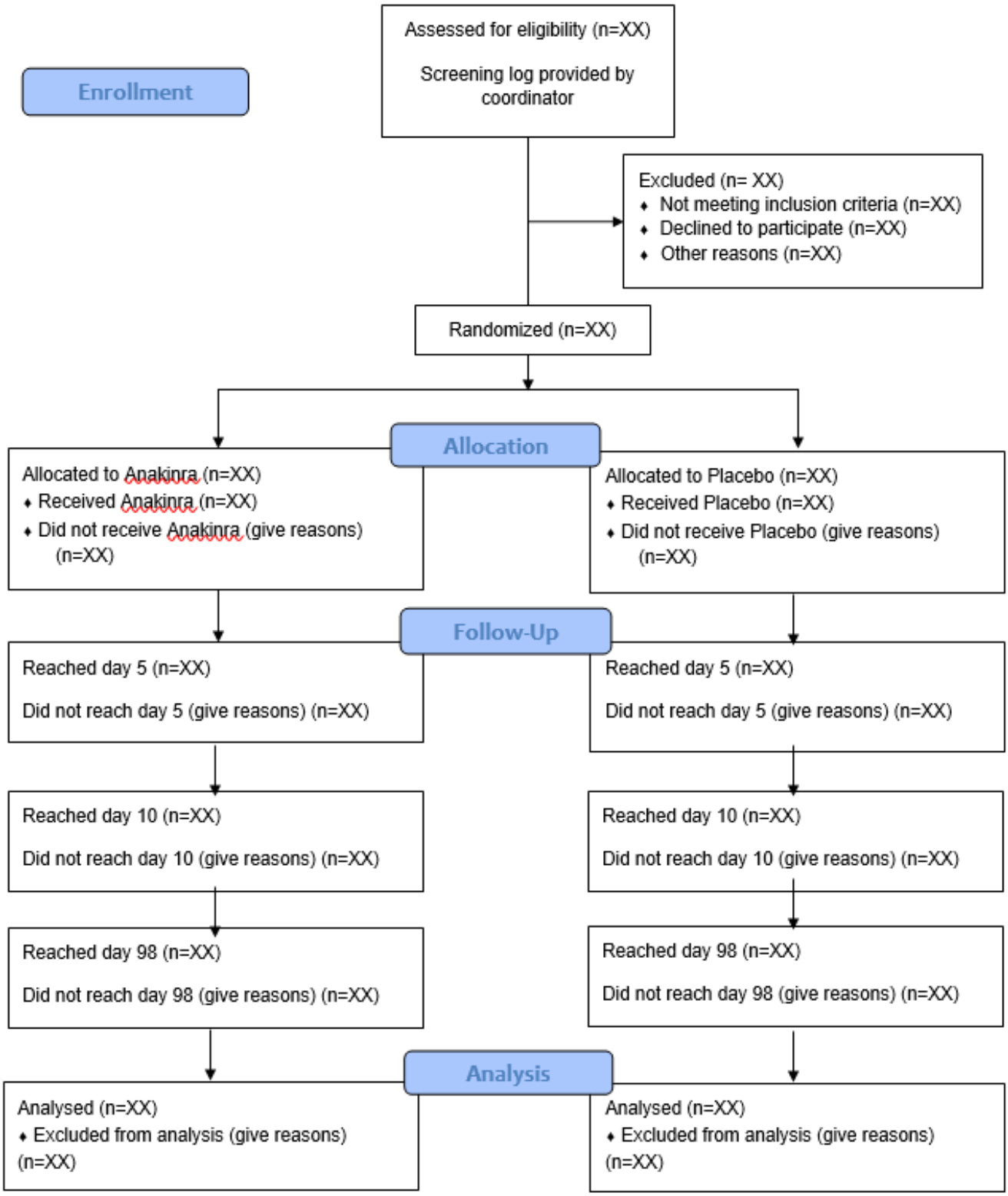
The SAP, code development, final dummy report, and all documentation regarding the interim analyses can be found in the IASO study folder.

9 Summary of Study Data

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, median, maximum, minimum and standard deviation. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported. All summary tables will be split by treatment allocation, and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

9.1 Subject Disposition

Note: screening details are to be provided by co-ordinators



9.2 Derived variables

9.2.1 Primary endpoint

Rescue therapy received by Day 10 = Yes or No for each participant.

9.2.1.1 Primary analysis

Full Analysis Population: all randomised patients who received at least one dose of IMP.

If the day 10 assessments were performed, the primary endpoint will be

- Yes, if medical/surgical rescue therapy is "yes" and the time difference between rescue therapy and first IV corticosteroid is <10 days
- No, if medical/surgical rescue therapy is "no" and the time difference between rescue therapy and first IV corticosteroid is >10 days

If the day 10 assessments were not performed, the primary endpoint will be missing

9.2.1.2 Secondary analysis

The same definition as it in the primary analysis with the randomised population.

Randomised population: all randomised patients regardless of whether IMP was received.

9.2.2 Secondary endpoints

1. Colectomy within 98 days = Yes or No for each participant

If Day 98 assessment was performed, the value =

- Yes, if colectomy is "yes" and the time difference between colectomy and first IV corticosteroid is <98 days
- No, if colectomy is "no" and the time difference between colectomy and first IV corticosteroid is >98 days

Note: checking with the Day 10 assessment too.

If Day 98 assessment was performed, the value = missing

2. Time to clinical response:

Time to clinical response is date from the first IV corticosteroid to clinical response.

Events: patients who had two consecutive days with MTWSI<10 without missing any assessments prior to the event; the date of first assessment of these two consecutive days will be used in the time to clinical response.

Censoring: date of the last consecutive assessment day 0.5 if day 1 assessment was missing; patients who had two consecutive days with MTWSI<10 but with missing assessment before will be censored at the last consecutive assessment.

3. Time to medical or surgical rescue therapy:

Time to medical or surgical rescue therapy, measured according to the time after the first dose of IV corticosteroids until the time that rescue therapy occurs (using definitions as set out in primary endpoint). Data will be captured up to the same time point as the primary endpoint.

9.3 Protocol Deviations

A listing of all major protocol deviation (eligibility, treatment error) will be provided. Additional information not recorded in the CRFs will be provided by the trial coordinators.

9.4 Demographic and Baseline Variables

The following demographic and baseline variables will be summarised according to Section 9 using all patients randomised.

9.4.1 Demographics

- Age at randomisation
- Sex
- Smoker (yes/no)

9.4.2 Stratification factors

- Previous or current therapy with any of immunomodulators, biologics, or oral janus kinase inhibitors (yes/no)
- Current or previous oral corticosteroid prescription(s) within 8 weeks prior to first dose of intravenous corticosteroids

9.4.3 Medical history

- Prior diagnosis of IBD at the point of hospitalisation
- Prior hospitalisation for ASUC
- Prior history of immunomodulators, anti-TNF therapy, and other biologic therapies
- Baseline use of immunomodulators, anti-TNF therapy, other biological therapies, steroids, and 5-ASA

- Use of immunomodulators, anti-TNF therapy, other biological therapies, steroids, and 5-ASA post randomisation

9.4.4 Scores and questionnaires

- MTWSI score
- EQ5D
- CUCQ-32
- Endoscopic Mayo score (baseline score)

9.5 Treatment Compliance

The detailed treatment received will be summarised. Whether they received the IV dose, the time between first IV and first IMP, the number of SC IMP doses received, and time between doses will be summarised.

10 Efficacy Analyses

We will report summary statistics on the primary and secondary endpoints (safety AE and SAE summary will be reported under Safety Analyses) according to treatment group assigned.

10.1 Primary Efficacy Analysis

The primary efficacy analysis will be based upon the Full Analysis Population.

10.1.1 Primary endpoint

The primary analysis will consist of 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, using logistic regression to adjust for important baseline covariates.

The covariates listed in Section 8.3.1 will be considered for the logistic regression model. If they are significant in the univariate analysis ($p<10\%$) or selected using stepwise regression with critical p-value=0.15), then they will be included in the model.

A listing will be included for those who did not have a rescue therapy variable due to not having day 10 assessment.

10.1.2 Secondary endpoints

The incidence of colectomy will be compared in a similar logistic regression model to estimate the effect of treatment with anakinra. The covariates listed in Section 8.3.1 will be considered for the model. If the model does not converge, a logit link will be used instead of an identity link. The odds ratio will be presented.

Reasons why participants did not complete day 98 assessments will be listed.

To test the burden of MTWSI, a random effects mixed model for repeated measurements will be fitted. The fixed effects will include treatment allocation, baseline MTWSI, time of assessments (days 1-5), and an interaction between treatment allocation and time. The dependent variable will be the total MTWSI score repeated from days 1 to 5. A random intercept will be fitted to allow the average MTWSI score to be higher or lower for each individual.

For the time to clinical response and time to medical or surgical rescue therapy variables, Kaplan-Meier curved will be produced and log rank tests will be performed. A cox model will be fit to the data, including treatment allocation and the two stratification factors.

10.2 Secondary Efficacy Analyses

The secondary analysis will be based upon the Randomised Population.

1. The same analyses performed previously will be repeated with this population – some of the secondary endpoints will have a different definition for the denominator due to the different population being used.
2. Complier Average Causal Effect (CACE) analysis will be used to assess the influence of the amount of treatment received, as distinct from treatment assigned.

A complier in the anakinra treatment arm for this analysis is defined as those who:

- Completed 5 days of treatment; or
- Completed day 5 treatment with missing doses; or
- Stopped treatment early with:
  - sufficient recovery to allow for cessation of IV steroids
  - decision to commence medical or surgical rescue therapy
  - hospital discharge

Compliance will be a binary outcome; yes if the criteria above is satisfied, and no if not. A list on "non-compliers" for this analysis will be provided. No covariates will be adjusted for this analysis.

$$\text{CACE} = \frac{\text{Day 10 rescue therapy rate in the anakinra arm whe were compliers}}{\text{Day 10 rescue therapy rate in the placebo arm who would have complied}}$$

The Day 10 rescue therapy rate in the placebo who would have complied will be derived based on the following assumptions:

- Randomisation has worked, i.e. the proportion of compliers is the same in the two arms of the trial, so the number of controls who would have been 'non compliers with the treatment' (if they had been offered it), is the same as the number of non-compliers with the treatment who were offered it
- Compliers get treatment if and only if randomly allocated to treatment, and non-compliers never get the treatment regardless of allocation
- Being offered a treatment does not affect your outcome

3. Subgroup analysis on the primary endpoint will be carried out, as defined in Section 8.3.2

11 Safety Analyses

This will be based on safety population for all data included in the dataset lock.

11.1 Adverse Events

- Incidence of SAEs, AEs measured until Day 10 (+3) following commencement of IMP treatment
- Lists of SAEs and infections
- Listing of AEs
- AE/SAE incidence by treatment arms
- Summary of AEs by severity and treatment allocation
- Summary of AEs by System Organ Class and treatment allocation
- Listing of AEs probably or possibly related to IMP

11.2 Clinical Laboratory Evaluations

11.2.1 Standard care bloods

The following standard care bloods were collected at baseline and days 1-5 and will be summarised according to section 9 and also presented with a spaghetti plot for

each measurement by treatment allocations for all patients received at least one dose of IMP:

- Monocyte count
- Neutrophil count
- Lymphocyte count
- Total WBC count
- Platelet levels
- Albumin levels
- Haemoglobin levels
- CRP levels

11.2.2 Research sample collection

Research blood samples were collected at baseline and days 1-5. Stool samples were collected at baseline and day 5.

The number of expected samples and received samples will be provided, with reasons why samples were not collected.

12 Analysis on exploratory outcome measures

Patient reported quality of life (EQ-5D-5L and CUCQ-32) at baseline and 3 and 6 months

Summary scores/sub scores for each questionnaire will be derived based on the corresponding questionnaire manual. The analyses will be based on Full Analysis Population.

12.1 Descriptive statistics

Summary statistics (mean, std, median, p25-p75, range) of each score at baseline, month 3, month 6 by treatment allocation

12.2 Mixed model for repeated assessments

The following fixed effects will be included:

- Treatment allocation
- Baseline score
- Time of assessment (3 months and 6 months)
- Interaction between treatment allocation and time of assessment

- Stratification factors

The dependent variable is the summary score at month 3 and month 6, and the summary score of change from baseline at month 3 and month 6.

12.2.1 Impact of need for rescue therapy and for colectomy

Fixed effects to be considered are:

- Baseline score
- Rescue therapy received at Day 10 assessment including the patient received the treatment on day 11
- Time of assessment
- Interaction between rescue therapy x time of assessment with and without treatment allocation
- Interaction between treatment allocation and time of assessment

Assuming the colectomy was performed prior to month 3 QoL assessment for all patients. The same analyses with the variable rescue therapy received replaced by the variable colectomy received

13 Further exploratory analyses

13.1 Predicting need for rescue therapy or colectomy

The analyses will be based on the randomised population.

13.1.1 Validation of existing score

The outcome used will be the need for rescue therapy or colectomy

Contingency tables of the existing cut points will be provided, so that the sensitivity and specificity can be assessed. The predictors will be used univariately in a logistic regression model with a corresponding ROC curve. The model results will be presented, and the ROC curve will also display the area under the curve (AUC).

13.1.1.1 Oxford index (1996)

Predictors: After 3 days of treatment (Day 3 assessment in the IASO CRF): frequent stools, raised CRP

Cut points: frequent stools (>8/day) (this will be assessed as >7/day for our data due to the variable grouping), or raised CRP (>45 mg/l) with and with treatment allocation

13.1.1.2 CRP/albumin ratio (CAR) (Gibson et al , 2018)

Predictors: day 3 assessment in the IASO CRF: CAR; and CAR and stool frequency

Cut points: CAR>0.85; CAR>0.85 and stool frequency >3 (Dublin Index)

13.1.2 Exploring new predictors

The outcomes will be:

1. Day 10 rescue therapy including both medical and surgical treatment
2. Surgery by day 98

Variables assessed at baseline and the first 3 days will be considered univariately. In particular:

Baseline:

Phenotype

- Age at Day 0 (date of dose 1(IV))
- Age at diagnosis (approximate age at initial UC diagnosis)
- Sex
- Smoking status
- Prior IMM (stratification 1: previous or current therapy with any of immunomodulators)
- Steroid prior to admission (stratification 2: previous or current oral corticosteroid)
- Symptom duration prior to admission
- Stool frequency
- Previous hospitalisation for ASUC
- Symptom Severity (MTWSI) Score Collection
- Previous hospitalisation for ASUC
- Symptom Severity (MTWSI) Score Collection

Endoscopy data

- Mayo score (where available)

Treatment

- Use of IV methylprednisolone vs IV hydrocortisone

Lab data

- CRP
- Hb
- WCC
- Albumin
- CRP:Albumin ratio
- Neutrophil count
- Monocyte count:
- Lymphocyte count
- Platelet levels

Change from Day 0 defined as $\frac{\textbf{Assessment at Day 1}}{\textbf{Assessment at Day 0}}$ **:**

- CRP
- Hb
- WCC
- Albumin
- CRP:Albumin ratio
- Neutrophil count
- Monocyte count:
- Lymphocyte count
- Platelet levels
- MTWSI score

Variables considered at Day 1, Day 2, Day 3 together with the baseline variables:

- CRP
- Hb
- WCC
- Albumin
- CRP:Albumin ratio
- Neutrophil count
- Monocyte count:

- Lymphocyte count
- Platelet levels

13.2 Success of medical rescue therapy

The population is all patients who had rescue therapy at day 10 assessment.

13.2.1 Validation of existing score

13.2.1.1 Cacheux W, Seksik P, Lemann M, et al. Predictive factors of response to cyclosporine in steroidrefractory ulcerative colitis. Am J Gastroenterol 2008;103:63742

The outcome is time from rescue therapy until surgery (assessed at day 98) or censored at the date of withdrawal or day 98 if no surgery had been performed.

A cox model will be fit to the data, with the following factors to be considered univariately:

- CRP>45mg/L at the last available time point before rescue therapy
- Mayo 2 vs Mayo 3

13.2.1.2 Australian study

Australian study of 54 patients found that a Mayo endoscopic score of 2 (as opposed to 3) was predictive of avoidance of colectomy within 12 months.

The binary outcome is surgery by day 98.

A contingency table for MAYO score 2 and MAYO score 3 will be presented. A logistic regression model will be fit to the data with MAYO score as a predictor, and a corresponding ROC curve with the AUC will be displayed.

The factors to be considered include:

- Mayo 2 vs Mayo 3

13.2.1.3 CRP/albumin ratio

A CRP/albumin cut off 0.37 at hospital discharge predicted subsequent colectomy within 12 months with an area under receiver operating curve of 0.73. Pre-treatment CRP and albumin levels were not predictive of colectomy.

The binary outcome is surgery by day 98.

A contingency table for CRP/albumin ratio 0.37 will be presented. A logistic regression model will be fit to the data with CRP/Albumin ratio as a predictor, and a corresponding ROC curve with the AUC will be presented.

The factors to be considered include:

- CRP/albumin ratio 0.37 at the last available time point before rescue therapy

13.2.2 Exploring new predictors

The same baseline variables considered under section 13.1.2 together with the lab data assessed at the last available time point before rescue therapy.

The outcomes will be:

1. Time from rescue therapy until surgery
2. Surgery by day 98

Similar further exploratory analysis for each arm will be performed

14 Figures

The following figures will be produced:

- A CONSORT diagram showing patient disposition
- Plot of 95% CI of the absolute difference of rescue therapy (primary endpoint)
- Spaghetti plots to show the change in standard care bloods over time
- Plot of 95% CI of the absolute difference of colectomy (98 day)
- Kaplan Meier curves for time to event variables
- Spaghetti plots for EQ5D, CUCQ-32, and MTWSI scores over time

15 Reporting Conventions

Pvalues $\geq$0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

16 Technical Details

The trial statistician will be responsible to develop a program to produce the dummy report (using the dummy concealment list). Once they are happy with the code, they will input the real concealment list.

The SAP is based on Version 3.0 of the protocol. The software package R version 3.6.1 is in use at the time of writing, but if upgrade will be documented. Copies of the code written will be stored. Each report and individual table of graph will have:

- The date and time included
- The name of the code file that produced the analysis
- The author
- A log capturing the version of the software and any external addon code used.
- Population used

The version control system Git will be used and individual code files will also have comments that convey:

- the author
- the date and time of writing
- description of any revisions
- references to inputs and outputs
- reference to any parent code file that runs the child code file

A reviewing statistician will independently reproduce the following:

- Primary outcome summary statistics

17 Summary of Changes to the Protocol

Amendment No.	Protocol version no.	Date	Details of changes made
1	1.1	18 September 2017	Modified Section 11.4 and changed units/value of eGFR as part of the response to the MHRA review.
2	1.2	13 October 2017	ISRCTN number added, emc website link removed from Section 11.1.1.8
3	2.0	25 May 2018	Update to the number of centres in the trial (Section 9.2)
4	3.0	30 October 2018	- Updated Trial Statistician - Realignment of secondary/exploratory objectives and addition of one exploratory outcome - Expansion of safety secondary outcome to include AEs - Addition of a timing window (± 1 day) for collection of baseline patient-reported questionnaires and alignment of wording related to subsequent questionnaire collection - Changed requirements for Stool sample collection at baseline - Addition of option to receive paraffin-embedded tissue from sites from routine biopsies - Minor updates to eligibility criteria - Clarification of the order/timing of randomisation - Exemption of participants from D5 stool sample collection following colectomy - Addition of updated funder disclaimer - Update to include 2018 Data Protection Act - Clarification regarding timing of first IMP dose and administration of IV corticosteroids - Administrative updates

18 Listing of Tables, Listings and Figures

A listing of the tables, listings, and figures are given in the following document:

meta_table_v0.1.csv