CLINICAL TRIAL PROTOCOL

A Phase II, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of TJ301 (FE 999301) Administered Intravenously in Patients with Active Ulcerative Colitis

Protocol Number:	CTJ301UC201
Investigational Medicinal Product:	TJ301 (solution for injection), also referred to as FE 999301 and Olamkicept
Indication:	Active Ulcerative Colitis
Phase:	2
Investigators:	Multicenter, international, across Mainland China, Taiwan, Republic of Korea and Australia
Coordinating Investigator	Prof. Dr. Minhu Chen Chair, Department of Gastroenterology and Hepatology Vice President The First Affiliated Hospital, Sun Yat-sen University 58 Zhongshan Road, Guangzhou, China
Expert committee	Prof. Dr. Stefan Schreiber Institute for Clinical Molecular Biology University Hospital Schleswig-Holstein Schittenhelmstrasse 12, 24105 Kiel, Germany
Name and Address of Sponsor:	Leading Biopharm Limited **Sponsor Contact:** Yin Liu Suite 802, OmniVision Park West Tower 88 Shangke Road, Pudong, Shanghai 201210, China Tel: + 86 135 0178 1723
GCP Statement:	This trial will be performed in compliance with GCP.

APPROVAL

REPRESENTATIVES OF SPONSOR

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation (ICH) E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

Yin Liu, MD
Clinical Medical Director

Date

Taylor B. Guo, PhD
Chief Science Officer

Date

REPRESENTATIVES OF CRO

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation (ICH) E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

Jiali Liu
Data Management Manger
Mosim Co., Ltd

Date

Weiyan Dai
Biostatistics Manager
Mosim Co., Ltd

Date

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the Sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in this protocol.
- Terms outlined in the Clinical Study Site Agreement.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in this protocol.

_____

Signature of Investigator Date

_____

Investigator's Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State)

_____

Location of Facility (Country)

VERSION OF PROTOCOL OR PROTOCOL AMENDMENT

Document	Date of issue
V1.0	22 Feb 2017
V1.1	16 May 2017

SYNOPSIS

TITLE OF TRIAL

A Phase II, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of TJ301 (FE 999301) Administered Intravenously in Patients with Active Ulcerative Colitis

Coordinating Investigator
Prof. Dr. Minhu Chen
Chair, Department of Gastroenterology and Hepatology
Vice President
The First Affiliated Hospital, Sun Yat-sen University
58 Zhongshan Road, Guangzhou, China

Expert committee
Prof. Dr. Stefan Schreiber
University Hospital Schleswig-Holstein Arnold-Heller-Str. 3 24105 Kiel Germany

Investigators

Multicenter, international across Mainland China, Taiwan, Republic of Korea and Australia.

TRIAL SITES

The trial will be conducted at 25-30 sites globally.

PLANNED TRIAL PERIOD	CLINICAL PHASE
First patient first visit: 3rd Quarter 2017 Last patient last visit: 1st Quarter 2020	2

OBJECTIVES

Primary Objective

- To explorate the safety and efficacy of TJ301 in patients with active ulcerative colitis.

Secondary Objectives

- To investigate the pharmacokinetics (PK) of TJ301 in patients with active ulcerative colitis.
- To investigate the pharmacodynamics (PD) of TJ301 in patients with active ulcerative colitis.
- To investigate immunogenicity of TJ301 in patients with active ulcerative colitis.

Exploratory Objectives

- To explorate the relationship between PKand PD of TJ301 in patients with active ulcerative colitis.

ENDPOINTS

Primary Endpoints

- Clinical and endoscopic remission at Week 12, defined as a full Mayo score ⩽2, no individual subscore >1, rectal bleeding subscore = 0.
- Adverse events, vital signs, 12-lead Electrocardiography (ECG), and clinical safety laboratory abnormalities.

Secondary Endpoints

- Clinical and endoscopic response (decrease from Baseline in full Mayo score≥3 and ≥30%, including decrease from Baseline in rectal bleeding subscore≥1 or rectal bleeding subscore ≤1) at Week 12.
- Clinical remission at Weeks 4, 6, 8, 10, and 12 defined as a stool frequency subscore=0, rectal bleeding subscore = 0, and 9-point partial Mayo score ≤1.
- Clinical response (decrease from Baseline in 9-point partial Mayo score≥2 and ≥30%, including decrease from Baseline in rectal bleeding subscore≥1 or rectal bleeding subscore ≤1) at Weeks 4, 6, 8, 10, and 12.
- Mucosal healing defined as Mayo endoscopic subscore = 0 or 1 at Week 12.
- Change from Baseline to Weeks 4, 6, 8, 10, and 12 in 9-point partial Mayo score.
- Change from Baseline to Week 12 in full Mayo score.
- Change from Baseline to Week 12 in modified Mayo score (=full Mayo score excluding Physician's Global Assessment (PGA) subscore).
- Change from Baseline to Weeks 4, 6, 8, 10, and 12 in PGA score.
- FDA-defined remission at Week 12, defined as Stool frequency subscore=0, Rectal bleeding subscore=0, and Endoscopy subscore =0 or 1.
- Immunogenicity: Anti-TJ301 antibodies.
- PK subgroup: AUC_{inf}, AUC_t, $\%AUC_{ext}$, C_{max}, t_{max}, CL, V_z, λ_z, $t_{½}$, and MRT (if applicable).
- Peak and trough (pre-infusion) TJ301 serum concentration.

Exploratory Endpoints

- Change from Baseline to Weeks 4, 8, and 12 in exploratory biomarkers (erythrocyte sedimentation rate [ESR], C-reactive protein (CRP), IL-6, IL-6/sIL-6R complex, neutrophil and platelet count, faecal calprotectin).

Study Design

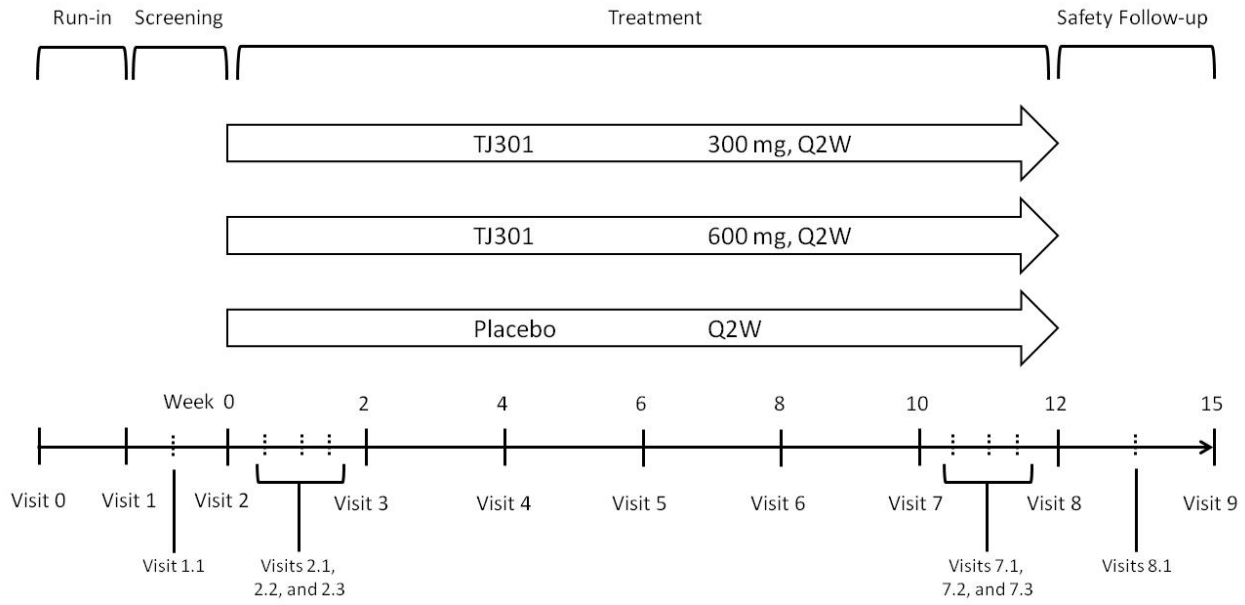
This is a multicenter, randomized, double-blind, placebo-controlled phase II study.

The trial includes a Run-in Period (if stable conventional treatment needed), a 4-week Screening Period, a 12-week Treatment Period, and a 3-week Safety Follow-up Period to Day 105.

90 patients will be centrally, dynamically, randomly assigned to 3 groups (1:1:1) to receive 600mg TJ301 biweekly (Q2W), 300mg TJ301 Q2W or placebo Q2W. TJ301 or placebo administrations will occur on Days 0, 14, 28, 42, 56, and 70. Randomisation will be stratified by prior corticosteroids treatment (yes/no) and consent to participate in PK substudy (yes/no).

During the treatment period and the follow-up period, patients should be on stable conventional treatment for UC in double-blind except for those who cannot tolerate the stable conventional treatment. Conventional treatment for UC can be the concomitant UC treatment or UC treatment previously received by the patient, including corticosteroids at no more than 20 mg prednisone (or equivalent), and/or with medications containing 5-aminosalicylates (5-ASA), and/or with azathioprine (AZA)/mercaptopurine (6-MP).

Study Flowchart



There will be 9~10 main visits at the investigational site during the study:

- Visit 0: Run-in period: at an optional visit (Visit 0), decision will be made if patients need stable conventional UC treatment to meet the following criteria: with corticosteroids stable for at least 2 weeks prior to Randomization at no more than 20 mg prednisone (or equivalent), and/or with medications containing 5-aminosalicylates (5-ASA) at no less than 2 g 5-ASA per day for at least 3 months and stable for at least 4 weeks prior to Randomization, and/or with azathioprine (AZA) at no less than 1.5 mg/kg/day or mercaptopurine (6-MP) at no less than 0.75 mg/kg/day for at least 6 months and stable for at

least 6 weeks prior to Randomization. If patients already met the criteria, they will directly enter the Screening Period (Visit 1). If not, they will need stable conventional UC treatment during the Run-in Period except those who cannot tolerate the medications mentioned above.

- Visit 1: Screening Visit, start of Screening Period (Days -28 to -1 prior to Visit 2)
- Visit 2: Randomisation Visit (Baseline), start of 12-week Treatment Period
- Visits 3-7: 5 visits during 12-week Treatment Period
- Visit 8: End of Treatment (EoT) Visit, completion of 12-week Treatment Period
- Visit 9: Safety Follow-up Visit, scheduled at 35 days after the last dose of IMP (Day 105).

Clinical assessments of disease activity will take place at Visit 1 (Screening Visit), Visit 2 (Randomisation Visit), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8), Visit 7 (Week 10), and Visit 8 (Week 12). During Screening and at Visit 8 (Week 12), assessments of disease activity will also include endoscopy (colonoscopy or sigmoidoscopy); mucosal biopsies for assessment of mucosal healing, histology, immunohistochemistry will be collected during endoscopy at these time points.

TJ301 PK will be assessed in a subgroup of patients in Mainland China (24 patients, 8 per arm; electronically assigned at randomisation and consenting to the extra procedures). Blood samples for PK subgroup will be collected as follows:

- At 1st dose: pre-dose and 0.5, 1, 2 (end of infusion), 6, 48, 144 (Day 6), and 240 (Day 10) h after the start of the 1st administration;
- At the 2nd, 3rd, 4th, and 5th administrations blood samples will be collected pre-dose and at the end of infusion;
- At 6th dose: pre-dose and 0.5, 1, 2 (end of infusion), 6, 48, 144 (Day 76), 240 (Day 80), 336 (Day 84), 480 (Day 90), and 840 h (Day 105) after the start of the 6th administration.

The actual sampling time will be recorded.

For patients completing the last dose of IMP, a Safety Follow-up Visit will be scheduled to Day 105 (Week 15). For patients not completing the trial, a Safety Follow-up Visit will be scheduled 35 days (5.8 - 6.6 half-lives of TJ301) after the last dose of IMP.

NUMBER OF PATIENTS

In total, 90 patients with active UC will be enrolled competitively, and randomised equally into three arms with TJ301 (two dose levels) or placebo.

CRITERIA FOR INCLUSION / EXCLUSION

Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Male and female patients 18-70 (inclusive) years of age.
2. Active UC confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy at Screening, with extending > 15-cm past the anal verge from endoscopy.
3. Active UC with a full Mayo score⩾5 and a rectal bleeding subscore ≥1 at screening.
4. During Day -35 to Day -6 prior to Randomisation, an endoscopy subscore ≥2.
5. Treated with conventional non-biological UC therapy: with corticosteroids stable for at least 2 weeks prior to Randomization at no more than 20 mg prednisone (or equivalent), and/or with medications containing 5-aminosalicylates (5-ASA) at no less than 2 g 5-ASA per day for at least 3 months and stable for at least 4 weeks prior to Randomization, and/or with azathioprine (AZA) at no less than 1.5 mg/kg/day or mercaptopurine (6-MP) at no less than 0.75 mg/kg/day for at least 6 months and stable for at least 6 weeks prior to Randomization.
6. A female subject has been sterilized or has been menopausal, or the subject has no pregnancy plan during the trial and voluntarily adopts effective contraceptive measures.
7. The patient is able and willing to comply with the requirements of this trial protocol.
8. The subject should be able to read and write to understand and fill out Patient Diary.
9. Voluntarily signed Informed Consent obtained before any trial-related procedures are performed.

Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Pregnant or breastfeeding women.
2. Contraindication to colonoscopy or sigmoidoscopy.
3. Allergies to any component of TJ301.
4. History of colostomy, colectomy or partial colectomy.
5. Current diagnosis of inflammatory bowel disease unclassified, Crohn's disease, ischemic colitis, fulminant colitis and/or toxic megacolon, patients with ulcerative colitis limited to the rectum (ulcerative proctitis), infective enteritis, amebic bowel disease and intestinal schistosomiasis.
6. History of malignancy other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma *in situ* of the cervix. If the Screening colonoscopy shows evidence of dysplasia or a malignancy, the patient is not eligible.
7. Primary or secondary immunodeficiency including neutropenia (absolute neutrophil count

<1500/μL); or lymphopenia (absolute lymphocyte count <500/μL).

8. Moderate to severe anaemia (haemoglobin <9 g/dL), or thrombocytopenia (platelet count <75 000/μL), or serum creatinine >2 mg/dL.
9. Autoimmune disease besides UC, with the exceptions of Sjogren's syndrome or hypothyroidism.
10. Clostridium (C.) difficile positive at screening visit or treated for C. difficile within the 4 weeks prior to Randomization.
11. Known clinically relevant chronic liver disease. Impaired hepatic function in the absence of a diagnosis of primary sclerosing cholangitis (serum transaminases >2.5 x upper limit of normal [ULN], alkaline phosphatase >2.5 x ULN, or abnormalities in synthetic liver function tests judged by the investigator to be clinically significant), or a diagnosis of primary sclerosing cholangitis, serum transaminases >3 x ULN, alkaline phosphatase >3 x ULN, or abnormalities in synthetic liver function tests (total bilirubin >1.5 x ULN) judged by the investigator to be clinically significant.
12. Serious underlying disease other than UC in the opinion of the investigator.
13. History of drug addiction within the last 1 year or current drug addiction or use of illicit drugs.
14. Any indication of the regular use of more than 40 grams of alcohol every day.
15. Smokers who smoke more than 10 cigarettes per day.
16. Known concurrent acute or chronic viral hepatitis B or C infection or human immunodeficiency virus (HIV) infection.
17. Presence or history of active tuberculosis (TB) or latent TB infection, defined as 1) a positive QuantiFERON-TB Gold test at Screening, or 2) a positive T-spot test within 4 weeks of Randomisation and evidence of current or previous pulmonary tuberculosis by chest X-ray within 12 weeks of Randomisation.
18. Positive immunoglobulin M antibody titres in the presence of negative immunoglobulin G titres to Epstein-Barr virus (EBV).
19. If clinical suspicion of cytomegalovirus (CMV), cytomegalovirus testing should be undertaken. Subjects with intestinal mucosa biopsy positive for cytomegalovirus at screening are to be excluded.
20. Receiving any investigational therapy or any approved therapy for investigational use within 30 days or 5 half-lives prior to Randomization (whichever is longer).
21. Currently taking any medications other than those allowed per protocol guidelines.
22. Infections (including diverticulitis) requiring treatment with antibiotics, antivirals, or antifungals within 14 days prior to Randomisation.
23. Any prior use of biologic drugs.

24. Received any live (attenuated) vaccines within 30 days prior to Randomisation.
25. Recent treatment with medium-to-high-dose intravenous corticosteroids (methylprednisolone 60 mg/day or hydrocortisone 300 mg/day) within 8 weeks prior to Randomisation or oral corticosteroids of more than 20 mg prednisone (or equivalent) within 30 days prior to Randomisation.
26. Receipt of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil within 30 days prior to Randomisation.
27. Treatment with therapeutic enema or suppository, other than required for endoscopy preparation, within 14 days prior to the screening endoscopy and during the remainder of the trial.

Investigational Medicinal Product (IMP)

The IMP in this trial is TJ301 (FE 999301, Olamkicept (proposed INN)) (15 mg/mL in solution for injection [25 mM histidine, 200 mM sucrose, 0.1 mg/mL Polysorbate 20 in aqueous solution]). The placebo is the solution for injection [25 mM histidine, 200 mM sucrose, 0.1 mg/mL Polysorbate 20 in aqueous solution] without TJ301.

Both placebo and TJ301 should be stored at -20±5 °C and thawed at the site by site personnel (blind to study randomisation) and diluted in 250 mL 5% (w/v) glucose. The infusion time is 2 hours.

The following concentrations and infusion volumes of TJ301 and placebo will be used:

Dose group	Vials	Drug volume (mL)	5% (w/v) glucose(mL)	TJ301 (mg/mL)	Infusion volume (mL)
Placebo	8 vials Placebo	40	250	0	290
300 mg	4 vials Placebo and 4 vials TJ301	40	250	1.03	290
600 mg	8 vials TJ301	40	250	2.07	290

STATISTICAL METHODS

Sample Size

A sample size of N=72 (n=24 per treatment/placebo arm) patients is expected to achieve a power of 83% of detecting a trend ($p<0.05$, one-sided) if the true remission rate difference (at Week 12) between the placebo and highest dose groups (600 mg Q2W) is 30% (10% for the placebo and 40% for the highest dose) using Pearson's chi-square test without continuity correction. The trial also

has 70% power to reach a statistically significant result ($p<0.05$, one-sided) in case the remission rate difference between placebo and treatment (300 mg Q2W and 600 mg Q2W combined together) is 20% (10% vs 30%). Considering the dropout rate of approximately 20%, a total of 90 patients will be enrolled competitively.

Data Analyses

Quantitative variables will be described with the number of non-missing values, mean, standard deviation (SD), median, and minimum/maximum values. Qualitative variables will be described with the number and percentage of patients with each qualitative characteristic. Missing values will not be included in the calculation of percentages. All data will be listed by individual patient and study visit.

The primary efficacy endpoint is clinical and endoscopic remission at Week 12. This binary outcome (remission status=yes/no) variable will be analysed by a logistic regression model. A patient with missing data on the remission status will be assumed to be not in remission.

All dichotomised secondary endpoints will be analysed using a repeated logistic regression model and continuous endpoints will be analysed using a repeated measures Analysis of Covariance (ANCOVA) model.

In addition, patients in both the placebo and the treatment groups will be split into subgroups based on the baseline level of IL-6/sIL-6R complexes. Comparison in endpoints will be made for different subgroups.

Safety analyses will be summarized descriptively by treatment groups. No statistical testing for comparison of treatment groups will be performed for safety variables.

The PK parameters will be derived using noncompartmental method. The PK of TJ301 will be summarized using descriptive statistics.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

ANCOVA	Analysis of Covariance
Anti-TNF	Anti-Tumour Necrosis Factor
5-ASA	5-Aminosalicylate
AZA	Azathioprine
ß-HCG	beta-Human Chorionic Gonadotrophin
CMV	Cytomegalovirus
CRO	Contract Research Organisation
CRP	C-Reactive Protein
EBV	Epstein-Barr virus
e-CRF	Electronic Case Record Form
ECG	Electrocardiogram
EoT	End-of-Treatment
ESR	Erythrocyte Sedimentation Rate
FAS	Full Analysis Set
Fc region	Fragment Crystallisable Region
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEENT	Head, Eyes, Ears, Nose, and Throat
HIV	Human Immunodeficiency virus
HPA	Hypothalamic-Pituitary-Adrenal
IBD	Inflammatory Bowel Disease

ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1
IL-6	Interleukin 6
IL-6R	IL-6 Receptors
IMP	Investigational Medicinal Product
ITT	Intention-to-Treat
IRB	Institutional Review Board
i.v.	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
6-MP	6-Mercaptopurine
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per Protocol
PRO	Patient Reported Outcome
PT	Preferred Term
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
sIL-6R	Soluble IL-6 Receptor
SOC	System Organ Class
SRC	Safety Review Committee
SUSAR	Suspected, Unexpected Serious Adverse Reaction

TB	Tuberculosis
UC	Ulcerative Colitis
ULN	Upper Limit of Normal
WHO	World Health Organization

Definition of Terms

Bowel movement	A single defecation event with a beginning and end (as interpreted by the patient), which may include single or multiple stools.
Mayo Score	Full Mayo Score: A composite disease activity score consisting of four items or subscores: stool frequency (relative to normal), rectal bleeding, physician's global assessment, and endoscopic appearance (range 0-12; higher scores being worse). 9-point Partial Mayo Score: The sum of the stool frequency, rectal bleeding, and physician's global assessment subscores (range 0-9). 6-point Partial Mayo Score: The sum of the stool frequency and rectal bleeding subscores (range 0-6).
Randomisation	Patient is randomly assigned to a treatment group and given a unique patient number
Sponsor	Leading Biopharm Limited
Screened	Patient who has signed informed consent and has undergone at least one screening assessment

Definition of Pharmacokinetic Terms

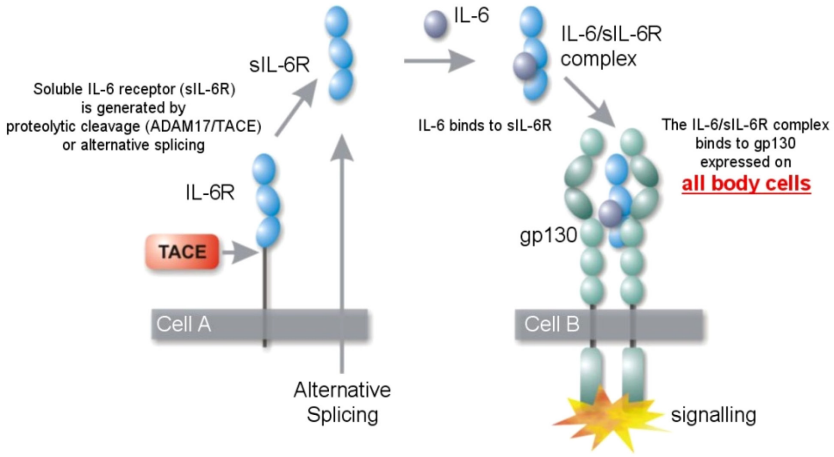
AUC_{inf}	Area under the concentration-time curve to infinity
AUC_t	Area under the concentration-time curve from time zero up to time t, where t is the last time point at which the concentration is above the lower limit of quantification
%ExtrapAUC	Percentage of AUC that is due to extrapolation from the last measurable concentration
C_{max}	Maximum concentration observed
t_{max}	Time of maximum observed concentration (C_{max})
CL	Total systemic clearance
V_z	Volume of distribution associated with the terminal phase
λ_z	First-order rate constant associated with the terminal (log-linear) portion of the concentration-time curve
$t_{½}$	Elimination half-life
MRT	Mean residence time
F	Bioavailability

1 INTRODUCTION

1.1 Background

Interleukin 6 (IL-6) is a pleiotropic cytokine produced by hematopoietic and non-hematopoietic cells, e.g. in response to infection and tissue damage. IL-6 is believed to be a key mediator in diseases such as rheumatoid arthritis (RA), psoriasis and inflammatory bowel disease (IBD; i.e. Crohn's disease and ulcerative colitis [UC]).

IL-6 exerts its multiple biological activities through two main signalling pathways. One is the so-called classic ligand-receptor pathway via membrane-bound IL-6 receptors (IL-6R) present mainly on hepatocytes and certain leukocytes. The second is the *trans*-signalling pathway *via* circulating soluble IL-6R (sIL-6R) originating from proteolytic cleavage of the membrane-bound IL 6R or from alternative splicing (1)(2). While the classic IL-6 signalling is involved in the acute inflammatory response, *trans*-signalling is mainly involved in chronic inflammation and has been shown to prevent disease-promoting mucosal T-cell populations from going into apoptosis. A schematic presentation of the *trans*-signalling pathway of IL-6 is shown in Figure 1.



TACE: tumour necrosis factor alpha converting enzyme
ADAM: A disintegrin and metalloprotease

Figure 1 Trans-signalling Pathway of IL-6

Patients with Crohn's disease and UC have been found to produce increased levels of IL-6 when compared with controls, the IL-6 levels being correlated to clinical activity (3)(4)(5)(6). Crohn's disease and UC patients have also been found to have increased levels of sIL-6R and consequently, IL 6/sIL-6R complex in serum (4)(5)(6).

TJ301 (FE 999301, Olamkicept (proposed INN)) is a first-in-class, selective IL-6 trans-signalling inhibitor and anti-inflammatory biologic that is under development for the treatment of UC and Crohn's disease. TJ301 is a selective IL-6/sIL-6R complex trap consisting of two complete extracellular domains of gp130, the common signal transducer of IL-6-type cytokines, dimerised by

fusion to the fragment crystallisable region (Fc region) of human immunoglobulin G1 (IgG1). TJ301 targets and neutralises the IL-6/sIL-6R complex thereby inhibiting the *trans*-signalling pathway, without any interaction with either IL-6 or IL-6R individually, which is different from other anti-IL6 or anti-IL6R products in development to block IL-6 two signaling pathways. TJ301 is expected to be as effective as existing biologics but safer and more suited for early and long-term use.

1.2 Scientific Justification for Conducting the Trial

The safety, tolerability and pharmacokinetic (PK) properties of TJ301 (FE 999301) have been investigated in Germany in two phase 1, single- and multiple-ascending dose clinical studies in healthy and Crohn's disease subjects with up to 4 weeks of weekly intravenous (i.v.) infusion. These studies showed dose-proportional systemic exposure, in the dose range of 0.75 mg to 750 mg, with a mean terminal half-life of approximately 5 days and no apparent dose-dependent trends in the incidence or nature of adverse events. Furthermore, a cohort of patients with quiescent Crohn's disease demonstrated similar systemic exposure to that in healthy subjects, for corresponding doses of 75 mg, 300 mg, and 750 mg in the single-ascending-dose trial.

The purpose of this proof-of-concept trial is to assess the safety, efficacy, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of two different doses of i.v. infusions of TJ301 in patients with active UC. The ability to induce remission of TJ301 will be investigated in the 12-week double-blind treatment period of the study.

1.3 Benefit / Risk Aspects

For patients with active UC, 5-aminosalicylate (5-ASA) is considered a first-line treatment, either as oral or topical (e.g. suppositories, enema) formulations. 5-ASA has a benign safety profile with dosing in active disease of up to several grams a day, but is not effective in all patients.

Oral, systemic corticosteroids are used for induction of remission in patients not responding to 5-ASA. Corticosteroids have frequent and occasionally serious side effects, e.g. hypothalamic-pituitary-adrenal (HPA)-axis suppression, hyperglycaemia/insulin resistance, cataracts, and osteoporosis (notably, IBD itself is a risk factor for osteopenia/osteoporosis, with Crohn's patients being most affected), and systemic corticosteroids are therefore undesirable in maintenance treatment. Immunosuppressive drugs, such as azathioprine (AZA) or 6-mercaptopurine (6-MP) (i.e. thiopurines), are used as steroid-sparing agents in steroid-dependent or steroid-refractory patients, in induction as well as maintenance treatment (7)(8), but are associated with an increased risk for malignancies (9). Since thiopurines and corticosteroids are not effective in all patients and especially in the moderately to severely active IBD patient population, there is a need for novel, effective and safe second- and even third-line treatment options.

In conclusion, patients with active UC are representative of the target population for TJ301, and should present the opportunity to detect a larger effect due to more pronounced disease activity at Baseline.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

- To explorate the safety and efficacy of TJ301 in patients with active ulcerative colitis.

Secondary Objectives

- To investigate the pharmacokinetics of TJ301 in patients with active ulcerative colitis.
- To investigate the pharmacodynamics of TJ301 in patients with active ulcerative colitis.
- To investigate immunogenicity of TJ301 in patients with active ulcerative colitis.

Exploratory Objectives

- To explorate the relationship between pharmacokinetics and pharmacodynamics of TJ301 in patients with active ulcerative colitis.

2.2 Endpoints

Primary Endpoints

- Clinical and endoscopic remission at Week 12, defined as a full Mayo score ≤2, no individual subscore >1, rectal bleeding subscore = 0.
- Adverse events, vital signs, 12-lead Electrocardiography (ECG), and clinical safety laboratory abnormalities.

Secondary Endpoints

- Clinical and endoscopic response (decrease from Baseline in full Mayo score ≥3 and ≥30%, including decrease from Baseline in rectal bleeding subscore ≥1 or rectal bleeding subscore ≤1) at Week 12.
- Clinical remission at Weeks 4, 6, 8, 10, and 12 defined as a stool frequency subscore=0, rectal bleeding subscore = 0, and 9-point partial Mayo score ≤1.
- Clinical response (decrease from Baseline in 9-point partial Mayo score ≥2 and ≥30%, including decrease from Baseline in rectal bleeding subscore ≥1 or rectal bleeding subscore ≤1) at Weeks 4, 6, 8, 10, and 12.
- Mucosal healing defined as Mayo endoscopic subscore = 0 or 1 at Week 12.
- Change from Baseline to Weeks 4, 6, 8, 10, and 12 in 9-point partial Mayo score.
- Change from Baseline to Week 12 in full Mayo score.
- Change from Baseline to Week 12 in modified Mayo score (=full Mayo score excluding Physician's Global Assessment (PGA) subscore).

- Change from Baseline to Weeks 4, 6, 8, 10, and 12 in PGA score.
- FDA-defined remission at Week 12, defined as Stool frequency subscore=0, Rectal bleeding subscore=0, and Endoscopy subscore =0 or 1.
- Immunogenicity: Anti-TJ301 antibodies.
- PK subgroup: AUC_{inf}, AUC_t, $\%AUC_{ext}$, C_{max}, t_{max}, CL, V_z, λ_z, $t_{½}$, and MRT (if applicable).
- Peak and trough (pre-infusion) TJ301 serum concentration.

Exploratory Endpoints

- Change from Baseline to Weeks 4, 8, and 12 in exploratory biomarkers (erythrocyte sedimentation rate [ESR], C-reactive protein (CRP), IL-6, IL-6/sIL-6R complex, neutrophil and platelet count, faecal calprotectin).

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Trial Design Diagrams

A schematic overview of trial design is shown in Figure 2.

3.1.2 Overall Design

This is a multicenter, stratified randomized, double-blind, placebo-controlled phase II study.

The trial includes a Run-in Period (if stable conventional treatment needed), a 4-week Screening Period, a 12-week double-blind Treatment Period, and a Safety Follow-up Period of 3 weeks to Day 105.

90 patients will be centrally, dynamically, randomly assigned to 3 groups (1:1:1) to receive 600mg TJ301 biweekly (Q2W), 300mg TJ301 Q2W or placebo Q2W. Randomisation will be stratified by prior corticosteroids treatment (yes/no) and consent to participate in PK substudy (yes/no). TJ301 or placebo administrations will occur on Days 0, 14, 28, 42, 56, and 70.

During the double-blind period and the follow-up period, patients should be on stable conventional treatment for UC.

There will be 9 ~ 10 main visits at the investigational site during the study:

- Visit 0: Run-in Period: at an optional visit (Visit 0), decision will be made if patients need stable conventional UC treatment to meet the following criteria: with corticosteroids stable for at least 2 weeks prior to Randomization at no more than 20 mg prednisone (or equivalent), and/or with medications containing 5-aminosalicylates (5-ASA) at no less than 2 g 5-ASA per day for at least 3 months and stable for at least 4 weeks prior to Randomization, and/or with azathioprine (AZA) at no less than 1.5 mg/kg/day or mercaptopurine (6-MP) at no less than 0.75 mg/kg/day for at least 6 months and stable for at least 6 weeks prior to Randomization. If patients already met the criteria, they will directly enter the Screening Period (Visit 1). If not, they will need stable conventional UC treatment during the Run-in Period except those who cannot tolerate the medications mentioned above.
- Visit 1: Screening Visit, start of Screening Period (Days -28 to -1 prior to Visit 2)
- Visit 2: Randomisation Visit (Baseline), start of 12-week Double-blind Treatment Period
- Visits 3-7: 5 visits during 12-week Double-blind Treatment Period
- Visit 8: End of Treatment (EoT) Visit, completion of 12-week Double-blind Treatment Period
- Visit 9: Safety Follow-up Visit, scheduled at 35 days after the last dose of IMP (Day 105).

Clinical assessments of disease activity will take place at Visit 1 (Screening Visit), Visit 2 (Randomisation Visit), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8), Visit 7 (Week 10), and Visit 8 (Week 12). During Screening and at Visit 8 (Week 12), assessments of disease activity will also include endoscopy (colonoscopy or sigmoidoscopy); mucosal biopsies for assessment of mucosal healing, histology, immunohistochemistry will be collected during endoscopy at these time points.

TJ301 PK will be assessed in a subgroup of patients in Mainland China (24 patients, 8 per arm; electronically assigned at randomisation and consenting to the extra procedures). Blood samples for PK subgroup will be collected in as follows:

- At 1st dose: pre-dose and 0.5, 1, 2 (end of infusion), 6, 48, 144 (Day 6), and 240 (Day 10) h after the start of the 1st administration;
- At the 2nd, 3rd, 4th, and 5th administrations blood samples will be collected pre-dose and at the end of infusion;
- At 6th dose: pre-dose and 0.5, 1, 2 (end of infusion), 6, 48, 144 (Day 76), 240 (Day 80), 336 (Day 84), 480 (Day 90), and 840 h (Day 105) after the start of the 6th administration.

The actual sampling time will be recorded.

The schedule of blood sampling for PK assessment allows the evaluation of PK profiles after single dose and after multiple doses in patients with UC. Considering the terminal plasma half-life of 5.3 – 6.0 days for TJ301 in healthy volunteers, the last blood sample will be collected at 840 hours (5.8~6.6 half-lives of TJ301) after the last dose. Also due to the long half-life of TJ301, the scheduled sparse blood sampling would be able to capture the PK profile of TJ301.

In order to ensure that standard therapy is not withheld from patients not gaining sufficiently from IMP treatment, patients suffering a worsening in disease after Visit 5 are to be withdrawn. Worsening will be defined as an increase from last visit in Mayo rectal bleeding subscore ≥1, over 3 consecutive days (Appendix 1). Such worsening should be evaluated by the Investigator and confirmed by endoscopy (no improvement or worse) prior to deciding whether or not to withdraw the patient.

For patients not completing the trial, a Safety Follow-up Visit will be scheduled 35 days (5.8 - 6.6 half-lives of TJ301) after the last dose of IMP. For patients completing the 12-week Treatment Period, likewise a Safety Follow-up Visit will be scheduled at 35 days after the last dose of IMP (Days 105).

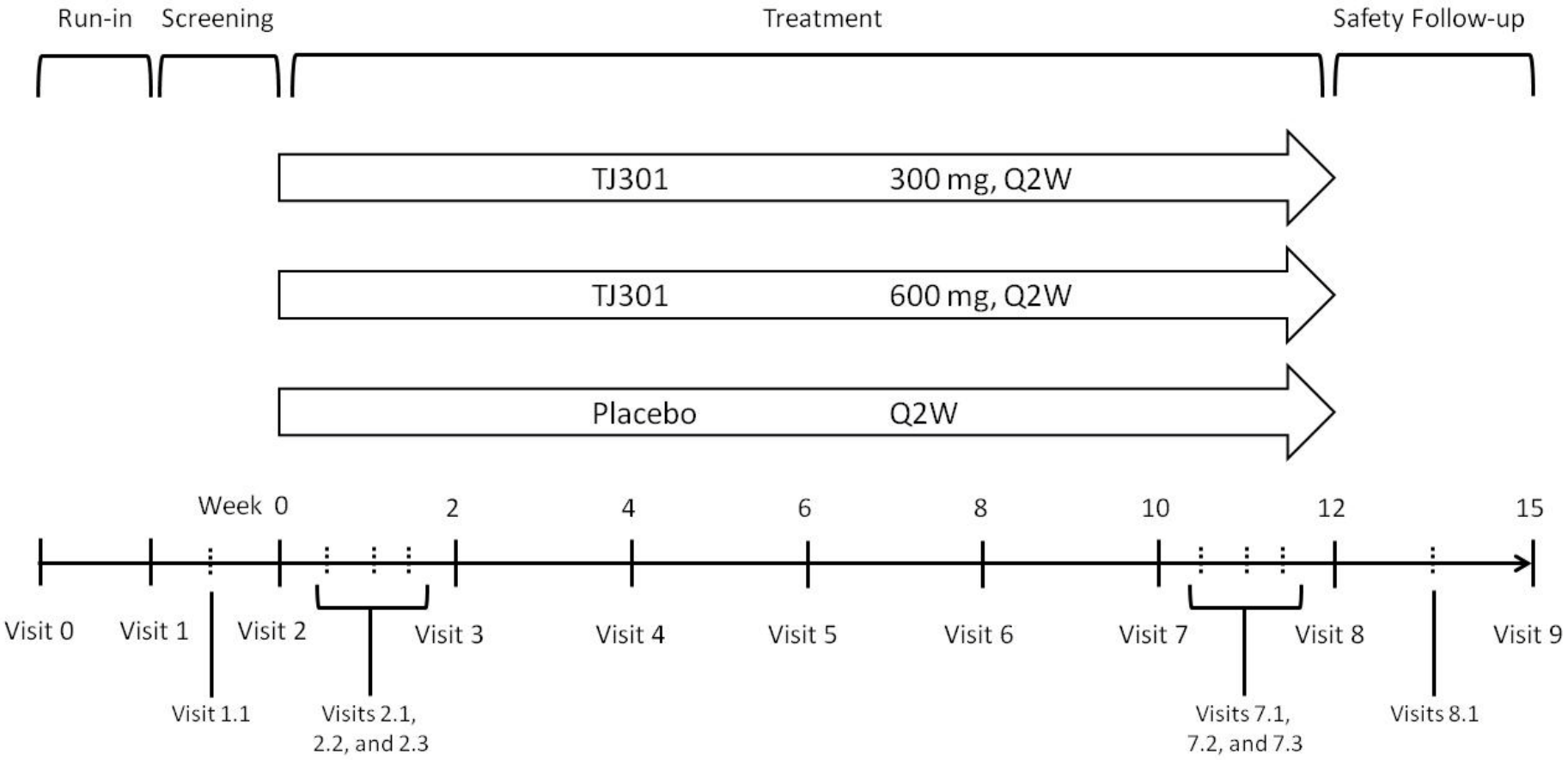


Figure 2 Overview of Trial Design

3.1.3 Trial Schedule

First patient first visit is planned for Third Quarter 2017 and last patient last visit is planned for First Quarter 2020. The expected total duration of the trial is approximately 2.5 years.

3.2 Planned Number of Patients

In total, 90 patients with active UC at approximately 25-30 investigational sites globally will be enrolled competitively and randomised equally into three arms with TJ301 (two dose levels) or placebo.

3.3 Safety Review Committee

A Safety Review committee (SRC) will be established. The SRC is an expert advisory group commissioned and charged with the responsibility of evaluating, primarily, cumulative safety data at regular intervals. The SRC will review blinded data and provide recommendations to the Sponsor based on their evaluation.

During the conduct of the trial, the responsibilities of the SRC will be to periodically review safety data, evaluate any safety concerns, and make recommendations to the Sponsor regarding trial conduct and possible trial modifications. The SRC will comprise at least a medical monitor, a physician and a pharmacologist. All members have experience and expertise in their field of practice.

A SRC Working Procedure will be prepared and signed prior to enrolment of the first patient. The charter will outline the specific purpose and functions of the SRC-related to monitoring the safety of patients in the trial. This charter will also describe the procedures for data extraction and data delivery conventions to and from the SRC members for review purposes.

3.4 Discussion of Overall Trial Design

3.4.1 Trial Design

This trial is designed as a randomised, double-blind, placebo-controlled proof-of-concept trial of TJ301. Patients will be on concomitant treatment with stable doses of corticosteroids, or immunomodulators, or 5-ASA/sulfasalazine – all first- or second-line standard of care in UC – for at least the duration of the 12-week Treatment Period (i.e. up to the primary endpoint). Two dose levels of TJ301 will be investigated, and as discussed in Section 3.4.4, modelling of the effect on a PD biomarker, based on PK measurements over a wide range of serum concentrations of TJ301, suggests that the chosen dosages may show a dose-dependent clinical efficacy.

The typical duration of induction treatment in active UC, both in clinical practice and in clinical trials, is at least 8 weeks. The novel mechanism of action with TJ301, with blockade of only IL-6 *trans*-signalling, may influence the time to a clinically relevant endpoint such as clinical remission. In order to capture the full extent of the potential treatment effect, the primary endpoint will be assessed at Week 12. As shown in the recent proof-of-concept trial with etrolizumab (10) in a

similar trial population as the one proposed with TJ301, placebo response was higher earlier during the treatment course (at Week 6 as opposed to Week 10). Thus, more substantive 'true' response and remission rates can be expected with longer treatment duration.

3.4.2 Selection of Endpoints

The prospectively defined primary efficacy endpoint will be a binary endpoint of clinical and endoscopic remission at Week 12, defined as a full Mayo score ≤2, no individual subscore >1, and rectal bleeding subscore = 0. The full Mayo score (range, 0-12; higher score is worse) is based on the clinician's scoring of clinical signs and symptoms, as well as endoscopic scoring of gross colonic mucosal inflammation. While there is no validated scale for scoring the severity of inflammation or clinical symptoms in UC, the Mayo score has been extensively used in earlier clinical trials in UC, and shows a good correlation between the full Mayo score and the clinician-rated components only (partial Mayo score without endoscopy; see Section 7.1.1 for details). The partial Mayo score without endoscopy can be used to accurately predict inflammatory activity, and the evolution of a treatment effect even in the absence of endoscopy.

Nevertheless, the endoscopic component of the Mayo score allows a direct assessment of the inflammatory activity, which is suitable in a proof-of-concept setting. This should allow a more robust correlation between clinical efficacy outcomes, PK parameters, and PD effects.

3.4.3 Blinding

A central, computer-based randomisation procedure is used to eliminate selection bias. To reduce the risk of breaking the blind, IMP thawing and reconstitution will be carried out at the trial site by blinded site personnel, independent of the Investigator and the Sponsor. The appearance of the reconstituted IMP, as well as the infusion volume (290 mL) will be identical for all treatment groups.

In order to reduce bias as much as possible, the trial is double-blind, keeping all subjects and the investigator blinded to the treatment. The randomisation list will not be available to any person involved in the conduct and evaluation of the trial until the trial database is locked.

3.4.4 Selection of Doses in the Trial

The safety and tolerability of TJ301 have been investigated in phase 1, single- and multiple-ascending dose studies in both healthy subjects and patients with quiescent IBD (Crohn's disease) up to 750 mg without any concern. Pharmacokinetic results indicate dose proportionality in maximal concentration obtained (C_{max}) and overall exposure (AUC) with a terminal half-life of approximately 4.7 days.

The doses and dose frequency selected for this trial are within a dose range that is considered safe and tolerable in healthy subjects and patients, trying to limit the number of i.v. infusion events.

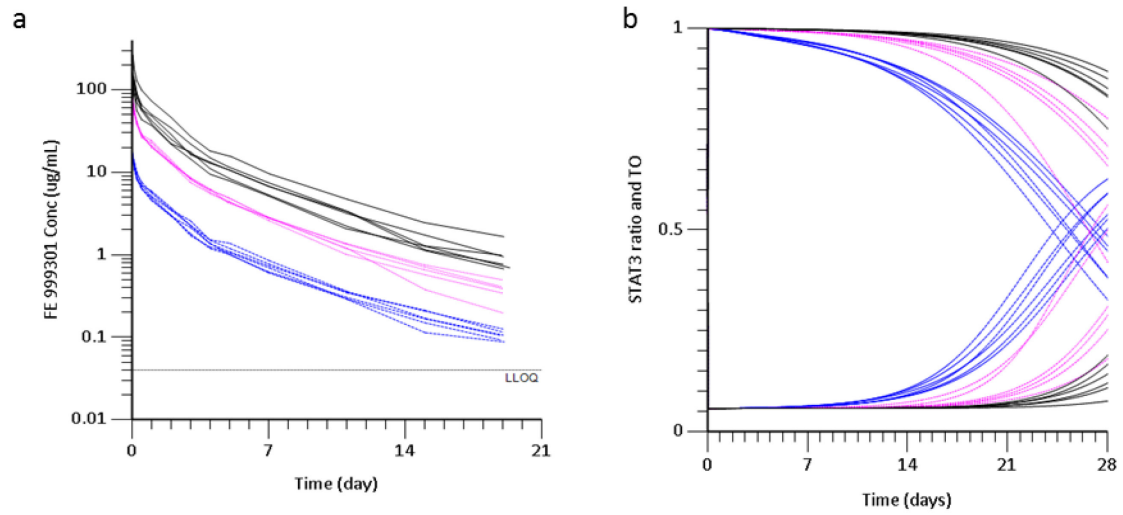
Evidence from treatment with infliximab and etanercept indicate that a higher dose requirement in IBD compared to RA and psoriasis and may also vary between disease states. The low systemic

exposure in IBD can partly be explained by demographics of the patient population, development of antibodies to the drug and administration of concomitant immunomodulators, but could also be related to a disease state.

Lamina propria mononuclear cells obtained from surgical colon specimens from patients with Crohn's disease and UC showed that both CD4+ T-cells and macrophages produced increased amounts of IL-6 compared to controls (11). sIL-6R was found to be released via shedding from the surface of macrophages and mononuclear cells with increased production associated with elevated levels of IL-6. Mucosal T-cells from IBD patients have showed strong evidence for IL-6 *trans*-signalling with activation of STAT-3, and the anti-apoptotic factors bcl-2 and bcl-xl. Treatment with TJ301 is anticipated to induce apoptosis of disease-perpetuating T-cells (12), which are assumed to induce long-lasting secretion of matrix-degrading substances such as chemokines and matrix metalloproteinases, which promote transmural inflammation. The turnover of T-cells may influence the dosing frequency. Treatments of IBD patients normally employ a less frequent or lower dose, when clinical remission is achieved.

The activity of the drug has, in the phase 1 programme, been explored using an *ex vivo* assay measuring the level of activation (phosphorylation) of the second messenger STAT-3. The relationship between exposure (Figure 3a) and efficacy is not known. However, based on *ex vivo* experiments, target saturation resulting in a suppression of STAT-3 activation back to baseline levels is expected to occur above an exposure of 1 µg/mL. Thus, the dose levels for this trial were selected to test levels of exposure around the threshold.

The 75 mg dose every other week is, according to simulations, anticipated to suppress the second messenger signal to baseline level for a duration of at least one week and single dose data suggest approximately 80% occupancy after 14 days (Figure 3b). Both the 300 mg and 600 mg dose administered every other week are anticipated to suppress the activation of the IL-6/sIL-6R second messenger signal STAT-3 to baseline, as the trough levels are expected to be >1 µg/mL. The highest dose of 600 mg is selected to likely cover the highest anticipated dose in the therapeutic range of TJ301.



Blue line: 75 mg. Magenta line: 300 mg. Black line: 600 mg.

Figure 3 a) Dose Proportional Pharmacokinetics of TJ301 and b) pSTAT-3/STAT 3 Ratio and Target Occupancy (TO) after Single Doses of TJ301

This trial is to investigate the efficacy of TJ301 *versus* placebo added on top of standard of care, in the induction of response and remission in patients with active UC. The two doses selected are within the range of doses investigated in phase 1 with dose proportionality in systemic exposure, and with no evident safety signals. The two doses are selected to give exposure above (300 and 600 mg) full target saturation (expected at the theoretical threshold of 1 µg/mL at trough). The selected dose levels may enable elucidation of dose response.

3.4.5 Selection and Timing of Dose for Each Patient

During the 12-week Treatment Period, dosing will be infusions every 2 weeks, as administered by trial personnel at the trial site. Dosing is fixed-dose throughout the trial.

In the multiple dosing parts of the phase I study of TJ301, the maximum dose of TJ301 was set as 600 mg weekly for 4 consecutive weeks (4 doses totally). In this study, TJ301 will be administered at up to 600 mg every two weeks for 12 consecutive weeks (6 doses totally). The concentration-time curves from the phase I study indicated very limited accumulation of TJ301 in plasma after multiple dosing. Although there will be 2 more doses in this study compared with the phase I study, the averaged plasma concentration of TJ301 will be very similar between the two studies. Therefore the proposed maximum doses (600 mg Q2W) can be considered safe and tolerable in patients. In addition, usually it takes at least 8 weeks for the biologics targeting UC, such as infliximab, golimumab, etc., to induce remission in patients with UC. Thus a 12-week treatment period is

proposed for TJ301 in this study with the purpose that patients to be enrolled will be more likely to benefit from treatment.

3.4.6 Withdrawal Criteria

In addition to the patient's right to withdraw from the trial at any time, as well as withdrawal at the Investigator's discretion as discussed in Section 4.4, the SRC (Section 3.3) will review blinded data, for safety.

In order to ensure that standard therapy is not withheld from patients not gaining sufficiently from IMP treatment, patients suffering a worsening in disease after Visit 5 are to be withdrawn. Worsening will be defined as an increase from last visit in Mayo rectal bleeding subscore ≥1, over 3 days (Appendix 1). Such worsening should be evaluated by the Investigator and confirmed by endoscopy (no improvement or worse) prior to deciding whether or not to withdraw the patient.

3.4.7 Follow-up Procedures

For patients completing the trial, a Safety Follow-up Visit will be scheduled on Day 105 (Week 15). For patients not completing the trial, a Safety Follow-up Visit will be scheduled 35 days (5.8 - 6.6 half-lives of TJ301) after the last dose of IMP.The procedures to be performed during the Safety Follow-up Visit are described in Section 6.3.

At the end of the trial patients will be treated for their UC at the discretion of the Investigator.

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

This trial is designed to include adult and elderly male and female outpatients with active, UC. Patients who fulfil all of the inclusion criteria (Section 4.1.1) and none of the exclusion criteria (Section 4.1.2) are eligible for inclusion in the trial.

4.1.1 Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Male and female patients 18-70 (inclusive) years of age.
2. Active UC confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy at Screening, with extending > 15-cm past the anal verge from endoscopy.
3. Active UC with a full Mayo score ⩾5 and a rectal bleeding subscore ≥1 at screening.
4. During Day -35 to Day-6 prior to Randomisation, an endoscopy subscore ≥2.
5. Treated with conventional non-biological UC therapy: with corticosteroids stable for at least 2 weeks prior to Randomization at no more than 20 mg prednisone (or equivalent), and/or with medications containing 5-aminosalicylates (5-ASA) at no less than 2 g 5-ASA per day for at least 3 months and stable for at least 4 weeks prior to Randomization, and/or with azathioprine (AZA) at no less than 1.5 mg/kg/day or mercaptopurine (6-MP) at no less than 0.75 mg/kg/day for at least 6 months and stable for at least 6 weeks prior to Randomization.
6. A female subject has been sterilized or has been menopausal, or the subject has no pregnancy plan during the trial and voluntarily adopts effective contraceptive measures.
7. The patient is able and willing to comply with the requirements of this trial protocol.
8. The subject should be able to read and write to understand and fill out Patient Diary.
9. Voluntarily signed Informed Consent obtained before any trial-related procedures are performed.

4.1.2 Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Pregnant or breastfeeding women.
2. Contraindication to colonoscopy or sigmoidoscopy.
3. Allergies to any component of TJ301.
4. History of colostomy, colectomy or partial colectomy.
5. Current diagnosis of inflammatory bowel disease unclassified, Crohn's disease, ischemic colitis, fulminant colitis and/or toxic megacolon, patients with ulcerative colitis limited to the rectum (ulcerative proctitis), infective enteritis, amebic bowel disease and intestinal schistosomiasis.

6. History of malignancy other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma *in situ* of the cervix. If the Screening colonoscopy shows evidence of dysplasia or a malignancy, the patient is not eligible.
7. Primary or secondary immunodeficiency including neutropenia (absolute neutrophil count <1500/μL); or lymphopenia (absolute lymphocyte count <500/μL).
8. Moderate to severe anaemia (haemoglobin <9 g/dL), or thrombocytopenia (platelet count <75, 000/μL), or serum creatinine >2 mg/dL.
9. Autoimmune disease besides UC, with the exceptions of Sjogren's syndrome or hypothyroidism.
10. Clostridium (C.) difficile positive at screening visit or treated for C. difficile within the 4 weeks prior to Randomization.
11. Known clinically relevant chronic liver disease. Impaired hepatic function in the absence of a diagnosis of primary sclerosing cholangitis (serum transaminases >2.5 x upper limit of normal [ULN], alkaline phosphatase >2.5 x ULN, or abnormalities in synthetic liver function tests judged by the investigator to be clinically significant), or a diagnosis of primary sclerosing cholangitis, serum transaminases >3 x ULN, alkaline phosphatase >3 x ULN, or abnormalities in synthetic liver function tests (total bilirubin >1.5 x ULN) judged by the investigator to be clinically significant.
12. Serious underlying disease other than UC in the opinion of the investigator.
13. History of drug addiction within the last 1 year or current drug addiction or use of illicit drugs.
14. Any indication of the regular use of more than 40 grams of alcohol every day.
15. Smokers who smoke more than 10 cigarettes per day.
16. Known concurrent acute or chronic viral hepatitis B or C infection or human immunodeficiency virus (HIV) infection.
17. Presence or history of active tuberculosis (TB) or latent TB infection, defined as 1) a positive QuantiFERON-TB Gold test at Screening, or 2) a positive T-spot test within 4 weeks of Randomisation and evidence of current or previous pulmonary tuberculosis by chest X-ray within 12 weeks of Randomisation.
18. Positive immunoglobulin M antibody titres in the presence of negative immunoglobulin G titres to Epstein-Barr virus (EBV).
19. If clinical suspicion of cytomegalovirus (CMV), cytomegalovirus testing should be undertaken. Subjects with intestinal mucosa biopsy positive for cytomegalovirus at screening are to be excluded.
20. Receiving any investigational therapy or any approved therapy for investigational use within 30 days or 5 half-lives prior to Randomization (whichever is longer).
21. Currently taking any medications other than those allowed per protocol guidelines.

22. Infections (including diverticulitis) requiring treatment with antibiotics, antivirals, or antifungals within 14 days prior to Randomisation.
23. Any prior use of biologic drugs.
24. Received any live (attenuated) vaccines within 30 days prior to Randomisation.
25. Recent treatment with medium-to-high-dose intravenous corticosteroids (methylprednisolone 60 mg/day or hydrocortisone 300 mg/day) within 8 weeks prior to Randomisation or oral corticosteroids of more than 20 mg prednisone(or equivalent) within 30 days prior to Randomisation.
26. Receipt of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil within 30 days prior to Randomisation.
27. Treatment with therapeutic enema or suppository, other than required for endoscopy preparation, within 14 days prior to the screening endoscopy and during the remainder of the trial.

4.2 Method of Assigning Patients to Treatment Groups

4.2.1 Recruitment

Approximately 25-30 sites will participate in this trial.

Each trial site will require potential patients to undergo a Screening Visit prior to randomisation to a treatment group. Each patient will receive a unique screening number which must be entered in a screening log that must be maintained at each trial site. The screening number will be allocated sequentially in the order in which the patients are screened. The results of each screening should be recorded in the screening log. Selected data for screened patients should also be entered in the electronic case record form (e-CRF), along with the reason for screening failure if the patient is not randomised to treatment.

Under no circumstances will patients screened in the trial be permitted to be re-screened for a second time in this trial, except who need Run-in Period to stabilize the dose of concomitant treatment per protocol.

4.2.2 Randomisation

After all applicable screening assessments have been performed, patients who have met all inclusion criteria and none of the exclusion criteria will be centrally, dynamically, randomly allocated to one of the three groups and will receive a unique computer-generated randomisation number.

At the Randomisation Visit (Visit 2), patients will be centrally, dynamically randomised in a 1:1:1 fashion to each of the three arms, namely placebo, TJ301 300 mg, or TJ301 600 mg, by validated Interactive Web Response System (IWRS). Randomisation will be stratified by prior corticosteroids treatment (yes/no) and consent to participate in PK substudy (yes/no). . This information will be

collected at Visit 1 and will be used at Visit 2 for randomisation by stratification based on these factors.

In addition, only some patients in Mainland China will enter the PK subgroup. Patients in PK subgroup (N=24, 8 for each arm) will be centrally, dynamically randomised in a 1:1:1 fashion to each of the three arms, namely placebo, TJ301 300 mg, or TJ301 600 mg.

4.3 Restrictions

4.3.1 Prior and Concomitant Therapies

Details of all concomitant medication will be recorded in the e-CRF, along with the main reason for prescription. In addition, prior treatment for UC within 12 months of Visit 1 (Screening) will be recorded.

4.3.2 Prohibited Therapy

Patients will be prohibited from taking any other IMP or undergo any other investigative treatment during the trial from the time the informed consent form is signed through to at least the Follow-up Visit, or any other IMP within 30 days or 5 half-lives prior to Visit 2 (whichever is longer).

The following previous or concomitant medications are disallowed during the trial:

- Immunomodulating/suppressing drugs, including JAK inhibitors (NB: AZA and 6-MP are allowed as per inclusion criteria, see Section 4.1.1).
- Antibiotics, when given as treatment for UC relapse.
- Any biologic drugs.
- Any live (attenuated) vaccines.

4.3.3 Other Restrictions

Patients on stable-dose concomitant treatment for UC at Visit 2 must remain on a stable dose throughout the trial except for patients on corticosteroids; tapering of corticosteroids is allowed at the discretion of the Investigator.

4.4 Withdrawal Criteria

The patients have the right to withdraw from the trial at any time for any reason, without the need to justify their decision. However, the Investigator should record the reason for the patient's withdrawal, if possible. The Investigator also has the right to withdraw patients.

Patients will be withdrawn in the following circumstances:

- A patient's desire to withdraw for any reason.
- Loss to follow-up (every effort must be made to contact the patient; a certified letter must be sent or phone calls on three separate days must be made).

- An adverse event which, in the opinion of the Investigator and/or Sponsor, necessitates withdrawal.
- A patient's substantial non-compliance (e.g. visits non-compliance) after agreement with the Sponsor.
- The Investigator's opinion that continuing the patient in the trial is not appropriate. The Investigator may withdraw a patient at any time if it is considered to be in the patient's best interest.
- Patients suffering a worsening in disease after Visit 5 are to be withdrawn. Worsening will be defined as an increase from the last visit in Mayo rectal bleeding subscore ≥1, over 3 consecutive days. Such worsening should be evaluated by the Investigator and confirmed by endoscopy (no improvement or worse) prior to deciding whether or not to withdraw the patient.

Patients discontinued from the trial will be invited to a Safety Follow-up Visit 35 days (5.8 - 6.6 half-lives of TJ301) after the last dose of IMP as soon as possible after a decision of discontinuation has been taken. At these visits, the Investigator will obtain all the required details and document the date of the premature termination and the main reason in the e-CRF.

In case the patient has withdrawn consent, no new data can be entered into the e-CRF and data are recorded in the medical records only. Correction of previous data entries and/or entering of data related to visits/procedures done prior to but made available after withdrawal of consent (e.g. laboratory results) will be allowed unless the patient disapproves it.

Any withdrawal must be fully documented in the e-CRF and source documents, registered in the e-CRF as discontinued, and followed by the Investigator/Investigative Staff. If the reason for discontinuation is an adverse event, the specific event will be recorded in the e-CRF. Withdrawn patients will not be replaced.

In case the Investigator becomes aware of any serious adverse events (SAEs) or related non-serious adverse events in a withdrawn patient after trial completion these will be reported to the Sponsor (Section 8.5).

The Sponsor may temporarily or permanently discontinue the trial at an investigational site at any time for safety, ethical, compliance or other reasons. If this is necessary, the Sponsor will endeavour to provide advance notification to the site. If the site or trial is suspended or discontinued, the Investigator/Investigative Staff will be responsible for promptly informing the Independent Ethics Committee (IEC) that this has happened. If required by local regulations, the Sponsor will be responsible for informing the IEC of trial or site discontinuation. In such an event, all trial data and unused IMP must be returned to the Sponsor.

5 TREATMENTS

5.1 Treatments Administered

The IMP in this trial is TJ301 (15 mg/mL in solution for injection [25 mM histidine, 200 mM sucrose, 0.1 mg/mL polysorbate 20 in aqueous solution]).

- Active substance: TJ301
- Provide by: Leading Biopharm Limited
- Manufacturer: Octoplus Development B.V. (now as Dr. Reddy's Research &Development B.V.) , Netherlands
- Application form: intra-venous Infusion
- Formulation: 15 mg/mL, 5mL vials, Solution for injection
- Packaging /units per package: diluted in 250 mL 5% (w/v) glucose for infusion
- Storage (incl. specific storage guidance): TJ301 is stored at -20±5°C
- Market authorisation: No

The placebo is the solution for injection [25 mM histidine, 200 mM sucrose, 0.1 mg/mL polysorbate 20 in aqueous solution] without TJ301.

- Active substance: No
- Provide by: Leading Biopharm Limited
- Manufacturer: Octoplus Development B.V. (now as Dr. Reddy's Research &Development B.V.), Netherlands
- Application form: intra-venous Infusion
- Formulation: 15 mg/mL, 5mL vials, Solution for injection
- Packaging /units per package: diluted in 250 mL 5% (w/v) glucose for infusion
- Storage (incl. specific storage guidance): Placebo is stored at -20±5°C
- Market authorisation: No

Both placebo and TJ301 should be stored at -20±5°C and thawed at the site by site personnel (blind to study randomisation) and diluted in 250 mL 5% (w/v) glucose (1.03 mg/mL TJ301 for the 300 mg group, 2.07 mg/mL TJ301 for the 600 mg group and 0 mg/mL TJ301 for the placebo group). The infusion time is 2 hours.

The following concentrations and infusion volumes of TJ301 and placebo will be used:

Dose group	Vials	Drug volume (mL)	5% (w/v) glucose(mL)	TJ301 (mg/mL)	Infusion volume (mL)
Placebo	8 vials Placebo	40	250	0	290
300 mg	4 vials Placebo and 4 vials TJ301	40	250	1.03	290
600 mg	8 vials TJ301	40	250	2.07	290

5.2 Characteristics and Source of Supply

All IMP is provided by the sponsor and handled according to the principles of Good Manufacturing Practice (GMP).

5.3 Packaging and Labelling

Packaging and labelling of IMP will be performed under responsibility of Leading Biopharm Limited or entrusted CRO in accordance with GMP/GCP and national regulatory requirements.

All IMP will be labelled with trial specific labels each containing a unique IMP number.

A self-adhesive tear-off label will be included and is to be affixed to the drug accountability form maintained at the trial site.

5.4 Conditions for Storage and Use

The Investigator will ensure that all medicinal products will be stored at the trial sites in appropriate conditions in a secure location with controlled access. The storage condition for placebo and TJ301 is -20±5 °C and thawed at the pharmacy and diluted in 250 mL 5% (w/v) glucose. When reconstituted for infusion, the finally diluted IMPs should be stored at 15-25 °C and used as soon as possible within 3 hours of preparation. The IMP will be administered as i.v. infusions every 2 weeks for 12 weeks (i.e. 6 infusions in total). An infusion volume of 290 mL will be used. The infusion time will be 2 hours. Following the first and second i.v. infusion, the patient will be monitored for infusion reactions at the site for three hours after infusion. For the remaining infusions, the patient will be monitored for one hour post-infusion only, since clinical experience in this field has shown that this is sufficient for patients receiving frequent infusions.

The temperature in the storage compartment shall be monitored every working day with a thermometer and the values shall be documented. Deviations in storage temperature must be reported without delay, and the medicinal products must not be used until further instructions from the Sponsor are received.

5.5 Blinding/Unblinding

5.5.1 Blinding

In order to reduce bias as much as possible, the trial is double-blind, keeping all subjects, the Investigator, and all staff involved in the conduct of the trial blinded to the treatment administered.

Patients will be centrally, dynamically randomised using Interactive Web Response System (IWRS). The randomisation list will not be available to any person involved in the conduct (Section 5.1) and the scientists analysing blood samples for TJ301 (Section 3.4.3), and evaluation of the trial until the trial database is locked.

The bioanalytical laboratory staff is authorized to receive the randomization list prior to the study conclusion to determine which samples should be analyzed for TJ301 according to standard operating procedures.

5.5.2 Unblinding of Individual Patient Treatment

An emergency decoding possibility, computer-based or other, will be available to the Investigator and to designated persons at the Sponsor. Breaking of the blind for individual patients in emergency situations is an Investigator responsibility. As far as the emergency permits, the need to break the blind will be communicated to the Sponsor.

The unblinding in emergency situations is only permitted in case of a suspected, unexpected serious adverse reaction (SUSAR) or other important adverse event, when the knowledge of the IMP in question is required for therapeutic decisions for the management of the patient. As far as the emergency permits, the need to break the blind will be agreed by the Investigator and the Sponsor. The Investigator who unblinds a treatment must record the reason and date for unblinding before the treatment code can be broken. The Investigator must record the event of unblinding in the patient's medical record, including the reason for unblinding, but not the treatment allocation if this can be avoided.

In case of accidental unblinding, the same documentation as for emergency unblinding must be obtained.

If the Sponsor needs to unblind a treatment, the reason and the date of opening should be recorded with signature, following corporate standard operational procedures for unplanned unblinding of clinical trial patients. It should be recorded in the subject's source documents that the code is broken, why, when and by whom.

If it is necessary to unblind an individual patient's treatment for the purposes of expedited reporting to the authorities and/or IECs, only those individuals within the Sponsor whose responsibility it is to report this information will know the identity of the IMP. Every attempt will be made to ensure that all other trial and site staff will remain blinded throughout the course of the trial.

Information on whether the blind has been broken for any patients must be collected before the database is declared clean and is released to the statistician.

5.6 Treatment Compliance

5.6.1 Dispensing and Accountability

IMP will only be dispensed to patients who meet the eligibility criteria and are randomised to a treatment group in the trial. The Investigator (or his/her blinded designated personnel, e.g. trial nurse) will maintain a patient Drug Dispensing Log detailing the IMP numbers and dates of IMP used for each patient during the course of the trial. Used IMP vials and infusion bags will be saved for drug accountability. The dispensing will be captured in the e-CRF and will be verified by a Monitor (a Sponsor representative) during the trial and signed off by the Investigator (or his/her designated personnel, e.g. trial nurse).

A site Drug Accountability Log will be maintained by site personnel. This log will be monitored by a Monitor during the trial. The log will be signed off by the Investigator at the end of the trial.

5.6.2 Assessment of Compliance

The IMP will be administered to the patient by authorised trial staff at the trial sites and the procedure will be documented in a separate Dispensing Log, provided by the Sponsor or CRO.

In order to know how much IMP that has been given to each patient, an infusion pump will be used. The pump will give the exact amount given per patient. The data from the pump will be captured in the source documents.

5.7 Return and Destruction of Medicinal Products and Auxiliary Supplies

Used medicinal products can be destroyed at the trial site in accordance with local requirements and when site operating procedures permits after the drug accountability has been finalised, signed-off by the Investigator, and verified by the Monitor.

Unused IMP vials must be returned to the Sponsor for destruction after drug accountability has been finalised, signed-off by the Investigator, and verified by the Monitor, at the end of the trial.

6 TRIAL PROCEDURES

6.1 Trial Flowchart

The trial includes a Run-in Period (if stable conventional treatment needed), a 4-week Screening Period, a 12-week double-blind Treatment Period, and a 3-week Safety Follow-up Period to Day 105. All periods are associated with evaluations and procedures that must be performed at specific time points, as described in Sections 6.2 through 6.4. The Time and Events Schedule (Table 1) summarises the frequency and timing of trial events. The Patient Distribution Plan and PK, Anti-TJ301 antibodies and Biomarker Samples Schedule are presented in Figure 4 and Figure 5, respectively.

Table 1 Time and Events Schedule

Trial Activity	**Run-in**	**Screening Period**		**Treatment Period**													**Follow-up Period**	
Week				0		1		2	4	6	8	10				12		15
Day(s)		-28 to -6	-5 to -1	0	*2*	*6*	*10*	14	28	42	56	70	72	76	80	84	90	105
Allowed window for visit (days)						*±1*	*±1*	±1	±1	±2	±2	±2			±1	±2	±2	±2
Visits	**Visit 0 Stabilization**	**Visit 1 Screening**	**Visit 1.1 Baseline**	**Visit 2 Baseline**	***V2.1***	***V2.2***	***V2.3***	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	***V7.1***	***V7.2***	***V7.3***	**V 8 (EoT Visit)**	***V8.1***	**V 9 (Safety Follow-up Visit)**
Informed consent	•	•[a]																
Inclusion/exclusion criteria		•		•														
Stable conventional treatment	•	•	•	•				•	•	•	•	•				•		•
HIV, HBV, HCV, EBV, CMV test		•																
TB test		•																•
Randomisation				•														
Demographics	•	•																
Alcohol and tobacco habits		•																
Medical and surgical history		•																
UC medical history, confirmation of UC diagnosis, and previous UC therapy	•	•																
Urine screening for drugs of abuse		•																
Endoscopy[b] including biopsy sampling		•[c]														•		
Diary dispensing		•	•	•				•	•	•	•	•						
Diary review[d]			•	•				•	•	•	•	•				•		
Efficacy evaluation (full Mayo score)				•												•		
Efficacy evaluation (9-point partial Mayo score)				•				•	•	•	•	•				•		
Blood sampling for PK assessments[e]				•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Faeces sampling for calprotectin				•					•		•					•		

Trial Activity	**Run-in**	**Screening Period**		**Treatment Period**													**Follow-up Period**	
Week				0		1		2	4	6	8	10				12		15
Day(s)		-28 to -6	-5 to -1	0	*2*	*6*	*10*	14	28	42	56	70	72	76	80	84	90	105
Allowed window for visit (days)						*±1*	*±1*	±1	±1	±2	±2	±2			±1	±2	±2	±2
Visits	**Visit 0 Stabilization**	**Visit 1 Screening**	**Visit 1.1 Baseline**	**Visit 2 Baseline**	***V2.1***	***V2.2***	***V2.3***	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	***V7.1***	***V7.2***	***V7.3***	**V 8 (EoT Visit)**	***V8.1***	**V 9 (Safety Follow-up Visit)**
Blood sampling for biomarkers[f]				•					•		•					•		
Blood sampling for anti-TJ301 antibodies				•				•	•		•					•		•
Clinical laboratory tests[g]			•					•	•	•	•	•				•		•
Pregnancy test[h]			•													•		•
Stool sample for *Clostridium difficile* assay		•																
Physical examination[i]		•	•						•		•					•		•
Vital signs[j]		•	•					•	•	•	•	•				•		•
12-lead ECG			•					•	•	•	•	•				•		•
Concomitant medications documented		•	•	•				•	•	•	•	•				•		•
Adverse events documented				•				•	•	•	•	•				•		•
IMP administration[k]				•				•	•	•	•	•						

a. If not already signed the ICF during the Run-in Period

b. Including mucosal biopsies. During screening, diagnostic colonoscopy or flexible sigmoidoscopy, at the discretion of the Investigator (if no diagnostic colonoscopy with serial biopsy has been performed within one year of screening, a full colonoscopy is required, to exclude malignancy), centrally read. Endoscopy conducted within 35 days before Randomisation is acceptable. At Visit 8, flexible sigmoidoscopy, centrally read.

c. The screening endoscopy should be performed at Day -35 to Day -6 prior to Randomisation.

d. The scores for stool frequency and rectal bleeding will be calculated as an average based on scores collected from the Patient daily Diary, for up to 5, but at least 3 days prior to each applicable visit. If the patient undergoes bowel preparation for endoscopy any of the days before a visit, the stool frequency and rectal bleeding subscore for that day(s) should be considered missing. In addition, the stool frequency and rectal bleeding subscore will be considered missing for the day of all endoscopies and the day after.

e. For Mainland China PK subgroup only. At 1st dose: pre-dose and 0.5, 1, 2 (end of infusion), 6, 48, 144 (Day 6), and 240 (Day 10) h after the start of the 1st administration; At the 2nd, 3rd , 4th, and 5th administrations blood samples will be collected pre-dose and at the end of infusion; At 6th dose: pre-dose and 0.5, 1, 2 (end of infusion), 6, 48, 144 (Day 76), 240 (Day 80), 336 (Day 84), 480 (Day 90), and 840 h (Day 105) after the start of the 6th administration.

f. Biomarkers erythrocyte sedimentation rate [ESR], C-reactive protein (CRP), neutrophil and platelet count tests will be be analysed in local sites. IL-6, IL-6/sIL-6R complex, and faecal calprotectin tests will be analysed in central lab. At Visits 2 and 8, the patient should be in a fasting state (≥8 hours).

g. Includes haematology, clinical chemistry, coagulation tests, and urinalysis assessments. Clinical laboratory test should be conducted -5 to -1 days prior to Randomisation.

h. Serum pregnancy test at Visit 1 and urine pregnancy test at Visits 8 and 9.

i. A complete physical examination will be performed at Visits 1 (Screening) and 9 (Follow-up). Body weight only will be measured at Visits 1.1, 4, 6 and 8.

j. Includes blood pressure (measured after the patient has been in a seated position for ≥3 minutes of rest), pulse, respiratory rate, and body temperature.

k. IMP administration should be the last procedure of each IMP administration visit. The infusion time will be 2 hours.

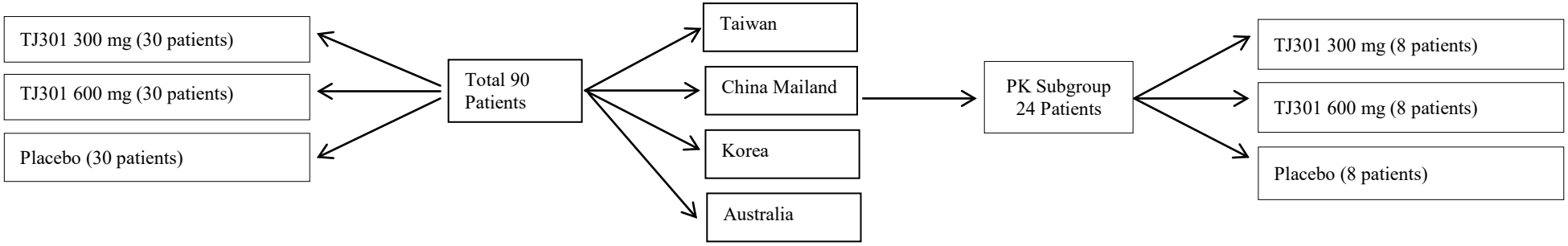


Figure 4 Patients Distribution Plan

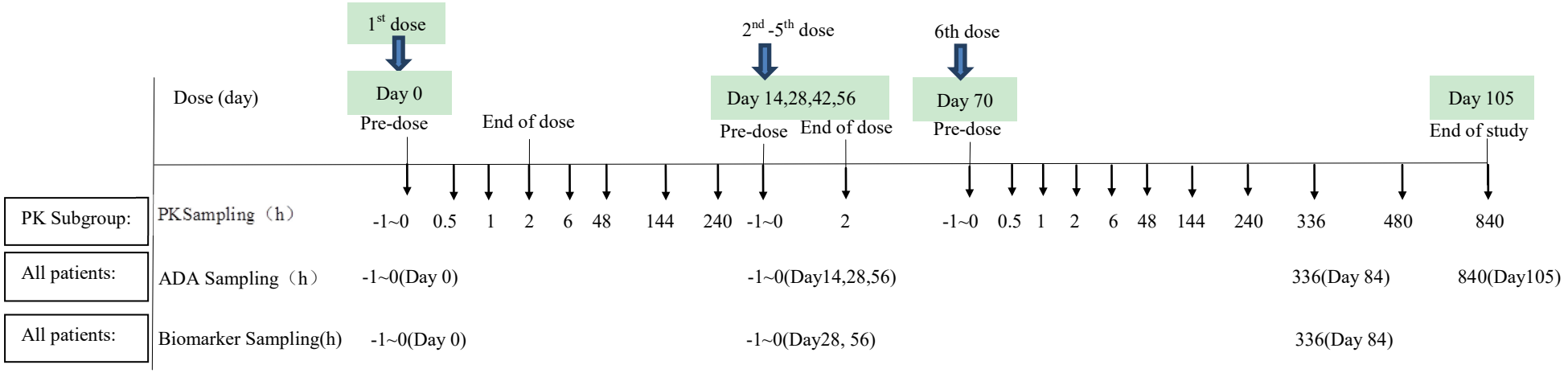


Figure 5 PK, Anti-TJ301 Antibodies and Biomarker Samples Schedule

6.2 Visit 0 to 8

6.2.1 Run-in Period (Stabilization Period, Visit 0)

This is an optional visit for those patients need stable conventional UC treatment to meet the following criteria: with corticosteroids stable for at least 2 weeks prior to Randomization at no more than 20 mg prednisone (or equivalent), and/or with medications containing 5-aminosalicylates (5-ASA) at no less than 2 g 5-ASA per day for at least 3 months and stable for at least 4 weeks prior to Randomization, and/or with azathioprine (AZA) at no less than 1.5 mg/kg/day or mercaptopurine (6-MP) at no less than 0.75 mg/kg/day for at least 6 months and stable for at least 6 weeks prior to Randomization.

If patients already met the criteria as above, they will directly enter the Screening Period (Visit 1). If not, they will need stable conventional UC treatment during the Run-in Period except those who cannot tolerate the medications mentioned above.

- Signing ICF (prior to any trial-related activities)
- Demographics (gender, date of birth, race and ethnic origin) and relevant medical and surgical history
- Confirmation of UC diagnosis, UC medical history
- To stabilize conventional treatment.

6.2.2 Screening Period (Days -28 to -1 prior to Visit 2)

At the Screening Visit (Visit 1), information will be collected for evaluation of trial eligibility by provided information as follows:

- Signing ICF (prior to any trial-related activities), if not already signed the ICF during the Run-in Period
- Inclusion criteria and exclusion criteria
- HIV, HBV, HCV, TB, EBV, and CMV test
- Demographics (gender, date of birth, race and ethnic origin) and relevant medical and surgical history
- Alcohol and tobacco habits
- Medical and surgical history
- Confirmation of UC diagnosis, UC medical history
- Urine screening for drugs of abuse

- Diagnostic colonoscopy or sigmoidoscopy, with mucosal biopsies. A full colonoscopy with serial biopsies with no signs of malignancy must have been performed within the last 12 months prior to screening (if this has not been performed, the screening endoscopy must be a full colonoscopy). The screening endoscopy should be performed -35 to -6 days prior to Randomisation. Endoscopic evaluation will be confirmed by a central, expert reader independent of the Investigator and the Sponsor.
- Stool sample for *Clostridium difficile* assay
- Complete physical examination
- Vital signs measurements (including pulse, respiration rate, body temperature, and systolic and diastolic blood pressure measured with the patient in a seated position after ≥3 minutes of rest)
- Concomitant medications documented, including previous and concomitant UC therapy.

At the Screening Visit, a Paper Diary (Appendix 3) will be dispensed to the patients to be used for the reporting of daily stool frequency and rectal bleeding (blood in stool). Patients will be instructed on the use of the Paper Diary. The Paper Diary will be returned at each visit.

During screening, diagnostic colonoscopy or flexible sigmoidoscopy, at the discretion of the Investigator (if no diagnostic colonoscopy with serial biopsy has been performed within one year of screening, a full colonoscopy is required, to exclude malignancy), will be centrally read. Endoscopy conducted within 2 months before Randomisation is acceptable.

Another visit, Visit 1.1, is scheduled after Visit 1. At Visit 1.1, the following procedures will be performed:

- Clinical laboratory test (blood and urine sampling)
- Serum beta-human chorionic gonadotropin (ß-HCG) pregnancy test
- Physical examination (body weight only)
- Vital signs measurements (including pulse, respiration rate, body temperature, and systolic and diastolic blood pressure measured with the patient in a seated position after ≥3 minutes of rest)
- 12-lead electrocardiogram (ECG)
- Diary dispensing
- Diary review
- Concomitant medications documented.

The patient should be instructed to come to next visit in a fasting state (≥8 hours).

6.2.3 Baseline Visit (Visit 2)

As one of the Baseline Visit, the following procedures will be performed:

- All inclusion and exclusion criteria (Section 4.1)
- Randomisation
- Efficacy evaluation (9-point partial Mayo Score and full Mayo Score)
- Blood sampling for PK assessments
- Faeces sampling for calprotectin
- Blood sampling for exploratory biomarkers (the blood sampling must be taken when the patient is in a fasting state [≥8 hours])
- Blood sampling for anti-TJ301 antibodies
- Diary dispensing
- Diary review
- Concomitant medications documented
- Adverse events documented
- IMP 1st administration.

6.2.4 12-week Treatment Period (Visits 3 to 8)

During the 12-week Treatment Period, the following data will be collected, as indicated in Table 1:

- Endoscopy (sigmoidoscopy) (Visit 8)
- Efficacy evaluation (9-point partial Mayo Score without endoscopy at all visits, full Mayo Score at Visit 8)
- Blood sampling for PK assessments (all visits)
- Faeces sampling for calprotectin (Visits 4, 6, and 8)
- Blood sampling for exploratory biomarkers (Visits 4, 6, and 8; At Visit 8, the blood sampling must be taken when the patient is in a fasting state [≥8 hours])
- Clinical laboratory test (blood and urine sampling; all visits)
- Urine pregnancy test (Visit 8)
- Blood sampling for anti-TJ301 antibodies (Visits 3, 4, 6, and 8)
- Physical examination (Visits 4, 6, and 8; body weight only)
- Vital signs (all visits)
- 12-lead ECG (all visits)
- Diary dispensing (Visits 3-7)
- Diary review (all visits)
- Concomitant medications documented (all visits)
- Adverse events documented (all visits)

- IMP administration (Visits 3-7).

For Visit 8, the patient should be instructed to come to the visit in a fasting state (≥8 hours).

6.2.5 PK Visits

TJ301 PK will be assessed in a subgroup of patients in Mainland China (24 patients, 8 per arm; electronically assigned at randomisation and consenting to the extra procedures). Blood samples for PK subgroup will be collected in as follows:

- At 1st dose: pre-dose and 0.5, 1, 2 (end of infusion), 6, 48, 144 (Day 6), and 240 (Day 10) h after the start of the 1st administration;
- At the 2nd, 3rd, 4th, and 5th administrations blood samples will be collected pre-dose and at the end of infusion;
- At 6th dose: pre-dose and 0.5, 1, 2 (end of infusion), 6, 48, 144 (Day 76), 240 (Day 80), 336 (Day 84), 480 (Day 90), and 840 h (Day 105) after the start of the 6th administration.

The actual sampling time will be recorded.

Acceptable time window of blood sampling for PK shows as below:

- 0 h sampling needs occur within 1 h before administration,
- the time windows between 0.25 h and 2 h post dosing are ‘theoretical timepoint ±3 min,
- the time windows between 2 h and 12 h post dosing are ‘theoretical timepoint ±10 min,
- the time windows between 12 h and 24 h post dosing are ‘theoretical timepoint ±20 min,
- the time window of 48 h post dosing is ‘theoretical timepoint ±1 hour,
- the time window of 144 h post dosing is ‘theoretical timepoint ±24 hour,
- the time window of 240 h post dosing is ‘theoretical timepoint ±24 hour,
- the time window of 336 h post dosing is ‘theoretical timepoint ±24 hour,
- the time window of 480 h post dosing is ‘theoretical timepoint ±24 hour,
- the time window of 840 h post dosing is ‘theoretical timepoint ±24 hour.

Sampling exceeding the specified time range mentioned above will be treated as a protocol deviation.

At Visits 2.1, 2.2, 2.3, 7.1, 7.2, 7,3, and 8.1, no other data will be collected.

6.3 Safety Follow-up Visit (Visit 9)

For patients completing the trial, a Safety Follow-up Visit will be scheduled on Day 105 (Week 15). For patients not completing the trial, likewise a Safety Follow-up Visit will be scheduled at 35 days after the last dose of IMP.

At the Safety Follow-up Visit, the following data will be collected:

- Blood sampling for PK assessments
- Blood sampling for anti-TJ301 antibodies
- Clinical laboratory test (blood and urine sampling)
- Urine pregnancy test
- TB test
- Complete physical examination
- Vital signs
- 12-lead ECG
- Concomitant medications documented
- Adverse events documented.

6.4 Unscheduled Visits

The patient may be called in for additional unscheduled visits due to safety reason at the discretion of the Investigator or the Sponsor, unless the patient has withdrawn his/her consent. The patient may also contact the site due to safety reason for an unscheduled visit. The unscheduled visit may include additional collection of blood samples for safety reasons. The unscheduled visit may also include additional assessments deemed necessary by the Investigator such as laboratory samples, ECGs, or other procedures which were missed at a previous visit. All unscheduled visits should be described (including the reason for the visit) and documented in the medical/source record, and in the e-CRF.

7 TRIAL ASSESSMENTS

7.1 Assessments Related to Endpoints

7.1.1 Clinical and Endoscopic Disease Activity (Mayo Score)

The full Mayo score (13) is a composite disease activity score consisting of four items or subscores: stool frequency (relative to normal), rectal bleeding, physician's global assessment, and endoscopic appearance. The overall range of the full Mayo score is 0-12 (higher scores being worse) and each subscore has a range of 0-3 (Table 2). The scores for stool frequency and rectal bleeding will be calculated as an average based on scores collected from the Patient daily Diary, for up to 5, but at least 3 days prior to each applicable visit. If the patient undergoes bowel preparation for endoscopy any of the days before a visit, the stool frequency and rectal bleeding subscore for that day(s) should be considered missing. In addition, the stool frequency and rectal bleeding subscore will be considered missing for the day of all endoscopies and the day after. The physician's global assessment and endoscopic appearance scores will be collected in the e-CRF.

The prospectively defined primary efficacy variable of clinical and endoscopic remission (defined as a full Mayo score ≤2, no individual subscore >1, rectal bleeding subscore = 0), will be used and is in accordance with guidelines and literature (14) (15).

The 9-point partial Mayo score, defined here as the sum of the stool frequency, rectal bleeding, and physician's global assessment subscores (range 0-9; higher scores being worse) is used for efficacy assessment at all site visits starting at Visit 2. The secondary endpoints based on the 9-point partial Mayo score which correlates well with the full Mayo score (16), should accurately predict the evolution of the effect on mucosal inflammation even in the absence of endoscopy at most site visits. Lastly, for the purpose of analysing patient-reported symptoms only, the 6-point partial Mayo score, defined as the sum of the stool frequency and rectal bleeding subscores (range 0-6; higher scores being worse) will be employed.

In parallel to the investigator scoring, endoscopic scoring (endoscopic component of the Mayo score) will be performed through centralised reading for efficacy assessment. Investigator evaluation must be verified by blinded central reader, with a second blinded central reader in case of lack of agreement. Note that the criteria of endoscopic appearance assessment in this study are DIFFERENT from the original criteria in (13). The Endoscopy subscore is modified so that a value of 1 does not include friability. Personnel responsible for endoscopic evaluation should NOT refer to the original criteria.

The endoscopy completed at Screening and Visit 8 (Week 12) will be sent to a central reading center selected by the Sponsor. The central reading center will be independent of the Investigator and the Sponsor. Endoscopic qualifying score will be reported to the Investigator and the Sponsor (or the Sponsor's representative) and will be uploaded to a database. The database will be maintained by an independent third-party contract research organisation (CRO).

Table 2 Full Mayo Scale Subscores

Components	Subscore	Severity	Score
CLINICAL RESPONSE (Patient's Symptoms)	Stool Frequency[a] (daily)	Normal number of stools for patient	0
		1 to 2 stools more than normal	1
		3 to 4 stools more than normal	2
		≥5 stools more than normal	3
	Rectal Bleeding[b] (daily)	No blood seen	0
		Streaks of blood with stool	1
		Obvious blood with stool	2
		Blood alone passes	3
	Physician's Global Assessment	Normal	0
		Mild disease	1
		Moderate disease	2
		Severe disease	3
ENDOSCOPIC RESPONSE (Objective Evidence of Inflammation)	Endoscopic Appearance[c]	Normal	0
		Mild disease	1
		Moderate disease	2
		Severe disease	3

[a] Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.
[b] The daily bleeding score represents the most severe bleeding of the day.
[c] Endoscopic appearance: Normal, Mild (erythema, decreased vascular pattern, granularity), Moderate (marked erythema, loss of vascular pattern, any friability, erosions), Severe (spontaneous bleeding, ulceration).
Note: endoscopic appearance is not part of the partial Mayo score. In addition, the criteria of endoscopic appearance assessment in this study are DIFFERENT from the original criteria in (13). The Endoscopy subscore is modified so that a value of 1 does not include friability.

Image handling and instructions for endoscopy will be provided to the central reading center from all investigational sites directly or from the sponsor (or CRO).

The patient reported Mayo subscores comprise stool frequency and rectal bleeding. They are collected for up to 5, but at least 3 days prior to each trial visit throughout the trial by the patient at home, and they are collected in both screening and treatment periods. The Mayo Score is not copyrighted. The patient reported Mayo subscores will be collected in electronic format (FDA 21 CRF part 11 compliant) via the use of a Paper Diary.

7.1.2 Physical Examinations

A complete physical examination including general appearance, head, eyes, ears, nose, and throat (HEENT), neck, cardiovascular, thorax/lungs, breasts, abdomen, genitourinary, musculoskeletal, lymph nodes, skin, neurological and mental status examination, height (at Screening only), and

body weight will be performed by the Investigator or a delegated Sub-Investigator (a medically licensed qualified trial team member) at Visits 1 (Screening) and 9 (Follow-up). Body weight only will be measured at Visits 1.1, 4, 6 and 8.

The same individual should preferably perform all physical examinations for a patient during the course of the trial. The Investigator will evaluate the clinical significance. Pre-existing conditions diagnosed through assessments and examinations at the screening visit or during the screening period are not adverse events, but are recorded as medical history. If any clinically significant abnormal findings are discovered after informed consent or any pre-existing conditions worsen during the trial, these must be recorded as adverse events.

7.1.3 Vital Signs

Vital signs will be measured at Visits 1, 1.1, 3, 4, 5, 6, 7, 8 and 9 and will include blood pressure (measured after the patient has been in a seated position for ≥3 minutes of rest), pulse, respiration rate, and body temperature.

The Investigator should evaluate the clinical significance of the results. Clinically significant abnormal findings will be reported as adverse events.

7.1.4 Clinical Safety Laboratory Parameters

Laboratory parameters: urinalysis (dipstick), urine pregnancy test, urine drug panel, haematology, clinical chemistry, coagulation, serum pregnancy test, TB, HIV, HBV, HCV, EBV, and CMV infection test, Clostridium difficile assay, erythrocyte sedimentation rate [ESR], C-reactive protein (CRP), neutrophil and platelet count, and biopsy samples (Appendix 2) will be measured at local sites according to the schedule in Table 1.

Anti-TJ301 antibodies, Pharmacokinetics TJ 301, IL-6, IL-6/sIL-6R complex, and faecal calprotectin tests will be analysed in central lab; sample collection methods and handling procedures will be described in a separate laboratory manual.

The Investigator will review the laboratory results and evaluate and document whether the results are normal or abnormal and whether abnormal results are non-clinically significant or clinically significant. Pre-existing clinically significant conditions diagnosed as a result of the screening procedures must be recorded as medical history. If any clinically significant abnormal findings are discovered after informed consent or any pre-existing conditions worsen during the trial, these must be recorded as adverse events. The laboratory report will be signed and dated by the Investigator.

For female subjects, a serum ß-HCG and a serum pregnancy test will be conducted at the Screening Visit (Visit 1) and urine pregnancy tests will be conducted at visit 8 and Follow-up visit.

7.1.5 Electrocardiogram

In this trial, a routine 12-lead ECG will be performed at Visits 1, 1.1, 3, 4, 5, 6, 7, 8, and 9. The ECG measurements will include heart rate and PR, QRS, and QT intervals. The Investigator will

evaluate the clinical significance of the ECGs. Clinically significant abnormal findings will be reported as adverse events.

7.2 Trial-specific Blood and Faeces Sampling

Blood sampling for exploratory biomarkers (ESR, IL-6, IL-6/sIL-6R complex, and neutrophil and platelet count), faeces sampling for calprotectin assessment, and blood samples for TJ301 and anti-TJ301 antibodies will be performed according to the schedule in Table 1.

7.3 Other Assessments

Not applicable.

7.3.1 Demography

Demographic data will be collected at the Screening Visit, including gender, date of birth, race, and ethnic origin (to the extent allowed by local regulations).

7.3.2 Medical and Surgical History

Information on clinically significant previous and concomitant illnesses, other than UC, or any clinically significant signs or symptoms that are present before informed consent, or pre-existing conditions identified through findings from assessments and examinations done during the Screening Visit will be recorded as medical and surgical history at Screening. For planned procedures/hospitalisations during the trial, documentation should be completed at the time of the Screening.

7.3.3 Ulcerative Colitis History and Previous Therapy for Ulcerative Colitis

The date of diagnosis of UC, as well as previous and concomitant treatments for UC, will be recorded separately in the e-CRF during the Screening Visit.

7.3.4 Concomitant Medication Review

Data concerning concomitant medications and procedures will be collected throughout the trial at all site visits. These data will be obtained at scheduled or unscheduled trial visits based on information provided spontaneously by the patient or as a result of questioning the patient.

7.3.5 Urine Screening for Drugs of Abuse

At the Screening Visit, a urine drug screening (e.g. cocaine, barbiturates, amphetamines, opiates, benzodiazepine, and cannabinoids) will be performed. Clinical significance of a positive urine drug screen will be assessed by the Investigator.

7.4 Drug Concentration Measurements

In PK subgroup, TJ301 levels will be monitored during the course of the trial. The clearance of TJ301 can potentially be affected not only by the presence of anti-TJ301 antibodies but also by disease activity including protein loss through severely inflamed colonic mucosa (21).

7.5 Handling of Biological Samples

A central laboratory will be used in this trial for Anti-TJ301 antibodies, TJ 301 PK, IL-6, IL-6/sIL-6R complex, and faecal calprotectin tests. Sampling tubes, material for shipment of the samples, and a laboratory manual detailing all sample collection and shipment procedures will be provided and distributed to the trial sites by the central laboratory.

Except for PK subgroup patients, the total amount of blood planned to be collected from each patient who will be enrolled during the course of the trial is approximately 200 mL.

For PK subgroup, the total amount of blood planned to be collected from each patient during the course of the trial is approximately 300 mL.

8 ADVERSE EVENTS

8.1 Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient participating in a clinical trial. It includes:

- Any unfavourable and unintended sign, symptom or disease temporally associated with the use of the IMP, whether or not considered to be caused by the IMP.
- Adverse events commonly observed and adverse events anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality, vital sign or finding from physical examination assessed as clinically significant by the Investigator (pre-existing conditions diagnosed through assessments and examinations at the screening visit or during the screening period are not adverse events, but are recorded as medical history).
- Accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures.
- Overdoses and medication errors with and without clinical consequences.

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

The Investigator must monitor the condition of the patient throughout the trial from the time of obtaining informed consent until the last visit.

The sources of adverse events cover:

- The patient's response to questions about his/her health (a standard non-leading question such as "How have you been feeling since your last visit?" is asked at each visit).
- Symptoms spontaneously reported by the patient.
- Investigations and examinations where the findings are assessed by the Investigator to be clinically significant changes or abnormalities.
- Other information relating to the patient's health becoming known to the Investigator (e.g. hospitalisation).

8.2.2 Recording of Adverse Events

The Investigator must record all adverse events in the Adverse Event Log provided in each patient's e-CRF with information about:

- Adverse event
- Date of onset (time can be recorded, if applicable)
- Intensity

- Causal relationship to IMP
- Action taken to IMP
- Other action taken
- Date and time of outcome
- Outcome
- Seriousness

Each of the items in the Adverse Event Log is described in detail in the following sections.

Adverse Event

Adverse events should be recorded as diagnoses, if available. If not, separate signs and symptoms should be recorded. One diagnosis/symptom should be entered per record.

If a patient suffers from the same adverse event more than once and the patient recovers in between the events, the adverse events should be recorded separately. If an adverse event changes in intensity, a worst-case approach should be used when recording the event, i.e. the highest intensity and the longest duration of the event.[a]

Note the following: A procedure is not an adverse event; the reason for conducting the procedure is. Hospitalisation is not an adverse event; the reason for hospitalisation is. Death is not an adverse event, but the cause of death is (an exception is sudden death of unknown cause, which is an adverse event).

Date and Time of Onset

The date of onset is the date when the first sign(s) or symptom(s) were first noted. If the adverse event is an abnormal clinically significant laboratory test or outcome of an examination, the onset date is the date the sample was taken or the examination was performed.

For pre-existing clinically significant conditions (diagnosed or observed as a result of the screening procedures) becoming worse after IMP administration, the date of onset is the date the worsening began.

[a] Exception: an adverse event with onset after enrolment but before the first IMP administration (i.e. a pre-treatment adverse event), which changes in intensity after IMP administration, must be recorded as two separate events. The initial adverse event should be recorded with outcome "not recovered" and the date and time of outcome is when the intensity changed. The second adverse event should be recorded with date and time of onset when the intensity changed.

Intensity

The intensity of an adverse event must be classified using the following 3-point scale:

Mild: Awareness of signs or symptoms, but no disruption of usual activity.

Moderate: Event sufficient to affect usual activity (disturbing).

Severe: Inability to work or perform usual activities (unacceptable).

Causal Relationship to IMP

The possibility of whether the IMP caused the adverse event must be classified as one of the following:

Reasonable possibility:

There is evidence or argument to suggest a causal relationship between the IMP and the adverse event. The adverse event may occur as part of the pharmacological action of the IMP or may be unpredictable in its occurrence.

Examples:

- adverse events that are uncommon but are known to be strongly associated with IMP exposure.
- adverse events that are not commonly associated with IMP exposure, but the event occurs in association with other factors strongly suggesting causation, such as a strong temporal association or the event recurs on rechallenge.

No reasonable possibility:

There is no reasonable evidence or argument to suggest a causal relationship between the IMP and the adverse event.

Examples:

- known consequences of the underlying disease or condition under investigation.
- adverse events common in the trial population, which are also anticipated to occur with some frequency during the course of the trial, regardless of IMP exposure.

Action Taken to IMP

The action taken to the IMP in response to an adverse event must be classified as one of the following:

- No change (medication schedule maintained or no action taken)
- Withdrawn
- Interrupted

Other Action Taken

Adverse events requiring therapy must be treated with recognised standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

If medication is administered to treat the adverse event, this medication should be entered in the Concomitant Medication Log.

Date of Outcome

The date the patient recovered or died, or disease condition worsens.

Outcome

The outcome of an adverse event must be classified as one of the following:

- Recovered (fully recovered or the condition has returned to the level observed at initiation of trial treatment)
- Recovered with sequelae (resulted in persistent or significant disability/incapacity)
- Recovering
- Not recovered
- Worse
- Fatal.

8.3 Adverse Events of Special Interest

Adverse events of special interest include adverse events observed in earlier clinical development of TJ301 and those resulting from blocking IL-6 signaling shown by other drugs or investigational products.

Certain side effects were observed early on during the clinical development program for TJ301, including infusionrelated reactions, headache, nasopharyngitis, myalgia, diarrhoea, cough, and decreased neutrophil count. In addition, certain side effects were characterized during the clinical development of other IL-6 inhibitors (e.g. tocilizumab) and have been shown to be mechanistically linked to its mode of action and its effect on inflammation. These side effects include neutropenia, thrombocytopenia, elevation of liver enzymes, lipid disorders (elevation of total cholesterol), severe infection (including tuberculosis), and gastrointestinal perforation.

8.4 Pregnancy and Pregnancy Outcome

If a pregnancy occurs at any time after signing the informed consent form, the IMP should be immediately stopped and the Sponsor must be informed immediately.

Note that pregnancy itself is not an SAE, and should not be reported via the e-CRF. Contact details for the follow up on the pregnancy should be provided with the report. The Sponsor may request additional pregnancy-specific follow-up information once the pregnancy has been notified.

The mother and the foetus must be followed-up at least until the birth of the infant and one month after the birth of the infant (also pregnancy following paternal IMP exposure). In general, the follow-up will include the course; duration and the outcome of the pregnancy as well as neonatal health. If a pregnancy results in an abnormal outcome (birth defect/congenital anomaly), this must be reported as an SAE to the Sponsor according to the procedure described in Section 8.5.2. Any outcome which the Investigator and/or the Sponsor considers to be related to the IMP will be treated as an expedited report.

In cases in which a foetus may have been exposed through transmission of the IMP via semen following paternal exposure, and the pregnancy results in an abnormal outcome (birth defect/congenital anomaly) this must be reported as an SAE to the Sponsor according to the procedure described in Section 8.5.2.

8.5 Serious Adverse Events

8.5.1 Serious Adverse Event Definition

Serious Adverse Events during the Trial

An event is defined a serious adverse event if it:	Guidance
results in **death**	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within four weeks after the treatment ends and irrespective of the causal relationship to the IMP. The death of a patient enrolled in a trial is *per se* not an event, but an outcome.
is **life-threatening**	The term life-threatening refers to an adverse event in which the patient was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death if it were more severe.
requires in-patient **hospitalisation** or prolongation of existing hospitalisation	The term hospitalisation means that the patient was admitted to hospital or that existing hospitalisation was extended as a result of an event. Hospitalisation describes a period of at least 24 hours. Over-night stay for observation, stay at emergency room or treatment on an out-patient basis do not constitute a hospitalisation. However, medical judgement must always be exercised and when in doubt the case should be considered serious (i.e. if case fulfils the criterion for a medically important event). Hospitalisations for administrative or social purposes do not constitute an SAE. Hospital admissions and/or surgical operations planned before trial inclusion are not considered adverse events, if the illness or disease existed before the patient was enrolled in the trial, provided that the condition did not deteriorate during the trial.
results in persistent or significant **disability/incapacity**	Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. In doubt, the decision should be left to medical

An event is defined a serious adverse event if it:	Guidance
	judgement by the Investigator.
is a **congenital anomaly/birth defect**	Congenital anomaly/birth defect observed in any offspring of the patient conceived during treatment with the IMP.
is an **important medical event**	Important medical events are events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include adverse events that suggest a significant hazard, contraindication or precaution, occurrence of malignancy or development of drug dependency or drug abuse. Medical and scientific judgement should be exercised in deciding whether events qualify as medically important. Important medical events include any suspected transmission of an infectious agent via a medicinal product. Any organism virus or infectious particle (e.g. prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product.

8.5.2 Collection, Recording and Reporting of Serious Adverse Events

SAE Reporting by the Investigator

All SAEs must be reported **immediately** to the Sponsor or CRO as soon as it becomes known to the Investigator and not later than within 24 hours of their knowledge of the occurrence of the SAE. Investigators will be notified by the Sponsor or CRO of all SAEs that require prompt submission to their Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor or CRO. The Sponsor or CRO will ensure that all SAEs are reported to the appropriate regulatory authorities.

The Investigator is responsible for submitting the completed SAE Report Form to the regulatory body with the fullest possible details **within 3 calendar days** of his/her knowledge of the SAE.

The SAE Report Form is included in the e-CRF system, and must be completed and submitted according to the instructions provided on the form. In case the e-CRF cannot be accessed and hence the SAE Report Form cannot be filled in within the e-CRF system, a paper SAE Report Form should be used and sent to the Sponsor.

The information on the form must be transferred to the e-CRF when the e-CRF is up and running again.

Completion of the Demographics, Adverse Event Log, Medical History Log and Concomitant Medication Log are mandatory for initial reports and for follow-up reports if any relevant changes have been made since the initial report. Data entries must have been made in the e-CRF for the Sponsor to access the information.

Additional information relevant to the SAE such as hospital records, results from investigations, e.g. laboratory parameters (that are not already uploaded in the e-CRF), invasive procedures, scans and x-rays, and autopsy results can be faxed or scanned and e-mailed to the Sponsor using the contact details in the section above. In any case this information must be supplied by the Investigator upon request from the Sponsor. On any copies provided, such details such as patient's name, address, and hospital ID number should be concealed and instead patient number should be provided.

The Investigator will supply the Sponsor and the IEC with any additional requested information such as results of post-mortem examinations and hospital records.

CRO contact information:

Zhijia Han

E-mail: zhijia.han@tigermed.net

Sponsor contact information:

Yonghong Jia

E-mail: yonghong.jia@3rdventure.com

Expedited Reporting by the Sponsor or CRO

The Sponsor or CRO will report all adverse events that are **serious, unexpected and with a reasonable possible causality to the IMP** as judged by either the Investigator or the Sponsor to the relevant parties within the stipulated timelines. The expectedness is assessed by the Sponsor according to the Investigator's Brochure.

SAEs will be considered reportable regardless of whether or not the IMP was used in accordance with the provisions in the protocol and the Investigator's Brochure.

8.6 Follow-up of Adverse Events and Serious Adverse Events

8.6.1 Follow-up of Adverse Events with Onset during the Trial

During the trial, the Investigator must follow-up on each adverse event until it is resolved or until the medical condition of the patient is stable.

After the patient's last visit, the Investigator must follow-up on any adverse event classified as serious or considered to have a reasonable possible causality to the IMP until it is resolved/recovered or until the medical condition of the patient is stable. All such relevant follow-up information must be reported to the Sponsor and CRO. If the event is a chronic condition, the Investigator and the Sponsor may agree that further follow-up is not required.

8.6.2 Collection of Serious Adverse Events with Onset after Last Trial Visit

If an Investigator becomes aware of an SAE after the patient's last visit (this includes withdrawn patients, Section 4.4), and he/she assesses the SAE to have a reasonable possible causality to the IMP, the case will have to be reported to the Sponsor and CRO, using the contact information, regardless how long after the end of the trial this takes place.

9 STATISTICAL METHODS

All statistical analyses will be detailed in a separate Statistical Analysis Plan (SAP).

9.1 Determination of Sample Size

This is a proof-of-concept trial not aimed at confirming evidence of primary efficacy but rather at exploring preliminary indications of efficacy (not *per se* restricted to primary only) and safety with the aim of informing a decision about proceeding into full development. The exploratory nature of this trial requires a minimum number of patients to be exposed, yet without losing the possibility of inferring meaningful conclusions.

A sample size of N=72 (n=24 per treatment/placebo arm) patients is expected to achieve a power of 83% of detecting a trend ($p<0.05$, one-sided) if the true remission rate difference (at Week 12) between the placebo and highest dose groups (600 mg Q2W) is 30% (10% for the placebo and 40% for the highest dose) using Pearson's chi-square test without continuity correction. The trial also has 70% power to reach a statistically significant result ($p<0.05$, one-sided) in case the remission rate difference between placebo and treatment (300 mg Q2W and 600 mg Q2W combined together) is 20% (10% vs 30%). Considering the dropout rate of approximately 20%, a total of 90 patients will be enrolled competitively.

9.2 Patient Disposition

All patients screened and randomised will be accounted for. All post-randomisation discontinuations will be summarised by reason for discontinuation. The number of patients screened and not randomised will be presented.

9.3 Protocol Deviations

The criteria for protocol deviations considered major with the implication of data exclusions from the Per Protocol (PP) analysis will be determined prior to database lock and unblinding.

9.4 Analysis Sets

9.4.1 Intention-to-Treat Analysis Set

The Intention-to-treat (ITT) analysis set will include all randomised patients with treatment assignment according to the planned randomisation.

9.4.2 Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomised patients with at least one Post-baseline 9-point partial Mayo score value with treatment assigned according to the planned randomisation.

9.4.3 Per Protocol (PP) Analysis Set

The PP analysis set will consist of FAS patients who had no major protocol violations that would impact efficacy analysis with treatment assigned according to the planned randomisation.

9.4.4 Safety Analysis Set

The Safety analysis set will include all randomised patients who received at least one dose of IMP, with treatment assignment according to actual treatment received.

9.4.5 PK Analysis Set

The PK analysis set will consist of patients in PK subgroup who have at least one after-dose measurable plasma sample.

9.5 Trial Population

9.5.1 Demographics and other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all patients in the ITT, FAS, PP, and Safety analysis sets by treatment group.

9.5.2 Medical History, Concomitant Medication and Other Safety Evaluations

Medical history will be coded by system organ class (SOC) and preferred term (PT) using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarised for all patients in the ITT, FAS, and Safety analysis sets by treatment group.

The number and percentage of patients with medical history conditions will be summarised by SOC and PT.

9.6 Endpoint Assessments

9.6.1 General Considerations

Due to exploratory nature of this proof-of-concept trial, statistical testing will be performed both at the one-sided 20% and the one-sided 5% level. However, if the direction of the hypothesis is not self-evident, or two-sided in nature (e.g. testing for an interaction term), two-sided tests will be performed.

Quantitative variables will be described with the number of non-missing values, mean, standard deviation (SD), median, and minimum/maximum values. Qualitative variables will be described with the number and percentage of patients with each qualitative characteristic. Missing values will not be included in the calculation of percentages. All data will be listed by individual patient and study visit.

The efficacy data will be descriptively summarized and used for exploratory purposes only.

The Mayo subscores for stool frequency and rectal bleeding will be calculated as an average based on scores collected from the Patient daily Paper Diary, for up to 5, but at least 3 days prior to each applicable visit. If the patient undergoes bowel preparation for endoscopy any of the days before a visit, the day(s) should be censored from mean stool frequency and rectal bleeding subscore calculations for that visit.

9.6.2 Primary Endpoint

The primary efficacy endpoint is clinical and endoscopic remission (defined as a full Mayo score ≤2, no individual subscore >1, rectal bleeding subscore = 0) at Week 12 in the ITT population. This binary outcome (remission status=yes/no) variable will be analysed by a logistic regression model with treatment and the randomisation-stratification factors (prior corticosteroids treatment and consent to participate in PK substudy) as fixed effects and the baseline full Mayo score as covariate. A patient with missing data on the remission status will be assumed to be not in remission. Sensitivity analyses, using different analyses sets and missing data handling, will be detailed in the SAP.

9.6.3 Secondary and Exploratory Endpoints

All dichotomised secondary endpoints will be analysed using a repeated logistic regression model using Generalized Estimating Equations (GEE) with treatment, the randomisation-stratum, and visit as factors, the respective baseline score as covariate, and allowing for a treatment by visit interaction for the FAS and PP analysis set.

Continuous endpoints (e.g. change from Baseline in 6-point/9-point partial or full Mayo Score) will be analysed using a repeated measures Analysis of Covariance (ANCOVA) model for the FAS and PP analysis set using the same adjustments as above.

Endpoints assessed at only one post-baseline visit will be analysed using the cross-sectional equivalents, i.e. a logistic regression (similar to the primary endpoint) for binary endpoints, and ANCOVA for continuous endpoints (without adjusting for visit, and without a visit by treatment interaction).

If applicable, AUC_{inf}, AUC_t, %ExtrapAUC, C_{max}, t_{max}, CL, V_z, λ_z, $t_{½}$ and MRT for TJ301 after the initial dose at Visit 2 (Week 0) will be calculated by non-compartmental analysis using WinNonlin V7.0 or above.

For all patients, serum peak and trough (pre-infusion) TJ301 concentrations over time will be presented as descriptive statistics.

Exploratory exposure-response modelling of the effect of TJ301 on biomarkers and efficacy assessments may be performed and used for optimisation of dose in future trials.

9.7 Extent of Exposure and Treatment Compliance

Descriptive summaries of the number of days dosed with study drug will be provided for each treatment group. The summaries will be provided for the Safety analysis set.

9.8 Safety

9.8.1 General Considerations

Safety parameters will be evaluated for the safety analysis data set.

Complete data listings and summary tables will be created for all safety information and include adverse events, concomitant medications, vital signs, clinical laboratory test values, and 12-lead ECG.

For safety data, Baseline will be defined as the last observed value collected prior to the start of treatment. No statistical testing for comparison of treatment groups will be performed for safety variables.

9.8.2 Adverse Events

A pre-treatment adverse event will be defined as an adverse event which occurs between signing the informed consent form and before the first dose of the IMP. A treatment-emergent adverse event (TEAE) will be an adverse event which occurs in the time interval from time of start of the first dose of the IMP up to 28 days after the Follow-up Visit. If an adverse event on Day 0 occurs before administration of IMP, it will be recorded as a pre-treatment adverse event. A post-treatment adverse event is any adverse event occurring after the patient's last visit (see also Section 8.6.2).

Treatment-emergent adverse events will be tabulated by SOC and PT using the currently available MedDRA version. The total number of patients reporting an adverse event, the percentage of patients (%) with an adverse event, and the number of events (E) reported will be presented.

Summary tables will be prepared for:

- All adverse events
- Adverse events by causality (reasonable possible/no reasonable possible)
- Adverse events leading to death
- Adverse events by intensity
- Adverse drug reactions by intensity
- SAEs
- Adverse events leading to withdrawal

A separate data listing will be provided of pre-treatment and post-treatment adverse events.

9.8.3 Safety Laboratory Variables

Clinical laboratory variables will be presented by using both summary statistics.

10 DATA HANDLING

10.1 Source Data and Source Documents

Source Data – International Conference on Harmonisation (ICH) Definition

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents - ICH Definition

Source documents are defined as original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Trial-specific Source Data Requirements

For each patient allocated to treatment, the Investigator will indicate in the hospital/medical source records that the patient participates in this trial and the date of obtaining the informed consent. The records should document data on the condition of the patient at the time the patient is enrolled in the trial to enable verification of eligibility. Signed and dated informed consent will be stored and archived according to local requirements. In addition the following information, at the minimum, will also be recorded in the hospital/medical source records for each patient:

- Documentation of signed and dated Informed Consent
- Patient's name and date of birth
- Screening/randomisation number
- Body weight and height
- Dosing of IMP – date of first and last dose
- Occurrence of any adverse events/SAEs (including description and duration)
- Medical history
- Date of UC diagnosis
- Date of each visit
- Any assessment performed
- Any concomitant therapy
- Status of the patient at the end of trial

- Reason for discontinuation/withdrawal, if applicable

The following documents collected during the trial should be stored and archived together with the patient's hospital/medical records or in the Investigator File as agreed upon prior to the trial start at each trial site:

- Laboratory print-outs from central and local laboratory – evaluated, signed, and dated by the Investigator or a delegated Sub-Investigator
- ECG print-outs/reports – evaluated, signed, and dated by the Investigator or a delegated Sub-Investigator
- Patient dispensing logs of IMP
- Evaluations of physical examinations
- Collection of laboratory samples
- Demographics

For withdrawals, all available e-CRF data should be monitored and source data verified. Source data verification (SDV) will be handled the same way for withdrawn patients as for completed patients.

10.2 Electronic Case Record Form

An e-CRF system provided by an independent third-party CRO will be used for data capture. The system is validated and access at all levels to the system is granted/revoked following the Sponsor's procedures, in accordance with regulatory and system requirements.

Data should be entered into the system timely after the patient has attended a visit or after the data become available, as applicable.

The Investigator will approve/authorise the e-CRF entries for each patient with an electronic signature which is equivalent to a handwritten signature.

The e-CRF system and the database will be hosted at the independent third party CRO. After the trial database is declared clean and released to the statistician, a final copy of the database will be stored at the Sponsor. The Investigator will also receive a copy of the trial site's final and locked data (including audit trail, electronic signature and queries) as write-protected PDF-files produced by the independent third party CRO. The PDF-files will be stored on a CD and will be provided to the Investigator before access to the e-CRF is revoked.

Errors occurring in the e-CRF will be corrected electronically. Such corrections/modifications will be automatically tracked by an audit trail detailing the date and time of the correction and the name of the person making the correction.

10.3 Use of Patient Reported Outcome Instruments

A Paper Diary will be used by the patients for the reporting of daily bowel movement frequency and rectal bleeding (blood in stool) for the calculation of Mayo score at each visit. Patients will be instructed on the use of the Paper Diary. This will include symptom reporting (stool frequency, blood in stool) throughout the trial. The Paper Diary should be completed by the patient every evening starting the evening of the day of Visit 1. A separate manual on the use of the system will be provided to each investigational site.

10.4 Data Management

A set of data management documents will be created under the responsibility of the Sponsor or CRO. The data management plan will be issued before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation.

The data management documents will describe captured methods, who is authorised to enter the data, decisions about ownership of data, source data storage, which data will be transferred (including timing of transfers), the origin and destination of the data and who will have access to the data at all times.

10.5 Provision of Additional Information

On request, the Investigator will provide the Sponsor and CRO with additional data relating to the trial, duly anonymised and protected in accordance with applicable requirements.

11 MONITORING PROCEDURES

11.1 Periodic Monitoring

The Monitor will contact and visit the Investigator periodically to ensure adherence to the Protocol, International Conference on Harmonisation (ICH)-Good Clinical Practice (GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy, and verifiability of e-CRF entries compared to source data. The Investigator will permit the Monitor direct access to all source data, including medical records, and/or documents in order to facilitate data verification. The Investigator will co-operate with the Monitor to ensure that any discrepancies that may be identified as resolved. The Investigator is expected to be able to meet the Monitor during these visits. When the first patient is allocated to treatment at the trial site, a monitoring visit will take place shortly afterwards. For this trial, the frequency of the monitoring visits is intended to be approximately every 6-8 weeks. Frequent monitoring is expected when new patients have been included; thereafter there may be longer intervals between the visits. The frequency of monitoring is also dependent on the number of patients at each trial site.

One hundred percent SDV will be performed. The SDV process and definition of key variables to be monitored will be described in detail in the Monitor's Plan for the trial.

11.2 Audit and Inspection

The Investigator will make all the trial-related source data and records available at any time to quality assurance auditor(s) mandated by the Sponsor, or CRO, or to domestic/foreign regulatory inspectors or representatives from IECs who may audit/inspect the trial.

The main purposes of an audit or inspection are to assess compliance with the trial protocol and the principles of ICH-GCP including the Declaration of Helsinki and all other relevant regulations.

The patients must be informed by the Investigator and in the Informed Consent Documents that authorised Sponsor representatives and representatives from regulatory authorities and IECs may wish to inspect their medical records. During audits/inspections the auditors/inspectors may copy relevant parts of the medical records. No personal identification apart from the screening/randomisation number will appear on these copies.

The Investigator should notify the Sponsor without any delay of any inspection by a regulatory authority or IEC.

11.3 Confidentiality of Patient Data

The Investigator will ensure that the confidentiality of the patients' data will be preserved. In the e-CRF or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by an identification system, which consists of an assigned number in the trial. Documents that are not for submission to the Sponsor (e.g. the confidential patient identification

code and the signed Informed Consent forms), will be maintained by the Investigator in strict confidence.

12 CHANGES IN THE CONDUCT OF THE TRIAL

12.1 Protocol Amendments

Any change to this Protocol will be documented in a Protocol Amendment, issued by the Sponsor or CRO, and agreed upon by the Investigator and the Sponsor prior to its implementation.

Protocol amendments will be submitted for notification of IECs and Regulatory authorities, in accordance with local regulations. An approval by the IECs is required for a substantial amendment, e.g. one which could affect the safety of the patients, or which entails a change to the scope/design of the trial.

Changes to the protocol to eliminate immediate hazard(s) to trial patients may be implemented prior to IEC approval.

12.2 Deviations from the Protocol

Deviations from the Protocol should not occur. If deviations occur, the Investigator must inform the Monitor, and the implications of the deviation must be reviewed and discussed. Any deviation must be documented (or included in e-CRF data). In addition, a set of deviations must be accompanied by a description of the deviation, the relevant dates (start and stop), and the action taken. A Log of Protocol Deviation Reports will be maintained by the Sponsor or CRO. Deviation reports and supporting documentation must be kept in the Investigator's File and in the Trial Master File.

12.3 Premature Trial Termination

Both the Investigator (with regard to his/her participation) and the Sponsor reserve the right to terminate the trial at any time. Should this become necessary, the procedures will be agreed upon after consultation between the two parties. In terminating the trial, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the best interests of the patients. Regulatory authorities and IECs will be informed.

In addition, the Sponsor reserves the right to terminate the participation of individual trial sites. Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter patients at an acceptable rate.

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data and information collected during this trial will be reported in a clinical trial report prepared by the Sponsor or CRO and submitted for comments and signature to the Investigator.

13.2 Confidentiality and Ownership of Trial Data

Any confidential information relating to the IMP or the trial, including any data and results from the trial will be the exclusive property of the Sponsor. The Investigator and any other persons involved in the trial will protect the confidentiality of this proprietary information belonging to the Sponsor.

13.3 Publications and Public Disclosure

13.3.1 Publication Policy

At the end of the trial, one or more manuscripts for joint publication may be prepared in collaboration between the Investigator(s) offered authorship and the Sponsor. In a multi-site trial based on the collaboration of many sites, any publication of results must acknowledge all sites. Results from multi-site trials must be reported in entirety in a responsible and coherent manner and results from subsets should not be published in advance or without clear reference to the primary publication of the entire trial. The Sponsor reserves the right to be last author(s) in all publications related to this trial, with a maximum of three employees of the Sponsor per publication. In the event of any disagreement in the content of any publication, both the Investigator's and the Sponsor's opinion will be fairly and sufficiently represented in the publication.

Any external CRO or laboratory involved in the conduct of this trial has no publication rights regarding this trial.

If the Investigator wishes to independently publish/present any results from the trial, the draft manuscript/presentation must be submitted in writing to the Sponsor for comment prior to submission. Comments will be given within three months from receipt of the draft manuscript. This statement does not give the Sponsor any editorial rights over the content of a publication, other than to restrict the disclosure of the Sponsor's intellectual property. If the matter considered for publication is deemed patentable by the Sponsor, scientific publication will not be allowed until after a filed patent application is published. Under such conditions the publication will be modified or delayed at the Investigator's discretion, to allow sufficient time for the Sponsor to seek patent protection of the invention.

13.3.2 Public Disclosure Policy

International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public, clinical trials registry. Thus, it is the responsibility of the Sponsor to register the trial in appropriate registries.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Independent Ethics Committee

An IEC will review the protocol and any amendments and advertisements used for recruitment. The IEC will review the patient information sheet and the informed consent form, their updates (if any), and any written materials given to the patients. A list of all IECs to which the protocol has been submitted and the name of the committee chairmen will be included in the clinical trial report.

14.2 Regulatory Authority Authorisation/Approval/Notification

The regulatory permission from Regulatory authorities to perform the trial will be obtained in accordance with local regulations. All ethical and regulatory approvals must be available before a patient is exposed to any trial-related procedure, including screening tests for eligibility.

14.3 End-of-Trial and End-of-Trial Notification

End-of-Trial is defined as the date the last patient performs the last visit in the trial. At the end of the trial, the regulatory authorities and IECs will be notified about the trial completion according to national requirements. In addition, a summary of the clinical trial report will be provided when available and within one year of trial completion (defined as Last Patient Last Visit).

14.4 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, in compliance with the approved protocol, GCP, and applicable regulatory requirements.

14.5 Patient Information and Consent

An English master version of the Patient Information and Informed Consent documents will be provided for translation and adaptation into local languages. If changes are made to the Patient Information and Informed Consent documents by the IEC and/or the trial sites, the amended documents must be submitted back to the Sponsor for approval.

The patient will receive a copy of the patient information and his signed consent.

The Investigator will obtain a freely given written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the trial which are relevant to the patient's decision to participate. The trial patient must be given ample time to consider participation in the trial, before the consent is obtained. The informed consent form must be signed and dated by the patient before he is exposed to any trial-related procedure, including screening tests for eligibility. The Investigator will also sign and date the form.

The Investigator will explain that the patients are completely free to refuse to enter the trial or to withdraw from it at any time, without any consequences for their further care and without the need to justify their decision.

If new information becomes available that may be relevant to the trial patient's willingness to continue participation in the trial, a new patient information and informed consent form will be forwarded to the IECs (and regulatory authority, if required). The trial patients will be informed about this new information and re-consent will be obtained.

Each patient will be informed that the monitor(s), quality assurance auditor(s) mandated by the Sponsor, or regulatory authority inspector(s), in accordance with applicable regulatory requirements, may review his/her source records and data. Data protection will be handled in compliance with ICH guideline, local laws, and local regulations.

14.6 Compliance Reference Documents

The Declaration of Helsinki, the consolidated ICH-GCP, and other national law(s) in the participating countries shall constitute the main reference guidelines for ethical and regulatory conduct.

15 LIABILITIES AND INSURANCE

15.1 ICH-GCP Responsibilities

The responsibilities of the Sponsor, the Monitor and the Investigator are defined in the ICH-GCP consolidated guideline, and applicable regulatory requirements in the country where the trial takes place. The Investigator is responsible for adhering to the ICH-GCP responsibilities of investigators, for dispensing the IMP in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the trial.

15.2 Liabilities and Insurance

In case of any damage or injury occurring to a patient in association with the IMP or the participation in the trial, the Sponsor has contracted an insurance which covers the liability of the Sponsor, the Investigator and other persons involved in the trial in compliance with the laws in the countries involved.

16 ARCHIVING

16.1 Investigator File

The Investigator is responsible for maintaining all the records (protocol and protocol amendments, completed e-CRFs, signed informed consent forms, relevant correspondence, and all other supporting documentation), which enable the conduct of the trial at the site to be fully understood, in compliance with ICH-GCP. The study site should plan on retaining such documents for approximately 15 years after study completion. The study site should retain such documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Patient identification codes (patient names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to Sponsor. The Investigator must contact Sponsor prior to disposing of any study records.

16.2 Trial Master File

The Sponsor will archive the Trial Master File in accordance with ICH-GCP and applicable regulatory requirements.

17 REFERENCES

1. Rose-John S, Scheller J, Elson G, Jones SA. 2006. Interleukin-6 biology is coordinated by membrane-bound and soluble receptors: role in inflammation and cancer. J Leukoc Biol. 2006; 80(2):227-236.

2. Waetzig GH, Rose-John S. Hitting a complex target: an update on interleukin-6 trans-signalling. Expert Opin Ther Targets. 2012;16(2):225-236.

3. Gustot T, Lemmers A, Louis E, Nicaise C, Quertinmont E, Belaiche J, Roland S, Van Gossum A, Devière J, Franchimont D. Profile of soluble cytokine receptors in Crohn's disease. Gut. 2005;54(4):488-495.

4. Nancey S, Hamzaoui N, Moussata D, Graber I, Bienvenu J, Flourie B. Serum interleukin-6, soluble interleukin-6 receptor and Crohn's disease activity. Dig Dis Sci. 2008;53(1):242-247.

5. Reinisch W, Gasché C, Tillinger W, Wyatt J, Lichtenberger C, Willheim M, Dejaco C, Waldhör T, Bakos S, Vogelsang H, Gangl A, Lochs H. Clinical relevance of serum interleukin-6 in Crohn's disease: single point measurements, therapy monitoring, and prediction of clinical relapse. Am J Gastroenterol. 1999;94(8):2156-2164.

6. Mitsuyama K, Toyonaga A, Sasaki E, Ikeda H, Harada K, Tateishi H, Nishiama T, Tanikawa K. Soluble interleukin-6 receptors in inflammatory bowel disease: relation to circulating interleukin-6. Gut. 1995;36(1):45-49.

7. Dignass A, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, Danese S, D'Hoore A, Gassull M, Gomollón F, Hommes DW, Michetti P, O'Morain C, Oresland T, Windsor A, Stange EF, Travis SP; European Crohn's and Colitis Organization (ECCO). The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohn’s Colitis 2010 Feb;4(1):28-62.

8. Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, D'Haens G, D'Hoore A, Mantzaris G, Novacek G, Oresland T, Reinisch W, Sans M, Stange E, Vermeire S, Travis S, Van Assche G. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis. 2012 Dec;6(10):991-1030.

9. Smith MA, Irving PM, Marinaki AM, Sanderson JD. Review article: malignancy on thiopurine treatment with special reference to inflammatory bowel disease. Aliment Pharmacol Ther. 2010 Jul;32(2):119-30.

10. Vermeire S, O'Byrne S, Keir M, Williams M, Lu TT, Mansfield JC, Lamb CA, Feagan BG, Panes J, Salas A, Baumgart DC, Schreiber S, Dotan I, Sandborn WJ, Tew GW, Luca D, Tang MT, Diehl L, Eastham-Anderson J, De Hertogh G, Perrier C, Egen JG, Kirby JA, van Assche G,

Rutgeerts P. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. Lancet. 2014 Jul 26;384(9940):309-18.

11. Reinecker HC, Steffen M, Witthoeft T, Pflueger I, Schreiber S, MacDermott RP, Raedler A. Enhanced secretion of tumour necrosis factor-alpha, IL-6, and IL-1 beta by isolated lamina propria mononuclear cells from patients with ulcerative colitis and Crohn's disease. Clin Exp Immunol. 1993 Oct;94(1):174-81.

12. Atreya R, Mudter J, Finotto S, Müllberg J, Jostock T, Wirtz S, et al. Blockade of interleukin 6 trans signalling suppresses T-cell resistance against apoptosis in chronic intestinal inflammation: Evidence in Crohn disease and experimental colitis in vivo. Nature Medicine 2000; 6(5):583-588.

13. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987 Dec 24;317(26):1625-9.

14. Dignass A, Eliakim R, Magro F, Maaser C, Chowers Y, Geboes K, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. J Crohns Colitis. 2012 Dec;6(10):965-90.

15. Travis SP, Dinesen L. Remission in trials of ulcerative colitis: what does it mean? Pract Gastroenterol 2010;30:17-20.

16. Dhanda AD, Creed TJ, Greenwood R, Sands BE, Probert CS. Can endoscopy be avoided in the assessment of ulcerative colitis in clinical trials? Inflamm Bowel Dis. 2012 Nov;18(11):2056-62.

17. Vande Casteele N, Feagan BG, Gils A, Vermeire S, Khanna R, Sandborn WJ, Levesque BG. Therapeutic drug monitoring in inflammatory bowel disease: current state and future perspectives. Curr Gastroenterol Rep. 2014 Apr; 16(4):378.

18. Steenholdt C, Brynskov J, Thomsen OØ, Munck LK, Fallingborg J, Christensen LA, Pedersen G, Kjeldsen J, Jacobsen BA, Oxholm AS, Kjellberg J, Bendtzen K, Ainsworth MA. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. Gut. 2014 Jun;63(6):919-27.

19. Fasanmade AA, Adedokun OJ, Ford J, Hernandez D, Johanns J, Hu C, Davis HM, Zhou H. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. Eur J Clin Pharmacol. 2009 Dec;65(12):1211-28.

20. Roblin X, Marotte H, Rinaudo M, Del Tedesco E, Moreau A, Phelip JM, Genin C, Peyrin-Biroulet L, Paul S. Association between pharmacokinetics of adalimumab and mucosal healing

in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2014 Jan; 12(1):80-84.

21. Brandse JF, Wildenberg M, de Bruyn JR, Wolbink GJ, Lowenberg M, Posioen C, van den Brink GR, D'Haens GR. Fecal Loss of Infliximab As a Cause of Lack of Response in Severe Inflammatory Bowel Disease. Gastroenterology. 2012;157:S-1.

APPENDICES

Appendix 1 – Calculation of Worsening

For a given day after Visit 4, the daily score for rectal bleeding will be calculated as an average based on scores collected from the Patient daily Paper Diary for 5 days prior to that day. If the patient undergoes bowel preparation for endoscopy during any of these 5 days, the rectal bleeding subscore for those day(s) should be considered missing. In addition, the rectal bleeding subscore will be considered missing for the day of all endoscopies and the day after. The daily score for rectal bleeding will be calculated for all the days until the EoT Visit.

Furthermore, for each day after Visit 4, the change in the daily subscore for rectal bleeding from the most recent visit will be calculated. This change will be referred to as the delta in the daily subscore for rectal bleeding for that day.

Examples:

- Assume that for a patient, Day 30 is between Visit 4 and Visit 5, then the delta in the daily score for rectal bleeding at the Day 30 will be calculated as the change in the daily score for rectal bleeding at Day 30 from the daily score for rectal bleeding at Visit 4 (see Section 7.1.1).

- Assume that for a patient, Day 52 is between Visit 5 and Visit 6, then the delta in the daily score for rectal bleeding at the Day 52 will be calculated as the change in the daily score for rectal bleeding at Day 52 from the daily score for rectal bleeding at Visit 5.

Worsening will be defined as an increase from last visit in Mayo rectal bleeding subscore $\geq$1, over 3 consecutive days. Such a worsening should be evaluated by the Investigator and confirmed by endoscopy (no improvement or worse) prior to decision for withdrawal of patient.

Appendix 2 – Laboratory Parameters

The following laboratory parameters will be measured.

Laboratory parameters: urinalysis (dipstick), urine pregnancy test, urine drug panel, haematology, clinical chemistry, coagulation, serum pregnancy test, TB, HIV, HBV, HCV, EB, and CMV infection test, Clostridium difficile assay, erythrocyte sedimentation rate [ESR], C-reactive protein (CRP), neutrophil and platelet count, and biopsy samples will be measured at local sites.

Anti-TJ301 antibodies, Pharmacokinetics TJ 301, IL-6, IL-6/sIL-6R complex, and faecal calprotectin tests will be analysed in central lab; sample collection methods and handling procedures will be described in a separate laboratory manual.

Routine Haematology:

- Haematocrit (Hct)
- Haemoglobin (Hb)
- Mean cellular haemoglobin (MCH)
- Mean cellular haemoglobin concentration (MCHC)
- Mean cellular volume (MCV)
- Platelet count
- Red blood cell (RBC) count

White blood cell (WBC) count including absolute counts of neutrophils, lymphocytes, monocytes, eosinophils and basophils.

Routine Clinical Chemistry:

- Alanine transaminase (ALT)
- Albumin
- Alkaline phosphatase (AP)
- Aspartate transaminase (AST)
- Bicarbonate
- Bilirubin – direct (only if total bilirubin is outside the normal range)
- Bilirubin – total
- Calcium
- Chloride
- Creatinine
- C-Reactive protein (CRP)
- Gamma glutamyl transferase (GGT)
- Glucose
- Insulin

- HbA1c
- Potassium
- Total cholesterol, LDL cholesterol, HDL cholesterol
- Triglycerides
- Protein - total
- Sodium

Coagulation Tests:

- Activated partial thromboplastin time (aPTT)
- Prothrombin time
- International Normalised Ratio (INR)
- Fibrinogen

Urinalysis (dipstick):

- Glucose
- Bilirubin
- Ketone
- Specific Gravity
- Blood
- pH
- Protein
- Urobilinogen
- Nitrite
- Leucocytes

Pregnancy Tests:

- Serum pregnancy test, as applicable
- Urine pregnancy test, as applicable

Exploratory Biomarkers:

- From blood: C-reactive protein (CRP), ESR, IL-6, IL-6/sIL-6R complex, neutrophil and platelet count
- From faeces: calprotectin

Pharmacokinetics:

- TJ301 in serum

Urinalysis (microscopic, if applicable):

- Sediment, cells, casts

Other Laboratory Assessments:

- Urine screening for drugs of abuse (e.g. cocaine, barbiturates, amphetamines, opiates, benzodiazepine, and cannabinoids)
- HIV (HIV-1/2 Antigen and Antibodies)
- HBV (Hepatitis B Surface Antigen)
- HCV (Hepatitis C Antibody)
- TB (QuantiFERON-TB Gold; or T-spot test plus chest X-ray)
- EBV [Viral capsid antigen (VCA)-IgM test and VCA-IgG test]
- CMV (if applicable; CMV DNA load by real-time polymerase chain reaction assay)
- *Clostridium difficile* (*Clostridium difficile* toxin assay)
- Anti-TJ301 antibodies

Appendix 3 – Patient Diary (blank sample)

Patient Diary

Subject Name: _____/

Site name: _____/

Site Number: _____/

Screening No. _____ **Randomization No.** _____/

Diary Dispensing Date ☐☐☐☐☐☐☐☐ (yyyymmdd)

Next Visit Date ☐☐☐☐☐☐☐☐(yyyymmdd)

Please read the flowing questions and answer them as per your personal status.
Please ask your responsible investigator for the study if you have any questions.

1. Which option below best describes your Stool Frequency today? Please choice one only.
   a) Normal number of stools b) 1 to 2 stools more than normal
   c)3 to 4 stools more than normal d) ≥5 stools more than normal

Date(mmdd)								
Your answer								
Date(mmdd)								
Your answer								

2. Which option below best describes your Rectal Bleeding today? Please choice one only.
   a) No blood seen b) Streaks of blood with stool
   c) Obvious blood with stool d) Blood alone passes

Date(mmdd)								
Your answer								
Date(mmdd)								
Your answer								

Patient Diary

1. Do you have any unable/uncomfortable feeling during these days? No ☐, Yes☐,
   If yes, please fill in below.

Start date☐☐☐☐(mmdd) End date☐☐☐☐(mmdd) Please describe it._____/
Start date☐☐☐☐(mmdd) End date☐☐☐☐(mmdd) Please describe it._____/
Start date☐☐☐☐(mmdd) End date☐☐☐☐(mmdd) Please describe it._____/
Start date☐☐☐☐(mmdd) End date☐☐☐☐(mmdd) Please describe it._____/

2. Do you have any concomitant medications (including medications for UC) during these days? No ☐, Yes☐, If yes, please fill in below.

Drug name	Start date	End date	Route	Frequency	Strength	Dose per time (mg/g/ml)

Subject Signature: _____ **Date(yyyy/mm/dd):** _____/_____/_____

Instructions for recording the number of stools and their worst rectal bleeding over a 24-hour period:

Definition of Stool	A stool is defined as a trip to the toilet when the patient has either a bowel movement, or passes blood alone, blood and mucus, or mucus only.
Rectal Bleeding	Patients should indicate the most severe category that describes the amount of blood they had in their stools for a given day. Among the categories of rectal bleeding, “streaks of blood with stool” means streaks of blood with stool less than half the time, “obvious blood with stool” means obvious blood (more than just streaks) or streaks of blood with stool most of the time. Patients should select “No Blood Seen” in the rectal bleeding section if they do not have stool during a given day.

Appendix 4 – Summary of Changes for Version 1.1

The main purpose for revising the CTJ301UC201 protocol is to include the following changes:

- Remove Germany and add Australia as countries/regions since the Sponsor decided to conduct the study at sites in Mainland China, Taiwan, Korea and Australia instead of sites in Mainland China, Taiwan, Korea and Germany.
- Add “Version of Protocol or Protocol Amendment”.
- Clarify stratification factors in randomization.
- Update the name of IMP Manufacturer.
- Add more information on detection of HIV, HBV, HCV, EBV, CMV, and TB.
- Update inclusion criteria considering subjects should be able to understand and fill out Patient Diary.
- Update the timing when Endoscopy should be performed.
- Update exclusion criteria considering patients with latent TB infection should be excluded from this study.
- Add TB test at Safety Follow-up Visit.
- Add Blood sampling for anti-TJ301 antibodies at Visit 3.
- Modify the randomisation-stratification factors.

- Add the statement that the criteria of endoscopic appearance assessment in this study is DIFFERENT from the original criteria. Personnel responsible for endoscopic evaluation should NOT refer the original criteria.
- Add instructions for filling out Patient Diary.
- Add description of adverse events of special interest.
- Correct typographical errors.

Editorial changes and updates to style and formatting have been made to improve clarity and consistency throughout the document. Noteworthy changes are described in the table below. Changes in sections were also made in the protocol synopsis and elsewhere in the document, as applicable.

Section Number	Changed from	Changed to	Rationale
Secondary Endpoints	Not applicable.	• Change from Baseline to Week 12 in modified Mayo score (=full Mayo score excluding Physician's Global Assessment (PGA) subscore). • Change from Baseline to Weeks 4, 6, 8, 10, and 12 in PGA score.	Recommended by FDA guidance 'Ulcerative Colitis: Clinical Trial Endpoints', issued in August 2016. Use of the full Mayo Score (including Physician's Global Assessment (PGA) subscore) is

		• FDA-defined remission at Week 12, defined as Stool frequency subscore=0, Rectal bleeding subscore=0, and Endoscopy subscore =0 or 1.	not recommended by the FDA as endpoint measures to support a marketing application.
Throughout the protocol	glucocorticosteroids	corticosteroids	'corticosteroids' is more appropriate than 'glucocorticosteroids'.
Cover page, Synopsis, 6.1	Germany	Australia	Sponsor decided to conduct the study at sites in Mainland China, Taiwan, Korea and Australia instead of sites in Mainland China, Taiwan, Korea and Germany
Version of Protocol or Protocol Amendment	Not applicable.		"Version of Protocol or Protocol Amendment" is added.
3.1.2, also in Synopsis, 4.2.2 and 9.6.2	90 patients will be centrally, dynamically, stratified randomly (by elevated ≧3 mg/L) CRP levels, and stable conventional treatment (prior treatment with amino salicylates, corticosteroids, and immunosuppressive drugs)) assigned to 3 groups (1:1:1) to receive 600mg TJ301 biweekly (Q2W), 300mg TJ301 Q2W or placebo Q2W.	90 patients will be centrally, dynamically, randomly assigned to 3 groups (1:1:1) to receive 600mg TJ301 biweekly (Q2W), 300mg TJ301 Q2W or placebo Q2W. Randomisation will be stratified by prior corticosteroids treatment (yes/no) and consent to participate in PK substudy (yes/no).	Randomisation stratification is clarified.

3.1.2, also in Synopsis, 6.1 and 6.2.5	0.5, 1, 1.5, 6	0.5, 1, 2 (end of infusion), 6	Change the PK sampling at 1.5 hour to 2 hour (end of infusion).
3.3	The DSMC is an expert advisory group commissioned and charged with the responsibility of evaluating, primarily, cumulative safety data at regular intervals and ensuring that the benefit-risk assessment of the IMP continues to be favourable.	The SRC is an expert advisory group commissioned and charged with the responsibility of evaluating, primarily, cumulative safety data at regular intervals.	It is more appropriate to use SRC rather than DSMC as the name of the committee, since the purpose of the committee is to review safety data.
3.4.7, also in Synopsis	For patients not completing the trial, a Safety Follow-up Visit will be scheduled 35 days (5.8 - 6.6 half-lives of TJ301) after the last dose of IMP. For patients completing the trial, likewise a Safety Follow-up Visit will be scheduled to Day 105 (Week 15).	For patients completing the trial, a Safety Follow-up Visit will be scheduled on Day 105 (Week 15). For patients not completing the trial, a Safety Follow-up Visit will be scheduled 35 days (5.8 - 6.6 half-lives of TJ301) after the last dose of IMP.	Editorial change.
4.1.1, also in Synopsis	During Day -60 to Day -6 prior to Randomisation, an endoscopy subscore ≥2.	During Day -35 to Day -6 prior to Randomisation, an endoscopy subscore ≥2.	The endoscopy results obtained within 60 to 35 days prior to Randomisation may not be reliable as baseline.
4.1.1, also in Synopsis	at no less than 3 g 5-ASA per day	at no less than 2 g 5-ASA per day	To meet Taiwan guideline.

4.1.1, also in Synopsis	Not applicable.	The subject should be able to read and write to understand and fill out Patient Diary.	Inclusion Criterion 8 is added. To get reliable patient-reported Mayo subscorevia Patient Diary, the subjects should be able to understand and fill out Patient Diary.
4.1.2, also in Synopsis	indeterminate colitis	inflammatory bowel disease unclassified	The term “inflammatory bowel disease unclassified” is more popularly used than “indeterminate colitis” recently.
4.1.2, also in Synopsis	Presence or history of active tuberculosis (TB).	Presence or history of active tuberculosis (TB) or latent TB infection, defined as 1) a positive QuantiFERON-TB Gold test at Screening, or 2) a positive T-spot test within 4 weeks of Randomisation and evidence of current or previous pulmonary tuberculosis by chest X-ray within 12 weeks of Randomisation.	Patients with latent TB infection should be excluded from this study.
5.1	Manufacturer: OctoPlus N.V.	Manufacturer: Octoplus Development B.V.	The name of IMP manufacturer is corrected.
5.1, also in Synopsis, 5.4, 6.1	The infusion time is 2 hour±3 min.	The infusion time is 2 hours.	For some sites, it may be difficult to control the dosing time within ±3 min.
5.5.2	If the Sponsor needs to unblind a treatment, the reason and the date of opening with signature should be	If the Sponsor needs to unblind a treatment, the reason and the date of opening should be recorded with signature, following corporate	If the Sponsor needs to unblind a treatment, it should be recorded in the source documents.

	recorded, following corporate standard operational procedures for unplanned unblinding of clinical trial patients. It should be recorded in the source documents that the code is broken, why, when and by whom.	standard operational procedures for unplanned unblinding of clinical trial patients. It should be recorded in the subject's source documents that the code is broken, why, when and by whom.	
6.1, Table 1	Not applicable.	Add TB test at safety follow-up visit. Add Blood sampling for anti-TJ301 antibodies at Visit 3. Remove physical examination on V3, V5 and V7.	TJ301 may increase the risk for TB. An ADA sampling is added on Day14 (Visit 3). Physical examination every 4 weeks is sufficient.
6.1, Annotation a for Table 1	The screening endoscopy should be performed at Day -60 to Day -6 prior to Randomisation.	The screening endoscopy should be performed at Day -35 to Day -6 prior to Randomisation.	The endoscopy results obtained within 60 to 35 days prior to Randomisation may not be reliable as baseline. Some other footnotes for Time and Events Schedule have been updated.
6.2.3	Not applicable.	Add diary dispensing and diary review	Missed in V1.0.
7.1.1	Not applicable.	Note that the criteria of endoscopic appearance assessment in this study are DIFFERENT from the original criteria in (13). The Endoscopy subscore is modified so that a value of 1 does not	To emphasize that the criteria of endoscopic appearance assessment in this study is DIFFERENT from the original criteria of endoscopic

		include friability. Personnel responsible for endoscopic evaluation should NOT refer to the original criteria.	appearance assessment.
8.3	Not applicable.	Adverse events of special interest include adverse events observed in earlier clinical development of TJ301 and those resulting from blocking IL-6 signaling shown by other drugs or investigational products. Certain side effects were observed early on during the clinical development program for TJ301, including infusion-related reactions, headache, nasopharyngitis, myalgia, diarrhoea, cough, and decreased neutrophil count. In addition, certain side effects were characterized during the clinical development of other IL-6 inhibitors (e.g. tocilizumab) and have been shown to be mechanistically linked to its mode of action and its effect on inflammation. These side effects include neutropenia, thrombocytopenia, elevation of liver enzymes, lipid disorders (elevation of total cholesterol), severe infection (including tuberculosis), and gastrointestinal perforation.	Adverse events observed for TJ301 and other IL-6 inhibitors can be regarded as adverse events of special interest.
8.5.2	Haiyan Liu E-mail: haiyan.liu@tigermed.net	Zhijia Han E-mail: zhijia.han@tigermed.net	CRO contact information is updated.

Appendix 2	• TB, HIV, HBV, HCV EB, and CMV infection • Immunoglobulin M antibody titres in the presence of negative immunoglobulin G titres to Epstein-Barr virus Cytomegalovirus biopsies (if applicable)	• HIV (HIV-1/2 Antigen and Antibodies) • HBV (Hepatitis B Surface Antigen) • HCV (Hepatitis C Antibody) • TB (QuantiFERON-TB Gold or T-spot test plus chest X-ray) • EBV [Viral capsid antigen (VCA)-IgM test and VCA-IgG test] CMV (if applicable; CMV DNA load by real-time polymerase chain reaction assay)	Add more detailed instruction for screening of TB, HIV, HBV, HCV EBV, and CMV infection.