Clinical Study Protocol

Drug Substance	Tralokinumab CAT-354
Study Code	D2211C00001
Edition Number	1.0
Date	

A phase IIa, randomised, double-blind, placebo-controlled, parallel-arm, multicenter study to evaluate the efficacy and safety of tralokinumab (CAT-354), a recombinant human monoclonal antibody directed against interleukin-13 (IL-13), as add-on therapy, on clinical response in patients with active, moderate-to-severe, ulcerative colitis

Sponsor: AstraZeneca AB,

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

A phase IIa, randomised, double-blind, placebo-controlled, parallel-arm, multicenter study to evaluate the efficacy and safety of tralokinumab (CAT-354), a recombinant human monoclonal antibody directed against interleukin-13 (IL-13), as add-on therapy, on clinical response in patients with active, moderate-to-severe, ulcerative colitis

International Co-ordinating Investigator or Principal Investigator or National Co-ordinating Investigator

Study site(s) and number of patients planned

This study will be conducted at approximately 30 study sites in approximately 8 European countries. The target is to randomise 110 patients.

Study period		Phase of development
Estimated date of first patient enrolled	Q1	IIa
Estimated date of last patient completed	Q1	IIa

Objectives

Primary objective

The primary objective of the study is to assess the effect of tralokinumab compared with placebo in patients with active ulcerative colitis (UC) by assessment of clinical response, as defined by the Mayo score, at week 8.

Secondary objectives

- To assess change in Mayo score from baseline to week 8.
- To assess mucosal healing at week 8.
- To assess change in partial Mayo score from baseline to week 4, 8, 12, 16, 20, and 24.
- To assess the proportion of patients in clinical remission, as defined by the Mayo score, after 8 weeks.

- To assess histology in biopsies from colonic mucosa at baseline and week 8.
- To assess markers of disease activity and intestinal leakiness in serum and faeces at baseline, week 4, 8, 12, 16, 20, and 24.
- To assess the pharmacokinetics and immunogenicity of tralokinumab.

Safety objective

To evaluate the safety and tolerability of tralokinumab by assessment of reported Adverse Events (AE), safety laboratory values, electrocardiograms, vital signs, weight, and physical examination findings.

Pharmacogenetic objective

To collect and store DNA for future exploratory research into genes/genetic variation that may influence response to treatment of UC (ie, distribution, safety, tolerability and efficacy) and/or predisposition to, or progression of UC.

Study design

This is a phase IIa, randomised, double-blind, placebo-controlled, parallel-arm, multicenter study to evaluate the efficacy and safety of 300mg tralokinumab sc. All patients will continue background therapy for UC as per local standard of care in addition to the investigational product (IP).

Target patient population

110 adult patients are planned to be randomised. Patients should have moderate to severe UC (Mayo score 6-12) and with a valid diagnosis at least 90 days prior to randomisation and receiving background UC therapy.

Investigational product, dosage and mode of administration

Tralokinumab (CAT-354) 300 mg will be administered as 2 sc 150 mg injections every 2 weeks during a 12 week period.

Comparator, dosage and mode of administration

Placebo will be given as 2 sc injections every 2 weeks during a 12 week period.

Background medications, dosage and mode of administration

IP will be given as add-on medication for patients treated for UC according to the local standard of care. Accepted background medications for UC are:

- 5-ASA containing medications,
- purine analogues (azathioprine or 6-mercaptoprurine), and/or

- low dose glucocorticosteroids (≤ 20 mg oral prednisolone or equivalent daily).

All enrolled patients must receive at least 5-ASA containing medications, with the exception of patients refractory to 5-ASA containing medications or unable to tolerate 5-ASA containing medications.

The dose of background therapy may be decreased during the study, but administration of IP must be discontinued if intensified therapy for UC is regarded medically necessary by the investigator.

Duration of treatment

Following a one week enrolment period, patients will be randomised to 12 weeks double-blind treatment. Thereafter patients will enter 12 weeks follow-up off-treatment. The total length of the study is 25 weeks.

Outcome variable(s):

Primary Efficacy variable

Clinical response is defined as a decrease in Mayo score from baseline of at least 3 points and at least 30% with an accompanying decrease in the sub score for rectal bleeding of at least 1 point or absolute sub score for rectal bleeding of 0 or 1.

Secondary variables

- Change from baseline in Mayo score.
- Mucosal healing, defined as an improvement of the endoscopy subscore (from the Mayo score) from 3 or 2 to 0 or 1 point, or from 1 to 0 points.
- Change from baseline in partial Mayo score.
- Clinical remission, defined as Mayo score of 2 or lower with no individual sub-score exceeding 1 point.
- Histologic disease activity: modified Riley score.
- Markers of disease activity and intestinal leakiness in serum and faeces: CRP and albumin (in serum), calprotectin (in faeces).
- Immunogenicity: incidence of anti-drug antibodies (ADA) to tralokinumab in serum.
- Plasma pharmacokinetics (PK) parameters.
- Adverse events, safety laboratory variables, ECG, vital signs (BP, pulse, and temperature), weight, and physical examination.

Statistical methods

Primary variable, clinical response at week 8, and the secondary variables, mucosal healing and clinical remission at week 8, will be analyzed using the Cochran-Mantel-Haenszel chi-square test, stratified by glucocorticosteroid-refractory status.

Change from baseline in Mayo score and partial Mayo score will be treated as either ordered categorical variables or as continuous variables, depending on the distribution of the data. Mayo score will be analyzed using either ANCOVA or cumulative logit methodology. Partial Mayo score will be analyzed using repeated measures analysis. Repeated measures analysis will also be used to analyze change from baseline in markers of disease activity (CRP, calprotectin) and change from baseline intestinal leakiness (albumin). Modified Riley score will be compared between groups using a stratified Wilcoxon test, with baseline score as the stratification variable.

Safety variables will be presented descriptively.

All efficacy analyses will be based on the full analysis set, safety analyses will be addressed with the safety analysis set.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug antibodies
AE	Adverse event (see definition in Section 6.4.1)
ALP	Alkaline phophatase
ALT	Alanine aminotransferase
ASA	Aminosalicylic Acid
AST	Aspartate aminotransferase
AZA	Azathioprine
cc	cubic centimeters
CD	Crohn's Disease
CP	Centipoise
CMV	Cytomegalovirus
CRF	Case Report Form (electronic/paper)
CRP	C-reactive Protein
CSA	Clinical Study Agreement
CSR	Clinical Study Report
DAE	Discontinuation of Investigational Product due to Adverse Event
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
EMA	European Medicine Agency
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
Ig	Immunoglobulin
IL	Interleukin
IP	Investigational Product

Abbreviation or special term	Explanation
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LIMS	Laboratory Information Management System
LLOQ	Lower Limit of Quantification
LSLV	Last Subject Last Visit
MHC	Major Histocompatibility Complex
NKT-cell	Natural Killer T-cell
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
PGx	Pharmacogenetic research
PI	Principal Investigator
mRNA	Messenger Ribonucleic Acid
SAE	Serious Adverse Event (see definition in Section 6.4.2).
SNP	Single Nucleotide Polymorphism
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
UCGHQ	Ulcerative Colitis Global Health Question
ULN	Upper limit of normal
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

1.1.1 Ulcerative Colitis (UC)

UC is one of the two main types of inflammatory bowel disease (IBD), the other being Crohn's disease (CD). UC is characterized by relapsing and remitting inflammation of the colon, including rectum, restricted to the mucosa. The inflammatory process results in the most common presenting symptoms: rectal bleeding and diarrhea with or without mucus (Danese and Fiocchi 2011). Most UC patients have mild disease confined to the distal colon and rectum. Mild UC frequently responds well to medical treatment. Moderate disease is found in 30% of patients, while severe disease affects 10%. Patients with moderate to severe UC may experience serious life-threatening complications. In addition to the immediate effects of disease flares, these patients are at risk of developing long-term life-threatening complications. Long-term studies indicate that approximately 50% of UC patients relapse in any given year. The loss of disease control over time results in considerable impact on patients' quality of life and their use of healthcare resources.

1.1.2 Current management of UC

Current medical management of UC aims at inducing and maintaining remission. Therapy is tailored to the individual patient. Alternatives include 5-aminosalicylic acid containing medications (5-ASA), glucocorticosteroids, and purine analogues including azathioprine (AZA) and 6-mercaptopurine. Methotrexate, cyclosporine and monoclonal antibodies targeting tumor necrosis factor α (anti-TNF-α), e.g. infliximab, are also frequently used at more severe stages of the disease.

Topical and oral 5-ASA containing medications are used to induce and maintain remission in mild and moderate UC. Patient compliance and the diagnosis should be reconsidered in patients failing to respond to 5-ASA containing medications. Treatment is frequently escalated if symptoms do not improve within 10-14 days, or if the patient does not tolerate 5-ASA (Burger and Travis 2011).

Steroids are added when 5-ASA containing medications fail. The 5-ASA therapy may be discontinued, depending on response and tolerability. Episodes of severe UC accompanied by systemic symptoms are often treated with intravenous steroid therapy, with the addition of one or more of the other classes of drugs as required.

Patients responding well to initial therapy with glucocorticosteroids are subsequently switched to maintenance therapy with 5-ASA or immunomodulators to avoid the long-term systemic side effects of glucocorticosteroids.

Anti-TNF-α therapy may be added in patients with moderate or severe UC and insufficient response to conventional therapy. Anti-TNF-α therapy can be used both to induce and to maintain remission. Complete or partial surgical removal of the large bowel (colectomy) may

be required in severe disease refractory to treatment. Successful induction and maintenance therapy lowers the incidence of, and delays the time to, colectomy among UC sufferers. Virtually all patients eventually require intensified therapy due to the progressive nature of UC. UC therefore remains an area of significant unmet need, as even with infliximab therapy approximately 20% of patients will be hospitalized each year and 10% of patients will undergo colectomy within a year of receiving infliximab (Sandborn et al 2009).

1.1.3 Interleukin-13 (IL-13) in UC

IL-13 is a multifunctional cytokine secreted by activated T-cells. It up-regulates the expression of MHC class II and CD23, and induces IgE isotype switching of B-cells. IL-13 has been found to be critical for the pathogenesis of asthma independent of IgE and eosinophils (Wills-Karp et al 1998).

IL-13 signals through the IL-13Ra1 receptor, which is dimerised with IL4R. IL-13 also binds to IL-13Ra2, which is membrane bound, but also exists, at least in rodents, in a soluble form. The transcription factor STAT6 is activated downstream of IL-13 receptor binding (Palmer-Crocker et al 1996).

IL-13 is expressed at higher level in *in vitro* stimulated lamina propria mononuclear cells (LPMCs) from colon resections of patients suffering from ulcerative colitis, compared with LPMCs from healthy controls or patients with CD (Fuss et al 2004). Natural killer T-cells (NKT-cells) from UC patients expressed higher levels of IL-13 when stimulated with anti-CD2/anti-CD28 compared to cells from CD patients or controls. Functional assessment on cytotoxicity and CD1d stimulation, suggest that NKT-cells in the lamina propria of UC patients are stimulated by CD1d interaction and produce IL-13 which in turn enables NKT-cells to lyse epithelial cells and potentially contribute to the disease pathology in UC (Fuss et al 2004).

Reported IL-13 treatment effects on the epithelial barrier *in vitro* include increased rate of apoptosis, decreased electrical resistance and increased permeability of mannitol (Heller et al 2005). An increase of the pore forming protein claudin-2 was also observed, as have been reported by others (Weber et al 2010). This was also seen in patient biopsy material where claudin-2 had a 10-fold higher expression in active IBD compared to controls (Prasad et al 2005, and Zeissig et al 2007). Phosphorylated STAT-6 is increased in colon biopsies from UC patients compared to healthy controls, and IL-13 induced claudin-2 expression can be inhibited by a STAT-6 inhibitor in colon epithelial cells in vitro (Rosen et al 2011). Expression of tight junction proteins occludin, claudin-1, and claudin-4 were decreased in UC samples (Heller et al 2005).

In a clinical study of UC, IFNβ1was given to patients weekly for 12 weeks and LPMCs were collected from responders and non-responders and stimulated with anti-CD2/antiCD28 antibodies. Beside a general improvement for rectal bleeding scores, the induction of IL-13 in LPMCs was decreased significantly in the responder group, while it was not affected in the non-responders (Mannon et al 2011). IL-13 levels have also been shown to be elevated in

biopsies from UC patients in active disease compared to UC patients in clinical remission (Inoue et al 1999).

In a mouse model of oxazolone induced colitis, in which the phenotype resembles UC, blockade of IL-13 by injection of soluble Fc coupled IL-13Ra2 suppress the colitis (Heller et al 2005). The authors also locate the main source for IL-13 to NKT-cells and that the phenotype is dependent on the presence of NKT-cells.

In summary, IL-13 is a cytokine produced in high amounts by NKT-cells in UC and the effect of IL-13 may play a central role in the pathophysiology of UC (Danese and Fiocchi 2011).

1.1.4 Tralokinumab

The human anti-IL-13 monoclonal antibody tralokinumab potently and selectively neutralizes human IL-13. Tralokinumab has been evaluated in Phase 1 and Phase 2 studies as part of a clinical development program in moderate to severe asthma. Tralokinumab has shown an acceptable safety and tolerability profile in the clinical studies conducted to date, and has also exhibited efficacy measured as a statistically significant increase in forced expiratory volume in 1 second (FEV_1) compared with placebo in a Phase 2a study. Please refer to the tralokinumab Investigator Brochure (IB) for details on clinical and preclinical studies performed, as well as full efficacy and safety data. Assuming IL-13 is involved in the pathogenesis of UC, as suggested by pre-clinical data, tralokinumab may prove to be a useful new therapy for UC.

Periostin is a matricellular protein secreted by bronchial epithelial cells in response to IL-13. Asthma patients with high periostin serum levels had greater improvement in lung function when administered a monoclonal antibody against IL-13 than did patients with low periostin levels (Corren et al 2011). Clinical studies will show if periostin can be used to predict response also to tralokinumab therapy, in asthma and/or in UC.

1.2 Research hypothesis

Administration of tralokinumab as an addition to background therapy to outpatients with moderate to severe UC is hypothesized to result in better efficacy than the administration of background therapy alone, and to be associated with an acceptable safety profile.

1.3 Rationale for conducting this study

Tralokinumab has been shown to be a potentially safe and efficacious therapy for moderate to severe asthma in phase I and phase IIa studies. Tralokinumab targets IL-13, and IL-13 has been implicated in the pathogenesis of UC (Danese and Fiocchi 2011). Moderate to severe UC represents an area of unmet medical need as currently available therapies frequently fail to prevent significant morbidity and mortality. This study will evaluate if tralokinumab has potential as a novel therapy for UC when added to standard therapies.

1.4 Benefit/risk and ethical assessment

There is an unmet medical need for new therapies for use in subjects with moderate to severe UC not achieving long-term remission on standard therapy. Tralokinumab is a monoclonal antibody in development for the treatment of moderate to severe asthma targeting IL13. IL13 is an emerging target for the treatment of UC based on preclinical data (see section 1.1.3). In a previous study in subjects with asthma (Study MI-CP199), treatment with tralokinumab showed evidence of a beneficial clinical effect compared with placebo.

In preclinical studies tralokinumab has been administered intravenously at doses up to 100mg/kg weekly to cynomolgus monkeys for 26 weeks without adverse effects (IB section 4.3.2.1.3). In a pilot embryofoetal toxicity study in cynomolgus monkeys, and in a pre- and post-natal development study in which the neonates were followed for one (1) month post partum, no adverse effects were noted after weekly intravenous administration of tralokinumab 100mg/kg (IB section 4.3.4).

In clinical studies completed to date, tralokinumab was generally well tolerated. A number of possible risks have been identified that are described in the current IB and measures are in place in this study to protect participating subjects as follows:

- Subjects will be closely monitored during the course of the study with clinic visits every other week during the treatment period and daily diary recordings of symptoms of UC and use of medication for UC. Administration of investigational product (IP) will be discontinued if intensified therapy for UC is regarded medically necessary by the investigator. Intensified therapy will then be administered according to the local standard of care to ensure patients receiving placebo, or not responding to tralokinumab, receive appropriate care.

- One acute hypersensitivity reaction, characterized by increased wheezing, shortness of breath, and facial pruritus, was reported in an asthmatic subject following the first IV infusion of tralokinumab (10mg/kg) in Study CAT-354-0603. However, in Study MI CP199, no hypersensitivity reactions were reported following repeat sc dosing. As a precautionary measure in this study, subjects will be monitored for immediate drug reactions; vital signs will be taken immediately after administration of IP and at least every 30 minutes thereafter. For the first 4 doses of IP, subjects will remain at site for a minimum of 2 hours or until stable, whichever is later. For the fifth and subsequent doses of IP, subjects will remain at site for a minimum of 1 hour or until stable, whichever is later. Discharge from site will be determined by the investigator. Medical equipment to treat acute anaphylactic reactions will be immediately available in this study, and study personnel will be trained to recognize and treat anaphylaxis (Appendix F).

- Neutralization of IL-13 might theoretically cause a worsening of parasitic infestation, and therefore subjects either with untreated systemic parasitic infestations or a recent history of parasitic infection will be excluded. Furthermore,

the study will only be conducted in territories where parasitic infections are rare. Subjects with other clinically significant infections will also be excluded.

- No evidence of formation of ADAs has been detected in previous clinical studies; however, subjects will be monitored for the presence of such antibodies.

- Study participants will undergo endoscopic assessment with biopsy collection twice during the study. However, biopsies will only be collected if biopsy collection is not associated with significant discomfort or unacceptable medical risk to the individual patient.

The information gained from this study will have significant value in determining whether tralokinumab has the potential to be developed as a therapy for moderate to severe UC. Previous clinical experience with tralokinumab shows no major safety or tolerability concerns and appropriate measures have been instituted in this study to protect subjects from possible risks that have been identified and to monitor subjects closely. Hence, the current risk/benefit ratio is favourable and justifies the administration of tralokinumab in this study.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to assess the effect of tralokinumab compared with placebo in patients with active UC by assessment of clinical response, as defined by the Mayo score, at week 8.

2.2 Secondary objectives

- To assess change in Mayo score from baseline to week 8.

- To assess mucosal healing at week 8.

- To assess change in partial Mayo score from baseline to week 4, 8, 12, 16, 20, and 24.

- To assess the proportion of patients in clinical remission, as defined by the Mayo score, after 8 weeks.

- To assess histology in biopsies from colonic mucosa at baseline and week 8.

- To assess markers of disease activity and intestinal leakiness in serum and faeces at baseline, week 4, 8, 12, 16, 20, and 24.

- To assess the pharmacokinetics and immunogenicity of tralokinumab.

2.3 Safety objective

To evaluate the safety and tolerability of tralokinumab by assessment of reported Adverse Events (AEs), safety laboratory values, electrocardiograms, vital signs, weight, and physical examination findings.

2.4 Exploratory objectives

- To assess transcription of selected genes by measuring mRNA levels in peripheral blood, and to assess IL-13 and other cytokines, and periostin, in serum at baseline, 4, 8, 12, 16, 20, and 24 weeks.
- To assess mechanism based biomarkers and the levels of IL-13 and other cytokines in colonic mucosa, both in areas of active disease and in unaffected mucosa, at baseline and week 8.
- To assess the efficacy of 300mg tralokinumab and placebo in patients receiving different background therapies for UC at baseline, by assessment of clinical response.
- To assess the efficacy of 300mg tralokinumab and placebo in subgroups of patients with different prior history of and treatment for UC, by assessment of clinical response.
- To assess the concordance between the investigator reported Mayo score and the patient reported UCGHQ score.

2.5 Pharmacogenetic objective

To collect and store DNA for future exploratory research into genes/genetic variation that may influence response to treatment of UC (i.e. distribution, safety, tolerability and efficacy) and/or predisposition to, or progression of UC.

3. STUDY PLAN AND PROCEDURES

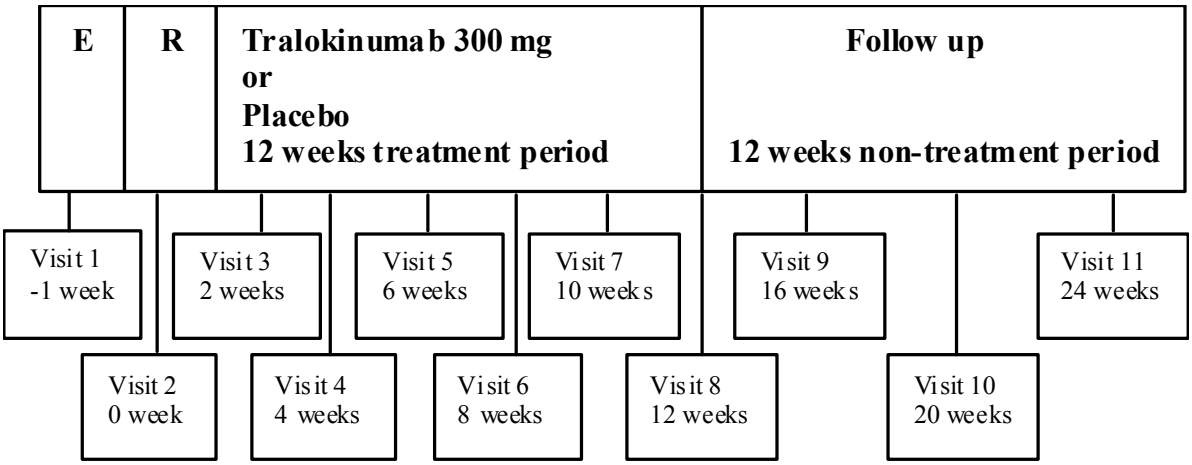
This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a phase IIa, randomised, double-blind, placebo-controlled, parallel-arm, multicenter study to evaluate the efficacy and safety of 300mg tralokinumab sc. All patients will continue background therapy for UC as per local standard of care in addition to the IP. The IP will be given as 2 sc 150mg injections every 2 weeks during the 12-week period.

Approximately 110 patients will be randomised.

Figure 1 Study Flow chart



Visit 2: The day of randomisation and administration of first dose is considered as DAY 1.

3.1.1 Study Periods

Enrolment period (E; Visit 1 – Visit 2, during week – 1)

The Enrolment Visit (Visit 1) will take place 2-7 days before the randomisation at Visit 2.

The purpose of the enrolment period is to ensure patient eligibility. Informed Consent will be obtained prior to conducting any study related assessments or activities. The patient will be assessed against inclusion and exclusion criteria applicable at Visit 1 (inclusion criteria 1, 2, 3, 5, 6, 7 and exclusion criteria 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 18, 21, 22, 23, and 24).

Screening for tuberculosis will be performed according to local standard practice at each study site.

An endoscopy with biopsy sampling will be performed after the HIV, hepatitis B, hepatitis C and TB screening results have been reported negative, and before randomisation at Visit 2.

Patients will be instructed to monitor their symptoms of disease and record those in a Diary Card (see Section 6.1.1).

12-weeks Treatment Period: Randomisation (R, Visit 2, Week 0, DAY 1) and Treatment Visits (Visits 3 - 8)

Randomisation Visit and Visit 6 (week 8) will start with administration of the Ulcerative Colitis Global Health Question (UCGHQ) to the patient prior to any other assessments (see section 6.5.1).

On the Randomisation Visit assessment of eligibility criteria will continue. The patient will be assessed against inclusion and exclusion criteria applicable at randomisation (all inclusion and exclusion criteria except exclusion criterion 2).

If applicable, a blood sample for optional genetic research will be collected after signing of a separate Informed Consent.

Laboratory blood sampling including PK, ADA, biomarkers, and calprotectin in faeces will be done and shipped to a central laboratory. Pharmacokinetic (PK) samples should be collected before administration of IP. The exact timing of each sc injection and each PK sampling collection is to be recorded at each visit.

Eligible patients will be randomised to either tralokinumab (300mg) or placebo administered in 2 sc injections. An unblinded qualified designee, who is not involved in the management of the patients, will inject the investigational product into the sc tissue of the anterior thigh or abdomen. The site of injection will be assessed during all treatment visits (see Section 6.4.10.1).

Treatment Visits are scheduled every 2 weeks. IP should be administered only on scheduled study visits within the accepted time window (+/-5 days). IP must not be administered if the visit window has been missed. The administration of IP should be resumed at the next scheduled treatment visit.

Vital signs (blood pressure, pulse rate, and temperature) will be obtained before and after administration of IP during all treatment visits (see Section 6.4.9).

Follow-up Period: 12-weeks Non-Treatment Period (Visits 9- 11)

During the 12-week Follow-up Period there are 3 visits every 4 weeks (+/-5 days). The End of Study visit is Visit 11.

As per Study Plan UCGHQ, physical examination, ECG, partial Mayo score, a laboratory panel, sampling for: PK, immunogenicity, biomarkers, and follow up of any AEs/ SAEs will be performed.

At visit 9 the last assessment of the IP injection site will be performed.

Between scheduled study visits, patients may come on unscheduled visit due to experience of deterioration of health status. During unscheduled visit patients' health status will be assessed (physical examination, and/or vital signs, and/or AE/SAE, whatever applicable).

Table 1 Study Plan

VISIT	**1**	**2** [h]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Week	-1	0	2	4	6	8	10	12	16	20	24
Visit window (days)	-7 to -2	0	±5	±5	±5	±5	±5	±5	±5	±5	±5
Informed Consent	X										
Inclusion/exclusion criteria	X	X									
Demographic data	X										
Medical/surgical history	X										
Disease specific characteristics	X										
Nicotine use	X										
Vital signs		X	X	X	X	X	X	X			X
Physical examination	X	X		X		X		X	X	X	X
BMI (weight and height[a])	X							X			X
12-lead ECG		X						X			X
Laboratory assessments [b]	X	X		X		X		X	X	X	X
TB screening [c]	X										
Contraception control [d]	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test serum-βHCG [d]	X										
Urine Pregnancy test	X	X	X	X	X	X	X	X	X	X	X
ADA serum sampling		X				X		X	X		X
PK serum sampling		X		X		X		X	X	X	X
Cytokine and periostin serum sampling [e]		X		X		X		X	X	X	X
mRNA blood sampling		X		X		X		X	X	X	X
Calprotectin in faeces		X		X		X		X	X	X	X
Mayo score including Endoscopy		X[g]				X					
Biopsy sampling		X[g]				X					
Partial Mayo score		X [i]		X		X [i]		X	X	X	X

VISIT	**1**	**2** [h]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Week	-1	0	2	4	6	8	10	12	16	20	24
Visit window (days)	-7 to -2	0	±5	±5	±5	±5	±5	±5	±5	±5	±5
Randomisation		X									
IP administration		X	X	X	X	X	X	X			
Vital signs monitoring after IP administration		X	X	X	X	X	X	X			
Injection site assessment after IP administration		X	X	X	X	X	X	X	X		
Diary Card for registration of symptoms: D-dispensed; C-collected	D	C/D		C/D		C/D		C/D	C/D	C/D	C
Diary Card review		X	X	X	X	X	X	X	X	X	X
Administration of PRO Question- UCGHQ		X				X					X
AEs / SAEs	X	X	X	X	X	X	X	X	X	X	X
Tryptase serum sampling[j]		X [j]	X [j]	X [j]	X [j]	X [j]	X [j]	X [j]	X [j]		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Informed Consent for Optional Genetic Research; PGx blood sampling [f]		X									

[a] Height should be measured only on visit 1. BMI on Visit 8 and Visit 11 will be calculated based on height measurement from Visit 1.
[b] The laboratory parameters to be collected are specified in Table 9 and Table 10.
[c] Assessed according to local standard of care as determined by local guidelines.
[d] The selected method of contraception should be entered in medical records. Accepted methods of contraception are shown in Table 2. Blood pregnancy test will be done on all female patients who are not postmenopausal or hysterectomised (for definition see Section 4.1, point 6).
[e] The biomarkers are specified in Table 8.
[f] Informed Consent for Optional Genetic Research must be obtained before blood collection.
[g] Baseline endoscopy to be performed after the HIV, hepatitis B, hepatitis C and TB screening results have been reported negative, and before randomisation.
[h] Baseline measurements at Visit 2 (just prior to randomisation /dosing).
[i] Determined from Mayo score.
[j] If an anaphylactic reaction occurs during or within a 24-hour period after administration of IP, serum for assessment of tryptase will be collected as soon as possible after the event, at 60 minutes ± 30 minutes after the event, and at discharge.

3.2 Rationale for study design, doses and control groups

3.2.1 Overall rationale and study population

The study is designed to evaluate the clinical efficacy and safety of tralokinumab as compared to placebo as add on therapy, in patients with moderate to severe UC receiving background therapy.

Patients exhibiting insufficient response to the therapy, or exhibiting significant worsening, are at all times allowed to discontinue IP and receive intensified therapy for UC in accordance with the local standard of care. The study design thereby minimizes the medical risk to patients randomised to receive placebo, as all patients at all times receive the local standard of care therapy for UC in addition to the IP.

The patient population was chosen based on preclinical and clinical data indicating a pivotal role of IL-13 in the pathogenesis of UC, and since patients with moderate to severe UC represent an unmet medical need. Only patients managed in the outpatient setting are eligible for the study. Patients with a severe disease flare requiring hospitalization need treatment with intensive therapies such as intravenously administered glucocorticosteroids, immunomodulatory therapies, or surgery. Hence only outpatients with moderate or severe UC are eligible to participate in this study.

3.2.2 Study design

The overall design of the study is similar to the previously performed studies ACT1 and ACT2 contributing to the registration of infliximab for UC (Rutgeerts et al 2005).

The study is double-blinded, but tralokinumab and placebo are visually distinct. Hence an unblinded qualified designee not otherwise involved in the management or assessment of patients will administer the IP. See section 5.4.1 for details on the methods used to ensure blinding.

Placebo is an adequate comparator to establish proof of principle, and is also the comparator recommended by the EMA guideline for clinical studies in UC (EMEA, Ref CHMP/EWP/18463/2006).

3.2.3 Primary, secondary and exploratory endpoints

The primary endpoint is clinical response at 8 weeks, defined as a decrease in Mayo score (Schroeder et al 1987) from baseline of at least 3 points and at least 30% with an accompanying decrease in the sub score for rectal bleeding of at least 1 point or absolute sub score for rectal bleeding of 0 or 1. The primary endpoint has been used in phase II and III trials of other agents, and has been successfully employed in pivotal trials resulting in the registration of novel therapies for the treatment of UC. Clinical response as defined is therefore considered a robust marker of clinical benefit among patients suffering from UC.

Secondary endpoints include mucosal healing, change in Mayo score, change in partial Mayo score, proportion of patients achieving remission, histological disease activity, and markers of disease activity (CRP in serum and calprotectin in faeces) and a marker of intestinal leakage (albumin in serum). The endpoints aim to provide additional information on the disease activity in the tralokinumab arm compared with the placebo arm to further characterise the efficacy of tralokinumab compared with placebo.

The pharmacokinetic profile and the immunogenicity of tralokinumab are included as secondary endpoints to investigate if treatment at the proposed dose results in adequate exposure to test the medical hypothesis. The PK and Immunogenicity of tralokinumab 300mg sc has not previously been defined in patients with UC, only in patients with asthma.

Safety and tolerability are included as a secondary endpoint to investigate if administration of tralokinumab 300mg sc results in an acceptable safety profile.

The exploratory endpoints include evaluation of mechanism based biomarkers, cytokine levels, and the collection of genetic data. The mechanism based biomarkers planned to be evaluated include claudin-2 and STAT6 phosphorylation. Activation of the transcription factor STAT6 by IL-13 may be involved in the pathogenesis of UC (see section 1.1.3), and expression of the pore forming protein claudin-2 and other proteins will also be evaluated to gain insight to the tralokinumab mechanism of action and the pathogenesis of UC. Measuring the levels of phosphorylated STAT6 and claudin-2 by immunohistochemistry, as well as the messenger ribonucleic acid (mRNA) levels of claudin-2 using polymerase chain reaction, in both unaffected and affected mucosa before and after the administration of tralokinumab will test the proposed mechanism of action of tralokinumab in UC, as well as the biology underlying the pathogenesis of UC.

Cytokine levels will be evaluated using a multiplex assay in serum, and in both affected and unaffected mucosa to further the understanding of UC and the tralokinumab mechanism of action.

The optional genetic testing will focus on single nucleotide polymorphisms (SNPs) with the potential to have a clinically significant impact on the response to therapy, such as SNPs in the IL-13 receptors.

Analysing mRNA levels in peripheral blood may provide insight into how the transcription of studied genes changes with tralokinumab therapy, and if the levels of transcription of selected genes at baseline affect efficacy or safety outcomes.

In summary the exploratory analyses performed in this study aim to investigate the pharmacology of tralokinumab in UC and the pathogenesis of UC, and to improve patient selection in future studies by evaluation of potentially suitable biomarkers.

3.2.4 Dosing and study duration

In study MI-CP199 tralokinumab 150mg, 300mg and 600mg sc was administered to patients with moderate to severe asthma. FEV_1 showed a trend to improve in all treatment arms

compared with placebo, but FEV_1 was similar in the 300mg and 600mg treatment arms. FEV_1 improved more in the 300mg and 600mg treatment arms than in the 150mg treatment arm. Tralokinumab was associated with acceptable safety profile at all three doses, but the incidence of diarrhoea was significantly higher in the 600mg arm than in the 150mg and 300mg arms. See the tralokinumab IB for further details on efficacy and safety in study MI-CP199.

The PK/PD profile for tralokinumab has not been defined in UC, but is assumed to be similar to that in asthma. Since the 600mg dose was associated with an increased incidence of diarrhoea, which is a particularly undesirable adverse effect in UC, and since efficacy measured as FEV_1 was similar at 300mg and 600mg in study MI-CP199, the 300mg dose was selected for this study.

The primary endpoint will be assessed at 8 weeks to provide efficacy results comparable to other biologic drugs approved or in development for the treatment of UC.

Treatment will continue for 12 weeks to ensure the tralokinumab steady state is achieved, which will provide a better understanding of the safety profile of tralokinumab to be expected during long-term administration to patients with UC.

The 12-week safety follow-up after the last IP administration is appropriate given the pharmacokinetic profile of tralokinumab demonstrated in previous studies. Also efficacy parameters will be collected for 12 weeks beyond the last IP administration, since a previous asthma study (MI-CP199) suggested tralokinumab efficacy may be prolonged beyond what would be expected based on PK data (IB section 5.1.2.1.1.2).

4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule. Inclusion and exclusion criteria will be assessed on Visit 1 and Visit 2.

4.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures.

2. Male and female patients aged 18 – 65 years.

3. Diagnosis of ulcerative colitis verified with endoscopy and biopsy at least 90 days prior to randomisation.

4. Non-hospitalized patients with moderate-severe UC, Mayo score of ≥ 6 including an endoscopy sub-score of at least 2 (based on baseline endoscopy), including patients with extensive or left-sided subtypes of UC (Satsangi et al 2006).

5. Treated with medication containing 5-ASA at a stable dose for at least 2 weeks prior to randomisation, or previously treated with medication containing 5-ASA at maximum dose without significant improvement, or unable to tolerate 5-ASA containing medication.

   In addition the following concomitant treatments for UC are allowed at randomisation:

   - A stable low dose of glucocorticosteroids (≤ 20mg prednisolone or equivalent daily) since at least 4 weeks,

   And/or

   - A stable dose of purine analogue (azathioprine or 6-mercaptopurine) therapy since at least 12 weeks.

6. Females of childbearing potential who are sexually active with a nonsterilized male partner must use highly effective contraception from enrolment, and must agree to continue using such precautions from enrolment visit through follow-up visits/end of study. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

   - Females of childbearing potential are defined as those who are not surgically sterile (i.e. bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses without an alternative medical explanation).

   - A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in Table 2.

7. Non-sterilized males or sterilized males who are ≤ 1 year post-vasectomy who are sexually active with a female partner of childbearing potential must use a highly effective method of contraception (see Table 2) from enrolment visit through follow-up visits /end of study.

Table 2 Highly effective Methods of Contraception

Barrier Methods	Hormonal Methods [a]
Male condom plus spermicide	Progestin-releasing implants (eg Implanon™ , Norplant™)
Intrauterine device with copper-banded coils	Medroxyprogesterone for depot injection (eg Depo-Provera™)
Bilateral tubal occlusion or ligation	Combined oral contraceptives with fixed doses of progestin and estrogen during each treatment cycle
	Cerazette™ (desogestrel), the only accepted progestin only pill
	Transdermal system with a combination of progestin and estrogen (eg Evra™ patch)
	Progestin-releasing intrauterine system (eg Mirena™)
	Intravaginal device with a combination of progestin and estrogen (eg NuvaRing™)

[a] Hormonal methods of contraception must have been used consistently for 3 months prior to study entry to be considered highly effective methods of contraception.

4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
2. Previous enrolment in the present study.
3. Participation in another clinical study with an IP, including biological agents, during the last 4 months or 5 half-lives, whichever is the longest.
4. Previous receipt of tralokinumab.
5. Pregnant or breastfeeding women.
6. History of subtotal colostomy with ileorectostomy or colostomy with ileoanal pouch, Kock pouch, or ileostomy for UC or any planned bowel surgery.
7. Current diagnosis of indeterminate colitis, CD, ischemic colitis, fulminant colitis and/or toxic megacolon and patients with UC limited to the rectum (ulcerative proctitis).

8. Patients who received systemic intravenously glucocorticosteroids or medium to high dose of oral glucocorticosteroids (>20mg prednisolone or equivalent daily) within 8 weeks before randomisation.

9. Patients receiving total parenteral nutrition.

10. Patients who received anti-TNF α treatment within 12 weeks before randomisation.

11. Use of cyclosporine A, tacrolimus, methotrexate, or mycophenolate mofetil for UC within 30 days before randomisation, or use of topical therapy for UC within 2 weeks before randomisation.

12. Patients who received a live attenuated vaccine within 4 weeks before randomisation.

13. History of a clinically significant infection (eg, requiring antibiotics or antiviral medications) within 4 weeks prior to randomisation.

14. History of an untreated systemic helminth parasitic infestation; diagnosis of a helminth parasitic infestation within 6 months prior to enrolment; history of living with a person known to have had a helminth parasitic infestation within 12 months prior to enrolment.

15. Positive hepatitis B surface antigen or hepatitis C virus antibody serology. Subjects with a history of hepatitis B vaccination without history of hepatitis B are allowed to enrol.

16. Positive human immunodeficiency virus (HIV) test at enrolment or subject taking antiretroviral medications, as determined by medical history and/or subject's verbal report.

17. Patients who in the opinion of the investigator have evidence of active tuberculosis, either treated or untreated, or latent tuberculosis without completion of an appropriate course of treatment or appropriate ongoing prophylactic treatment. Evaluation will be according to the local standard of care as determined by local guidelines and may consist of history and physical examinations, chest x-ray, and/or tuberculosis test (eg, purified protein derivative or QuantiFeron test).

18. Previous medical history or evidence of an uncontrolled intercurrent illness that in the opinion of the investigator may compromise the safety of the patient in the study or interfere with evaluation of the IP or reduce the patient's ability to participate in the study.

19. Any clinically relevant abnormal findings in physical examination, electrocardiogram (ECG), vital signs, haematology, clinical chemistry, or urinalysis during enrolment period, which in the opinion of the investigator or medical

monitor may compromise the safety of the patient in the study or interfere with evaluation of the IP or reduce the patient's ability to participate in the study.

20. Evidence of active liver disease, including bilirubin, aspartate transaminase, alanine transaminase, or alkaline phosphatase > 2 upper limit of normal (ULN).

21. History of cancer and colorectal dysplasia, except for basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy ≥ 12 months prior to randomisation or other malignancies treated with apparent success with curative therapy ≥ 5 years prior to randomisation.

22. History of any known primary immunodeficiency disorder excluding asymptomatic selective immunoglobulin A (IgA) or immunoglobulin G (IgG) subclass deficiency.

23. History of drug addiction, drug abuse (including cannabinoids), alcohol abuse or other circumstances which in the investigators judgement may compromise the patient's ability to comply with the study requirements.

24. Major surgery within 8 weeks prior to randomisation, or planned in-patient surgery or hospitalisation during the study period.

Regarding exclusion criteria for PGx blood sampling (optional participation), see Appendix D.

The procedures for withdrawal of incorrectly enrolled patients are described in Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

- Patients should abstain from blood donation during the whole study.
- Prohibited concomitant medications are listed in Section 5.6.2.
- Fertile and sexually active patients or their partners should use highly effective contraceptive methods (see Table 2) throughout the study and at least 12 weeks after the last administration of IP. See inclusion criteria 6 and 7 for details and definitions, and section 13.3 for actions to be taken in case of pregnancy.
- See section 13.3.2 about sperm donation and fathering a child.

5.2 Patient enrolment and randomisation and initiation of investigational product

The Principal Investigator will:

1. Obtain signed informed consent from the potential patient or their legal representative before any study specific procedures are performed.

2. Assign potential patients a unique enrolment number, beginning with 'E#'.

3. Determine patient eligibility. See Sections 4.1 and 4.2.

4. Assign eligible patients unique randomisation codes (patient numbers) received via IVRS/IWRS.

The E-code will be used to identify the patient throughout the study participation. Patient eligibility will be established before treatment randomisation.

Randomisation codes will be assigned at Visit 2, after all inclusion/exclusion criteria have been evaluated. The code will be assigned via an Interactive Voice Response System (IVRS) or an Interactive Web Response System (IWRS).

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

Enrolled patients will be listed on the enrolment log. Patients may only be enrolled into the study once.

5.2.1 Procedures for randomisation

A randomisation list will be prepared using a validated computer program (GRand). Patients will be randomised to treatment with either tralokinumab or placebo in a ratio of 1:1.

Randomisation to IP will be done via an IVRS/IWRS at Visit 2. The IVRS/IWRS will sequentially allocate the treatment and provide the randomisation number and the appropriate kit ID from those available at the study site. The randomisation is carried out at the study level and the assigned randomisation numbers and the associated kit IDs will not be sequential within a study site. Forced randomisation is not allowed.

5.3 Procedures for handling patients incorrectly enrolled or randomised

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

Where patients that do not meet the inclusion and/or exclusion criteria are enrolled in error, or incorrectly started on treatment, or where patients subsequently fail to meet the restrictions

during the study (see section 5.1), the investigator should inform the Study Physician immediately. The Study Physician is to ensure all such contacts and subsequent decisions are appropriately documented.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The study will be conducted in a double blind fashion. Tralokinumab and placebo are visually distinct from one another. Tralokinumab appears to be slightly opalescent, whereas placebo appears to be a clear solution. There is also a difference in viscosity between the active and placebo IP. Active IP has a viscosity of approximately 13 centipoise (cP), whereas placebo IP has a viscosity of approximately 1 cP.

The sponsor staff, the patients, and the investigators involved in the treatment of patients or in the clinical evaluation of patients will not be aware of the treatment received (International Conference on Harmonisation [ICH] E9).

IP will be handled by an unblinded IP manager/pharmacist at the study site and will be administered by an unblinded study staff member who will not be involved in the management or evaluation of study patients. Handling and administration of IP could be delegated the same study staff member.

The staff responsible for the dose preparation and administration of IP must have appropriate training in the subcutaneous administration of drugs.

An unblinded Site Monitor will be unblinded to perform IP accountability.

5.4.2 Methods for unblinding the study

During the whole study period no member of the blinded study team at AstraZeneca, at MedImmune or at the investigational sites or any Contract Research Organization handling data will have access to the randomisation scheme. Exception from this rule are relevant persons at MedImmune Clinical Research Pharmacy Services (CRPS) or their designee, where the information is needed to package study medication, and the Patient Safety departments at MedImmune and AstraZeneca.

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to IP manager or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS manual that will be provided to each study site.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff. Instructions for unblinding an individual patient's IP are contained in the IVRS/IWRS manual.

In the event that the treatment allocation for a patient becomes known to the investigator or other study staff involved in the management of the patients, or needs to be known to be able

to treat the patient for an AE, the sponsor must be notified immediately by the investigator and preferably, before unblinding.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational products

Table 3 Identity of IPs

IP	Dosage form and strength	Manufacturer
Tralokinumab (CAT-354)	300mg Formulated at a nominal concentration of 150mg/mL in [redacted] See Table 4 for full list of excipients.	MedImmune
Placebo	Placebo contains the same excipients, in the same concentration only lacking tralokinumab	MedImmune

Table 4 Tralokinumab (CAT-354) composition

Ingredient	Concentration	Unit Formula per 150 mg Vial (nominal)
Active Ingredient		
CAT-354	150mg/mL	150mg
Other Ingredients		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

The IP (tralokinumab and placebo) is filled into 3ml glass vials, stoppered, and sealed with an aluminium overseal.

IP will be supplied to the site as kits containing one vial per kit. Each kit has a unique number that is identical to the printed number on the vial label within the kit.

Materials Safety Data Sheets will be provided detailing procedures required for the safe handling of the IP.

5.5.2 Doses and treatment regimens

Patients will receive either:

- Tralokinumab (CAT-354) 300mg will be administered during study visits as 2 (two) sc 150mg injections every 2 weeks for 12 weeks starting from Visit 2 (week 0),
- Placebo will be administered during study visits as 2 (two) sc injections every 2 weeks for 12 weeks starting from Visit 2 (week 0).

Sites will be supplied also with needles and syringes required for IP administration. **Do not use any other materials other than those provided by the MedImmune.**

More details regarding handling of drug supplies and accountability for the IP will be provided separately.

Any defects with the IP must be reported immediately to the MedImmune Product Complaint Department (see Table 5) by the unblinded IP Manager/pharmacist and further notification to the unblinded Site Monitor. All defects will be communicated to MedImmune and investigated further with the Product Complaint department. During the investigation of the product complaint, all IP must be stored at labelled conditions unless instructed otherwise.

Defects may be related to component, product, and packaging and labelling issues. The table below includes, but is not limited to, descriptions of product complaints that should be reported.

Table 5 Complaint Categories Descriptions

Complaint Category	Brief Description
Component Issue	Defect in container or dosing mechanism of IP. The component defect may be damaged, missing or broken. Component examples include vials, stoppers and caps.
Product Issue	Defect in the product itself. The product appearance has visual imperfections such as foreign particles, crystallization, discoloration, turbidity, insufficient volume or anything that does not apply to the product description.
Packaging/Labelling Issue	Defect in the packaging or labelling of the product. The packaging or labelling defects may be damaged, unreadable, or missing label.

When reporting a product complaint, be prepared to provide the following information:

- Customer Information (reporter name, address, contact number, date of complaint),
- Product Information (product name, packaging kit number or lot number, expiry date, clinical protocol number),
- Complaint Information (complaint category, description).

Table 6 Product Complaint Department Contact Information

Email	
Phone	
Fax	
Mail	MedImmune, LLC

5.5.2.1 Dose Preparation

The IP should be equilibrated for a minimum of 30 minutes/maximum of 1 hour to room temperature then swirled GENTLY 5-10 times to mix prior to use.

The IP Vials MUST NOT be inverted during swirling.

The dose of IP for administration must be prepared using an aseptic technique by the unblinded pharmacist/unblinded study site staff as follows:

1. The IP is viscous therefore it should be confirmed that all the contents are at the bottom of the vial before attempting to withdraw liquid from the vial. The vial may require gentle tapping on the side to dislodge any liquid that may be held in the stopper recess.
2. The IP should be withdrawn (slowly) from the vial into the 1 ml hypodermic syringe, using a 19G x 1½ inch hypodermic needle.

When withdrawing the IP, the vial should be tilted at an angle to ensure that 1mL can be extracted.

3. Syringe should be inverted and tapped to remove all air bubbles.
4. The 19G needle will be changed to the 27G x ½ inch hypodermic needle. New needle will be capped until administration.

The syringe must be prepared immediately for administration so that it does not require any further labelling but maintains the blind.

5.5.2.2 Treatment Administration

The first day of dosing is considered Day 1 (Week 0). IP (tralokinumab or placebo) must be administered during study visit, the same day the IP is assigned. If there is a delay in the administration of IP such that it will not be administered within the specified timeframe, the study monitor must be notified *immediately*.

The IP will be administered by 2 sc injections. An unblinded qualified study staff member, who will not be involved in the management of the patients, will inject the IP into the sc tissue of the anterior thigh or abdomen.

Two injections (150mg per injection) are required in order to administer tralokinumab at the required dose of 300mg. Therefore at each administration (tralokinumab or placebo) 2 separate injection sites on the anterior thigh or abdomen at least 3cm apart should be used. Injection sites should be rotated at each visit.

The IP will be administered via a 27-gauge syringe. The person administering the dose will wipe the skin surface of the anterior thigh or abdomen with alcohol and allow to air dry. The skin will be pinched to isolate the sc tissue from the muscle. The needle will be inserted at a 90-degree angle approximately halfway into the sc tissue. The IP will be slowly injected (at least 5-second duration is recommended) into the sc tissue using gentle pressure. The area should not be massaged after injection.

5.5.2.3 Monitoring of Dose Administration

Vital signs (blood pressure, temperature, and pulse rate) will be obtained before IP administration on all treatment visits. After IP administration, patients will be monitored for immediate drug reactions; vital signs will be taken immediately after administration of IP and at least every 30 minutes thereafter. For the first 4 doses of IP, patients will remain at site for a minimum of 2 hours or until stable, whichever is later. For the 5^{th}, 6^{th}, and 7^{th} doses of IP, patients will remain at site for a minimum of 1 hour or until stable, whichever is later. The investigator will determine if and when a patient can be discharged from the study site.

As with any antibody, allergic reactions to administration of tralokinumab are possible. The World Health Organization has categorized anaphylaxis into 2 subgroups, which are clinically indistinguishable: immunologic (IgE-mediated and non-IgE-mediated [eg, IgG and immune complex mediated]) and nonimmunologic (Johansson et al 2004).

The clinical criteria for defining anaphylaxis for this study are listed in Appendix F, together with a guide to the signs and symptoms and management of acute anaphylaxis. Appropriate drugs, such as epinephrine, antihistamines, glucocorticosteroids etc, and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and study staff should be trained to recognize and treat anaphylaxis according to local guidelines.

If an anaphylactic reaction occurs (see Appendix F), a blood sample will be drawn from the patient as soon as possible after the event, at 60 minutes ± 30 minutes after the event, and at discharge for analysis of serum tryptase.

5.5.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

5.5.4 Storage

The IP will be shipped to study sites and stored under controlled temperature: 2-8°C.

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the study kit specifies the appropriate storage. IP must be kept in the original outer package in a secure area with restricted access.

The IP must not be frozen. It is preferred that an on-site refrigerator has an electronic temperature monitoring system or chart recorder. At minimum, the on-site refrigerator must have daily monitoring of the minimum/maximum temperature.

5.6 Concomitant and post-study treatment(s)

Medications considered necessary for the patient's safety and well being with the exception of drugs listed in section 5.1, may be given at the discretion of the investigator. Concomitant medications must be recorded in the appropriate sections of the eCRF.

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

5.6.1 Background medications

IP will be given as add-on medication for patients treated for UC according to the local standard of care. Accepted background medications for UC are:

- 5-ASA containing medications,
- purine analogues (azathioprine or mercaptoprurine), and/or
- low dose glucocorticosteroids (≤ 20 mg oral prednisolone or equivalent daily).

All enrolled patients must receive at least 5-ASA containing medications, with the exception of patients refractory to 5-ASA containing medications or unable to tolerate 5-ASA containing medications (see section 4.1 Inclusion criteria, bullet 5).

Administration of IP must be discontinued if intensified therapy for UC is regarded medically necessary by the investigator (see section 5.8, bullets 7a and 7b). Intensified therapy includes surgery for UC, increased daily doses of background therapy for UC or the addition of any

new therapies for UC (listed in section 5.6.2). Intensified therapy should be according to the local standard of care considering the patients condition.

The daily doses of background therapy for UC may be decreased in response to clinical improvement or tolerability issues, as per local standard of care. The daily dose of background therapy for UC may not be increased, see previous paragraph.

The background UC medication is not regarded as study drug, and will not be provided by AstraZeneca or MedImmune.

5.6.2 Prohibited medications during study

Medication not allowed from Visit 1 and throughout the study:

- Drugs which affect GI pathology, function and integrity, including NSAIDs (with the exception of occasional use up to 1 day/week),
- Antibiotics (except for treatment of acute illness),
- Intravenous glucocorticosteroids,
- Oral glucocorticosteroids at a daily dose higher than the daily dose administered during the enrolment period,
- Anti-TNFs,
- Immunosuppressives (excluding the background medications specified in section 5.6.1),
- Interferons,
- Immunoglobulin or blood products,
- Live attenuated vaccines.

Administration of IP must be discontinued if prohibited medications are to be administered to the patient (see section 5.8, particularly bullets 7a and 7b).

5.7 Treatment compliance

The administration of all IP should be recorded in the appropriate sections of the eCRF.

IP is administered during study visits by study site staff, who will monitor compliance.

5.7.1 Accountability

MedImmune will provide the investigators with IP using designated distribution centers. MedImmune will provide the investigator(s) with adequate stock quantities of IP and the stock

levels will be maintained via the IVRS/IWRS as vials are used. The study drug provided for this study will be used only as directed in the study protocol.

The unblinded IP Manager/pharmacist is required to maintain accurate IP accountability records. The study staff will account for all study drugs dispensed to patients. Upon completion of the study, copies of IP accountability records will be returned to AstraZeneca. As per the MedImmune 's procedures unused IP will be returned to the local depot and destroyed upon authorization by the MedImmune.

Study site staff, if applicable, or the AZ monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery and destruction should be signed.

5.8 Discontinuation of Investigational Product

Patients may be discontinued from IP in the following situations:

1. Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment,

2. Incorrect enrolment (i.e., the patient does not meet the required inclusion/exclusion criteria),

3. Pregnancy,

4. Experienced an event, which in the opinion of the investigator and/or AstraZeneca, contraindicated further dosing such as illnesses or complications, e.g. anaphylactic reaction to the IP or other safety reasons,

5. Adverse Event,

6. Severe non-compliance to study protocol,

7. Development of any study specific criteria for discontinuation:

    (a) Patient with insufficient therapeutic response and thus in need of intensified therapy for UC prescribed at the discretion of the investigator,

    (b) Patient with insufficient therapeutic response or in need of surgery.

5.8.1 Procedures for discontinuation of a patient from investigational product

A patient who decides to discontinue IP will always be asked about the reason(s) and the presence of any adverse events.

If the patient is discontinued from IP, the scheduled study visits, data collection and procedures should continue according to the study protocol until study completion. Alternatively, if the patient does not agree to this option, a modified follow up through eg,

regular telephone contacts or a contact at study completion should be arranged, if agreed to by the patient and in compliance with local data privacy laws/practices. The approach taken should be registered in the eCRF.

If a patient is withdrawn from study, see Section 5.9.

5.9 Withdrawal from study

Patients are at any time free to withdraw from study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4) and the patient should return diary cards.

Withdrawn patients will not be replaced.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

The principal investigator ensures the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The principal investigator will sign the electronic Case Report Form. A copy of the completed electronic Case Report Forms will be archived at the study site.

Data from the central laboratories assessments will be either loaded into WBDC or returned to AstraZeneca directly as datasets, and validated to ensure that it is consistent with the clinical data. Any queries on the data will be raised and resolved within the WBDC system or other designated systems.

6.1.1 Diary Card

Patients will collect information in a Diary Card related to symptoms of ulcerative colitis and changes in concomitant medications from the Enrolment Visit and continuing throughout the study. The Diary Card is aimed to facilitate for the patient to remember his/her symptoms of disease and any change in concomitant medication. The Diary Cards will be reviewed at every visit by the investigator. Information entered by the patient in the Diary Card will facilitate recording data needed to determine the partial Mayo score.

6.2 Data collection at enrolment and follow-up

6.2.1 Enrolment procedures

During the enrolment period (up to randomisation) the following data will be collected and recorded in the appropriate sections of the eCRF:

- Demographics (including sex, date of birth /or age), race and/or ethnic group
- Medical and surgical history
- Nicotine use (current/former/never user)
- Concomitant medications
- Physical examination, vital signs, weight, and height measurements
- 12-lead ECG
- Disease specific characteristic
- Mayo score and Partial Mayo score (see Section 6.3.1) from baseline endoscopy examination
- Modified Riley score reading local and central (Geboes et al 2000) from biopsies collected during baseline endoscopy
- Collection of blood, urine, and faeses samples for laboratory variables listed in Table 8, Table 9, and Table 10.
- Urine pregnancy test for females of childbearing potential
- Completion of UCGHQ
- Adverse Events and Serious Adverse Events.

6.2.2 Follow-up procedures

During the follow-up period from Visit 9 to Visit 11, the following data will be collected according to Study Plan (Table 1):

- Physical examination, vital signs, and weight measurements
- Partial Mayo score
- Completion of UCGHQ
- 12-lead ECG

- Collection of blood, urine, and faeses samples for laboratory variables listed in Table 8, Table 9, and Table 10.
- Urine pregnancy test for females of childbearing potential
- Concomitant medications
- Adverse Events and Serious Adverse Events.

6.3 Efficacy

6.3.1 Mayo Score

The investigator will assess Mayo score at Visit 2 (baseline) and at Visit 6 (Week 8). Mayo score is a combined endpoint consisting of the summarized scoring from four sub-score areas: stool frequency, rectal bleeding, endoscopy findings and the physician's overall assessment of the same in addition to abdominal discomfort and patient's general sense of well-being. The below scoring system will be used (Lewis et al 2008, and Schroeder et al 1987):

Stool frequency (Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency)

0	Normal number of stools per day for this patient
1	1-2 stools per day more than normal
2	3-4 stools per day more than normal
3	5 or more stools per day more than normal

Rectal bleeding (The daily bleeding score represents the most severe bleeding of the day)

0	No blood seen
1	Streaks of blood with stool less than half the time
2	Obvious blood with stool most of the time
3	Blood alone passes

Findings of endoscopy

0	Normal or inactive disease
1	Mild disease (erythema, decreased vascular pattern, mild friability)
2	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3	Severe disease (spontaneous bleeding, ulceration)

Physician's global assessment (PGA) (The physician's global assessment acknowledges the 3 other criteria, the patient's recall of abdominal discomfort and general sense of well-being)

0	Normal
1	Mild disease
2	Moderate disease
3	Severe disease

Mayo score is assessed on the study visit day by the following procedure:

- For stool frequency and rectal bleeding the average symptom severity over the previous 3 days as reported in the Diary Card and during the visit is used to calculate the Mayo score. Diary Cards will be used for daily recording of symptoms between visits.
- Endoscopy subscore represents the endoscopy conducted on the study visit day.

6.3.1.1 Partial Mayo Score

Partial Mayo score is assessed by the investigator at the study Visits 2 (baseline), 4 (week 4), 6 (week 8), 8 (week 12), 9 (week 16), 10 (week 20), and 11 (week 24).

Partial Mayo score is the combined endpoint consisting of the summarized scoring from three sub-score areas: stool frequency, rectal bleeding and the physician's overall assessment of the same in addition to abdominal discomfort and patient's general sense of well-being.

The same scoring system as for Mayo score, with the exception of the endoscopy sub-score, will be used (Lewis et al 2008).

6.3.2 Endoscopy

Endoscopic assessments are scheduled during the enrolment period (baseline) and Visit 6 at week 8. Colonoscopy is the preferred procedure, but if the full extent of the disease can be assessed and unaffected mucosa can be visualized, and photographs and biopsies can be taken using flexible sigmoidoscopy, then flexible sigmoidoscopy is an acceptable alternative. Flexible sigmoidoscopy is not an acceptable alternative under any other circumstances.

Patients will be prepared for endoscopy according to local practice. All medications administered in preparation for and during the endoscopy will be recorded as concomitant medications in the eCRF.

Photographs will be taken of the areas from which biopsies are collected. The photographs will not have to be submitted to the sponsor, unless specifically requested, but should remain archived at the study site. The photographs may be reviewed at site by study monitors or auditors. The study sponsor will request copies of the photographs to be submitted for central

review and adjudication if the central pathology assessment of the collected biopsies does not align with the reported Mayo endoscopy scores reported in the eCRF.

6.3.2.1 Biopsy sampling

Biopsies will be collected during both endoscopies, but only if biopsy collection is not associated with significant discomfort or unacceptable medical risk to the individual patient.

The handling and shipping of the collected biopsy specimen is detailed in the Laboratory Manual.

Biopsies will be collected from areas with active disease/macroscopic inflammation, as well as from unaffected mucosa.

Biopsies for local assessment of disease histology

A biopsy will be collected from affected mucosa to allow local assessment of disease histology. Additional biopsies may be collected, e.g. for mapping of the extent of disease or assessment of incidentally found polyps, if required by local standard of care. The histology will be assessed according to a modified Riley score (Riley et al 1991, and Geboes et al 2000) to evaluate the disease activity, and will be recorded in the eCRF. If multiple biopsies are collected the highest score achieved by any biopsy should be reported on the eCRF. The baseline biopsy will also be used to confirm the UC diagnosis. The patient is not eligible to be randomised if the histology findings do not support a diagnosis of UC. Assessment of presence or absence of cytomegalovirus (CMV) infection by the local pathology laboratory is encouraged whenever such an infection is suspected.

The pathology report must be reviewed and signed by the investigator.

Biopsy sampling for central analysis

Six biopsies will be collected for central analysis from each patient at each endoscopy:

- Three in an area exhibiting active disease/macroscopic inflammation at baseline,
- Three in an area unaffected by disease/without macroscopic inflammation at baseline.

Biopsies should be collected from the same area of the intestine at baseline and at Visit 6 (week 8), whether the macroscopic appearance of the mucosa has changed between baseline and Visit 6 (week 8) or not.

Biopsies from the unaffected mucosa will not need to be collected if the patient exhibits pan-colitis, and no unaffected mucosa can be found.

The outcome of the central histology assessment will be entered into the eCRF, but will not influence patient study participation.

One or more of the collected biopsies will be utilized to examine if CMV infection is present in the mucosa, either by PCR or by immunohistochemistry, or both. The treating physician will be informed if CMV infection is suspected.

Table 7 Biopsy samples for central laboratory assessments

Biopsy #	Location	Medium	Assessments to be done
1.	At baseline unaffected mucosa	Phosphate-buffered 4% Formaldehyde	Central assessment of histology. Measurement of protein expression of STAT6-P, claudin-2, and other proteins using immunohistochemistry.
2.	At baseline unaffected mucosa	Allprotect Tissue Reagent	Multiplex measurement of cytokines (including IL-13) and other proteins.
3.	At baseline unaffected mucosa	Allprotect Tissue Reagent	Measurement of mRNA levels of STAT6, claudin-2 and other genes.
4.	At baseline affected mucosa	Phosphate-buffered 4% Formaldehyde	Central assessment of histology. Measurement of protein expression of STAT6-P, claudin-2, and other proteins using immunohistochemistry.
5.	At baseline affected mucosa	Allprotect Tissue Reagent	Multiplex measurement of cytokines (including IL-13) and other proteins.
6.	At baseline affected mucosa	Allprotect Tissue Reagent	Measurement of mRNA levels of STAT6, claudin-2 and other genes.

6.3.3 Markers of Disease Activity and Intestinal Leakiness, and mRNA levels

The laboratory samples collected to measure mRNA levels, and to assess disease activity (CRP, periostin, cytokines and calprotectin) and intestinal leakiness (albumin) are displayed in Table 8 by visit. These variables will be assessed at the central laboratories. For information on the collection, labelling, storage and shipment of samples, see the Laboratory Manual.

The faeces sample will consist of a dipstick rather than stool collection. Patients may collect the sample prior to the visit if properly trained in advance by site staff, but sample collection by site staff during the visit is preferred.

Table 8 Markers of Disease Activity and Intestinal Leakiness, and mRNA

VISIT	1	2	3	4	5	6	7	8	9	10	11
Week	-1	0	2	4	6	8	10	12	16	20	24
Albumin (serum)	X	X		X		X		X	X	X	X
CRP (serum)	X	X		X		X		X	X	X	X
Periostin (serum)		X		X		X		X	X	X	X
Cytokines (serum)		X		X		X		X	X	X	X
mRNA (blood)		X		X		X		X	X	X	X
Calprotectin (faeces)		X		X		X		X	X	X	X

6.4 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study at the site is familiar with the content of this section.

6.4.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.4.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix B to the Clinical Study Protocol.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse Events will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period.

SAEs will be recorded from the time of informed consent.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the last study visit are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collect for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum intensity of the AE
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- AE caused patient's withdrawal from study (yes or no)
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation

- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Causality assessment in relation to background medications
- Description of AE.

Intensity rating scale:

1 mild (awareness of sign or symptom, but easily tolerated)

2 moderate (discomfort sufficient to cause interference with normal activities)

3 severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Causality collection

The Investigator will assess causal relationship between IP and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IP?'

For SAEs causal relationship will also be assessed for other medications, the background medications and for study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'. A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study staff: *'Have you had any health problems since the you were last asked?'*, or disclosed in the patients diary, or revealed by observation

will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the Clinical Study Report. Deterioration as compared to baseline in protocol-mandated laboratory values, or vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value or a vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg. anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Wherever possible the outcome of microbial culture tests will be added to the reported infection term, eg. “staphylococcal pneumonia” or “culture negative suspected urinary tract infection” should be reported rather than “pneumonia” or “urinary tract infection” alone.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

NB. Cases where a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix E ‘Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy’s Law’, for further instructions.

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then investigators or other site staff member inform appropriate AstraZeneca representatives within one day, ie immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one**

calendar day of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site staff member inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

Once the Investigators or other site staff indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site staff member reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

6.4.5 Laboratory safety assessment

Clinical safety laboratory tests (except pregnancy tests) will be performed in a central clinical laboratory. For information on methods of collection, assessment, labelling, storage and shipment of samples, see the Laboratory Manual.

Urinary pregnancy tests will be performed at the site using a licensed test (dipstick). All samples should be taken by adequately trained study staff and handled in accordance with instructions.

Up to date reference ranges will be provided during the study and laboratory results will be compared to the laboratory standard normal ranges and flagged if they are outside the normal range.

For information on recording of AEs based on laboratory tests, see Section 6.4.3.

The laboratory reports should be signed, dated and retained at the study site as source data for laboratory variables.

Blood and urine samples for determination of clinical chemistry, haematology, urinalysis and other safety tests will be taken at the times indicated in Safety Laboratory Time Schedule table and Specification of Routine Safety Laboratory Tests table (Table 9 and Table 10).

Table 9 Safety Laboratory Time Schedule

VISIT	1	2	3	4	5	6	7	8	9	10	11
Week	**-1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**
Haematology	X	X		X		X		X	X	X	X
Clinical chemistry	X	X		X		X		X	X	X	X
S-beta hCG (Women)	X										
Urinalysis	X	X		X		X		X	X	X	X
Hepatitis B and C screening	X										
HIV screening	X										
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X
Tryptase serum sampling		X [1]	X [1]	X [1]	X [1]	X [1]	X [1]	X [1]	X [1]		
Local laboratory assessments:											
TB screening	X										

[1] If an anaphylactic reaction occurs (see Appendix F) during or within a 24-hour period after administration of IP, serum for assessment of tryptase will be collected as soon as possible after the event, at 60 minutes ± 30 minutes after the event, and at discharge.

Table 10 Specification of Routine Safety Laboratory Tests

Haematology	Clinical chemistry	Urinalysis
B-Haemoglobin (Hb)	S-Creatinine	U-Hb (dipstick)
B-Leukocyte count	S-Bilirubin (total)	U-Protein (dipstick)
B-Leukocyte differential count (neutrophils, lymphocytes (B- and T-cells), monocytes, eusinophils and basophils)	S-Alkaline phosphatase	U-Glucose (dipstick)
B-Platelet count	S-ASAT	U-Nitrites
B-Hematocrit	S-ALAT	U-Bilirubin
Mean corpuscular volume (MCV)	S-Albumin	
Mean corpuscular haemoglobin concentration (MCHC)	S-Potassium	Pregnancy test (dipstick)
	S-Sodium	
	S-Calcium (total)	Urine culture (if applicable) [1]
	S-Bicarbonate	
	S-Chloride	
	S-Gamma GT	
	S-Uric Acid	
	S-βhCG (Women) at screening only	

[1] Refer to 6.4.10.1.

NB. In case a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN please refer to Appendix E 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

For blood volume see Section 7.1.

6.4.6 Physical examination

Physical examinations will be performed by a physician or qualified designee. A complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities) and neurological systems.

A physical examination should be done according to schedule shown in Study Plan (Table 1).

Medically significant changes from the baseline/enrolment physical examination will be reported as AEs (refer to 6.4.3).

6.4.7 Weight and Height

The patient's weight will be recorded in kilogram (kg) with one decimal, and height will be measured in cm.

Measurements should be done with light clothing, and no shoes.

The patient's weight will be collected at Visit 1, Visit 8, and Visit 11. The patient's height will be collected only at Visit 1. Measurements allow the BMI to be calculated.

6.4.8 ECG

A 12-lead ECG will be taken (supine position, standard ECG with a recommended paper speed of 50mm/second covering at least 6 sequential beats) after the patient has been lying down resting for at least 5 minutes.

The principal investigator or delegated investigator is responsible for the overall interpretation and determination of clinical significance of any potential ECG findings, and whether the ECG is normal or not.

6.4.9 Vital signs

Vital signs like blood pressure, temperature, and pulse rate will be obtained on Visit 2, on all Treatment Visits, and on Visit 11 (Table 1).

6.4.9.1 Pulse and blood pressure

Blood pressure, pulse rate will be obtained before blood samples are taken. Patient should rest for at least 5 minutes before measurement. Patients should be seated and pulse rate will be

measured before blood pressure. Ideally, blood pressure should be measured with the same machine, at the same time of day, and by the same staff at each visit.

6.4.9.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated certified thermometer.

6.4.9.3 Vital signs after IP administration

After IP administration, patients will be monitored for immediate drug reactions; vital signs will be taken immediately after administration of IP and at least every 30 minutes thereafter. For the first 4 doses of IP, patients will remain at site for a minimum of 2 hours or until stable, whichever is later. For the 5th, 6th, and 7th doses of IP, patients will remain at site for a minimum of 1 hour or until stable, whichever is later. The investigator will determine if a patient can be discharged from the study site.

6.4.10 Other safety assessments

6.4.10.1 Assessment of Injection Sites

The site of injection will be assessed at every visit from Visit 2 to Visit 9. Blinded study site staff will perform the assessment before the injection and 30 minutes after the injection, as well as prior to discharge from the study site. Injection site reactions will be recorded as AEs according to the criteria described in Section 6.4.1.

6.4.10.2 Assessment of Urinary Tract Infections

Urine should be collected and submitted to the local laboratory for culture in case of clinical suspicion of urinary tract infection. Any microbial agent detected in the culture should be reported in the AE verbatim in the CRF (see also Adverse Events based on examinations and tests above).

6.5 Patient reported outcomes (PRO)

The PRO measure used in this study is the Ulcerative Colitis Global Health Question (UCGHQ).

6.5.1 Ulcerative Colitis Global Health Question (UCGHQ)

The Ulcerative Colitis Global Health Question (UCGHQ) was developed by AstraZeneca for this study to measure the effect UC symptoms have on patients' overall health. It is a self-reported question asking patients to rate their current health considering their ulcerative colitis (see Appendix G).

The UCGHQ will be used for exploratory purposes to assess the concordance between the investigator reported Mayo score and the patient reported UCGHQ score.

The paper version of UCGHQ will be completed by patients at Visit 2 (baseline), Visit 6, and Visit 11 (Table 1). Each study site will assign the responsibility for the administration of the

UCGHQ to a blinded study site staff (eg, a research nurse, study coordinator). AstraZeneca will provide relevant training in administration of the question.

The study staff will explain the significance and relevance of the data collection for participating patients so that they are motivated to comply with data collection method.

Instructions for completion of the UCGHQ question are as follows:

- The question must be completed prior to any visit assessments and before discussion of disease progress to avoid biasing the patient's response to the question.
- The question must be completed in private by the patient.
- The patient should be given sufficient time to complete the question.
- The patient should not receive help from relatives, friends or clinical staff to answer the question. However, if the patient is unable to read (eg, impaired vision or inability to read or write) the question may be read out by trained study staff and responses recorded.
- Study staff should be neutral in their response to any questions from the patient and not help the patient to choose an answer or interpret the question for the patient, but encourage them to respond to the question as best as he/she can.
- The patient should be told that there is no right or wrong answer to the question and that he/she should choose the response that best describes the patient's own experience.
- The UCGHQ should be returned to study staff and checked for completeness.
- Only 1 answer should be recorded.

The paper question will be sent in a pre-addressed envelope to AstraZeneca.

The exploratory PRO analysis will not be reported in the CSR, but in separate report.

6.6 Pharmacokinetics

For PK analyses, it is important that the time of each sc injection is recorded for each patient. Serum will be collected pre-dose according to the schedule of study procedures to measure trough tralokinumab levels.

6.6.1 Collection of samples

Blood samples for determination of tralokinumab concentration in serum will be taken at the times presented in the study plan Table 1. Whole blood is collected into serum gel tubes for

serum preparation. The serum obtained from whole blood samples at each time point will be dispensed equally between the tubes specified for PK (approximately 0.25ml/tube).

Samples will be collected, labelled, stored, and shipped as detailed in Laboratory Manual. For blood volume see Section 7.1.

6.6.2 Determination of drug concentration

Samples for determination of drug concentration in serum will be analysed by Quotient Bioresearch Ltd on behalf AstraZeneca, using an appropriate, validated, bioanalytical method. The method used will be an immunoassay using an anti-idiotype to tralokinumab to capture drug and an anti-human IgG_4 detection antibody. Full details of the analytical method used will be described in a separate bioanalytical report.

All placebo samples will be analysed.

6.7 Immunogenicity

Serum will be collected predose according to the schedule of study procedures to determine the immunogenicity of tralokinumab.

6.7.1 Collection of samples

Blood samples for determination of the immunogenicity of tralokinumab in serum will be taken at the times presented in the study plan Table 1. Whole blood is collected into serum gel tubes for serum preparation. The serum obtained from whole blood samples at each time point will be dispensed equally between the tubes specified for immunogenicity (approximately 0.25ml/tube).

Samples will be collected, labelled, stored, and shipped as detailed in Laboratory Manual. For blood volume see Section 7.1.

6.7.2 Immunogenicity analyses

The presence or absence of anti-tralokinumab antibodies will be determined in the serum samples at MedImmune Ltd., using an appropriate, qualified, bioanalytical method. The method used will be a homogeneous bridging immunoassay. Full details of the analytical method used will be described in a separate bioanalytical report.

All placebo samples will be analysed.

6.8 Pharmacogenetics

For details of procedure refer to Appendix D.

6.9 Pharmacogenomics and blood samples for exploratory analyses

Exploratory analyses on mRNA, cytokine levels including IL-13, periostin and other proteins will be evaluated to gain insight on the tralokinumab mechanism of action and the pathogenesis of UC.

6.9.1 Collection of samples

Blood samples for mRNA extraction and pharmacogenomic analyses, and blood samples for the determination of IL-13 and periostin in serum will be taken at the times presented in Table 6.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory manual. For blood volumes, see Section 7.1.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 11 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Central Laboratory assessments				
Safety	Clinical chemistry	3.5	7	24.5
	Clinical chemistry (screening sample)	7	1	7
	Haematology	2	8	16
mRNA analysis		5	7	35
Pharmacokinetic, Immunogenicity, Markers of Disease Activity and IL[1]		5	12	60
Optional Pharmacogenetics [2]		10	1	10
Local Laboratory assessments				
TB screening		3	1	3
Total				155.5

[1] IL is intestinal leakiness
[2] Optional, only to be collected after patient has signed separate informed consent

Additional samples may be required if:

- an anaphylactic reaction occurs during or within a 24-hour period after administration of IP. The blood volume drawn for those assessments can be approximately 14ml.
- patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN (refer to Appendix E). The blood volume can be at least approximately 12ml for first confirmation assessment.
- any of the other blood tests show abnormal results or give cause for concern.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

AstraZeneca will ensure all biological samples are returned to the source following the finalisation of the Clinical Study Report in all countries where it is a legal requirement.

7.2.1 Pharmacokinetic and immunogenicity samples

PK and immunogenicity samples will be retained for future use at MedImmune Ltd. or designee for a maximum of 25 years following the Last Subject's Last Visit. A summary of measured drug concentrations and immunogenicity results will be reported in the Clinical Study Report.

7.2.2 Biomarker samples

All blood, serum and plasma samples and all tissue biopsies collected to evaluate exploratory endpoints are considered biomarker samples.

AstraZeneca or a designee will retain key biological samples for investigation of the pharmacology of tralokinumab for a maximum of 25 years following the Last Subject's Last Visit. The results from the investigation of such samples will not be reported in the Clinical Study Report but in separate reports (e.g. bioanalytical, and biomarker reports) and in scientific publications as appropriate.

7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each study site keeps full traceability of collected biological samples from the patients while in storage at the study site until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca or designee biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

As collection of the pharmacogenetic sample is optional and not an integral part of the study then the patient may continue in the study.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

8.4 Informed consent

The Principal Investigator(s) at each study site will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a study site's Informed Consent Form, AstraZeneca and the study site's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the study site, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the study site.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other staff involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.

9.2 Training of study site staff

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised. AstraZeneca will provide training of study site staff during Investigator's Meeting and during Study Initiation Visits.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved. The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)

- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the investigator(s) or other staff at the study site needs information and advice about the study conduct.

9.3.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.4 Study agreements

The Principal Investigator at each study site should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.5 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study is expected to start in Q1 and to end by Q1 .

The study may be terminated at individual study sites if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the

entire study prematurely if concerns for safety arise within this study or in any other study with tralokinumab.

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data management will be performed by AstraZeneca Data Management Centre staff.

Data will be entered in the Web Based Data Capture (WBDC) system at the study site. Trained study staff will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF instructions. The eCRF instructions will also guide the study site in performing data entry. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be Source Data Verified (SDV), reviewed/ queried and updated as needed. The Principal Investigator is responsible for signing the eCRF and this can be delegated to a trained Investigator. The eCRF is signed electronically as per the eCRF instructions. The data will be validated as defined in the Data Management Plan.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

The data will be frozen and then locked to prevent further editing. When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked. A copy of the eCRF will be archived at the study site when the study has been locked.

Management of external data

The data collected through third party sources will be obtained and reconciled against study data.

The Data Management Centre determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable). Data Management will ensure that the data collection tool (eg, IVRS/IWRS etc) will be tested / validated as needed. External data reconciliation will be done with the clinical database as applicable.

Dictionary coding

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at Data Management Centre.

Medical coding is done using the most current version of MedDRA and AstraZeneca Drug Dictionary.

Serious Adverse Event (SAE) Reconciliation

SAE Reconciliation Reports are produced and reconciled with Patient Safety database and/or the Investigational Site.

Data Management of genotype data

Refer to Appendix D.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratories internal or external to AstraZeneca.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of efficacy variable(s)

Calculation of efficacy variables will be performed by Cognizant.

Baseline is defined as the most recent measurement obtained before administration of IP. In most cases this will be data from randomisation visit (Visit 2), but if no such value exists, most recent value prior to Visit 2 will be used. Change from baseline for all variables will be calculated by subtracting the baseline value from the visit value. Variables analyzed on the logarithmic scale will be log-transformed before change from baseline is calculated.

11.1.1 Mayo score

Mayo score will be calculated as the sum of the four sub-scores. If any of the four sub-scores are missing, total Mayo score will be missing. Mayo score ranges from 0-12, with higher scores indicating a more severe disease.

11.1.2 Partial Mayo score

Partial Mayo score will be calculated as the sum of the scoring from the three sub-score areas: stool frequency, rectal bleeding and the physician's global assessment. If any of the sub-scores are missing, partial Mayo score will be missing. Partial Mayo score ranges from 0-9, with higher scores indicating a more severe disease.

11.1.3 Clinical response at Week 8 based on Mayo score, the primary variable

A patient will be classified as a responder if the three criteria below are fulfilled at Week 8:

- Decrease in total Mayo score from baseline ≥3 points

- Decrease in total Mayo score from baseline ≥30%
- Decrease in the sub-score for rectal bleeding ≥1 or absolute sub-score for rectal bleeding of 0 or 1 point.

A patient discontinuing IP, requiring intensified therapy, or who underwent a colectomy or ostomy before week 8, or who have a missing Mayo score registration at week 8, will be classified as a non-responder.

11.1.4 Clinical remission at week 8 based on Mayo score

A patient will be classified as being in clinical remission if both the criteria below are fulfilled at week 8:

- Absolute Mayo score ≤2
- No individual subscore >1

A patient discontinuing IP, requiring intensified therapy, or who underwent a colectomy or ostomy before week 8, or who has a missing Mayo score registration at week 8, will be classified as in no remission.

11.1.5 Mucosal healing at week 8

Mucosal healing is defined as an improvement of the endoscopy sub-score (from the Mayo score) at week 8 from 3 or 2 to ≤1 point, or from 1 to 0 points.

A patient discontinuing IP, requiring intensified therapy, or who underwent a colectomy or ostomy before week 8, or who has missing endoscopy sub-score registration at week 8, will be classified as not have had mucosal healing.

11.1.6 Change from baseline in Mayo score

Change from baseline to week 8 in total Mayo score will be calculated as the score at week 8 minus the score at baseline. No imputation of missing values will be performed.

11.1.7 Change from baseline in partial Mayo score

Partial Mayo score will be assessed at week 4, 8, 12, 16, 20 and 24. Change from baseline to each assessment in partial Mayo score will be calculated as the score at the assessment minus the score at baseline. No imputation of missing values will be performed.

11.2 Calculation or derivation of safety variable(s)

Baseline is defined as the most recent measurement obtained before administration of IP. In most cases this will be data from randomisation visit (Visit 2), but if no such value exists, most recent value prior to Visit 2 will be used. Change from baseline will be calculated as the visit value minus the value at baseline. BMI will be calculated from height and weight.

11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.3 Calculation or derivation of pharmacokinetic variables

The pharmacokinetic (PK) analyses will be performed at MedImmune Ltd. The actual sampling times will be used in the PK calculations. PK parameters will be determined using standard non-compartmental methods. The following PK parameters will be determined:

- Areas under the time-concentration curves from zero to infinity and to last observation ($AUC_{(0\text{-infinity})}$; $AUC_{(0\text{-t})}$);
- Dose-normalised $AUC_{(0\text{-infinity})}$: ($AUC_{(0\text{-infinity})}$/D);
- Maximum observed concentration (C_{max});
- Dose-normalised C_{max}: (C_{max}/D);
- Time to C_{max} (T_{max});
- Terminal-phase elimination half-life ($t_{1/2}$);
- Apparent clearance (CL/F);
- Steady-state volume of distribution (V_{ss}/F).

Using the serum concentrations of tralokinumab, the pharmacokinetics of tralokinumab will be analyzed using the noncompartmental method as implemented in WinNonlin® Professional version 5.1 or higher.

Samples below LLOQ will be discarded from the non-compartmental analysis; a more elaborated statistical methodology will be used to handle LLOQ samples when performing population pharmacokinetic/pharmacodynamic (PK/PD) modeling.

Relationship between tralokinumab plasma concentration and effect on PD endpoints of interest (Mayo score, individual sub-scores) will be presented graphically and summarized through descriptive statistics by treatment arm (placebo vs. tralokinumab). Concentration-

effect relationships will be explored by population PK/PD analysis in NONMEM® version 6.2 or higher.

Full details of the population PK/PD analysis intended for this study will be described in a separate analysis plan. Derived PK parameters and the outcome of the PK/PD analysis may be presented in reports separate from the CSR.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA OR DELEGATE

12.1 Description of analysis sets

The treatment associated with a patient may differ depending on the type of analysis used for a particular analysis. The as-randomised approach and as-treated approach are defined as:

As-randomised: Each patient is assigned the patients randomised treatment i.e. the treatment associated with the randomisation code allocated to the patient, identified via the randomisation schedule.

As-treated: Each patient is assigned the patients actual treatment received the first time IP is administrated to the patient regardless of randomisation code.

12.1.1 Full analysis set

The full analysis set will include data from all randomised patients. Patients who were randomised but did not subsequently go on to receive study treatment will be included in the Full analysis set. Analyses of efficacy will be based on the full analysis set, and on the as-randomised approach.

12.1.2 Safety analysis set

The safety analysis set will include data from all patients who received at least one dose of randomised treatment and for whom any post dose data are available. Post dose data implies that there has been a contact in which there has been an opportunity to report any health problems. All safety analyses will be based on this analysis set, and on the as-treated approach.

12.2 Methods of statistical analyses

A statistical analysis plan will be prepared and finalized before clean file is declared.

Descriptive statistics for continuous data will include (but is not restricted to) n (number of values), mean, median, standard deviation, minimum and maximum value. Descriptive statistics for categorical data will include n, frequency, and percentage. These summaries will be given for placebo and tralokinumab separately.

Where appropriate, model-based point estimates will be presented together with their two-sided 95% confidence intervals. When variables are log-transformed prior to analysis, estimates and confidence intervals will first be constructed in the logarithmic scale. By taking the antilogarithms, estimates and confidence intervals for the true geometric means and ratios of true geometric means will be achieved.

To support the one-sided hypotheses of this trial, one-sided p-values will be presented in the analysis of the primary variable - clinical response at week 8, and in the analysis of the two secondary variables - mucosal healing and clinical remission at week 8. No adjustment for multiplicity will be made.

All efficacy analyses will be based on the full analysis set, safety analyses will be addressed with the safety analysis set.

12.2.1 Analysis of primary variable

The primary variable, clinical response at week 8, will be analyzed using a one-sided Cochran-Mantel-Haenszel (CMH) chi-square test, with glucocorticosteroid-refractory status as a stratification factor. The null hypothesis that the proportion of patients responding on tralokinumab is less than or equal to the proportion of patients responding on placebo will be rejected in favour of the alternative hypothesis, that the proportion of patients responding is higher on tralokinumab than on placebo, if the one-sided p-value is <0.05.

The number and proportion of patients responding in each treatment arm will be displayed. The difference in proportions between tralokinumab and placebo will be presented using point estimate and 95% confidence intervals.

A sensitivity analysis will be performed, where patients with biopsies from affected mucosa where the central pathology assessment reported normal histology at baseline, will be excluded.

To assess the impact of premature discontinuations from IP on the primary variable, time to discontinuation of IP may be analysed using Kaplan-Mayer curves. The time to discontinuation of IP will be calculated as the date of IP discontinuation minus the date of randomization +1 day.

In addition, clinical response at week 8 will be summarized descriptively based on the following grouping variables: glucocorticosteroid-refractory status (yes or no), time since first diagnosis (≤5years or >5 years), prior immunomodulatory therapy (yes or no), and affected area in colon (rectosigmoideum involvement only, left side involvement only or extensive involvement).

12.2.2 Analysis of secondary efficacy variables

12.2.2.1 Mucosal healing and clinical remission at week 8

Proportion of patients with mucosal healing and proportion of patients in clinical remission, will be analyzed and presented in the same way as the primary variable, except that no subgroup analyses will be performed.

12.2.2.2 Change from baseline in Mayo score

Depending on the distribution of the data, change from baseline to week 8 in Mayo score will be analyzed using either ANCOVA or cumulative logit methodology. Mayo score at baseline will be included as a covariate, and treatment and glucocorticosteroid-refractory status as factors in the model. Patients with no week 8 assessment and from which change from baseline cannot be calculated, will be excluded from the analysis.

Changes from baseline to all scheduled assessments in each individual subscore will be presented in shift tables.

12.2.2.3 Change from baseline in partial Mayo score

Repeated measures analysis will be used to analyze the change from baseline in partial Mayo score. The model will include treatment, glucocorticosteroid-refractory status, partial Mayo score at baseline, visit, and treatment by visit interaction as explanatory variables. The contrasts of interest are the differences at each visit between tralokinumab and placebo. Depending on the distribution of the data, partial Mayo score will be treated as either a continuous or as an ordered categorical variable.

12.2.2.4 Markers of disease activity (CRP, calprotectin) and intestinal leakiness (albumin)

Repeated measures analysis will be used to analyze the change from baseline in markers of disease activity and intestinal leakiness. The model will include treatment, baseline value, visit, and treatment by visit interaction as explanatory variables. The contrasts of interest are the differences at each visit between tralokinumab and placebo.

Markers of disease activity and intestinal leakiness will be log-transformed before analysis, unless otherwise is stated in the SAP. The number of CRP values below limit of quantification will be assessed before analysis to ensure the model appropriateness. In case of large number of values below limit of quantification another method of analysis should be considered for CRP, this method will be stated in the SAP.

12.2.2.5 Modified Riley score

Changes from baseline to week 8 in modified Riley score will be presented descriptively in shift tables. Modified Riley score at week 8 will be compared between the treatment groups using a stratified Wilcoxon test, with baseline score as the stratification variable.

Each area of the colon assessed will be analysed separately, unless otherwise is stated in the SAP.

12.2.3 Pharmacokinetics

Tralokinumab serum concentrations will be tabulated along with descriptive statistics. The incidence rate of anti-drug antibodies (ADA) to tralokinumab will be reported.

12.2.4 Exploratory objectives

Subgroup analyses of primary variable see section 12.2.1.

Additional explorative analyses of exploratory objectives will be performed separately by the sponsor.

12.2.5 Analysis of safety variables

Laboratory variables, vital signs, BMI, and associated changes from baseline for these measures will be summarized with descriptive statistics at each visit where collected. Individual changes from baseline in laboratory variables will be presented graphically. Physical examination and ECG will be tabulated.

AEs, SAEs, AEs with outcome death, and AEs leading to discontinuation of IP will be tabulated for each treatment arm.

12.2.6 Interim analyses

No interim analysis planned.

12.3 Determination of sample size

The sample size calculation in this study was done to demonstrate superior efficacy of 300 mg tralokinumab over placebo with regard to the primary variable, clinical response at week 8. Assuming that the true proportions of patients responding are 65% and 35% in tralokinumab and placebo respectively, and a one-sided test at $\alpha = 0.05$ with a power of 90%, this yields a planned sample size of 53 patients in each treatment arm. In total 110 patients will be randomised to yield 106 evaluable patients.

The sample size calculations were based on published data on two studies comparing 5 and 10 mg of infliximab, each to placebo, in patients with moderate to severe ulcerative colitis (Rutgeerts et al 2005). Based on the reported studies the study sponsor was given marketing authorization for infliximab in UC. Therefore an increase in the proportion of patients responding to therapy from 35% to 65% would be considered clinically relevant.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4**

In the case of a medical emergency the investigator may contact the Study Physician at the AstraZeneca Research and Development. If the Study Physician is not available, contact the Study Leader.

Name	Role in the study	Address & telephone number
,	Study Physician	AstraZeneca R&D Mölndal
	Study Leader	AstraZeneca R&D | Poland Clinical Operational Hub

13.2 Overdose

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site staff inform appropriate AstraZeneca representatives **within one day** ie, immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

Female subjects should refrain from becoming pregnant during the study and for 12 weeks following the last dose (see section 5.1).

If a patient becomes pregnant during the course of the study IP should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, investigators or other site staff inform appropriate AstraZeneca representatives **within one day** ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

13.3.2 Paternal exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 12 weeks following the last dose (see section 5.1).

Pregnancy of the subject's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented for conceptions occurring from the date of the first administration of IP until 12 weeks after the last administration of IP.

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